Antibodies to the Epidermal Growth Factor Receptor in Non–Small Cell Lung Cancer: Current Status of Matuzumab and Panitumumab

Mark A. Socinski

Abstract

Matuzumab and panitumumab are antibodies against the epidermal growth factor receptor (EGFR) that are being evaluated in several malignancies including non–small cell lung cancer (NSCLC). In phase I trials of single-agent matuzumab in patients with EGFR-positive cancer, three tumor responses were documented in esophageal squamous cell carcinoma as well as colorectal carcinoma. A phase I trial of matuzumab in combination with paclitaxel has been reported in 18 patients with EGFR-positive advanced NSCLC. Objective responses were seen in 4 of 18 (23%) patients. A randomized phase II trial is currently ongoing in second-line NSCLC with matuzumab in combination with pemetrexed. A large dose/schedule trial of single-agent panitumumab enrolled 96 patients with EGFR-positive solid tumors. No responses were seen in the 14 lung cancer patients evaluated; 5 of 39 patients with colorectal cancers had objective responses. A randomized phase II trial of carboplatin/paclitaxel with or without panitumumab in 166 patients with previously untreated advanced stage IIIB/IV NSCLC did not find any benefit for the panitumumab arm compared with the chemotherapy alone arm with regard to response rates, time to disease progression, or median survival time. The lack of a biomarker to identify a subset of NSCLC patients who may derive benefit from this agent limits any potential enthusiasm for further trials of panitumumab at this time in NSCLC.

Non–small cell lung cancer (NSCLC) remains the leading cause of cancer-related mortality in the U.S. (1). Although therapeutic advances have been made, the survival outcomes in advanced disease remain suboptimal. Unfortunately, 40% to 50% of patients present with stage III/IV NSCLC (2). Although prolongation of survival and palliation of symptoms is possible as a result of multiple lines of therapy, cure is not possible; median survival times and 1-year survival rates range from 8 to 12 months and 30% to 50%, respectively, depending on the clinical characteristics of the patient populations studied (2, 3). Further improvements in survival will require a better understanding of the biology of NSCLC in general, and of the specific molecular abnormalities of the individual patient’s tumor that may be targeted by novel therapeutics.

The epidermal growth factor receptor (EGFR) is frequently dysregulated in human malignancies and, in particular, NSCLC (4, 5). This receptor is a member of the ErbB family of transmembrane receptor kinases. Epidermal growth factor and transforming growth factor α are two of several known ligands (frequently overproduced in malignancies) that bind to this receptor and, after dimerization with other EGFRs or other ErbB family members, activate the internal tyrosine kinase domain and several downstream signal transduction cascades. This results in cellular proliferation by activation of the mitogen-activated protein kinase pathway and in resistance to apoptosis by Akt pathway activation. Because of its central role in these processes (e.g., angiogenesis) vital to the malignant process, EGFR is a therapeutic target of great interest in several epithelial malignancies (4). Theoretically, the EGFR pathway could be used by malignancies in several ways including up-regulation of the receptor itself, excessive ligand production or activating mutations which may be ligand-dependent or ligand-independent (constitutive). Understanding the biology as to how this pathway is being used in individual malignancies could explain why certain agents directed at the EGFR pathway have clinical activity. Diseases driven more by ligand overproduction may be best approached with an antibody which blocks the ligand-receptor interaction. Ford and colleagues (6) have recently shown that responses to cetuximab were seen in colorectal carcinoma patients with excessive ligand production. Alternatively, activating mutations in the kinase domain of EGFR have been described in advanced NSCLC (7). These mutations seem to make the EGFR pathway the dominant pathway in these malignancies and are associated with the clinical characteristics of female sex, adenocarcinoma histology, nonsmoking status, and Asian ethnicity (7). In patients with these activating EGFR mutations, the single-agent response rates to either gefitinib or erlotinib [EGFR tyrosine kinase inhibitors (TKI)] range from 60% to 80%, which is remarkable in this disease (7). It is also likely that up-regulation
of wild-type EGFR would identify a population of patients with sensitivity to EGFR TKIs but the optimal manner in which to identify these patients remains elusive (7, 8).

As suggested above, two major therapeutic strategies have been employed in the clinic designed to specifically inhibit this pathway. Monoclonal antibodies directed at the EGFR have been developed that compete with ligands for the binding sites on the extracellular aspect of this receptor (4). When ligand binding is inhibited, the pathway cannot be activated (assuming it is not constitutively activated by a mutation event). The first anti-EGFR antibody to validate this approach was cetuximab, which was shown to improve survival in colorectal (9) and head and neck (10) malignancies in combination with standard therapies. The second strategy has involved the use of small molecule TKIs of the internal tyrosine kinase domain, which thereby block the downstream signaling effects of this pathway. The first EGFR TKI approved was gefitinib, based on two large phase II trials that showed single-agent activity as well as a palliative effect in advanced refractory NSCLC (11, 12). Gefitinib was later withdrawn from the market after the Iressa Survival Evaluation in Lung Cancer phase III trial failed to reach its primary end point of survival (13). Erlotinib has been shown to improve survival in both advanced refractory NSCLC (14) and pancreatic cancer (15) in phase III trials, which validates this therapeutic strategy in selected human malignancies.

Matuzumab and panitumumab are anti-EGFR antibodies that have been evaluated or are currently under development in several malignancies including NSCLC. Table 1 compares and contrasts these two antibodies with cetuximab, the first monoclonal antibody to EGFR approved for use in human malignancies.

### Matuzumab

Matuzumab is a humanized IgG1 monoclonal antibody targeting EGFR (16). Its murine precursor, EMD-55900, was not suitable for clinical development because it was associated with human anti-human antibodies responses (16). Matuzumab binds to the EGFR with high affinity, competitively blocking natural ligands and thus inhibiting downstream EGFR-mediated signaling. Initial phase I trials of matuzumab as a single agent showed that it was well tolerated at doses of 400 to 1,600 mg administered weekly, every 2 weeks, or every 3 weeks (16). Dose-limiting toxicities occurred at 2,000 mg weekly and consisted of grade 3 headache and fever. As it is a humanized antibody, matuzumab does not induce autoantibodies, as murine or chimeric antibodies may do. Its half-life is 6 to 8 days, making it suitable for less frequent dosing. In preclinical xenograft models, substantial antitumor activity has been shown with matuzumab (16). Matuzumab has also been shown to induce antibody-dependent cell-mediated cytotoxicity (ADCC), which may contribute to its antitumor activity (16). In the phase I trials (16), tumor responses were documented in esophageal squamous cell carcinoma as well as in colorectal carcinoma (patients were selected for the trial based on positive staining for EGFR in the tumor specimens). The pharmacodynamic effect of matuzumab has been shown both in serial skin as well as tumor biopsies (17, 18). The effect consists of inhibition of phosphorylated (p)EGFR, pMAPK, and pAKT in both skin and tumor (18).

A phase I trial of matuzumab in combination with paclitaxel has been reported in patients with EGFR-positive advanced NSCLC (19). The design administered matuzumab i.v. weekly at 100, 200, 400, and 800 mg with paclitaxel 175 mg/m² i.v. every 3 weeks. Eighteen patients with stage IIIB/IV NSCLC were evaluated (nine previously untreated and nine previously treated). The median age was 63 years and all had Karnofsky performance status ≥60%. All patients had evidence of EGFR positivity in their previous tumor specimens; however, the degree of positivity for each of the individual patients was not reported. The maximum planned dose of matuzumab (800 mg weekly) was achieved without reaching the maximum tolerated dose (eight patients were treated at the 800 mg dose). There was no grade 3 matuzumab-related toxicity; grade 2 toxicities consisted of pruritus (two patients), bronchospasm (one patient), and hot flashes (one patient). Grade 1 or 2 acneiform skin rashes occurred in 14 patients (most of the grade 2 rashes were seen at the 800 mg dose level). Coadministration of paclitaxel did not alter the pharmacokinetics of matuzumab. Objective responses were seen in 4 of 18 (23%) patients (3 previously untreated and all were smokers). The authors concluded that the combination of paclitaxel at 175 mg/m² i.v. every 3 weeks with weekly matuzumab at 800 mg i.v. was well tolerated and active in patients with advanced NSCLC.

In a single-arm phase I/II trial, it may be difficult to ascertain the true activity of a regimen or agent due to the influence of patient selection. The data reported by Kollmannsberger and

### Table 1. Comparison of anti-EGFR monoclonal antibodies in clinical development (30–34)

<table>
<thead>
<tr>
<th>Property</th>
<th>Cetuximab</th>
<th>Matuzumab</th>
<th>Panitumumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affinity</td>
<td>3.9 × 10⁻¹⁰ mol/L</td>
<td>4 × 10⁻⁹ mol/L</td>
<td>5 × 10⁻¹¹ mol/L</td>
</tr>
<tr>
<td>Structure/type</td>
<td>Chimeric human IgG₁</td>
<td>Humanized IgG₁</td>
<td>Human IgG₂</td>
</tr>
<tr>
<td>Induces ADCC (in vitro)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Preclinical lung</td>
<td>Regression in combination</td>
<td>Regression with monotherapy</td>
<td>Regression in combination</td>
</tr>
<tr>
<td>t₁/₂</td>
<td>~4 d</td>
<td>~10 d</td>
<td>~5.7 d</td>
</tr>
<tr>
<td>Dosing</td>
<td>400 mg/m² loading; 250 mg/m²/wk</td>
<td>800-1,600 mg QW, Q2W, Q3W</td>
<td>2.5-9.0 mg/kg, QW, Q2W, Q3W</td>
</tr>
<tr>
<td>Administration</td>
<td>Diphenhydramine</td>
<td>None</td>
<td>QW, Q2W, Q3W</td>
</tr>
<tr>
<td>Pretreatment</td>
<td>~10%</td>
<td>&lt;1%</td>
<td>None</td>
</tr>
<tr>
<td>Rash grade 3/4</td>
<td>69-90%</td>
<td>64-80%</td>
<td>7%</td>
</tr>
<tr>
<td>Rash (all grades)</td>
<td>Infusion reactions (~3%);</td>
<td>NA</td>
<td>~80-100%</td>
</tr>
<tr>
<td>Warnings</td>
<td>interstitial lung disease (&lt;0.5%);</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>hypomagnesemia (~24%)</td>
<td></td>
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</table>
Prunaru et al. (19) were not dissimilar from the original data with paclitaxel alone in advanced NSCLC (20). Given this, a randomized phase II trial is currently ongoing following the design shown in Fig. 1. A second-line therapy population of patients with advanced NSCLC was chosen using pemetrexed alone (500 mg/m² i.v. every 3 weeks) as the control arm based on a previously reported phase III trial (21). Two doses and schedules of matuzumab are being evaluated on the investigational arms of this trial; 800 mg i.v. weekly and 1,600 mg i.v. every 3 weeks in combination with pemetrexed every 3 weeks. The primary end point of this trial is response rate with secondary end points outlined in Fig. 1. If a clear signal is seen in this trial, suggesting that matuzumab in combination with pemetrexed increases the efficacy of therapy over pemetrexed alone, an argument for a definitive phase III trial could be advanced.

**Panitumumab**

Panitumumab is a fully humanized IgG₂ monoclonal antibody directed at the EGFR and binding with high affinity (22). In preclinical models, panitumumab has been shown to block ligand binding, thereby inhibiting epidermal growth factor–dependent tumor cell activation and proliferation. As a single agent, panitumumab has also been shown to inhibit EGFR-overexpressing tumors in multiple xenograft models (23). As it is an IgG₂ antibody, it does not induce ADCC. In clinical trials involving panitumumab, weekly administration schedules were well tolerated at doses predicted to have antitumor activity based on modeling of preclinical data (23). The most common toxicity is a transient acneiform skin rash, typically grade 1 or 2. No human antihuman antibodies have been reported to date. A large dose/schedule trial of single-agent panitumumab has been reported by Weiner and colleagues (24). This trial enrolled 96 EGFR-positive solid tumor patients (predominantly colorectal but 14 lung cancer patients were included). The doses and schedules evaluated were 0.1 to 5.0 mg/kg weekly, 6.0 mg/kg every 2 weeks, and 9.0 mg/kg every 3 weeks. No dose-limiting toxicities were observed and the maximum tolerated dose was not reached in any of the cohorts. The most common toxicity was skin rash; however, only 7% of patients had grade 3 skin toxicity. No premedications were used and no hypersensitivity reactions occurred. No responses were seen in the lung cancer patients evaluated; 5 of 39 patients with colorectal cancers had objective responses.

A randomized phase II trial in previously untreated advanced stage IIIB/IV NSCLC has been reported comparing carboplatin (AUC 6 i.v. every 3 weeks) and paclitaxel (200 mg/m² i.v. every 3 weeks) with or without panitumumab (2.5 mg/kg weekly; ref. 25). The results of this trial are summarized in Table 2. The randomization was imbalanced in a 2:1 fashion favoring the panitumumab arm. The primary end point of the trial was time to disease progression. Almost all of the 166 patients entered on the trial had a performance status of 0 to 1; 60% had adenocarcinoma histology; and ~10% were nonsmokers. All baseline demographic factors seemed to be well-balanced between the two arms of this trial. As shown in Table 2, there did not seem to be any benefit with regard to time to disease progression, which was 4.2 months for the panitumumab arm compared with 5.3 months for the chemotherapy alone arm (P = 0.55). Likewise, there did not seem to be any benefit in response rate or median survival time for the panitumumab arm. There were no unexpected toxicities seen and panitumumab did not seem to alter the toxicity profile of the carboplatin/paclitaxel doublet. Grade 3 acneiform rashes occurred in 4% of the patients on the panitumumab arm. Although this was not a phase III trial, this well-conducted, randomized phase II trial was disappointing and dampened enthusiasm for further investigation of panitumumab in advanced NSCLC. The absence of an efficacy signal in this trial certainly suggests that panitumumab may have little or no activity in NSCLC in combination with chemotherapy and provided no rationale to move panitumumab into a phase III trial in NSCLC. The lack of a biomarker which may potentially identify a subset of NSCLC patients who may derive benefit from this agent limits any potential enthusiasm for further trials at this time in NSCLC.

Blumenschein and colleagues (26) have reported preliminary results of a phase IB trial involving the combination of carboplatin, paclitaxel, panitumumab, and AMG 706 in patients with advanced stage IIIB/IV NSCLC has been reported comparing carboplatin (AUC 6 i.v. every 3 weeks) and paclitaxel (200 mg/m² i.v. every 3 weeks) with or without panitumumab (2.5 mg/kg weekly; ref. 25). The results of this trial are summarized in Table 2. The randomization was imbalanced in a 2:1 fashion favoring the panitumumab arm. The primary end point of the trial was time to disease progression. Almost all of the 166 patients entered on the trial had a performance status of 0 to 1; 60% had adenocarcinoma histology; and ~10% were nonsmokers. All baseline demographic factors seemed to be well-balanced between the two arms of this trial. As shown in Table 2, there did not seem to be any benefit with regard to time to disease progression, which was 4.2 months for the panitumumab arm compared with 5.3 months for the chemotherapy alone arm (P = 0.55). Likewise, there did not seem to be any benefit in response rate or median survival time for the panitumumab arm. There were no unexpected toxicities seen and panitumumab did not seem to alter the toxicity profile of the carboplatin/paclitaxel doublet. Grade 3 acneiform rashes occurred in 4% of the patients on the panitumumab arm. Although this was not a phase III trial, this well-conducted, randomized phase II trial was disappointing and dampened enthusiasm for further investigation of panitumumab in advanced NSCLC. The absence of an efficacy signal in this trial certainly suggests that panitumumab may have little or no activity in NSCLC in combination with chemotherapy and provided no rationale to move panitumumab into a phase III trial in NSCLC. The lack of a biomarker which may potentially identify a subset of NSCLC patients who may derive benefit from this agent limits any potential enthusiasm for further trials at this time in NSCLC.

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Blumenschein and colleagues (26) have reported preliminary results of a phase IB trial involving the combination of carboplatin, paclitaxel, panitumumab, and AMG 706 in patients
with stage IIIB/IV NSCLC. AMG 706 is a multitargeted, small molecule TKI of the vascular endothelial growth factor receptor, platelet-derived growth factor, and kit. The design of the trial included three segments: carboplatin and paclitaxel with AMG 706 (a); panitumumab 9.0 mg/kg i.v. every 3 weeks with AMG 706 (b); and carboplatin, paclitaxel, panitumumab, and AMG 706 (c). The primary end point of the trial is safety and pharmacokinetics, with response rate as the primary secondary end point. Preliminary data for segments a and b have been reported. AMG 706 could be safely combined with panitumumab with the primary toxicity being grade 3 hypertension. A similar trial has been reported by Crawford and colleagues (27) of the combination of cisplatin, gemcitabine, panitumumab, and AMG 706. Preliminary data in 15 patients with advanced NSCLC suggested that these four agents could be safely combined. Given the negative randomized phase II trial shown in Table 2, one has to wonder about the contribution of panitumumab to platinum-based chemotherapy given with or without antiangiogenic agents.

**Summary and Conclusions**

It is clear that therapy directed at the EGFR is and will be an important part of the therapeutic armamentarium against advanced NSCLC and perhaps the earlier stages of the disease as well. The National Cancer Institute of Canada trial (BR.21) validated this pathway using erlotinib, a small molecule TKI of the EGFR (14). Although there is a clinical profile (nonsmokers, female gender, adenocarcinoma histology, Asian ethnicity) that identifies the patients who seem to derive greater benefit from EGFR-directed therapy, it is likely that a molecular profile will be defined that will predict which patients will derive the greatest benefit from effectively targeting this pathway. Leading candidates in this regard are those patients with activating mutations of the EGFR and those with high EGFR gene copy number as determined by fluorescence in situ hybridization (28, 29). These findings may identify a subgroup of patients in which the EGFR pathway is dominant in the pathogenesis of their disease.

Whether or not the blockade of the external domain of the EGFR with a monoclonal antibody will produce the same effect remains to be shown. The lead antibody in current clinical trials is cetuximab, and two phase III trials are ongoing, with one having completed its accrual, comparing standard chemotherapy (cisplatin/vinorelbine) with or without cetuximab in advanced stage IIIB/IV NSCLC. Both matuzumab and panitumumab have theoretical advantages over cetuximab as they are humanized or fully human antibodies with substantially lower risk of severe hypersensitivity reactions as a result. The current clinical data with matuzumab and panitumumab are not sufficient to make a judgment at the current time as to its potential utility in NSCLC. Completion of the trial outlined in Fig. 1 will be the first opportunity to see if there is sufficient activity to justify further study in NSCLC. On the other hand, panitumumab failed to show any hint of benefit in the first-line randomized phase II trial reviewed in Table 2. One concern about this trial is that it was done in an unselected patient population. Identification of a molecular signature predicting benefit from antibodies directed at the EGFR may enrich the population and might be helpful in defining the true role of the anti-EGFR antibodies in advanced NSCLC.

**Open Discussion**

**Dr. Alan Sandler:** I have yet to hear a rationale why the antibodies should work with chemotherapy when the TKIs don’t.

**Dr. Thomas Lynch:** There are the data in colorectal cancer, and then also in head and neck cancer with radiation.

**Dr. Sandler:** Right, but I have yet to see a positive study with an EGFR antibody in lung cancer. The German LUCAS study data of cetuximab and chemotherapy looked negative. But people are marching on with these drugs. To Angen’s credit, they have stopped looking at panitumumab based on the data.

**Dr. Renato Martins:** In squamous cell carcinoma of the head and neck, cetuximab is highly effective. The phase II data showing a 10% to 15% response rate in patients who progressed on chemotherapy do not give you the perspective of what can happen in (the) clinic in terms of prolonged responses on cetuximab. If there is some biological relationship between the squamous cell carcinoma of the head and neck and the squamous cell carcinoma that we see in the lung, then I don’t think we should be closing the lid on these agents.

**Dr. Lynch:** Is anyone aware of any data or work with these two drugs in combination with radiotherapy in lung cancer?

**Dr. Martins:** One niche that we really don’t explore is what we do with lung cancer patients who cannot tolerate full-dose cisplatin and have locally advanced disease. We know what is done in the community. They get carboplatin and paclitaxel given weekly. I think we all agree that that is not acceptable, particularly since the CALGB trial showed that carboplatin adds nothing to radiation. It would be an interesting scenario for patients who cannot get full-dose cisplatin to combine one of the antibodies with radiation and then follow that with three cycles of chemotherapy.

**Dr. Socinski:** I think in lung that is important. There is an RTOG trial with cetuximab and radiation in the good performance status patients as well as a randomized trial in CALGB that Dr. Govindan is running, with or without cetuximab. But I don’t know that these drugs are being developed in the stage III setting at this point.

**Dr. Lynch:** Dr. Heymach, you do a lot of antibody work. Do you think this ADCC mechanism is important? Could that be an explanation for why we are not seeing activity with panitumumab, if it lacks ADCC effects?

**Dr. John Heymach:** If there are differences between antibodies and TKIs, I believe they may have more to do with their mechanism of action on the EGFR, such as increased receptor cycling on the cell surface, rather than ADCC.

**Dr. Sandler:** No one has addressed my question as to why an antibody should actually work with chemotherapy if in fact the mechanism involves access to EGFR. We have already said that giving it concurrently should lock the cell into a resistant phase. If we are dependent now upon saying the antibodies work because of an immune-mediated response, that is not why they were supposed to work.

**Dr. Roy Herbst:** It is hard to answer that question but certainly antibodies are much more specific than the small molecules. At least you know with an antibody you are hitting just the one target, and with the small molecules you often don’t know what else you are hitting.


References


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