Review Article

EGFR-directed monoclonal antibodies in non-small cell lung cancer: how to predict efficacy?

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Abstract: Cetuximab improved survival when added to first-line platinum-based chemotherapy in patients with advanced non-small cell lung cancer. In order to determine those patients who will derive the greatest benefit from the addition of cetuximab, the associations of clinical and tumor features with clinical outcome were determined. High EGFR expression of tumor cells based on an immunohistochemistry score was shown to predict benefit of cetuximab. Among patients with high EGFR expression, the hazard ratio for death was 0.73 in favor of chemotherapy plus cetuximab compared to chemotherapy alone. Among patients with low EGFR expression, no difference in survival was observed between patients treated with chemotherapy plus cetuximab compared to those treated with chemotherapy alone. The treatment interaction test was significant. KRAS mutation status and EGFR copy numbers were without predictive value. Patients with EGFR-activating mutations in their tumors had longer survival independent of the use of cetuximab. In conclusion, EGFR expression levels lend themselves as predictive biomarkers for the selection of those patients who will benefit from the addition of cetuximab to first-line chemotherapy with platinum-based doublets.

Keywords: EGF receptor; monoclonal antibody; cetuximab; biomarker; lung cancer; targeted therapy

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Introduction

Targeted therapies offer new possibilities for the systemic treatment of advanced non-small cell lung cancer (NSCLC) (1,2). The epidermal growth factor receptor (EGFR) is of particular interest as a therapeutic target (3,4). EGFR is a member of the ErbB family of transmembrane tyrosine kinase receptors. EGF and transforming growth factor-alpha are ligands of EGFR. Ligand binding to the extracellular domain of the receptor causes a conformational change and dimerization of the receptor. This activates the intracellular tyrosine kinase and starts a cascade of intracellular events which result in cell proliferation, invasion, metastasis, angiogenesis, and decreased apoptosis. EGFR is de-regulated in many cancers including NSCLC. EGFR expression is detected in up to 85% of NSCLC and has been shown to be associated with poor prognosis.

Because activation of EGFR promotes tumor growth, blockade of EGFR by monoclonal antibodies or tyrosine kinase inhibitors (TKIs) should improve clinical outcome in patients with NSCLC (3,4). Anti-EGFR monoclonal antibodies bind to the surface of EGFR and completely block the binding of EGF. Antibody receptor complexes are internalized and degraded. This leads to EGFR down-regulation on the surface of tumor cells. Monoclonal antibodies may also act *via* immunological mechanisms such as antibody-dependent cellular cytotoxicity (5). TKIs inhibit receptor signaling through competitively blocking the binding of adenosine triphosphate to the cytoplasmic domain of the EGFR.

Many EGFR-directed TKIs and several EGFR-directed monoclonal antibodies are in clinical development (4,6). In phase III trials, both EGFR-directed TKIs (erlotinib,

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

gefitinib or afatinib) and cetuximab improved outcome in patients with advanced NSCLC (7-10). Treatment with a TKI until disease progression resulted in superior progression-free survival and improved quality 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 (8-10). EGFR-directed TKIs had shown efficacy as maintenance therapy (11,12) and also in patients previously treated with chemotherapy (13). EGFR-directed TKIs were approved in many countries, although the approved indications may slightly vary between countries. In the European Union, erlotinib and gefitinib were approved for the treatment of patients with EGFR-activating mutations independent of the treatment line, and erlotinib was also approved as maintenance therapy in patients with stable disease after first-line chemotherapy and for patients progressing after prior chemotherapy.

EGFR-directed monoclonal antibodies are cetuximab, matuzumab, panitumumab and necitumumab (*Table 1*). Cetuximab is a chimeric human-murine monoclonal IgG1 antibody. Matuzumab is a humanized monoclonal antibody. Panitumumab and necitumumab are fully human monoclonal antibodies. These antibodies were or are currently still being evaluated in clinical studies, primarily in combination with first-line chemotherapy in patients with advanced NSCLC (7,14-20). Currently, data from phase III trials with chemotherapy plus EGFR-directed monoclonal antibodies are available only for cetuximab (7,20). In order to increase the clinical benefit ratio of cetuximab, research focused on the characterization of predictive biomarkers. Here we discuss the current status of predictive biomarkers for cetuximab when added to first-line chemotherapy in patients with advanced NSCLC.

First-line chemotherapy plus cetuximab

Cetuximab was mostly studied in combination with first-line chemotherapy in patients with advanced NSCLC (7,14-20). Few studies also evaluated cetuximab as single agent in patients with advanced NSCLC and in combination with chemoradiotherapy in patients with locally advanced NSCLC.

Cetuximab is usually administered concurrently with chemotherapy and continued as 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. Cetuximab-related side effects such as acne-like skin rash, diarrhea or rare hypersensitivity reactions can be managed by prophylactic or therapeutic measures. Anti-allergic pre-medication is required before the first infusion and recommended for subsequent infusions. Skin rash can be managed by (prophylactic) application of crèmes and, in severe cases, topical or systemic administration of corticosteroids or antibiotics.

Phase II trials

Results from several single-arm phase II studies of cetuximab in combination with different platinum-based doublets were reported (14-16). Two randomized phase II trials suggested improved efficacy of chemotherapy plus cetuximab compared to chemotherapy alone (17,18). Another randomized phase II trial indicated similar outcome for the concurrent and the sequential administration of chemotherapy and cetuximab (19).

Phase III trials

Two randomized phase III trials compared chemotherapy plus cetuximab with chemotherapy alone in patients with advanced NSCLC (*Table 2*) (7,20). The FLEX trial demonstrated improved overall survival for chemotherapy plus cetuximab in patients who had some degree of EGFR expression in their tumors (7). The BMS099 trial failed to demonstrate an improvement in progression-free survival in unselected patients with advanced NSCLC (20).

The FLEX trial enrolled patients with advanced EGFR-positive NSCLC (7). Patients were screened for immunohistochemical EGFR expression by means of the DAKO kit and patients had to have at least one positively stained tumor cell in order to be eligible for enrollment into the trial. Eighty-five percent of the screened patients fulfilled this inclusion criterion. Other eligibility criteria were stage IV or stage IIIB with malignant effusion, age ≥18 years, ECOG performance status 0-2, adequate

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

		N	Response rate	Survival*			
				HR	Median (months)	1-year	P-value
FLEX (7,21) cisplatin plus vinorelbine ± cetuximab							
ITT	CT+ cetuximab	577	26%	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 (20) Carboplatin/taxane ± cetuximab							
	CT+ cetuximab	338	26%	0.89	9.7	n.r.**	0.17
	CT	338	17%		8.4	n.r.	
Meta-analysis (22)							
	CT+ cetuximab	1,003	n.r.	0.878	10.3	45%	0.17
	CT	1,015	n.r.		9.4	40%	

*primary endpoint in FLEX; secondary endpoint in BMS099; **n.r., not reported

organ functions, and the presence of at least one bidimensionally measurable tumor lesion. 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 six cycles and cetuximab was planned to be continued after the end of chemotherapy until disease progression or unacceptable toxicity. The primary endpoint was overall survival. Secondary endpoints included progression-free survival, response rate, safety, and quality of life.

Patients (n=1,125) had the following baseline characteristics: 70% male, 30% female; median age 60 (range, 18-83 years); ECOG performance status 0-1 and 2 in 73% and 17% of the patients, respectively; 47% adenocarcinoma, 34% squamous cell carcinoma, 16% other NSCLC; 84% Caucasians, 11% Asian ethnicity; 22% never-smokers. The two treatment arms were well balanced with regard to these baseline patient characteristics.

Patients treated with chemotherapy plus cetuximab had longer survival compared to those receiving chemotherapy alone. The hazard ratio was 0.87 (P=0.044), median survival times were 11.3 versus 10.1 months, and 1-year survival rates were 47% versus 42%. The survival benefit was seen across all major subgroups. In particular, the survival gain was observed in both patients with adenocarcinomas and those with squamous cell carcinomas. Acne-like rash as the main cetuximab-related side effect occurred in about two thirds of the patients but grade 3 was seen in only 10% of the patients. Infusion-related reactions were seen in 4% of the patients. Thus the FLEX trial indicated a survival gain at acceptable toxicity for patients treated with chemotherapy plus cetuximab.

The BMS099 phase III trial compared cetuximab added to chemotherapy with carboplatin plus a taxane (paclitaxel or docetaxel) with chemotherapy alone in unselected patients (n=676) with advanced NSCLC (20). 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. The hazard ratio was 0.90 (P=0.2) and median survival times were 4.4 months versus 4.2 months. The response rate was 26% with chemotherapy plus cetuximab compared to 17% with chemotherapy alone, and this difference did reach statistical significance (P=0.007). The trial was not sufficiently powered to detect a survival difference. Nevertheless, the hazard ratio of death was 0.89 and, therefore, in the range of the one seen in the FLEX trial.

In both phase III trials, cetuximab was administered

concurrently with chemotherapy and continued as single agent after completion of chemotherapy. The fact that response rates were 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 confirmed the efficacy of cetuximab when added to first-line platinum-based chemotherapy (22). This analysis included 2,018 patients from 4 randomized trials (LUCAS, BMS100, FLEX, BMS099). Overall survival was prolonged in patients treated with chemotherapy plus cetuximab with a hazard ratio of 0.878 (95% CI, 0.795-0.969; P=0.01). Progression-free survival and overall response rate were also improved with chemotherapy plus cetuximab compared to chemotherapy alone. Because the results were obtained from trials that used different chemotherapies, these results suggest that the survival benefit obtained with cetuximab is independent of the type of platinum-based chemotherapy used.

Studies on biomarker characterization

After the results of the phase III trials had become available, research focused on the characterization of predictive biomarkers for the selection of those patients who will derive the benefit from the addition of cetuximab to first-line chemotherapy. Besides clinical parameters, molecular tumor characteristics were of particular interest as potential biomarkers.

First-cycle rash

Among patients treated with chemotherapy plus cetuximab, patients who developed skin rash within 3 weeks of cetuximab treatment had prolonged survival compared to those who did not (hazard ratio 0.63; median survival times 15.0 versus 8.8 months) (23). First-cycle rash was seen in 56% of the patients who were alive at day 21. However, it remains unclear whether this early onset skin rash is predictive or only prognostic.

EGFR-activating mutations

EGFR-activating mutations were analyzed in tumor samples from 39% of the FLEX intent-to-treat population. Activating mutations were detected in 15% of the evaluable patients (24). These mutations were associated with longer survival in patients treated with chemotherapy plus cetuximab but also in patients treated with chemotherapy alone. Thus EGFR-activating mutations were of prognostic value but did not appear to predict benefit from cetuximab.

KRAS mutation status

Based on findings in colorectal carcinomas where KRAS wild-type predicts for benefit of cetuximab, initial studies in patients with advanced NSCLC focused on KRAS status as a potential predictive biomarker. KRAS status was analyzed in 395 tumor samples from FLEX patients and KRAS mutations were detected in 19% of the patients (24). A similar frequency of KRAS mutations (17%) was seen in the BMS099 trial (25). However, the KRAS wild-type did not predict benefit from cetuximab with regard to response rate, progression-free survival, or overall survival in patients enrolled into these phase III trials (24,25). Similarly, KRAS mutation status lacked predictive significance in SWOG phase II trials (26). Thus the findings in advanced NSCLC are different from those in colorectal carcinomas. Potential explanations for these differences are, firstly, differences in the frequencies and types of KRAS mutations between these two cancers, and, secondly, the greater molecular complexity of NSCLC.

EGFR copy numbers

EGFR gene copy numbers detected by fluorescent in situ hybridization (FISH) were also evaluated as potential biomarkers for cetuximab (24,25). In the FLEX trial and the BMS099 trial, EGFR FISH positivity did predict neither prognosis nor benefit from cetuximab (24,25).

The possibility of EGFR copy numbers as predictive biomarkers was raised by a phase II study in chemo-naive patients with advanced NSCLC treated with carboplatin plus paclitaxel and either sequential or concurrent cetuximab (27). In this trial, 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. Based on these findings, the ongoing SWOG S018 phase III trial aims at determining whether EGFR FISH analysis can be used to characterize those patients who will benefit from adding cetuximab to first-line chemotherapy. In this trial, patients with advanced NSCLC are randomized

to carboplatin/paclitaxel (with or without bevacizumab) plus cetuximab or chemotherapy (with or without bevacizumab) alone.

EGFR expression as a predictive biomarker

Cetuximab acts via binding to EGFR on the surface of tumor cells and the amount of EGFR might have an impact on the efficacy of cetuximab. Thus studies were performed to determine whether EGFR expression levels might lend themselves as predictive biomarkers with regard to cetuximab.

EGFR-positivity of tumor cells was required for inclusion into the FLEX trial. Immunohistochemical EGFR expression of tumor cells was assessed by means of the DAKO pharmDx^{TM} kit in all FLEX patients prior to study entry (7,21). Membrane staining intensity was divided into no staining, weak staining (1+), intermediate staining (2+), and strong staining (3+) as described (21). 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, characterization of predictive biomarkers for the selection of those patients who most likely will benefit from the addition of cetuximab to chemotherapy had become a major research area. Because studies failed to show a predictive role for KRAS status and EGFR copy numbers, the association of EGFR expression levels and clinical outcome was studied in more detail.

For this analysis, an immunohistochemistry (IHC) score based on both intensities and frequencies of the various staining intensities was established (21). The EGFR IHC score 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 (STEPP) method, the objective response rates were assessed in sliding windows across the range of the IHC score. The difference in response rates between the 2 treatment arms was then used to identify an IHC score threshold that allowed to discriminate between a patient subset with a substantial cetuximab benefit from a subset with no or only little benefit. Among patients with EGFR IHC scores above 150, the benefit from cetuximab appeared to increase with increasing EGFR IHC scores. An EGFR IHC score of 200 was selected as cut-off in order to characterize those patients who will derive a substantial benefit from cetuximab treatment. All efficacy endpoints and safety were then assessed in patients with low (IHC score <200) and in those with high (IHC score ≥200) EGFR expression.

High EGFR expression was detected in 31% and low EGFR expression in 69% of patients of the intent-to-treat population of the FLEX trial (21). Baseline characteristics were similar in both expression groups and in the treatment arms of both expression groups. Among patients with high EGFR expression in their tumors, patients treated with chemotherapy plus cetuximab had longer 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 times were 12.0 (95% CI, 10.2-15.2) and 9.6 months (95% CI, 7.6-10.6 months), and 1-year survival rates were 50% and 37%. Among patients with low EGFR expression in their tumors, survival was not different between the two treatment arms. The hazard ratio was 0.99 (P=0.88). Median survival times were 9.8 and 10.3 months, and 1-year survival rates were 45% and 44%. The treatment interaction test was significant (P=0.044). Therefore, there was an interaction between EGFR expression levels and treatment effect. The survival benefit obtained with chemotherapy plus cetuximab in patients with high EGFR expression was seen across all major histological subgroups and most other major subgroups. Thus cetuximab is currently the only targeted agent that when added to first-line chemotherapy improves survival of patients with squamous cell carcinomas.

Chemotherapy plus cetuximab was superior to chemotherapy alone also with regard to secondary efficacy endpoints in patients with high EGFR expression in their tumors (21). Among these patients, response rates were 42% and 28% for patients treated with and without cetuximab. Among patients with low EGFR expression, no differences in response rates were observed. The test of interaction was significant, indicating that tumour 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 of the overall FLEX safety population (21). 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 EGFR-directed monoclonal antibodies

Matuzumab, a humanized anti-EGFR monoclonal IgG1 antibody with a prolonged half-life, and panitumumab, a fully human anti-EGFR IgG2 monoclonal antibody, were also studied in phase I and II trials in patients with advanced NSCLC (28-32). However, data from phase III trials or on biomarker characterization are not available for these 2 antibodies.

Necitumumab, a recombinant human anti-EGFR monoclonal antibody, is currently evaluated in combination with chemotherapy in patients with advanced NSCLC. No data on predictive biomarkers with regard to necitumumab have been reported until now.

Conclusions

Monoclonal antibodies directed against the EGFR opened new opportunities in the treatment of patients with advanced NSCLC. Cetuximab added to first-line chemotherapy was shown to improve response rates in all randomized trials and to increase survival as demonstrated by the FLEX trial and the meta-analysis of randomized trials. The survival benefit obtained with cetuximab is limited to patients with EGFR expression in their tumors.

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