

# Anti-EGFR monoclonal antibodies in the treatment of non-small cell lung cancer

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## introduction

Lung cancer is the first cause of cancer-related death in the Western world and the mortality rate is rapidly increasing in Asia; 1.2 million cancer deaths worldwide were from lung cancer in 2002 [1]. There are primarily two major types of lung cancer: non-small-cell lung cancer (NSCLC) and small-cell lung cancer. More than 50% of NSCLC patients are candidates for systemic treatment with chemotherapy, either for advanced disease, or as adjuvant or neo adjuvant treatment, in addition to local therapy. Chemotherapy has, however, modest activity in NSCLC and, in the past few years, several drugs were developed that are more specific for NSCLC patients, targeting biological features of cancer cell.

The epidermal growth factor receptor (EGFR) is a member of the ErbB family of transmembrane tyrosine kinase receptors, which includes ErbB1 (or HER-1, or EGFR), ErbB2 (or HER-2/neu), ErbB3 (or HER-3), and ErbB4 (or HER-4). The expression of EGFR is common in a number of normal epithelial tissues and expression of EGFR is elevated in several solid tumors. In NSCLC, overexpression of EGFR has been reported to be present in over 50% of cases in several series. In addition to this, several retrospective studies have identified the expression of EGFR as a negative prognostic factor in patients with resected early NSCLC [2]. Several EGFR inhibitors have been developed in recent years [3], which can be mainly categorized into two classes: small molecules that are inhibitors of the intracellular tyrosine kinase domain by interfering with autophosphorylation by adenosine triphosphate (ATP), and monoclonal antibodies to the extracellular domain of the EGFR which are the focus of present article.

## clinical studies with monoclonal antibodies in NSCLC

Several monoclonal antibodies that target the EGFR are under development and currently under investigation in solid tumors. Table 1 summarizes the agents that have been studied in NSCLC.

Cetuximab (Erbix<sup>TM</sup>, C225) has already been approved for the treatment of patients with metastatic colorectal cancer and is also currently under study for patients with advanced NSCLC. A phase II study assessed the use of Erbix as monotherapy for

advanced NSCLC patients who progressed following one or more previous chemotherapy regimens [4]. Three patients (4.5%) responded to treatment. The median time to progression was 2.3 months and median survival was 9.6 months. Of the 66 patients enrolled, 32 remain alive. The six month survival rate was 64% and the one-year survival was 39%. Duration of response was 3.1 months while duration of non-progression (those patients achieving best clinical response of stable disease) was 4.7 months. Of the three responders, two were male with adenocarcinoma and one was female with poorly differentiated carcinoma. Rosell and colleagues conducted a randomized phase II study to evaluate the activity of cetuximab in combination with chemotherapy in patients with previously untreated advanced NSCLC [5]. Patients with EGFR-positive tumors were randomized to treatment with cisplatin and vinorelbine alone or in combination with cetuximab. The study included 86 patients with 43 in each arm. The response rate was 35% for patients in the cetuximab arm, compared to 28% with chemotherapy alone. The median survival was 8.3 months with combination therapy and 7 months with chemotherapy alone. The 1-year survival and disease stabilization rates also favored the cetuximab arm. Based on the results of this study, a phase III clinical trial, referred to as the FLEX trial, is currently ongoing to compare the efficacy of chemotherapy (cisplatin and vinorelbine) with or without cetuximab for advanced NSCLC. Furthermore, there are two ongoing randomized phase II studies that use the chemotherapy regimens carboplatin/paclitaxel and cisplatin/gemcitabine with or without cetuximab and a phase III study (CP02-0452) comparing the following 4 treatment arms: Cetuximab plus Docetaxel, Cetuximab plus Pemetrexed, Docetaxel alone, or Pemetrexed alone.

Panitumumab (ABX-EGF) is a fully humanized antibody against the EGFR. Crawford and colleagues reported the results of a phase I study that evaluated panitumumab in combination with carboplatin and paclitaxel [6]. The study included 21 patients with previously untreated advanced NSCLC. No pharmacokinetic interactions were noted between panitumumab and the chemotherapeutic agents. For the 19 evaluable patients, the median survival was an impressive 17 months, with a median time-to-progression of 7 months. These results require confirmation in larger trials. A randomized phase II clinical trial to evaluate the activity of panitumumab in combination with carboplatin and paclitaxel has recently been

**Table 1.** Monoclonal antibodies currently studied for the treatment of NSCLC

Agent	Target	Characteristics	Route	Latest studies
Cetuximab (Erbix™)	EGFR extracellular domain	Chimeric	IV	Phase III in advanced NSCLC ongoing
Panitumumab (ABX-EGF)	EGFR extracellular domain	Fully human	IV	Phase II in advanced NSCLC ongoing
Pertuzumab	Erb2 heterodimerization		IV	Phase II in advanced NSCLC ongoing
Matuzumab (EMD72000)	EGFR extracellular domain	Humanized	IV	Phase II in advanced NSCLC in combination with paclitaxel ongoing
Nimotuzumab (TheraCIM)	EGFR extracellular domain	Humanized	IV	Phase II in advanced NSCLC ongoing
MDX214	EGFR extracellular domain	Fully human	IV	Phase II in advanced NSCLC ongoing

Abbreviations: EGFR, epidermal growth factor receptor; NSCLC, non-small-cell lung cancer; IV, intravenous.

completed. The study randomized patients ( $n = 175$ ) to treatment with carboplatin and paclitaxel alone or in combination with panitumumab. The results are eagerly awaited.

Pertuzumab represents a new class of targeted therapy, referred to as a HER dimerization inhibitor or HDI. Pertuzumab inhibits dimerization of HER2 with ligand-activated EGFR, HER3 and HER4. Preclinical xenograft studies have demonstrated efficacy of pertuzumab in the treatment of NSCLC. Encouraging interim data from a phase II multi-center trial of single agent pertuzumab were recently presented [7]. The trial has enrolled 51 patients with advanced or recurrent NSCLC that progressed on or after at least one chemotherapy regimen. Pertuzumab was administered with an 840 mg IV loading dose with repeat doses of 420 mg IV every 3 weeks until progressive disease, death or toxicity. Median progression-free survival was three months and six-week progression-free survival was 27%. While no complete responses were observed, more than 40% of patients had stable disease (42%) at six weeks; 40% progressed.

Matuzumab (formerly EMD 72000) is a humanized monoclonal antibody specific for the EGFR. Matuzumab also inhibits signaling through the EGFR pathway and might also activate ADCC pathways [8]. Pharmacokinetic studies have demonstrated that both weekly and every-3-week dosing schedules of matuzumab are feasible. Matuzumab can be safely combined with paclitaxel in NSCLC, and the pharmacokinetics of matuzumab are unaltered by paclitaxel [9]. Based on the pharmacokinetic studies of every-3-week matuzumab, NSCLC patients who will receive matuzumab 1200 mg every 3 weeks plus paclitaxel are currently being enrolled in a phase II trial.

Nimotuzumab (TheraCIM) is an anti-EGFR humanized monoclonal antibody that is currently under investigation in a phase II trial for NSCLC. This randomized trial will compare the effects of the combination of nimotuzumab with radiation against radiation alone in patients with stage IIB and III disease who are found to be insufficiently fit to tolerate the standard-of-care or who are not amenable to treatment with curative intent.

### markers of sensitivity to EGFR inhibitors in NSCLC

Identification of patients who are likely to benefit from modern targeted therapies, such as anti-EGFR agents, is of paramount

importance for improving therapeutic strategies in oncology as well as for reducing financial burden of health care systems [10]. While a number of independent studies have identified predictive factors for response to small molecules TKIs in NSCLC, such as mutant EGFR genes and EGFR gene copy number [11], very limited data are available for monoclonal antibodies. In particular, Tsuchihashi et al. reported that in 35 patients participating in a cetuximab-monotherapy study for recurrent NSCLC, known predictive mutations to TKIs were identified in 2/13 patients with stable disease (del746–750), 1/21 with progressive disease (L861Q) and 0/1 with partial response [12]. In a different clinical model, i.e. metastatic colorectal cancer, we recently showed that response to anti-EGFR monoclonal antibodies is associated with an increase in EGFR gene copy number as evaluated by fluorescence-in situ-hybridization (FISH) [13]. This finding, together with the role of EGFR gene copy number in predicting outcome to small molecules TKIs in NSCLC [11] and the cost-effectiveness of FISH analysis in other cancer models [14], support further evaluation of EGFR gene copy number as a predictive factor to monoclonal antibodies in NSCLC.

### conclusions

In summary, targeted drugs, primarily the EGFR inhibitors, have added new effective agents to the therapeutic armamentarium for NSCLC. Qualitative and quantitative survival benefit has been demonstrated with small molecules TKIs, but also anti-EGFR monoclonal antibodies, even though in an earlier stage of clinical investigation, have demonstrated promising activity that warrants further studies of these agents. Mutations in the ATP-binding site, that have been consistently associated with clinical response to TKIs [11], do not seem to predict response to anti-EGFR therapy using monoclonal antibodies such as cetuximab [4, 12]. Moreover, it has recently been reported that two patients responded to gefitinib after failure of several chemotherapy regimens and cetuximab [15]. Taken together, these findings could suggest that monoclonal antibodies and TKIs have different mechanisms of action and might be effectively combined in order to broaden their spectrum of activity.

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