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REVIEW

EGFR-directed monoclonal antibodies in non-small cell lung cancer

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Abstract Several monoclonal antibodies directed against the epidermal growth factor receptor (EGFR) have been evaluated in patients with non-small cell lung cancer (NSCLC). Cetuximab, a chimeric monoclonal antibody, has been studied in combination with first-line chemotherapy in phase II and two phase III trials in patients with advanced NSCLC. The phase III FLEX trial demonstrated an increase in survival for cisplatin/vinorelbine plus cetuximab compared to chemotherapy alone in patients with advanced EGFR-expressing NSCLC. Cetuximab added to carboplatin/paclitaxel failed to improve progression-free survival in the BMS099 phase III trial. However, a meta-analysis of four randomized trials confirmed a significant survival benefit for platinum-based chemotherapy plus cetuximab compared to chemotherapy alone. High EGFR expression of tumor cells was then shown to predict the benefit of cetuximab, whereas KRAS mutations and EGFR fluorescent in situ hybridization analysis were without predictive value. Matuzumab and panitumumab have also been studied in phase II trials. Necitumumab, a fully human monoclonal antibody, is currently evaluated in combination with chemotherapy in two phase III trials in patients with advanced NSCLC. Cetuximab is also studied in combination with chemoradiotherapy in patients with locally advanced NSCLC.

Keywords EGF receptor · Monoclonal antibody · Cetuximab · Biomarker · Lung cancer · Targeted therapy

Introduction

Novel strategies to improve outcome in systemic treatment of non-small cell lung cancer (NSCLC) focus on targeted therapies and customized chemotherapy [1, 2]. Several molecular alterations have been studied as potential therapeutic targets. The greatest clinical advances have been achieved through inhibition of growth factor receptor signaling or inhibition of angiogenesis.

Activation of growth factor receptors promotes tumor growth and results in worse clinical outcome. Thus, blockade of these receptors should improve clinical outcome in patients with NSCLC. Blockade of receptors can be achieved through neutralizing ligands, inhibiting ligand binding, blocking the receptor tyrosine kinase, and other mechanisms.

Among growth factor receptors, the epidermal growth factor receptor (EGFR) is of particular interest as a potential therapeutic target [3, 4]. EGFR is a member of the ErbB family of transmembrane tyrosine kinase receptors, and its ligands include EGF and transforming growth factor-alpha. The binding of ligands to the extracellular domain of the receptor causes a conformational change and dimerization of the receptor which then activates the intracellular tyrosine kinase. The following cascade of intracellular events results in cell proliferation, invasion, metastasis, angiogenesis, and decreased apoptosis. EGFR is deregulated in many cancers including NSCLC. In NSCLC, EGFR expression is detected in up to 85 % of the tumors and has been shown to be associated with poor prognosis. EGFR inhibition in patients with NSCLC has focused on the use of EGFR-directed monoclonal antibodies or tyrosine kinase inhibitors. Pharmacokinetics, pharmacodynamics, and mode of action are different between antibodies and tyrosine kinase inhibitors.

Several EGFR-directed tyrosine kinase inhibitors are in clinical development, and some of them have entered clinical practice (see [5] for review). These drugs block receptor signaling through competitively blocking the binding of adenosine triphosphate to the cytoplasmic domain of the EGFR. Treatment with a tyrosine kinase inhibitor (erlotinib, gefitinib, or afatinib) until disease progression has resulted in superior progression-free survival and improved quality

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of life compared to platinum-based first-line chemotherapy (for a maximum of 6 cycles) in patients with advanced NSCLC and EGFR-activating mutations in their tumors. Gefitinib and erlotinib have already been approved for first-line therapy of patients with EGFR-activating mutations in many countries. In the European Union, erlotinib has also been approved as maintenance therapy and in the second- and third-line settings independent of the mutation status, whereas gefitinib has been approved for patients with EGFR-activating mutations independent of treatment line.

The second strategy to block EGFR signaling is the use of monoclonal antibodies [6]. Here, we review the current status of the clinical development of EGFR-directed monoclonal antibodies for the treatment of patients with NSCLC (Table 1).

EGFR-directed monoclonal antibodies

Anti-EGFR monoclonal antibodies inhibit signal transduction. They bind to the surface of the EGFR and competitively block the binding of EGF. Antibody receptor complexes are internalized and degraded. This leads to EGFR downregulation on the surface of tumor cells. Monoclonal antibodies may also act via immunological mechanisms such as antibody-dependent cellular cytotoxicity [7].

EGFR-directed monoclonal antibodies include cetuximab, matuzumab, panitumumab, necitumumab, and others. These monoclonal antibodies have been or are currently still being evaluated in clinical studies in patients with NSCLC, primarily in combination with first-line chemotherapy in patients with advanced NSCLC.

Cetuximab

Cetuximab (Erbitux®) is a chimeric human–murine monoclonal IgG1 antibody. It inhibits signal transduction through binding to the external domain of the EGFR and, thereby, blocking ligand binding. Cetuximab may also act via antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity [7]. Besides colorectal cancer and head and neck cancer, non-small cell lung cancer is the third major cancer type in which cetuximab has been evaluated. Cetuximab added to palliative chemotherapy has been studied in phase II and III trials in patients with advanced NSCLC (Table 2). Studies have also assessed cetuximab as a single agent in patients with advanced NSCLC and combined with chemoradiotherapy in patients with locally advanced (stage III) NSCLC, but phase III data in these settings have yet to be obtained.

Table 1 EGFR-directed monoclonal antibodies in advanced NSCLC

Monoclonal antibody	Clinical development	
	Phase	Status
Cetuximab	Phase III	Completed
Matuzumab	Phase II	Completed
Panitumumab	Phase II	Completed
Necitumumab	Phase III	Ongoing

Cetuximab is administered in patients with NSCLC like in those with other cancers. Cetuximab is given concurrently with chemotherapy and continued as a single agent after the end of chemotherapy. Following an initial loading dose of 400 mg/m^2, cetuximab is intravenously infused at weekly doses of 250 mg/m^2 until disease progression or unacceptable toxicity. Acne-like skin rash, diarrhea, and rare hypersensitivity reactions are the clinically relevant side effects of cetuximab. These side effects can be managed by prophylactic or therapeutic measures. Anti-allergy premedication is required before the first infusion and recommended for subsequent infusions. Skin rash can be managed by (prophylactic) application of creams and, in more severe cases, topical or systemic administration of corticosteroids or antibiotics.

Phase II trials

Several single-arm phase II studies evaluated cetuximab in combination with different platinum-based doublets [8–10]. Two randomized phase II trials suggested improved efficacy of chemotherapy plus cetuximab compared to chemotherapy alone [11, 12]. The Lung Cancer Cetuximab Study studied cisplatin plus vinorelbine with and without cetuximab in patients with advanced NSCLC who showed some degree of immunohistochemical EGFR expression in their tumors [11]. The second randomized phase II trial showed similar improvements when cetuximab was added to chemotherapy with a platin plus gemcitabine compared to chemotherapy alone in unselected patients with advanced NSCLC [12]. Another randomized phase II trial found similar outcomes for the concurrent and the sequential administration of chemotherapy and cetuximab [13].

The encouraging results of the phase II trials led to two phase III trials [14, 15]. The aim of these trials was to determine whether first-line chemotherapy combined with cetuximab results in superior outcome compared to chemotherapy alone in patients with advanced NSCLC.

Phase III trials

Two randomized open-label phase III trials compared chemotherapy plus cetuximab with chemotherapy alone in patients with advanced NSCLC (Table 2) [14, 15]. The FLEX trial demonstrated improved overall survival for cetuximab added to chemotherapy, whereas the BMS099

Table 2 Cetuximab combined with first-line chemotherapy in advanced NSCLC: phase III trials

		Number	Response rate (%)	Survival[a]			
				Hazard ratio	Median (months)	1 year (%)	*p* value
FLEX [14, 17] (cisplatin plus vinorelbine ± cetuximab)							
ITT	CT + cetuximab	557	36	0.87	11.3	47	0.04
	CT	568	29		10.1	42	
High EGFR score	CT + cetuximab	178	44	0.73	12.0	50	0.01
	CT	167	28		9.6	37	
Low EGFR score	CT + cetuximab	377	33	0.99	9.8	40	0.88
	CT	399	30		10.3	40	
BMS099 [15] (carboplatin/taxane)							
ITT	CT + cetuximab	338	26	0.89	9.7	n.r.	0.17
	CT	338	17		8.4	n.r	
Meta-analysis [16]							
ITT	CT + cetuximab	1003	n.r.	0.878	10.3	45	0.17
	CT	1015	n.r.		9.4	40	

n.r. not reported

[a] Primary endpoint in FLEX; secondary endpoint in BMS099

trial failed to demonstrate an improvement in progression-free survival.

The FLEX trial compared cetuximab added to first-line chemotherapy consisting of cisplatin plus vinorelbine with the same chemotherapy alone in patients with advanced EGFR-expressing NSCLC [14]. The primary endpoint of this trial was overall survival. Secondary endpoints included progression-free survival, response rate, safety, and quality of life. Eligibility criteria were stage IV or stage IIIB with malignant effusion, age ≥18 years, Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, adequate organ functions, the presence of at least one bidimensionally measurable tumor lesion, and EGFR expression on tumor cells. EGFR expression was determined by immunohistochemistry. In order to be eligible for inclusion into the FLEX trial, patients had to have at least one positively stained tumor cell in their tumors. Exclusion criteria were known brain metastases, previous exposure to EGFR-targeted therapy or monoclonal antibodies, major surgery within 4 weeks or chest irradiation within 12 weeks prior to study entry, active infection, pregnancy, and symptomatic peripheral neuropathy. Eligible patients were randomized to chemotherapy plus cetuximab or chemotherapy alone.

Chemotherapy consisted of cisplatin 80 mg/m^2 on day 1 plus vinorelbine 25 mg/m^2 on days 1 and 8 of 3-week cycles. Patients in the cetuximab arm received cetuximab with a loading dose of 400 mg/m^2, followed by weekly infusions of 250 mg/m^2. Chemotherapy was planned for a maximum of 6 cycles, but cetuximab was planned to be continued after the end of chemotherapy until disease progression or unacceptable toxicity.

At baseline, the patients (n=1,125) had the following characteristics: 70 % were male, median age was 60 years (range 18–83 years), ECOG performance status was 0–1 and 2 in 73 and 17 % of the patients, 47 % adenocarcinoma, 34 % squamous cell carcinoma, 16 % other NSCLC, 84 % were Caucasians, 11 % were of Asian ethnicity, and 22 % were non-smokers. The two treatment arms were well balanced with regard to these baseline patient characteristics.

Patients receiving chemotherapy plus cetuximab had longer survival compared to those receiving chemotherapy alone (hazard ratio, 0.87; p=0.044; median, 11.3 months versus 10.1 months; 1-year survival rates, 47 % versus 42 %). The survival benefit was seen across all major subgroups. Acne-like rash as the main cetuximab-related side effect occurred in the about two thirds of the patients, but grade 3 was seen in only 10 % of the patients. Infusion-related reactions were seen in only 4 % of the patients.

The BMS099 phase III trial compared cetuximab in combination with carboplatin plus a taxane (paclitaxel or docetaxel) with chemotherapy alone in unselected patients (n=676) with advanced NSCLC [15]. The primary endpoint was progression-free survival determined by a blinded independent radiology review committee. Progression-free survival was not different between the two treatment arms (hazard ratio, 0.90; p=0.2; median, 4.4 months versus 4.2 months). However, the response rate was higher in the chemotherapy-plus-cetuximab arm compared to the chemotherapy-alone arm (26 % versus 17 %, p=0.007). Although the trial was not powered for survival, the hazard ratio of death was 0.89 in favor of chemotherapy plus cetuximab and, therefore, in the range of the hazard ratio seen in the FLEX trial.

In both phase III trials, cetuximab was administered concurrently with chemotherapy and continued as a single agent after completion of chemotherapy. The fact that response rates have been higher with chemotherapy plus cetuximab in all trials indicates that cetuximab is active during the chemotherapy phase. The exact impact of cetuximab maintenance on the overall outcome, however, remains to be determined.

Meta-analysis of randomized trials

A meta-analysis based on 2,018 patients from four randomized trials confirmed the efficacy of cetuximab when added to first-line platinum-based chemotherapy [16]. The benefit was seen for overall survival (hazard ratio, 0.878; 95 % CI, 0.795–0.969; $p=0.01$), progression-free survival, and overall response rate. The results also suggest that the survival benefit obtained with cetuximab is independent of the type of platinum-based chemotherapy used.

EGFR expression as a predictive biomarker

Immunohistochemical EGFR expression of tumor cells was prospectively assessed by means of the DAKO pharmDx™ kit in all patients enrolled into FLEX [14]. Membrane staining intensity was divided into no staining, weak staining (1+), intermediate staining (2+), and strong staining (3+) as described [17]. The fractions of cells at the various staining intensities were determined. Patients had to have at least one positively stained tumor cell in order to qualify for inclusion into the FLEX trial. After the results of the FLEX trial had become available, research has focused on the characterization of predictive biomarkers for the selection of those patients who most likely will benefit from the addition of cetuximab to chemotherapy.

In order to determine whether EGFR expression levels of tumor cells might serve as predictive biomarkers, the association between EGFR expression based on an immunohistochemistry (IHC) score and clinical outcome has been studied [17]. The EGFR IHC score considered both intensities and their frequencies and was calculated on a continuous scale of 0–300 according to the following formula: EGFR IHC score=1×(% cells staining weakly [1+])+2×(% cells staining moderately [2+])+3×(% cells staining strongly [3+]). Using the subpopulation treatment effect pattern plot method, the objective response rate was assessed in sliding windows across the range of the IHC score. The difference in response rates between the two treatment arms was then used to identify an IHC score threshold that discriminated between a patient subset with a substantial cetuximab benefit from a subset with no or little benefit only. A tendency of higher benefit from chemotherapy plus cetuximab was seen for patients with EGFR IHC scores above 150. For further analysis, an EGFR IHC score of 200 was selected as cutoff in order to characterize those patients who will derive a substantial benefit which outweighed the risks associated with cetuximab treatment. All efficacy endpoints and safety were then assessed in patients with low EGFR expression (IHC score <200) and in those with high (IHC score ≥200) EGFR expression.

High EGFR expression was seen in 31 %, and low EGFR expression was seen in 69 % of the evaluable patients in the FLEX intent-to-treat population [17]. Baseline characteristics were similar in both expression groups and in the treatment arms of both expression groups. Among patients with high EGFR expression, patients treated with chemotherapy plus cetuximab had prolonged survival compared to those treated with chemotherapy alone. The hazard ratio was 0.73 (95 % CI 0.58–0.93, $p=0.011$), median survival was 12.0 months (95 % CI 10.2–15.2) versus 9.6 months (95 % CI 7.6–10.6), and 1-year survival rates were 50 versus 37 %. Among patients with low EGFR expression in their tumors, survival was not different between the two treatment arms (hazard ratio 0.99, $p=$ 0 88, median 9.8 and 10.3 months, 1-year survival rates 45 and 44 %). The treatment interaction test revealed a significant interaction between EGFR expression levels and treatment effect ($p=0.044$). The survival benefit achieved by the addition of cetuximab to chemotherapy in patients with high EGFR expression was seen across most subgroups including all major histological subgroups. Thus, cetuximab is currently the only targeted agent that, when added to first-line chemotherapy, improves the survival of patients with squamous cell carcinomas.

Consistent with findings on overall survival, secondary efficacy endpoints were in favor of chemotherapy plus cetuximab in patients with high EGFR expression in their tumors [17]. Response rates were 42 and 28 % for patients treated with and without cetuximab among patients with high EGFR expression, but no differences were seen among patients with low EGFR expression. The test of interaction was significant, indicating that tumor EGFR expression levels are predictive biomarkers also with regard to response to chemotherapy plus cetuximab. With regard to progression-free survival and time-to-treatment failure, the interaction tests did not reach statistical significance.

Toxicity according to treatment arm was similar in the high and low EGFR expression groups and also comparable to the toxicity seen in the overall FLEX safety population [17]. The incidences of cetuximab-related grade 3 acne-like rash were similar in both expression groups (10 and 11 % of patients, respectively) and, therefore, not different from the incidence seen in the intent-to-treat population.

In summary, patients with high EGFR expression achieved a survival gain without an increase in toxicity when cetuximab was added to chemotherapy. Therefore, patient selection based on EGFR expression levels results

in a clinically meaningful improvement in the risk benefit assessment of platinum-based first-line chemotherapy plus cetuximab in patients with advanced NSCLC.

Other parameters studied as potential biomarkers

Clinical and molecular tumor characteristics other than EGFR expression levels have also been studied whether they might serve as predictive biomarkers. The development of skin rash within 3 weeks of cetuximab treatment has been associated with longer survival, but it remains unclear whether this early-onset skin rash is predictive or only prognostic [18]. The presence of EGFR-activating mutations in the tumors has been associated with prolonged survival independent of cetuximab [19].

A KRAS mutation was detected in 19 and 17 % of the patients in the FLEX and BMS099 trials, respectively [19, 20]. The KRAS mutation status had no impact on response rate, progression-free survival, or overall survival [19, 20]. The lack of a predictive value of KRAS mutation status is consistent with findings of the SWOG phase II trials [21]. These findings are different from those in colorectal cancers, where wild-type KRAS predicts for the benefit of cetuximab, but might be explained firstly by differences in frequencies and types of KRAS mutations between NSCLC and colorectal cancer and, secondly by the greater molecular complexity of NSCLC.

The EGFR gene copy number detected by fluorescent in situ hybridization (FISH) may be another potential biomarker for EGFR-directed antibodies. This possibility has been raised by a phase II study in chemo-naive patients with advanced NSCLC treated with carboplatin plus paclitaxel and either sequential or concurrent cetuximab [22]. In this trial, EGFR FISH was assessed in 76 patients and classified as positive in 59 % of assessable patients. Patients with FISH-positive tumors had a higher disease control rate, longer progression-free survival, and longer survival compared to patients with FISH-negative tumors. In the FLEX and BMS099 trials, EGFR FISH positivity did predict neither prognosis nor benefit from cetuximab. Thus, further studies such as the ongoing SWOG S018 trial will help to clarify whether EGFR FISH analysis is a clinically useful biomarker with regard to cetuximab treatment. This randomized phase III study compares carboplatin/paclitaxel or carboplatin/paclitaxel/bevacizumab with or without concurrent cetuximab in patients with advanced NSCLC.

Cetuximab in stage III NSCLC

Cetuximab added to radiotherapy has improved the survival of patients with head and neck cancer compared to radiotherapy alone [23]. Likewise, cetuximab might also improve the outcome of radiotherapy or chemoradiotherapy in patients with locally advanced NSCLC, and therefore, phase II trials have been initiated. A randomized phase II trial (CALGB 30407) studied carboplatin, pemetrexed, and thoracic radiation (70 Gy) with or without cetuximab in 99 patients with unresectable stage III NSCLC [24]. Patients in both arms received 4 cycles of consolidation therapy with pemetrexed. Compared to historic controls, survival was improved in both arms but similar in both treatment arms. Median survival times were 19 and 22 months, respectively, and response rates were 71 and 73 %, respectively.

Matuzumab

Matuzumab is a humanized anti-EGFR monoclonal IgG1 antibody with a prolonged half-life. Its activity in preclinical models led to further evaluation in clinical trials in patients with cancer. The maximum tolerated doses of matuzumab were 1,600 mg/week as a single agent and 800 mg/week when combined with paclitaxel [25, 26]. As with cetuximab, acne-like rash was the main side effect of matuzumab.

A randomized phase II study compared pemetrexed plus matuzumab with pemetrexed alone as second-line therapy for patients with advanced non-small cell lung cancer [27]. Pemetrexed was given at 500 mg/m^2 every 3 weeks, and matuzumab was given at either 800 mg weekly or 1,600 mg every 3 weeks. The response rate was 11 % for patients treated with pemetrexed plus matuzumab and 5 % for those treated with pemetrexed alone. Patients receiving weekly matuzumab had higher response rate (16 versus 2 %) and a trend towards longer survival (12.4 versus 5.9 months) than those treated with matuzumab every 3 weeks. The combination of pemetrexed and matuzumab had an acceptable safety profile, with the most common grade 3/4 adverse event being neutropenia.

Panitumumab

Panitumumab is a fully human anti-EGFR IgG2 monoclonal antibody which does not induce auto-antibodies or antibody-dependent cellular cytotoxicity. It has shown antitumor activity in preclinical models and was studied at dosing schedules ranging from 1 to 3 weeks [28]. A randomized phase II trial in 175 patients with EGFR-positive advanced NSCLC could not demonstrate a benefit for panitumumab added to paclitaxel plus carboplatin compared to the same chemotherapy alone [29]. Rash, dry skin, pruritus, diarrhea, vomiting, stomatitis, and dizziness were more frequent in the panitumumab arm.

Necitumumab

Necitumumab (IMC-11 F8) is a recombinant human anti-EGFR monoclonal antibody and similar to cetuximab in structure. However, due to the absence of murine structures,

hypersensitivity reactions are anticipated to be less frequent with necitumumab compared to cetuximab. Currently, two phase III trials in patients with advanced NSCLC are recruiting patients. The INSPIRE trial (Clinical Trials.gov Identifier: NCT00982111) evaluates necitumumab in combination with cisplatin plus pemetrexed in patients with non-squamous cell NSCLC, and the SQUIRE trial (Clinical Trials.gov Identifier: NCT00981058) evaluates necitumumab in combination with cisplatin plus gemcitabine in patients with squamous cell NSCLC. The primary endpoint of both trials is survival.

Conclusion

Monoclonal antibodies directed against EGFR have opened new opportunities in the treatment of patients with NSCLC. Cetuximab added to first-line chemotherapy was shown to improve response rates in all randomized trials and to increase survival (FLEX trial, meta-analysis). High EGFR expression based on an IHC score has been shown to characterize those patients who benefit from the addition of cetuximab to chemotherapy. Matuzumab and panitumumab have been evaluated in phase II trials, and necitumumab is currently evaluated in two phase III trials.

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