Background: Upregulated expression and aberrant activation of the epidermal growth-factor receptor (EGFR) are found in lung cancer, making EGFR a relevant target for non-small-cell lung cancer (NSCLC). Treatment with anti-EGFR monoclonal antibodies (mAbs) is associated with modest improvement in overall survival in patients with squamous cell lung cancer (SqCLC) who have a significant unmet need for effective treatment options. While there is evidence that using EGFR gene copy number, EGFR mutation, and EGFR protein expression as biomarkers can help select patients who respond to treatment, it is important to consider biomarkers for response in patients treated with combination therapies that include EGFR mAbs.

Design: Randomized trials of EGFR-directed mAbs cetuximab and necitumumab in combination with chemotherapy, immunotherapy, or antiangiogenic therapy in patients with advanced NSCLC, including SqCLC, were searched in the literature. Results of associations of potential biomarkers and outcomes were summarized.

Results: Data from phase III clinical trials indicate that patients with NSCLC, including SqCLC, whose tumors express high levels of EGFR protein (H-score of ≥200) and/or gene copy numbers of EGFR (e.g. ≥40% cells with ≥4 EGFR copies as detected by fluorescence in situ hybridization; gene amplification in ≥10% of analyzed cells) derive greater therapeutic benefits from EGFR-directed mAbs. Biomarker data are limited for EGFR mAbs used in combination with immunotherapy and are absent when used in combination with antiangiogenic agents.

Conclusions: Therapy with EGFR-directed mAbs in combination with chemotherapy is associated with greater clinical benefits in patients with NSCLC, including SqCLC, whose tumors express high levels of EGFR protein and/or have increased EGFR gene copy number. These data support validating the role of these as biomarkers to identify those patients who derive the greatest clinical benefit from EGFR mAb therapy. However, data on biomarkers for EGFR-directed mAbs combined with immunotherapy or antiangiogenic agents remain limited.

Key words: non-small-cell lung cancer, squamous cell lung cancer, EGFR-directed monoclonal antibodies
Non-small-cell lung cancer (NSCLC) is a heterogeneous disease that accounts for ~85% of lung cancer diagnoses [1]. The different subtypes of NSCLC, which include adenocarcinoma and squamous cell lung cancer (SqCLC), are histopathologically distinct and can exhibit differential treatment responses, including in overall survival (OS) and toxicity [2–6]. SqCLC is associated with a significant unmet need; it can be very aggressive; patients tend to be older, present at a later stage, and have a high incidence of comorbidities [7, 8], all of which can reduce the effectiveness of treatment and increase toxicity [9]. This is exemplified by the currently available therapies of bevacizumab, nintedanib, and pemetrexed, which are available for the treatment of patients with NSCLC, but excluded for the treatment of patients with SqCLC due to unacceptably low levels of efficacy and/or high toxicity [3, 10]. Upregulated expression and aberrant activation of SqCLC due to EGFR protein expression and KRAS genetic alterations with NSCLC, but excluded for the treatment of patients by Universita degli Studi di Torino user Downloaded from https://academic.oup.com/annonc/article-abstract/29/8/1701/5037893

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EGFR protein expression

EGFR protein expression level has been assessed as a predictive biomarker for response to treatment with EGFR-directed mAbs in patients with NSCLC, including SqCLC.

FLEX clinical trial. The phase III FLEX clinical trial (NCT00148798) assessed the efficacy of cetuximab, an EGFR-directed mAb for the treatment of patients with advanced NSCLC, including those with SqCLC histology [23]. This trial compared cetuximab plus cisplatin–vinorelbine chemotherapy versus cisplatin–vinorelbine chemotherapy alone for the treatment of chemotherapy-naïve patients with advanced NSCLC that express EGFR in ≥1 positively immunostained tumor cell. Median OS was significantly increased by 1 month in patients treated with cetuximab plus chemotherapy compared with those who received chemotherapy alone [hazard ratio (HR)=0.87; 95% confidence interval (CI) 0.76–1.00; P=0.04] (Figure 1A). Similar results were reported in the subset of patients with SqCLC (34%) (HR=0.80; 95% CI 0.64–1.00) (Figure 1A) [23].

In a retrospective analysis of FLEX, the IHC H-score cut-off was used to assess EGFR expression as a predictor of response to cetuximab [26]. For patients with NSCLC in the EGFR high-expression group [H-score ≥200; n=345 (31%)], median OS was significantly increased by >2 months for those treated with cetuximab plus cisplatin–vinorelbine chemotherapy compared with cisplatin–vinorelbine chemotherapy alone (HR=0.73; 95% CI 0.58–0.93; P=0.011) (Figure 1A). Furthermore, no significant differences in OS were observed between treatments for patients in the EGFR low-expression group (n=776; 69%; HR=0.99). Similarly, median OS was significantly increased by >2 months in patients with SqCLC in the EGFR-high group treated with cetuximab plus cisplatin–vinorelbine chemotherapy compared with cisplatin–vinorelbine chemotherapy alone (HR=0.62; 95% CI 0.43–0.88) (Figure 1A). Contrary to the findings from the retrospective FLEX analysis, however, a phase III study of patients with NSCLC treated with docetaxel or pemetrexed with or without cetuximab did not show an interaction between H-score (200 cut-off) and OS (P=0.35) or progression-free survival (PFS) (P=0.71), although other cut-offs were not evaluated and the evaluators differed from those who developed the classification [27].

BMS099 clinical trial. In the phase III BMS099 clinical trial (NCT00112294), an accompanying trial to the FLEX trial that did not include restrictions on EGFR expression or histological subtypes, the addition of cetuximab to taxane–carboplatin chemotherapy...
significantly improved the overall response rate (ORR) compared with chemotherapy alone in patients with advanced NSCLC (25.7% versus 17.2%, respectively; \(P = 0.007\)) [28]. Median OS was also improved, although this did not reach statistical significance (9.69 months with cetuximab versus 8.38 months in the taxane–carboplatin arm (HR = 0.89; 95% CI 0.75–1.05; \(P < 0.1685\))). Improvement in PFS with the addition of cetuximab was only shown in a post hoc analysis of the SqCLC patient population (HR = 0.70; 95% CI 0.47–1.05). The contrasts in clinical benefit between the FLEX and BMS099 clinical trials supported the need for a biomarker for the selection of patients with NSCLC who would benefit from therapy with EGFR-directed mAbs.

SQUIRE clinical trial. The phase III SQUIRE trial (NCT00981058) compared necitumumab plus gemcitabine and cisplatin chemotherapy versus chemotherapy alone in chemotherapy-naïve patients with advanced SqCLC [25]. The primary end point of OS was significantly increased by >1 month in patients treated with necitumumab plus chemotherapy compared with chemotherapy alone (HR = 0.84; 95% CI 0.74–0.96; \(P = 0.01\)) (Figure 1B). Based on these results, necitumumab, in combination with cisplatin and gemcitabine, was granted approval by the United States Food and Drug Administration (FDA) for the front-line treatment of patients with metastatic SqCLC [29].

In a pre-specified exploratory analysis of SQUIRE that used the \(H\)-score to define EGFR high expression, the OS hazard ratio for treatment with necitumumab plus cisplatin–gemcitabine versus cisplatin–gemcitabine alone favored patients in the EGFR-high group (\(H\)-score ≥200; HR = 0.75; 95% CI 0.60–0.94) compared

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Figure 1. (A) Overall survival of patients with NSCLC treated with cetuximab plus chemotherapy, necitumumab plus chemotherapy, or chemotherapy alone. Patients with NSCLC and SqCLC (unselected and high EGFR expressing) treated with cetuximab plus chemotherapy or chemotherapy alone. (B) Patients with SqCLC (unselected and high EGFR expressing) treated with necitumumab plus chemotherapy or chemotherapy alone. (C) Patients with NSCLC (unselected, high EGFR expressing, EGFR FISH\(^+\)) and high EGFR expressing/SqCLC treated with cetuximab plus chemotherapy or chemotherapy alone. CI, confidence interval; EGFR, epidermal growth-factor receptor; FISH, fluorescence in situ hybridization; HR, hazard ratio; IHC, immunohistochemistry; NSCLC, non-small-cell lung cancer; SqCLC, squamous non-small-cell lung cancer. aPirker et al. [23]; bPirker et al. [26]; cThatcher et al. [25]; dPaz-Ares et al. [30]; eHerbst et al. [36]; fHirsch et al. [37].
with those in the EGFR-low group (H-score <200; HR = 0.90; 95% CI 0.75–1.07) [25]. Median OS was later shown to be significantly increased by >1.5 months for patients with EGFR-positive tumors (EGFR > 0) treated with necitumumab plus chemotherapy compared with chemotherapy alone (HR = 0.79; 95% CI 0.69–0.92; P = 0.002) (Figure 1B). Importantly, OS was not found to be longer in the 5% of patients with EGFR-negative tumors (HR = 1.52) [30]. Based on these results, necitumumab in combination with cisplatin and gemcitabine was approved by the European Medicines Agency (EMA) as a first-line treatment option for patients with advanced SqCLC expressing EGFR by IHC [31]. However, given that the subgroup of patients with EGFR-negative tumors only comprised ~5% of the study population, many physicians have questioned the need to assess EGFR expression before instituting necitumumab in clinical practice.

**INSPIRE clinical trial.** The INSPIRE trial (NCT00982111) further assessed the role of histology on the efficacy of necitumumab by comparing first-line necitumumab plus pemetrexed and cisplatin chemotherapy versus pemetrexed and cisplatin chemotherapy alone for the treatment of patients with advanced non-squamous NSCLC (i.e. adenocarcinoma, large-cell carcinoma, and other non-squamous histology) [32]. In contrast to the findings from SQUIRE, no significant differences were observed in OS between the two cohorts in the INSPIRE clinical setting. Median OS was 11.3 months in the necitumumab plus pemetrexed and cisplatin group versus 11.5 months in the pemetrexed and cisplatin group [HR = 1.01 (95% CI 0.84–1.21); P = 0.96]. In addition, there were no significant differences in OS between treatment groups in high and low EGFR protein expression groups (H-score ≥200 and <200, respectively).

The limited efficacy of necitumumab in patients with advanced non-squamous NSCLC (INSPIRE) compared with patients with SqCLC (SQUIRE) may be due to the lower frequency with which increases in EGFR gene copy number and protein levels are observed in tumors from patients with non-squamous NSCLC [11].

**Meta-analysis of two necitumumab and five cetuximab clinical trials.** A recent meta-analysis of seven phase III clinical trials of EGFR-directed mAbs (necitumumab and cetuximab) systematically reviewed available data to evaluate the efficacy and toxicity of this therapy plus chemotherapy versus chemotherapy alone for the treatment of patients with advanced NSCLC [33]. Treatment with EGFR-directed monotherapy plus chemotherapy significantly increased OS (HR = 0.90; 95% CI 0.84–0.95), PFS (HR = 0.93; 95% CI 0.87–0.98), and ORR (OR = 1.27; 95% CI 1.06–1.51) in patients with NSCLC compared with chemotherapy alone. In subgroup analyses, treatment with EGFR-directed mAbs in combination with chemotherapy was associated with improved OS in patients with SqCLC (HR = 0.84; 95% CI 0.76–0.92), in patients with NSCLC whose tumors had high EGFR expression, defined as H-score ≥200 (HR = 0.83; 95% CI 0.70–0.98), and in smokers (HR = 0.87; 95% CI 0.79–0.96). Furthermore, the association between treatment with EGFR-directed mAbs and OS, PFS, and ORR was highest among patients with SqCLC whose tumors had high EGFR expression (HR = 0.71; 95% CI 0.59–0.86).

**EGFR gene copy number and mutation**

**BMS099 clinical trial.** A retrospective, correlative analysis of data from the BMS099 clinical trial aimed to identify biomarkers for the selection of patients with advanced NSCLC who would most likely benefit from treatment with cetuximab [34]. Biomarkers analyzed included KRAS and EGFR mutations, EGFR protein expression, and EGFR gene copy number. Mutations in KRAS and EGFR were found in 17% (35 of 202) and 10% (17 of 166) of patients, respectively. EGFR protein expression was detected in 89% of patients (131 of 148), and FISH+ (FISH+ defined as ≥40% cells with ≥4 EGFR copies and gene amplification in ≥10% of analyzed cells) was detected in 52% of patients (54 of 104). However, there was no significant association between response to treatment and EGFR expression, mutation, or copy number. Similar results for KRAS and EGFR mutations and EGFR gene copy numbers were reported in a retrospective analysis of the FLEX trial [35].

**SWOG 0819 clinical trial.** The phase III SWOG 0819 trial (NCT00946712) compared cetuximab with carboplatin–paclitaxel chemotherapy versus carboplatin–paclitaxel chemotherapy alone in chemotherapy-naïve patients with advanced NSCLC [36]. Bevacizumab was allowed in either arm of the study if there were no contraindications, such as SqCLC. No significant differences were observed in PFS or OS among unselected patients (Figure 1C). However, the data suggested that patients with EGFR FISH+ tumors may have experienced a statistically insignificant trend toward a benefit in PFS (HR = 0.91; 95% CI 0.74–1.12) and OS (HR = 0.83; 95% CI 0.67–1.04).

In an exploratory analysis of the SWOG 0819 clinical trial that assessed EGFR-expression levels as a predictive biomarker for clinical response to therapy with cetuximab, tumors from patients with advanced SqCLC were characterized as FISH+ (defined as EGFR/centromeric region of chromosome ≥2 or ≥10% of cells with ≥15 EGFR copies and ≥40% of cells with four EGFR copies) or FISH− and as having high or low EGFR-expressing tumors, as assessed by IHC [37]. Patients with FISH+ SqCLC who were treated with cetuximab plus carboplatin–paclitaxel (n = 55; 17.1%) showed improved median OS of ~5 months compared with chemotherapy alone (n = 56; 17.4%; HR = 0.56; P = 0.01) (Figure 1C). Furthermore, patients with FISH+, high EGFR-expressing SqCLC who were treated with cetuximab plus carboplatin–paclitaxel (n = 30; 9.3%) showed improved median OS of ~7 months compared with chemotherapy alone (n = 28; 8.7%; HR = 0.32; P = 0.0004) (Figure 1C). Similarly, patients with high (H-score ≥200) EGFR-expressing SqCLC who were treated with cetuximab plus carboplatin–paclitaxel experienced improved median OS of ~3 months compared with chemotherapy alone (HR = 0.64; P = 0.03) (Figure 1C). No significant differences in OS were observed for the unselected and adenocarcinoma patient populations.

**SQUIRE clinical trial (NCT00981058).** In a pre-specified exploratory analysis of the phase III SQUIRE clinical trial that used FISH to assess EGFR gene expression, treatment with necitumumab plus cisplatin–gemcitabine versus cisplatin–gemcitabine alone was favored in patients in the EGFR FISH+ group (median OS 12.6 versus 9.2 months, respectively; HR = 0.70; 95% CI
EGFR-directed mAbs in combination with immunotherapy

Immunotherapy agents, or immune checkpoint inhibitors, are increasingly being used to treat patients with NSCLC, including SqCLC, and their use in combination with EGFR mAbs should be an important development for these patients. The identification of biomarkers to target the combinations to patients who will derive benefit is, therefore, an important step. Antibodies targeting the programmed death-1 (PD-1) receptor and its ligand, PD-L1, are among the currently approved immunotherapies for the treatment of patients with NSCLC, and several studies of immunotherapy agents for first-line treatment of patients with NSCLC are currently ongoing (Table 1). Pembrolizumab, a PD-1 inhibitor, is the standard first-line treatment in patients with NSCLC with PD-L1 expression levels ≥50%, and it is also indicated for second-line treatment in patients with NSCLC whose tumors express PD-L1 in ≥1% of tumor cells [38]. Nivolumab and atezolizumab, PD-1 and PD-L1 inhibitors, respectively, are recommended as preferred second-line therapy for patients with NSCLC who have previously received treatment with pembrolizumab [3, 39, 40]. Durvalumab is a PD-L1 inhibitor indicated for second-line therapy of patients with advanced urothelial cancer. Recent data suggest that it is likely to become the standard of care in patients with stage III NSCLC with no disease progression after platinum-based chemoradiation [41, 42].

Results from randomized phase III trials demonstrated that second-line treatment of patients with advanced NSCLC with pembrolizumab, nivolumab, and atezolizumab was superior to docetaxel with respect to OS after first-line treatment with platinum doublet chemotherapy [43–46]. Furthermore, the benefit of immunotherapy over chemotherapy was shown to increase with higher PD-L1 levels. Based on these findings, guidelines now recommend that patients with advanced metastatic disease be tested for PD-L1 expression once diagnosed [3]. However, routine implementation of PD-L1 testing in the clinical setting has been adversely affected by the different companion/complementary PD-L1 IHC assays that have been specifically developed for each of the approved anti-PD-1/anti-PD-L1 immunotherapies [47].

A phase Ib study (NCT02451930) has recently completed assessing the efficacy and safety of pembrolizumab and...
necitumumab combination therapy for second-line treatment of PD-L1-selected patients with stage IV NSCLC [48]. Escalating doses of necitumumab (600–800 mg) with pembrolizumab (200 mg) were administered on day 1 and every 3 weeks. The results suggest modest activity for the combination in a population with a high proportion of patients with PD-L1-negative tumors: median (95% CI) PFS was 4.1 (2.4–6.9) months and the 6-month OS (95% CI) rate was 74.7% (61.5–83.9). No additional studies of EGFR mAbs in combination with immunotherapy could be identified in patients with advanced NSCLC.

Tumor-infiltrating lymphocytes and tumor mutational burden have recently emerged as potential biomarkers for assessing the likelihood of benefit from immunotherapy (Table 2). A role for tumor mutational burden as a biomarker is supported by the increased clinical benefit from pembrolizumab, nivolumab, and atezolizumab versus chemotherapy in patients with NSCLC whose tumors express higher PD-L1 protein levels [44–46].

Table 2. Biomarkers for use with mAb therapy directed against EGFR, PD-1/PD-L1, and VEGF/VEGFR in NSCLC

<table>
<thead>
<tr>
<th>mAb</th>
<th>Biomarker</th>
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<tr>
<td>EGFR</td>
<td>EGFR protein expression</td>
<td>Significant increase in OS for cetuximab plus chemotherapy versus cisplatin–vinorelbine chemotherapy in patients with NSCLC whose tumors have high EGFR expression [26] and favored OS [27] versus pemetrexed and cisplatin [28]. The use of cetuximab–paclitaxel chemotherapy as first-line treatment in patients with NSCLC whose tumors express high levels of EGFR [29,30]. OS hazard ratio for nectumumab plus cisplatin–gemcitabine versus cisplatin–gemcitabine in patients with NSCLC whose tumors express high levels of EGFR [25].</td>
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<td></td>
<td>EGFR gene copy number</td>
<td>Improved PFS and OS for treatment with cetuximab plus carboplatin–paclitaxel chemotherapy in patients with NSCLC, including SquCLC, whose tumors are EGFR FISH+ [36]</td>
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<td>EGFR mutation</td>
<td>No significant association between mutations and response to cetuximab with chemotherapy in patients with NSCLC, including SquCLC [34]</td>
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<tr>
<td>PD-1/PD-L1</td>
<td>PD-L1 expression</td>
<td>Increased clinical benefit from second-line pembrolizumab, nivolumab, and atezolizumab versus chemotherapy in patients with NSCLC whose tumors express higher PD-L1 protein levels [44–46]</td>
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<td></td>
<td>Tumor mutational burden</td>
<td>Increased clinical benefit from pembrolizumab, nivolumab, and atezolizumab in patients with NSCLC whose tumors have a high tumor mutational burden versus patients whose tumors have a lower mutation load [49–52]</td>
</tr>
<tr>
<td>VEGF/VEGFR</td>
<td>Biomarkers are not currently available</td>
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EGFR, epidermal growth-factor receptor; FISH, fluorescence in situ hybridization; mAb, monoclonal antibody; NSCLC, non-small-cell lung cancer; OS, overall survival; PD-1, programmed death-1; PD-L1, programmed death ligand-1; PFS, progression-free survival; SquCLC, squamous cell lung cancer; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

EGFR-directed mAbs in combination with antiangiogenic agents

Similar to EGFR signaling, angiogenesis has been shown to play an important role in tumor growth and survival. Therefore, agents targeting this pathway (such as bevacizumab and ramucirumab) have been shown to play a role in advancing the treatment of patients with NSCLC. Bevacizumab, a humanized mAb directed against vascular endothelial growth factor (VEGF), was the first angiogenesis inhibitor approved for first-line treatment of patients with non-squamous NSCLC based on data from two studies that demonstrated >2 months of improvements in PFS and an improvement in OS, with results later replicated in Chinese patients with non-squamous NSCLC [53–55]. In a randomized phase II trial, cetuximab plus bevacizumab for the treatment of chemotherapy-naïve patients with advanced non-squamous NSCLC showed a prolonged median PFS of 6.05 months when combined with six cycles of chemotherapy [56]. It is important to note, however, that bevacizumab is contraindicated for treatment of patients with SquCLC due to a heightened risk of life-threatening pulmonary hemorrhage in this patient population [3,57].

Ramucirumab, a mAb directed against VEGF receptor 2, has subsequently been approved for use in combination with docetaxel for the treatment of patients with metastatic platinum-resistant NSCLC, including SquCLC. Ramucirumab has been shown to be effective as a second-line therapy, improving both OS and PFS. In the Phase III REVEL study (NCT01168973), ramucirumab 10 mg/kg + docetaxel 75 mg/m² every 3 weeks resulted in a median (95% CI) OS of 10.5 (9.5–11.2) months compared with placebo + docetaxel [58]. No clinical trials combining ramucirumab therapy with EGFR-directed mAbs are currently ongoing in patients with NSCLC.

Currently, there is no clear consensus on which specific patient groups may derive benefit from combined therapy with EGFR and VEGF receptor mAbs, particularly in patients receiving concurrent EGFR mAbs, which supports the need to establish predictive biomarkers in this setting. Unfortunately there are no clinically validated biomarkers that are predictive of antiangiogenic effectiveness in NSCLC [59], and further clinical trials are needed to establish robust biomarker data.
Conclusions

SqCLC is associated with a significant unmet need for additional therapeutic options. EGFR-directed mAbs necitumumab and cetuximab have been investigated for the treatment of patients with advanced NSCLC, including SqCLC, in several clinical settings. Treatment with EGFR mAbs combined with chemotherapy has been shown to significantly increase response rates and OS in patients with NSCLC, including SqCLC, although results may be considered clinically modest in the era of immunotherapy. These data strongly suggest a greater clinical benefit in patients with NSCLC, including SqCLC, whose tumors exhibit a high level of EGFR expression or gene copy number.

With multiple recent positive immunotherapy trials across different lines of treatment and different disease stages, the treatment landscape in NSCLC is rapidly changing. Two recent studies have shown superior PFS in patients with NSCLC treated with first-line platinum chemotherapy combined with a PD-1/PD-L1 mAb [60, 61]. Anticipating similar positive results in some of the ongoing trials assessing the efficacy of first-line platinum doublets combined with PD-1/PD-L1 mAbs in patients with advanced SqCLC (Table 1), it is reasonable to consider incorporating EGFR mAbs into chemo-immunotherapy regimens in biomarker-selected SqCLC patients. Similarly, biomarker studies in ongoing phase I/II studies evaluating PD-1/PD-L1 mAbs combined with EGFR mAbs may identify patients most likely to benefit from combined EGFR and PD-1/PD-L1 mAb treatment strategies in the first- or second-line settings.

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References

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