Review Article

Cetuximab in non-small-cell lung cancer

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Abstract: Cetuximab is a chimeric monoclonal antibody that is directed towards the epidermal growth factor receptor (EGFR). It has been evaluated in combination with first-line chemotherapy in several phase II and two phase III trials in patients with advanced NSCLC. The phase III FLEX trial demonstrated improved survival for cetuximab combined with cisplatin plus vinorelbine compared to chemotherapy alone. The BMS099 trial failed to show a significant improvement in progression-free survival but resulted in a hazard ratio for death similar to the one seen in the FLEX trial. A meta-analysis of four randomized trials confirmed the efficacy of cetuximab when added to chemotherapy. EGFR expression levels based on an immunohistochemistry score have recently been shown to predict benefit from cetuximab in the FLEX trial. In patients with high EGFR expression, patients had prolonged survival when treated with chemotherapy plus cetuximab compared to chemotherapy alone. In patients with low EGFR expression, outcome was not different between the two treatment arms. Thus platinum-based chemotherapy combined with cetuximab represents a new treatment option for patients with advanced NSCLC and high EGFR expression in their tumors. Cetuximab is also evaluated in combination with chemoradiotherapy in patients with stage III NSCLC.

Keywords: Targeted therapy; cetuximab; EGFR; NSCLC; monoclonal antibodies

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Introduction

Chemotherapy is well established in patients with non-small-cell lung cancer (NSCLC). Patients with completely resected NSCLC are considered for adjuvant chemotherapy and those with stage III disease receive chemotherapy as part of their multimodality therapy. Patients with advanced NSCLC are offered palliative chemotherapy with platinum-based doublets containing 3rd generation anticancer drugs (1-3). Palliative chemotherapy increases survival and decreases cancer-related symptoms compared to best supportive care alone (1). Cisplatin-based regimens are slightly superior to corresponding carboplatin-based protocols and are preferred in patients with good performance status (4). Elderly patients and patients with reduced performance should also be considered for palliative chemotherapy with well tolerated protocols (5). Following first-line chemotherapy, patients may be considered for maintenance therapy. Patients with progressive disease receive second-line therapy with docetaxel, pemetrexed, or epidermal growth factor receptor (EGFR)-directed tyrosine kinase inhibitors (3).

Two main strategies are investigated in order to improve outcome of systemic therapies in patients with advanced NSCLC (6,7). Firstly, customized chemotherapy based on biomarkers such as ERCC1 or BRCA1 is evaluated in clinical trials but currently still remains experimental. Secondly, targeted therapies focusing on the inhibition of angiogenesis or growth factor receptor systems have been evaluated in combination with palliative chemotherapy or as single agents (6,7). Bevacizumab added to first-line chemotherapy has been established as a treatment option for selected patients with advanced non-squamous cell NSCLC (3). Among growth factors, EGFR is of particular interest as a therapeutic target (8,9). EGFR is a member of the ErbB family of transmembrane tyrosine kinase receptors and is deregulated in many cancers including NSCLC. Activation of EGFR results in tumor growth, invasion, metastasis and poor prognosis. Thus blockade of the EGFR function by monoclonal antibodies, tyrosine kinase inhibitors and other strategies may improve outcome in patients with advanced NSCLC.

EGFR-directed tyrosine kinase inhibitors are small molecules which block the adenosine triphosphate binding site of the

Table 1 EGFR-directed monoclonal antibodies

Monoclonal antibodies	Clinical status
Cetuximab	Phase III, approval pending
Necitumumab	Phase III
Matuzumab	Phase II
Panitumumab	Phase II

cytoplasmic domain of the EGFR. Gefitinib and erlotinib have shown efficacy in patients with advanced NSCLC, particularly in those with EGFR-activating mutations in their tumors (10,11). Currently, they are established as a preferred treatment option for first-line therapy of patients with advanced NSCLC who harbor an EGFR-activating mutation in their tumors, as maintenance therapy, and as second- or third-line therapy in patients previously treated with chemotherapy (3).

Anti-EGFR monoclonal antibodies are in various stages of clinical development in patients with advanced NSCLC (*Table 1*) (12). These antibodies include cetuximab, matuzumab, panitumumab, and necitumumab. This review summarizes the current status of the clinical development of cetuximab in patients with NSCLC.

Cetuximab

Cetuximab (Erbitux®) is a chimeric human-murine monoclonal IgG1 antibody. Cetuximab blocks EGFR-mediated signal transduction through binding to the extracellular domain of the EGFR. Corresponding antibody receptor complexes are internalized and degraded which results in the down-regulation of the EGFR on the surface of tumor cells. Cetuximab may also act by means of antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity (13).

Cetuximab is usually administered as intravenous infusion at a loading dose of 400 mg/m^2 followed by weekly doses of 250 mg/m^2. Pre-medication with anti-allergic drugs is required prior to the first infusion and recommended for subsequent infusions. After the end of chemotherapy, cetuximab administration is usually continued until disease progression or unacceptable toxicity. Like with other EGFR-directed therapies, acne-like skin rash and diarrhea are the main side effects. Hypersensitivity reactions occur in fewer than 5% of the patients.

Cetuximab has been studied in combination with chemotherapy in several phase II and two phase III trials in patients with advanced NSCLC (14-21). Its evaluation in patients with stage III NSCLC is currently ongoing.

Phase I/II trials

Single-arm phase II trials evaluated the efficacy of cetuximab in combination with different platin-based doublets in unselected patients with advanced NSCLC (14-16). Two randomized phase II trials suggested that chemotherapy plus cetuximab is superior to chemotherapy alone (*Table 2*) (17,18).

The Lung Cancer Cetuximab Study (LUCAS) compared cetuximab added to cisplatin plus vinorelbine with chemotherapy alone in 86 chemo-naive patients with advanced NSCLC (17). EGFR expression was assessed by immunohistochemistry. In order to be eligible, patients had to have some degree of EGFR expression in their tumors. Patients treated with cetuximab had higher response rates (35% versus 28%), longer progression-free survival (hazard ratio 0.71, median 5.0 versus 4.6 months) and longer survival (median 8.3 versus 7.3 months) compared to patients receiving chemotherapy alone. Skin toxicity grade 3-4 occurred in 10% of the patients. The occurrence of skin rash appeared to be associated with higher response to chemotherapy plus cetuximab. These promising efficacy results of chemotherapy combined with cetuximab led to the decision to design the FLEX phase III trial.

The second randomized phase II trial compared cetuximab added to a platin (mostly carboplatin) plus gemcitabine with the same chemotherapy in patients with advanced NSCLC (18). In contrast to the LUCAS trial, patient eligibility was independent of EGFR expression. Chemotherapy plus cetuximab resulted in a higher response rate (28% versus 18%) and longer progression-free survival (median 5.1 versus 4.2 months) compared to chemotherapy alone.

The optimal scheduling of cetuximab in combination with carboplatin plus paclitaxel has also been evaluated in chemo-naive patients with advanced NSCLC (19). Cetuximab was administered either concurrent with chemotherapy or after chemotherapy. Response rates, progression-free survival and overall survival were similar in both arms. Median overall survival was 10.9 months in the concurrent arm and 10.7 months in the sequential arm. However, sensory neuropathy was higher in the concurrent arm compared to the sequential arm (15% versus 5%).

Phase III trials in advanced NSCLC

Two randomized open-label phase III trials determined the efficacy of cetuximab combined with first-line chemotherapy in patients with advanced NSCLC (*Table 2*) (20,21).

The FLEX phase III trial studied whether chemotherapy plus cetuximab was superior to chemotherapy alone in patients with advanced EGFR-expressing NSCLC (20). The primary endpoint was overall survival. Secondary endpoints were progression-free survival, response rate, safety, and quality of life. Eligibility criteria were stage IV or stage IIIB with malignant effusion, age ≥18 years, ECOG performance status 0-2, adequate organ function (bone marrow, kidney, liver, and heart), the presence of at least one bidimensionally measurable

Table 2 First-line chemotherapy with and without cetuximab in patients with advanced NSCLC: randomized trials

Randomized trials		
Phase II trials		
LUCAS (17)	Cisplatin/vinorelbine plus cetuximab	Cisplatin/vinorelbine
N	43	43
Response rate	35%	28%
Progression-free survival	5.0 months	4.6 months
Overall survival median	8.3 months	7.3 months
1-year	33%	26%
2-year	16%	0%
Canadian trial (18)	Platin/gemcitabine plus cetuximab	Platin/gemcitabine
N	65	65
Response rate	28%	18%
Progression-free survival	5.1 months	4.2 months
Overall survival median	12 months	9 months
1-year	50%	37.5%
Phase III trials		
FLEX (20)	Cisplatin/vinorelbine plus cetuximab	Cisplatin/vinorelbine
N	557	568
Response rate	36%	29%
Progression-free survival	4.8 months	4.8 months
Overall survival median	11.3 months	10.1 months
1-year	47%	42%
BMS099 (21)	Carboplatin/taxane plus cetuximab	Carboplatin/taxane
N	338	338
Response rate	26%	17%
Progression-free survival	4.4 months	4.2 months
Overall survival median	9.7 months	8.4 months

tumor lesion, and EGFR expression on tumor cells. EGFR expression was immunohistochemically assessed and eligible patients had to have at least one positively stained tumor cell. 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. Randomization was stratified by ECOG performance status (0-1 versus 2) and tumor stage (IIIB with malignant pleural effusion versus IV).

Patients received cisplatin 80 mg/m^2 on day 1 plus vinorelbine 25 mg/m^2 on days 1 and 8 of 3-week cycles for up to six cycles. Cetuximab was administered at a loading dose of 400 mg/m^2 followed by weekly infusions of 250 mg/m^2. After the end of chemotherapy, cetuximab was continued until disease progression or unacceptable toxicity.

The FLEX trial enrolled 1,125 patients with the following baseline characteristics: 70% male; median age 60 years (range 18-83 years); ECOG performance status 0-1 and 2 in 73% and 17% of the patients, respectively; 94% stage IV; 47% adenocarcinoma, 34% squamous cell carcinoma, 19% other NSCLC; 84% Caucasians, 11% Asian ethnicity; 22% never-smokers. The two treatment arms were well balanced with regard to these patient baseline characteristics. In both arms, the median number of chemotherapy cycles was four. Post-study treatment was similar in both arms except that EGFR-directed tyrosine kinase inhibitors were more frequently given to patients of the chemotherapy-alone arm compared to patients of the chemotherapy-plus-cetuximab arm (27% versus 17%).

The FLEX trial demonstrated superior survival for chemotherapy plus cetuximab compared to chemotherapy alone. The hazard ratio was 0.87 (P=0.04). Median survival

and 1-year survival rates were higher in patients of the chemotherapy-plus-cetuximab arm compared to those of the chemotherapy-alone arm (median 11.3 versus 10.1 months, 1-year survival 47% versus 42%). The survival benefit was seen across all major subgroups. Side effects attributed to cetuximab included acne-like skin rash (10% grade 3) and diarrhea (4% grade 3-4). Infusion-related reactions occurred in 4% of the patients. Treatment-related deaths were low in both arms.

The BMS099 phase III trial evaluated the efficacy of cetuximab in unselected patients with advanced NSCLC (21). In contrast to the FLEX trial, patients were enrolled independent of EGFR expression. Patients (n=676) were randomized to chemotherapy plus cetuximab or chemotherapy alone. Chemotherapy consisted of carboplatin (AUC 6) plus a taxane (either paclitaxel at 225 mg/m^2 over 3 hours every 3 weeks or docetaxel at 75 mg/m^2 every 3 weeks). Cetuximab was administered weekly at the standard doses. The primary endpoint was progression-free survival determined by a blinded Independent Radiology Review Committee. The patient characteristics at baseline were as followed: 41% female; median age 65; ECOG performance status 0, 1 and 2 in 33%, 65% and 1%, respectively. Progression-free survival determined by the Independent Radiology Review Committee was not different between the two treatment arms. The hazard ratio was 0.90. Median progression-free survival times were 4.4 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=0.0066). Based on the assessment by the investigators, progression-free survival was prolonged in the chemotherapy-plus-cetuximab arm compared to the chemotherapy-alone arm (median 4.3 versus 3.8 months, P=0.0015) but response rates were not different between the two treatment arms (28% versus 23%, P=0.132). The reasons for these discrepant findings between the Independent Radiological Review Committee and the investigators remain unclear. Although not powered for assessment of overall survival, the hazard ratio was 0.89 in favor of the chemotherapy-plus-cetuximab arm and thus in the range of the one seen in the FLEX trial.

Response rates were higher with chemotherapy plus cetuximab in all randomized trials. This indicates that cetuximab has activity during the chemotherapy phase. The impact of the maintenance phase of cetuximab on the overall outcome remains to be determined.

Meta-analysis in advanced NSCLC

A meta-analysis which included 2018 patients from 4 randomized trials confirmed the survival benefit of chemotherapy plus cetuximab compared to chemotherapy alone in the first-line setting in patients with advanced NSCLC (22). The hazard ratio was 0.878 (95% CI, 0.795-0.969; P=0.01). The meta-analysis also indicated longer progression-free survival and higher response rate for the combination. The results also suggest that the survival benefit of cetuximab is independent of the chemotherapy protocol because the meta-analysis was based on trials with different chemotherapy protocols: cisplatin plus vinorelbine (LUCAS, FLEX) (17,20), platin plus gemcitabine (18), and paclitaxel plus a taxane (BMS099) (21).

Cetuximab in stage III NSCLC

Based on the promising results in patients with stage IV NSCLC and its efficacy in combination with radiotherapy in patients with head-and-neck cancer (23), cetuximab has also been evaluated in combination with radiotherapy or chemoradiotherapy in patients with stage III NSCLC. 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 consolidation therapy with pemetrexed. Compared to historic controls, survival was prolonged in both arms with median survival times of 19 and 22 months, respectively. Response rates were 71% and 73%, respectively. Thus further evaluation of cetuximab in patients with stage III NSCLC is warranted and corresponding clinical trials are ongoing.

Other EGFR-directed monoclonal antibodies

Several anti-EGFR-directed monoclonal antibodies other than cetuximab have also been or are currently being evaluated. Matuzumab, a humanized anti-EGFR monoclonal IgG1 antibody with a prolonged half-life, has been studied (25-27). In a randomized phase II trial in the second-line setting, pemetrexed plus matuzumab (800 mg weekly or 1,600 mg every 3 weeks) was compared to pemetrexed (27). The response rate was 11% for patients receiving pemetrexed plus matuzumab and 5% for those receiving pemetrexed alone suggesting the efficacy of matuzumab. However, the clinical development of matuzumab has been discontinued.

Panitumumab, a fully human anti-EGFR IgG2 monoclonal antibody, did not indicate a benefit when added to carboplatin plus paclitaxel in a randomized phase II trial (28).

Necitumumab, a recombinant human anti-EGFR monoclonal antibody, is evaluated in two phase III trials in patients with advanced NSCLC. The INSPIRE trial compares necitumumab added to cisplatin plus pemetrexed with chemotherapy alone in patients with non-squamous NSCLC. The SQUIRE trial evaluates cisplatin plus gemcitabine with and without necitumumab in patients with squamous cell NSCLC.

Predictive biomarkers

After the efficacy of cetuximab in combination with chemotherapy has been established in patients with advanced NSCLC, research

Table 3 EGFR expression levels and overall survival in advanced NSCLC: analysis of data from the FLEX trial (30)

	High EGFR expression		Low EGFR expression	
	CT + cetuximab	CT	CT + cetuximab	CT
Hazard ratio (95%)	0.73 (0.58-0.93)		0.99 (0.84-1.16)	
Median survival, months	12.0	9.6	9.8	10.3
P value	0.011		0.88	
P value for interaction			0.044	

focussed on the characterization of biomarkers that would allow selecting those patients who will derive the greatest benefit from the addition of cetuximab to chemotherapy. To achieve this goal, both clinical and molecular tumor characteristics have been studied as potential biomarkers (29-33).

Among clinical parameters, the development of early-onset skin rash in patients who have been treated with cetuximab has been shown to be associated with longer survival (29). Because skin rash has rarely developed in patients treated with chemotherapy only, however, it is not possible to differentiate whether early onset-skin rash has predictive value or prognostic significance or even reflects a mixture of both.

Among molecular tumor features, EGFR status was of particular interest as potential biomarker (30). In the FLEX study, immunohistochemical EGFR expression of tumors was prospectively assessed by means of the DAKO pharmDxTM kit because patients required immunohistochemical evidence of EGFR expression in at least one tumor cell in order to be eligible for enrolment (20,30). Membrane staining intensity on a scale of 0 to 3+ and the fraction of tumor cells staining at each intensity were evaluated. Based on these data, an EGFR immunohistochemistry score on a continuous scale of 0-300 was calculated and compared with clinical outcome (30). Response rates were used to determine an outcome-based discriminatory threshold score for EGFR expression (30). High (score 200 or more) and low (score below 200) EGFR expression were seen in 31% and 69% of the FLEX patients, respectively. The associations between EGFR expression levels and survival are summarized in *Table 3*. Among patients with high EGFR expression, survival was longer for patients treated with chemotherapy plus cetuximab than for those treated with chemotherapy alone. The hazard ratio was 0.73 (95% confidence interval 0.58-0.93; P=0.011). The median survival times were 12.0 and 9.6 months, and the 1-year survival rates were 50% and 37%, respectively. In patients with low EGFR expression, survival of patients was similar between those treated with chemotherapy plus cetuximab and those treated with chemotherapy alone The hazard ratio was 0.99 (95% confidence interval 0.84-1.16; P=0.88). The median survival times were 9.8 and 10.3 months and the 1-year survival rates were 45% and 44%, respectively. The test for treatment interaction was significant with a p value of 0.044. Thus EGFR expression levels have been demonstrated to be predictive for the efficacy of chemotherapy plus cetuximab.

Several other tumor characteristics were studied as potential biomarkers. EGFR-activating mutations were analyzed in tumors obtained from 293 FLEX and 166 BMS099 patients (31,32). EGFR-activating mutations were detected in 15% and 10% of the patients, respectively. Mutations were associated with better prognosis in both treatment arms but did not predict benefit from cetuximab. Thus *EGFR* mutation status does not appear to be a clinically useful biomarker with regard to cetuximab in patients with advanced NSCLC. *EGFR* gene copy number detected by fluorescent in situ hybridization (FISH) has recently been suggested as another potential biomarker based on the results of a phase II trial (33). However, EGFR FISH positivity did not predict outcome in the FLEX trial and the BMS099 trial (31,32). Similarly, *KRAS* mutation status did not predict benefit from cetuximab in the two phase III trials (31,32).

In conclusion, high EGFR expression is the only biomarker that allows the characterization of those patients with advanced NSCLC who will derive a clinically meaningful benefit from the addition of cetuximab to first-line chemotherapy.

Conclusions

Cetuximab added to first-line chemotherapy improves outcome including survival in patients with advanced NSCLC. The analysis of data from the phase III FLEX trial indicated that EGFR expression based on an immunohistochemistry score is a predictive biomarker for cetuximab. Patients with high EGFR expression in their tumors benefit from the addition of cetuximab to first-line chemotherapy, whereas those with low expression do not.

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