Epidermal Growth Factor Receptor Inhibition in the Management of Squamous Cell Carcinoma of the Lung

GLENWOOD D. GOSS,a,b,c JOHANNA N. SPAANSa

aOttawa Hospital Research Institute, Ottawa, Ontario, Canada; bOttawa Hospital Cancer Centre, Ottawa, Ontario, Canada; cDepartment of Medicine, University of Ottawa, Ottawa, Ontario, Canada

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Squamous • Non-small cell lung cancer • Epidermal growth factor receptor • Small molecule • Monoclonal antibodies • Meta-analysis

ABSTRACT

Molecular therapies targeting epidermal growth factor receptor (EGFR) have had a profound impact on the management of advanced non-small cell lung cancer (NSCLC). EGFR inhibition with EGFR tyrosine kinase inhibitors (EGFR-TKIs) and anti-EGFR monoclonal antibodies (mAbs) in squamous NSCLC (sqNSCLC) remains controversial in patients whose tumors are not known to harbor EGFR mutations. Recent meta-analyses of EGFR-inhibition randomized trials that are adequately powered for histological subgroup analysis and anti-EGFR trials limited to patients with squamous histology afford the opportunity to revisit EGFR treatment in sqNSCLC. In unselected patients with sqNSCLC who are not eligible for chemotherapy, EGFR-TKI therapy is a valid treatment option over placebo or best supportive care, with improved progression-free survival noted in randomized controlled trials in both the first- and second-line setting and improved overall survival (OS) in the second-line setting. In patients eligible for chemotherapy, first-line combination regimens with anti-EGFR mAbs have been shown to improve OS over chemotherapy alone in patients with squamous histology in meta-analysis and more recently in the SQUIRE sqNSCLC trial (chemotherapy with and without necitumumab). In sqNSCLC patients who respond to induction chemotherapy, maintenance therapy with erlotinib delays disease progression and may improve the survival of patients with stable disease. In the second-line setting, survival outcomes are comparable between chemotherapy and EGFR-TKIs in meta-analysis, with the latter being more tolerable as a second-line therapy. Newer-generation EGFR-TKI therapies may further benefit patients with sqNSCLC who have failed first-line chemotherapy, given the positive trial results from LUX-Lung 8 (afatinib vs. erlotinib). EGFR is a valid therapeutic target in unselected/wild-type patients with squamous cell carcinoma of the lung. With the recent approval of immune checkpoint inhibitors in the second-line management of advanced sqNSCLC and their adoption as a new standard of care, there exists an opportunity for novel combination therapies to increase therapeutic efficacy and durable tumor control. As more targeted agents are approved, combination regimens that include an anti-EGFR agent should be evaluated, and the optimal sequencing of targeted therapies should be defined.

The Oncologist 2016;21:1–9

Implications for Practice: Anti-epidermal growth factor receptor (EGFR) therapies remain controversial in unselected/wild-type EGFR squamous non-small cell lung cancer (NSCLC). Recent meta-analyses and squamous-only NSCLC EGFR-inhibition trials have overcome the power limitations of early trials and can now inform the management of squamous NSCLC with anti-EGFR therapies. With the approval of immunotherapeutics in the second-line management of squamous NSCLC, there exists an opportunity for novel combination therapies to improve efficacy and durable tumor control. The optimal timing and sequencing of available second-line targeted therapies, however, have yet to be defined. This review analyzes randomized clinical trials of EGFR inhibition in NSCLC and meta-analyses of these trials, with a focus on patients with squamous histology.

INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths worldwide [1]. Non-small cell lung cancer (NSCLC) represents 85% of all lung cancers, of which 20%–30% are squamous cell carcinoma [2]. Up to two thirds of patients with NSCLC present with locally advanced or advanced disease that is not amenable to surgery and, if left untreated, has a median survival of 7 months [3]. In patients with advanced stage IIIb/IV NSCLC, chemotherapy has been shown to improve...
sensitizing EGFR mutations (19]. In the case of small molecule EGFR inhibitors, uptake has inhibition in unselected sqNSCLC remains controversial [18, 19]. Improvement in OS was limited to the 59% of patients who developed a first-cycle rash to erlotinib (6.2 vs. 4.1 months, HR 0.94, 95% CI 0.81–0.92) [38], a finding not unique to the EGFR-TKI trials [33–37], one large phase III placebo-controlled trial (TOPICAL) evaluated the role of erlotinib as a front-line management strategy in NSCLC patients not eligible for chemotherapy [38]. Although that study demonstrated improved progression-free survival (PFS) in patients receiving erlotinib (2.8 vs. 2.6 months adjusted PFS, HR 0.80, 95% confidence interval [CI] 0.68–0.93) in the full study population, the median OS between treatment arms did not differ (3.7 vs. 3.6 months, HR 0.94, 95% CI 0.81–1.10) [38]. Improvement in OS was limited to the 59% of patients who developed a first-cycle rash to erlotinib (6.2 vs. 4.1 months, HR OS 0.76, 95% CI 0.63–0.92) [38], a finding not unique to the study [39, 40]. Patients with nonadenocarcinoma histology (not limited to squamous) and a first-cycle rash also had longer OS (HR 0.77, 95% CI 0.61–0.97), albeit in the absence of improved OS (HR 0.91, 95% CI 0.72–1.15) [38]. Although it increased the rates of diarrhea, hair loss, and constipation, treatment with erlotinib significantly improved quality of life and disease-related symptoms, including chest pain and dyspnea [38], which in the context of advanced lung cancer are important considerations.

In patients eligible for chemotherapy, EGFR-TKI therapy is not recommended in the first-line setting in NSCLC patients whose tumors are not known to harbor EGFR mutations likely also contribute to the observed efficacy of EGFR-TKI therapy [24].

The ability to definitively establish EGFR inhibition as a viable therapeutic strategy in advanced sqNSCLC has been hampered by a lack of power in the early EGFR-inhibition trials, as patients with squamous histology usually made up only 20%–30% of the study population [13, 16, 25]. Recently, a number of meta-analyses of the early EGFR-inhibition trials in advanced NSCLC have been undertaken, allowing for subgroup analysis by NSCLC histology [18, 26–29]. Combined with emerging data from a number of clinical trials limited to patients with squamous histology [30, 31], a review of the current evidence for EGFR inhibition as a therapeutic strategy in sqNSCLC is timely. Herein, we present a summary of the evidence from randomized trials of EGFR inhibition with EGFR-TKIs and anti-EGFR mAbs in advanced sqNSCLC in the front-line setting and beyond. The aim of this review is to guide the future management of advanced sqNSCLC with EGFR-targeted therapies. However, with the recent publication of the sqNSCLC Checkmate 017 study findings showing improved survival with the anti-PD-1 inhibitor nivolumab over docetaxel (9.2 vs. 6.0 months, hazard ratio [HR] 0.59, p < .001) [32], immune checkpoint blockade is redefining the second-line treatment of sqNSCLC and has created therapeutic optimism for overall future management. Therefore, the anti-EGFR trial data presented in this review must be considered in the context of a rapidly evolving field of research in sqNSCLC.

EGFR Inhibition as First-Line Therapy in Advanced Squamous NSCLC

EGFR-TKI monotherapy

Despite the high proportion of patients with advanced NSCLC who are medically unfit to undergo chemotherapy, few randomized trials have evaluated the clinical efficacy of EGFR-TKIs over best supportive care (BSC). Although mainly limited to small phase II randomized trials [33–37], one large phase III placebo-controlled trial (TOPICAL) evaluated the role of erlotinib as a front-line management strategy in NSCLC patients not eligible for chemotherapy [38]. Although that study demonstrated improved progression-free survival (PFS) in patients receiving erlotinib (2.8 vs. 2.6 months adjusted PFS, HR 0.80, 95% confidence interval [CI] 0.68–0.93) in the full study population, the median OS between treatment arms did not differ (3.7 vs. 3.6 months, HR 0.94, 95% CI 0.81–1.10) [38]. Improvement in OS was limited to the 59% of patients who developed a first-cycle rash to erlotinib (6.2 vs. 4.1 months, HR OS 0.76, 95% CI 0.63–0.92) [38], a finding not unique to the study [39, 40]. Patients with nonadenocarcinoma histology (not limited to squamous) and a first-cycle rash also had longer PFS (HR 0.77, 95% CI 0.61–0.97), albeit in the absence of improved OS (HR 0.91, 95% CI 0.72–1.15) [38]. Although it increased the rates of diarrhea, hair loss, and constipation, treatment with erlotinib significantly improved quality of life and disease-related symptoms, including chest pain and dyspnea [38], which in the context of advanced lung cancer are important considerations.

In patients eligible for chemotherapy, EGFR-TKI therapy is not recommended in the first-line setting in NSCLC patients whose tumors are not known to harbor EGFR mutations
EGFR mutations, including those with squamous histology. NSCLC whose tumors are not known to harbor activating first-line treatment strategy in patients with advanced based chemotherapy doublets remain the most appropriate.

With chemotherapy in the TORCH trial in unselected NSCLC post hoc univariate analyses across all trials consistently reporting superiority over chemotherapy alone in the first-line setting, with NSCLC, EGFR-TKI therapy has also failed to demonstrate clinical as first-line treatment strategy in advanced NSCLC whose tumors are not known to harbor activating EGFR mutations, including those with squamous histology.

**EGFR-TKI Combination Therapy**

As part of a combined regimen with chemotherapy in unselected NSCLC, EGFR-TKI therapy has also failed to demonstrate clinical superiority over chemotherapy alone in the first-line setting, with no survival differences between treatments by NSCLC histology [47–50]. These findings have been supported in a meta-analysis of six randomized controlled trials, which showed that combination therapy in unselected patients with advanced NSCLC resulted in comparable OS of 10.6 vs. 11.0 months (HR OS 1.04, 95% CI 0.96–1.13) [51]. Antagonism between the cytostatic EGFR-TKI agent and cell cycle-dependent chemotherapeutics has been advanced as a mechanism to explain these findings [52], which have to date prevented concurrent administration of chemotherapy and EGFR-TKIs as first-line treatment. Although intercalated regimens have been investigated [53, 54], preliminary evidence suggests that the therapeutic benefit of this strategy will be limited to patients with activating EGFR mutations and adenocarcinoma histology [54], limiting its relevance in the management of advanced sqNSCLC.

**Anti-EGFR Monoclonal Antibody Therapy in Squamous NSCLC**

Anti-EGFR monoclonal antibodies have not been evaluated as monotherapy in the front-line management of patients with advanced NSCLC because of their limited single-agent activity (response rate ∼4%) [55]. As part of a combination regimen, four trials (BMS-099, FLEX [First-line Erlotinib in Lung Cancer], LUCAS [Lung Cancer Cetuximab Study], and BMS-100) have evaluated cetuximab, a chimeric (mouse:human) IgG1 monoclonal antibody against EGFR, versus chemotherapy alone as first-line treatment in advanced NSCLC (Table 1) [16, 17, 56, 57]. Although generally favoring combination therapy [16, 17], an overall survival benefit with the addition of cetuximab in unselected NSCLC has only recently been established in a meta-analysis, based on the pooled analysis of individual patient data from these four trials (10.3 vs. 9.4 months, HR OS 0.90, 95% CI 0.74–1.09) [26]. The superior efficacy of this combination regimen in patients with squamous histology may be caused by their high EGFR expression. Indeed, the results of the FLEX trial showed better OS (12.0 vs. 9.6 months) in patients with high EGFR expression, among whom patients with squamous histology were found to benefit most from cetuximab (11.2 vs. 8.9 months, HR 0.62, 95% CI 0.43–0.88) [58]. The potential benefit of cetuximab to patients with squamous histology, however, must be considered within the context of the increased grade 3 and 4 toxicities in NSCLC patients receiving combination therapy [58].

The modest clinical benefit in individual cetuximab and chemotherapy trials, combined with the increased toxicity of combination therapy, has until now limited its regulatory approval in the front-line setting. However, a large phase III trial of combination therapy of the second-generation IgG1 anti-EGFR fully human antibody necitumumab with cisplatin-gemcitabine chemotherapy in NSCLC patients with squamous histology (SQUIRE) has recently demonstrated improved overall survival over chemotherapy alone (11.5 vs. 9.9 months, HR OS 0.84, 95% CI 0.74–0.96) and was generally better tolerated than cetuximab, with fewer skin toxicities and thromboembolic events observed [31]. Given the lack of treatment options in the front-line setting for patients with squamous histology and the limited efficacy of conventional chemotherapy regimens, a reassessment of this combination strategy may be warranted, given the superior efficacy and improved tolerability of the newer EGFR mAbs.

In summary, even among patients whose tumors are not known to harbor EGFR mutations, EGFR inhibition is an important strategy in the front-line management of patients with advanced squamous NSCLC. In unselected chemotherapy-ineligible patients, single-agent EGFR-TKIs are a valid treatment option that may delay disease progression and improve disease-related symptoms over BSC. Where chemotherapy is a treatment option, unselected/EGFR wild-type squamous NSCLC patients should be managed with a platinum-based doublet, as data suggest superior outcomes with chemotherapy in the absence of EGFR mutations. Although concurrent use of EGFR-TKIs and chemotherapy may be antagonistic, adding anti-EGFR mAbs in the front-line setting has been shown to improve OS in sqNSCLC in meta-analysis, and more recently in the SQUIRE trial. Against a chemotherapy backbone, the addition of newer-generation anti-EGFR mAbs may be a valid therapeutic strategy in patients with squamous histology to improve treatment outcomes, given their improved tolerability as part of a combination regimen.

**EGFR INHIBITION AS SECOND/THIRD-LINE THERAPY IN ADVANCED SQUAMOUS NSCLC**

**EGFR-TKI Monotherapy**

Compared with placebo or BSC, second-line erlotinib has been shown to improve PFS and OS in both unselected patients with...
advanced NSCLC and those with tumors of squamous histology [13, 59]. The definitive BR.21 trial of erlotinib versus placebo in the treatment of advanced NSCLC patients who had failed one or two lines of chemotherapy showed that erlotinib improved OS in the full study population (6.7 vs. 4.7 months, HR OS 0.70, 95% CI 0.58–0.85) [13]. In subgroup analysis of the 222 patients with tumors of squamous histology, erlotinib was also shown to improve OS (5.6 vs. 3.6 months; HR OS 0.67, 95% CI 0.50–0.90) [59], an improvement comparable to that of second-line chemotherapy in patients with squamous histology [60]. A similar phase III trial with gefitinib (ISEL), however, did not show an overall survival benefit in either the full study population (HR OS 0.89, 95% CI 0.77–1.02) or patients with nonadenocarcinoma histology (HR OS 0.92, 95% CI 0.75–1.12), not limited to patients with squamous histology [25]. The reason for the different results obtained in BR.21 and ISEL is unclear and is a matter of ongoing debate [61].

Given the improved efficacy of the newer-generation small molecule inhibitors against EGFR, EGFR-TKIs will likely continue to play an important role in the management of patients with squamous histology who have failed induction chemotherapy. Supporting this contention are the recent results of the LUX-Lung 8 trial in patients with sqNSCLC that compared the second-generation pan-HER irreversible EGFR-TKI, afatinib, with erlotinib in the second-line setting. That trial demonstrated a statistically significant improvement in PFS (2.4 vs. 1.9 months, HR PFS 0.82, 95% CI 0.676–0.998) [30] and OS (7.9 vs. 6.8 months, HR 0.81, 95% CI 0.69–0.95) for afatinib versus erlotinib [30]. With the recent approval of PD-1 inhibitors in the second-line management of patients with squamous NSCLC (discussed later under Other Approaches), the identification of sqNSCLC patients most likely to benefit from EGFR-TKI therapy will be increasingly important. In this respect, the correlative translational studies being conducted under the LUX-Lung 8 trial will be particularly informative.

The role of second-line EGFR-TKI therapy in chemotherapy-eligible patients with unselected/wild-type EGFR sqNSCLC remains controversial. In this setting, a number of head-to-head trials comparing EGFR-TKIs to chemotherapy have been conducted, with mixed results (Table 2) [62–67]. One such trial compared survival in patients with advanced NSCLC treated with gefitinib or docetaxel after induction chemotherapy [66]. INTEREST was a large (n = 1,433) noninferiority trial in which patients were randomized 1:1 to daily oral gefitinib (250 mg) or 75 mg/m² intravenous infusions of docetaxel every 3 weeks until disease progression. The final analysis of OS established noninferiority of these two regimens (7.6 vs. 8.0 months, HR OS 1.02, 96% CI 0.905–1.15), with results being consistent across histologic subgroups, including patients with nonadenocarcinoma histology (6.4 vs. 6.9 months) [66]. Although another smaller second-line trial (n = 222) of erlotinib versus docetaxel did suggest a survival difference favoring docetaxel in patients with EGFR wild-type NSCLC tumors (8.2 vs. 5.4 months, adjusted HR OS 0.73, 95% CI 0.53–1.00, p = .05), among patients with sqNSCLC there was no difference in OS (HR OS 0.90, 95% CI 0.49–1.65) [64]. More recently, a meta-analysis of second-line EGFR-TKI versus chemotherapy trials has reported comparable overall survival of these two treatment strategies in unselected NSCLC patients (HR OS 1.00, 95% CI 0.92–1.08) and in the EGFR wild-type population (HR OS 0.96, 95% CI 0.77–1.19); however, results were not reported separately by histology [29].

In trials comparing EGFR-TKIs to chemotherapy, EGFR-TKI therapy is generally found to be more tolerable as second-line therapy [28, 29]. In the metastatic NSCLC setting, relief of disease-related symptoms and minimization of treatment-associated toxicities in successive lines of treatment is particularly important. Although the results from more recent trials using more sensitive EGFR mutation platforms that may better define EGFR wild-type and mutant subgroups suggest that chemotherapy may result in longer PFS in EGFR wild-type NSCLC, in most of these trials the OS remained comparable [64, 68]. With the recent approval of PD-1 inhibitors for sqNSCLC, chemotherapy is an even less attractive treatment alternative in the second-line setting and is no longer an appropriate comparator for future second-line trials.

### Anti-EGFR Monoclonal Antibodies

The limited single-agent activity of EGFR mAbs and concerns regarding toxicity of combination cytotoxic therapy beyond first-line therapy has limited investigations of anti-EGFR mAb therapies in the second-line management of advanced NSCLC, including those with squamous histology. This has been confirmed by the results of the SELECT trial, which showed no overall survival benefit by adding cetuximab to docetaxel or pemetrexed in pretreated patients with advanced NSCLC, with notable increases in adverse events across all histologies [69].

In summary, in the second-line setting, EGFR-TKIs have been shown to improve OS over BSC in patients with squamous histology and remain a therapeutic option for patients who are not eligible for chemotherapy. In second and subsequent lines of therapy, this represents and increasingly bigger proportion of the sqNSCLC population. EGFR-TKIs also remain a viable treatment alternative in the management of chemotherapy-eligible sqNSCLC patients who have failed first-line chemotherapy, given the comparable survival outcomes of EGFR-TKI

Table 1. Randomized trials of first-line cetuximab plus chemotherapy in advanced non-small cell lung cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
<th>n</th>
<th>HR OS (95% CI)</th>
<th>Squamous, n (%)</th>
<th>HR OS (squamous) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLEX</td>
<td>Cisplatin/vinorelbine with and without cetuximab</td>
<td>1,125</td>
<td>0.87 (0.76–1.00)</td>
<td>377 (33.5)</td>
<td>0.80 (0.64–1.00)</td>
</tr>
<tr>
<td>BMS 099</td>
<td>Paclitaxel/carboplatin with and without cetuximab</td>
<td>676</td>
<td>0.89 (0.75–1.05)</td>
<td>132 (19.5)</td>
<td>0.87 (0.60–1.13)</td>
</tr>
<tr>
<td>BMS 100</td>
<td>Gemcitabine/celexab or gemcitabine/carboplatin with and without cetuximab</td>
<td>131</td>
<td>0.84 (0.55–1.27)</td>
<td>28 (21.4)</td>
<td>—</td>
</tr>
<tr>
<td>LUCAS</td>
<td>Cisplatin/vinorelbine with and without cetuximab</td>
<td>86</td>
<td>0.71 (0.45–1.12)</td>
<td>36 (41.9)</td>
<td>—</td>
</tr>
</tbody>
</table>

*Intention-to-treat population.

Abbreviations: —, no data; CI, confidence interval; FLEX, First-line Erbitux in Lung Cancer; HR, hazard ratio; LUCAS, Lung Cancer Cetuximab Study; OS, overall survival.
and chemotherapy in the second-line setting. With the recent approval of anti-PD-1 agents as second-line therapy in patients with squamous histology, docetaxel will likely be relegated to third-line therapy moving forward. Although not directly comparable, the similar median survival of sqNSCLC patients receiving nivolumab (9.2 months) and the newer EGFR-TKI afatinib (7.9 months) in Checkmate 017 and LUX-Lung 8 trials, respectively, supports both of these targeted agents as valid treatment options in the second-line setting in the absence of results of their head-to-head comparison. The important issue is that for the first time there are multiple therapeutic options for advanced sqNSCLC in the second-line setting. The type of regimen (single agent vs. combination therapy) and sequencing of available targeted therapies that will optimize outcomes for sqNSCLC patients who have failed induction chemotherapy have yet to be defined, but new treatment opportunities exist for this historically neglected subgroup of NSCLC patients.

Table 2. Select randomized trials of second-line epidermal growth factor receptor tyrosine kinase inhibitor versus chemotherapy in advanced non-small cell lung cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population</th>
<th>Treatment</th>
<th>n</th>
<th>Squamous, n (%)</th>
<th>HR PFS (95% CI)</th>
<th>HR OS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISTANA</td>
<td>Korean</td>
<td>Gefitinib vs. docetaxel</td>
<td>161</td>
<td>28 (17.4)</td>
<td>0.73 (0.53–1.00)</td>
<td>0.87 (0.61–1.24)</td>
</tr>
<tr>
<td>V-15-32</td>
<td>Japanese</td>
<td>Gefitinib vs. docetaxel</td>
<td>490</td>
<td>78 (15.9)</td>
<td>0.90 (0.72–1.12)</td>
<td>1.12 (0.89–1.40)</td>
</tr>
<tr>
<td>TAILOR</td>
<td>Italian</td>
<td>Docetaxel vs. erlotinib</td>
<td>222</td>
<td>54 (24.3)</td>
<td>0.71 (0.53–0.95)</td>
<td>0.73 (0.53–1.00)</td>
</tr>
<tr>
<td>DELTA</td>
<td>Japanese</td>
<td>Erlotinib vs. docetaxel</td>
<td>301</td>
<td>—</td>
<td>1.22 (0.97–1.55)</td>
<td>0.91 (0.68–1.22)</td>
</tr>
<tr>
<td>INTEREST</td>
<td>Multinational</td>
<td>Gefitinib vs. docetaxel</td>
<td>1,466</td>
<td>361 (24.6)</td>
<td>1.04 (0.93–1.18)</td>
<td>1.02 (0.91–1.15)</td>
</tr>
<tr>
<td>TITAN</td>
<td>Multinational</td>
<td>Erlotinib vs. docetaxel or pemetrexed</td>
<td>424</td>
<td>154 (36.3)</td>
<td>1.19 (0.97–1.46)</td>
<td>0.96 (0.78–1.19)</td>
</tr>
</tbody>
</table>

*Favoring docetaxel.

Abbreviations: —, no data; CI, confidence interval; DELTA, Docetaxel and Erlotinib Lung Cancer Trial; HR, hazard ratio; INTEREST, Iressa NSCLC Trial Evaluating Response and Survival Versus Taxotere; ISTANA, Iressa as Second Line Therapy in Advanced NSCLC Korea; OS, overall survival; PFS, progression-free survival; TAILOR, Tarceva Italian Lung Optimization Trial; TITAN, Tarceva in Treatment of Advanced NSCLC.

EGFR INHIBITION AS MAINTENANCE THERAPY IN ADVANCED SQUAMOUS NSCLC

Up to half of the patients with advanced NSCLC who benefit from first-line chemotherapy are not eligible for second-line chemotherapy at the time of disease progression [6, 70]. Having squamous histology is a negative predictor for treatment beyond first-line therapy in advanced NSCLC, with only a third of patients with squamous histology receiving subsequent therapies [71]. Maintenance therapy has recently been introduced as a strategy in advanced NSCLC to enhance the number of patients receiving treatment beyond induction chemotherapy and improve survival outcomes in the 40%–50% of patients whose best response to chemotherapy is stable disease. Given the low likelihood of second-line treatment in patients with sqNSCLC, maintenance therapy is a particularly attractive therapeutic strategy. The use of EGFR-TKIs as long-term maintenance therapy is supported by preclinical data suggesting a relationship between cytotoxic resistance and activation of the EGFR pathway [72, 73] and by its manageable toxicity profile.

SATURN is the largest trial to date investigating EGFR-TKI treatment as maintenance therapy in unselected NSCLC patients with stable disease or partial/complete response (PR/CR) after induction chemotherapy. Among the 889 patients randomized, erlotinib was shown to improve PFS in both patients with stable disease (12.1 vs. 11.3 weeks, HR PFS 0.68, p < .0001) and those with PR/CR (12.4 vs. 11.1 weeks, HR PFS 0.74, p > .0059) [74]. Erlotinib was also found to delay disease progression in patients with squamous histology (n = 360), irrespective of response to induction chemotherapy (PFS HR 0.76, 95% CI 0.60–0.95) [75]. Improved OS, however, was noted only in the 55% of patients with stable disease (11.9 vs. 9.6 months, HR OS 0.72, 95% CI 0.59–0.89) [74]. Among patients with stable disease, the greatest overall survival benefit was in patients with tumors of squamous histology (HR OS 0.67, 95% CI 0.48–0.92) [74]. This trial has been criticized because of the high proportion of patients in the placebo arm who never received second-line treatment; however, it is unclear whether this is a shortcoming of the study or an accurate reflection of the treatment paradigm for patients with advanced NSCLC. In a smaller three-arm study of gemcitabine continuation maintenance or erlotinib switch maintenance, both erlotinib (PFS 2.9 vs. 1.9 months, HR 0.82, 95% CI 0.73–0.93) and gemcitabine (3.8 vs. 1.9 months, HR 0.55, 95% CI 0.43–0.70) were shown to improve PFS over observation, with the benefit being similar in patients with nonadenocarcinoma histology (erlotinib: PFS HR 0.88, 95% CI 0.72–1.08; gemcitabine: PFS HR 0.56, 95% CI 0.37–0.85) [76].

Clinical trials of maintenance gefitinib after induction chemotherapy have also demonstrated improved PFS in a number of studies [77, 78]; however, these have not translated into improved overall survival in the individual trials. The limited number of patients with squamous histology in the gefitinib trials [77, 78] has limited interpretation of these findings for this subgroup. However, in a recent meta-analysis of EGFR-TKI maintenance trials (erlotinib or gefitinib), EGFR-TKIs were shown to reduce the risk of disease progression in unselected patients with advanced NSCLC (PFS HR 0.63, 95% CI 0.50–0.76), with the benefit being similar in patients with nonadenocarcinoma histology (HR 0.77, 95% CI 0.64–0.90) [79].

In summary, maintenance therapy is a particularly attractive therapeutic strategy in advanced sqNSCLC given the low likelihood of receiving second-line therapy. EGFR-TKI maintenance trials suggest that these agents delay disease progression in patients who respond to first-line chemotherapy,
including those with squamous histology. Given the poor prognosis of patients with stable disease after induction chemotherapy, maintenance EGFR-TKIs may represent an important therapeutic strategy in the management of sqNSCLC. With the introduction of new targeted therapies in the second-line setting, the timing of additional therapies (immediate versus deferred until progression) and the sequencing of available treatments will need to be defined.

**Other Approaches in the Management of Squamous Cell Carcinoma of the Lung**

Although historically at a therapeutic disadvantage compared with patients with nonsquamous NSCLC, a number of treatment strategies for advanced sqNSCLC are being developed and are under clinical investigation. Although it is not possible to address these in depth, it is important to acknowledge these emerging strategies in the management of squamous cell carcinoma of the lung.

The poor outcomes following conventional cytotoxic chemotherapy and the lack of treatment alternatives in sqNSCLC have prompted the evaluation of combination therapies aimed at enhancing the efficacy of established cytotoxic therapies. In the first-line setting, combination therapy of a platinum doublet with agents such as irinotecan, a poly-ADP ribose polymerase inhibitor, has failed to demonstrate improved overall survival (ECLIPSE) [80]. In the second-line setting, the antiangiogenic inhibitor ramucirumab has recently been shown to improve survival by 1.4 months (10.5 vs. 9.1 months, HR OS 0.86, 95% CI 0.75–0.98) when used in combination with docetaxel in the REVEL study, with comparable efficacy noted in sqNSCLC in subgroup analysis (9.5 vs. 8.2 months, HR OS 0.88, 95% CI 0.69–1.13) [81]. The impact of this combination in the overall management of patients with squamous histology is, however, uncertain.

Treatment with combinations of targeted agents in the second-line setting has also been evaluated as a strategy to improve clinical outcomes over EGFR-TKI monotherapy. Although mostly limited to phase II trials [82–86], there is some evidence that combination therapies that target multiple pathways may enhance treatment efficacy in sqNSCLC. Although an OS benefit of this approach has yet to be established [87], results from a phase III trial of erlotinib and sunitinib in previously treated sqNSCLC patients demonstrated a numerically superior PFS with combination therapy (HR PFS 0.80, 95% CI 0.61–1.05) [88]. At this time, however, this combination regimen is not approved in the second-line setting.

Finally, a number of molecular targets other than EGFR have recently been identified in sqNSCLC using comprehensive genome analysis [89]. Although a number of therapies targeting these molecular aberrations are currently under investigation in the LUNG MAP master protocol [90], their approval for the management of patients with sqNSCLC may be several years away. Immunotherapies that target immune checkpoints are also increasingly being investigated in lung cancer. Encouraging data on two PD-1 inhibitors (nivolumab and pembrolizumab) and a PD-L1 inhibitor (MPDL3280A [atezolizumab]) in NSCLC have recently been published [32, 91–95], with atezolizumab receiving FDA breakthrough designation in NSCLC patients with PD-L1-positive tumors progressing after induction chemotherapy, based on encouraging preliminary results [96]. Pembrolizumab has also received breakthrough designation in the second-line management of advanced NSCLC based on the results of the phase Ib trial (KEYNOTE-001) [97]. More recently, nivolumab has received FDA approval as a second-line therapy for metastatic sqNSCLC [98] based on the superior OS of sqNSCLC patients treated with nivolumab compared with docetaxel (9.2 vs. 6.0 months, HR 0.59, p < .001) in CHECKMATE 017, a randomized open-label trial [32, 91]. Although these results are encouraging, given the shorter-than-expected survival in the docetaxel arm in CHECKMATE 017 compared with previous reports [60], these early results require external validation. Nonetheless, PD-1/PD-L1 therapies are particularly exciting because of durable responses in excess of 1 year that have been documented in a percentage of patients on trial [32]. Although these possibilities expand the treatment options for patients with advanced sqNSCLC who have failed chemotherapy, the treatment strategy that will optimize therapeutic outcomes using these agents has not yet been defined, and the unique toxicities associated with this class of immune-modulating agents are still under investigation.

**Discussion**

Despite their established efficacy in unselected/EGFR wild-type NSCLC, EGFR-TKIs are increasingly being used in biomarker-selected patients where their efficacy is more pronounced [99, 100]. This shift in the management strategy in advanced NSCLC puts patients with squamous histology at a disadvantage because of the belief that their tumors rarely harbor EGFR mutations, and further limits their treatment options. Accumulating data of EGFR inhibition in NSCLC has afforded the opportunity to revisit anti-EGFR treatment in sqNSCLC and has confirmed a role for these agents in sqNSCLC management. Combined with emerging data from trials limited to patients with squamous histology, the role of EGFR inhibition in patients with squamous cell carcinoma of the lung is being redefined.

In patients not eligible for chemotherapy, first-line EGFR-TKI treatment with erlotinib has been shown to improve quality of life and delay progression compared with BSC in unselected NSCLC. Erlotinib has also been shown to improve PFS and OS in patients with sqNSCLC who have failed first-line chemotherapy. Second-line EGFR-TKIs have survival outcomes comparable to those of chemotherapy and better tolerability in advanced NSCLC, including in wild-type disease and nonadenocarcinoma/squamous histology. Maintenance EGFR-TKI therapy has been shown to delay disease progression in patients who respond to induction chemotherapy and to improve survival in meta-analyses in unselected NSCLC and in patients with squamous histology and is an important therapeutic option for sqNSCLC patients who may deteriorate too quickly to be eligible for second-line chemotherapy.

In chemotherapy-eligible patients, EGFR inhibition is an important component of a first-line strategy in the management of patients with squamous histology. Specifically, in a meta-analysis of cetuximab trials and more recently in a large phase III trial with necitumumab, anti-EGFR mAbs in combination with chemotherapy were shown to improve PFS and OS in sqNSCLC. Although survival benefits are modest, they are...
suggest that EGFR alterations occur with a frequency of tyrosine kinase/Ras pathways, recent genomic analyses previously suspected. Specifically, in the two thirds of sqNSCLC genomic alterations of EGFR may be more common than pre-approved first-line therapy for advanced sqNSCLC. Noteworthy because they enhance the efficacy of the only approved first-line therapy for advanced sqNSCLC.

The biologic mechanism accounting for the efficacy of EGFR inhibition in sqNSCLC is likely multifactorial. First, genomic alterations of EGFR may be more common than previously suspected. Specifically, in the two thirds of sqNSCLC with activation of the phosphatidylinositol 3-kinase/receptor tyrosine kinase/Ras pathways, recent genomic analyses suggest that EGFR alterations occur with a frequency of ~9% [89]. This may, in part, explain the efficacy of EGFR inhibition in sqNSCLC in the early EGFR-TKI trials. Second, second-generation EGFR-TKIs, such as afatinib, which irreversibly bind to enzymatically active ErbB receptors, likely enable sustained Erb family blockade including receptor activation, dimerization, and resistance inhibition and account for their enhanced efficacy over erlotinib in sqNSCLC. Third, the improved efficacy of anti-EGFR mAbs in squamous cell carcinoma of the lung is mostly likely caused by their higher EGFR expression, which is consistent with the efficacy of anti-EGFR mAbs in other high-EGFR-expressing tumors such as squamous cell carcinoma of the head and neck.

Although EGFR inhibition is a valid therapeutic approach in the management of advanced sqNSCLC patients, the benefits are modest and overall prognosis remains poor. The evaluation of therapies aimed at novel molecular targets in sqNSCLC has recently been enabled by comprehensive genomic characterization by The Cancer Genome Atlas project. Moving forward, combination therapies targeting multiple oncogenic pathways appear to be a rational approach to improve therapeutic efficacy. Given the manageable toxicities of anti-EGFR therapies, combinations of EGFR inhibitors with other targeted agents is feasible. With the encouraging results of PD-1/PD-L1 immune checkpoint inhibition in NSCLC, including in squamous histology, anti-EGFR combination regimens that include an immune checkpoint inhibitor may be a valid strategy. In this respect, combination therapy with anti-EGFR monoclonal antibodies may be a rational therapeutic approach, given that anti-EGFR mAbs have been shown to activate a number of immune mechanisms resulting in cellular cytotoxicity [101]. The sequencing of available targeted therapies that will optimize outcomes for sqNSCLC patients has yet to be defined but offers exciting treatment opportunities in their future management.

With the encouraging results of PD-1/PD-L1 immune checkpoint inhibition in NSCLC, including in squamous histology, anti-EGFR combination regimens that include an immune checkpoint inhibitor may be a valid strategy.

CONCLUSION

Patients with advanced sqNSCLC have historically been at a therapeutic disadvantage. Recent meta-analyses have definitively established the role of anti-EGFR therapies in their treatment. Combined with the positive phase III results of newer anti-EGFR therapies, such as afatinib in the second-line setting and necitumumab in combination with chemotherapy in the first-line setting, EGFR-targeted therapies are a valid therapeutic strategy in sqNSCLC. As more targeted agents are approved, novel combination regimens that include an anti-EGFR therapy should be evaluated, and the optimal sequencing of available targeted therapies should be defined.

AUTHOR CONTRIBUTIONS

Conception/Design: Glenwood D. Goss, Johanna N. Spaans
Provision of study material or patients: Johanna N. Spaans
Collection and/or assembly of data: Glenwood D. Goss, Johanna N. Spaans
Data analysis and interpretation: Glenwood D. Goss, Johanna N. Spaans
Manuscript writing: Glenwood D. Goss, Johanna N. Spaans
Final approval of manuscript: Glenwood D. Goss, Johanna N. Spaans

DISCLOSURES

Glenwood D. Goss: AstraZeneca, Roche, Boehringer Ingelheim Pharmaceuticals, Inc., Bristol-Myers Squibb, Pfizer (C/A, H), AstraZeneca (RF). The other author indicated no financial relationships. (C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (O) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

REFERENCES


65. Okano Y, Ando M, Asami K et al. Randomized phase III trial of erlotinib (E) versus docetaxel (D) as second- or third-line therapy in patients with advanced non-small cell lung cancer (NSCLC) who have wild-type or mutant epidermal growth factor (EGFR). Docetaxel and Erlotinib lung cancer trial (DELTALancet Oncol 2013;14:1326–1333.