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Targeted therapies inhibiting the epidermal growth factor receptor (EGFR) have been introduced in the treatment of patients with advanced non–small-cell lung cancer (NSCLC). Many inhibitors of the EGFR have been developed, targeting either the extracellular receptor domain with antibodies or the intracellular tyrosine kinase binding domain with small molecules. The tyrosine kinase inhibitor (TKI) gefitinib (Iressa) was the first targeted drug to be registered for the treatment of NSCLC after failure of chemotherapy. Given concurrently together with platinum combination chemotherapy both TKIs gefitinib and erlotinib (Tarceva) failed to increase activity. Sequential targeted therapy after chemotherapy is currently being investigated further. Studies with the monoclonal antibody cetuximab (Erbitux) combined with chemotherapy are ongoing. Side effects of the small molecules are mainly skin rash and diarrhea, whereas the antibodies do not give diarrhea. Selection of patients, based on molecular markers and patient characteristics, has become an important issue for the further development of these drugs, given there is activity in a relatively small group of patients with NSCLC. Newer drugs inhibiting more than one receptor pathway are being investigated in order to find activity in a broader group of patients.

Lung cancer is the leading cause of cancer-related death, with 1.2 million cancer deaths due to lung cancer in the year 2002 in the western world.[1] More than 50% of non-small-cell lung cancer (NSCLC) patients are candidates for systemic treatment with chemotherapy, either for advanced disease or as adjuvant or neoadjuvant treatment in addition to local therapy in earlier stages. Chemotherapy has, however, modest activity in NSCLC.[2] In the past few years several new drugs that more specifically work on cancer cell targets have shown activity in NSCLC. The most-investigated target is the epidermal growth factor receptor (EGFR). This receptor is a member of the ErbB family of transmembrane tyrosine kinase receptors, which includes ErbB1 (or HER1, or EGFR), ErbB2 (or HER2/neu), ErbB3 (or HER3), and ErbB4 (or HER4). 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 this receptor as a negative prognostic factor in patients with resected early NSCLC.[3] Clinical Studies With EGFR Inhibitors in NSCLC Several EGFR inhibitors have been developed in recent years[3]; they can mainly be categorized into two classes: monoclonal antibodies to the extracellular domain of the EGFR receptor, or small molecules which are inhibitors of the intracellular tyrosine kinase (TKI) domain, interfering with autophosphorylation by ATP. Other molecules, however, have also been developed, including vaccines.[4] Single Agents

- Gefitinib- Gefitinib (Iressa) is the first molecularly targeted agent to be registered for advanced NSCLC. This registration has been based on two large randomized phase II studies, the IDEAL 1 and 2 studies.[5] Gefitinib was given orally in continuous dosing. In IDEAL 2, performed in the United States, patients had to have received a platinum compound and docetaxel (Taxotere). In total 221 patients were randomized to receive either 250 or 500 mg of gefitinib daily. Gefitinib was well tolerated at 250 mg/d and it induced antitumor activity in approximately 10% of patients. There was no significant difference in response or survival between the two dosages, but toxicity was higher at the 500-mg/d dose. These results compare favorably with chemotherapy, which induces far more side effects and probably a similar level of activity.[6] In the second study (IDEAL 1) conducted mainly in Europe and Japan, patients with one or two prior chemotherapy regimens, including a platinum compound, were also randomized to receive gefitinib at 250 or 500 mg daily.[7] Response rate approached 20% and was similar in both arms, symptom improvement was 40%, and this was higher in patients who had an objective response. Again, side effects were in general well tolerated, but were more severe with the 500-mg dose. In a multivariate analysis it became apparent that female patients, patients with histology of adenocarcinoma, and those
who had previously received hormonal or immunologic therapies had significantly higher chances of response. In a large extended access program gefitinib has been made available in the past years, and as a result, several reports have been published based on this experience. Patients were given 250 mg daily; inclusion and assessments were relatively loose in this program. In general, the response rate was, however, similar to or somewhat lower than the IDEAL studies in these reports.[8-10] Gefitinib is active in first line, with a level of activity not clearly higher than that observed after chemotherapy failure.[10-12] Patients with brain metastases[13-15] and elderly patients[16,17] can benefit from this treatment. Patients with poor performance status may also be candidates for gefitinib treatment and results were particularly promising in Chinese patients.[17,18] Principal side effects of gefitinib are skin rash, acneiform changes of the skin, and diarrhea. Diarrhea was actually the dose-limiting toxicity in phase I studies. Most toxicities are National Cancer Institute Common Toxicity Criteria grade 1 or 2. As a rare but serious side effect, interstitial lung disease has been observed in patients receiving gefitinib. Worldwide, the incidence of interstitial lung disease is about 1% (2% in the Japanese postmarketing experience and about 0.3% in a US expanded access program). Approximately one-third of the cases were fatal.[5] A recent article gives detailed information for the practicing oncologist on how to deal with gefitinib toxicities, and what to expect in terms of activity and patient selection.[19] A randomized phase III study (ISEL) comparing gefitinib at 250 mg daily vs placebo in 1,692 patients refractory to chemotherapy failed to demonstrate an improvement of survival with gefitinib in the overall population (median 5.6 vs 5.1 months, $P = .11$) or in patients with adenocarcinoma (6.3 vs 5.4 months, $P = .07$). There was, however, benefit in Asians and never-smokers.[20] Another study (BR19) randomizing stage IIIB NSCLC patients to receive gefitinib or placebo after chemoradiation and consolidation chemotherapy was closed after an unplanned interim analysis because it did not show a survival benefit for gefitinib at a daily dose of 250 or 500 mg.[21]

**Erlotinib**-Erlotinib (Tarceva) is another TKI, with slightly different pharmacologic characteristics than gefitinib. A phase II study in advanced NSCLC has been performed in 57 patients.[22] A response rate of 12.3% was obtained in this study of patients with prior chemotherapy. Response did not appear to be correlated to the extent of prior exposure to chemotherapy. Survival was correlated to occurrence and degree of skin toxicity. Furthermore, there was no relationship with EGFR expression. The BR21 study randomized patients who had failed one or two prior chemotherapy regimens to receive placebo or erlotinib at 150 mg daily.[23] The study randomized 731 patients in a 2:1 ratio to receive erlotinib or placebo. Approximately half of the patients were randomized as second-line and half as third-line treatment. In this study an improvement in survival was obtained in the erlotinib arm: patients on placebo had a median survival of 4.7 months whereas those on erlotinib had a median survival of 6.7 months ($P = .001$). The response rate with erlotinib was 8.9%. Toxicity was as expected with this dose of erlotinib, and was acceptable, consisting mainly of skin toxicity and diarrhea. These side effects were in the range observed with the higher doses of gefitinib in the IDEAL studies.[7,24] Major symptoms (cough, dyspnea, and pain) were significantly improved by erlotinib treatment compared to placebo. This important study brought erlotinib to registration by the US Food and Drug Administration in November 2004 and by the European Union on September 21, 2005, for the treatment of second- and third-line advanced NSCLC. In view of the positive results obtained with erlotinib, the results with gefitinib are disappointing and somewhat surprising. Gefitinib and erlotinib are very similar compounds with some differences in pharmacologic properties. It seems plausible that the choice of dose may have played a role in determining the different outcome of the ISEL and the BR21 studies. The dose of erlotinib used was 150 mg/d, which corresponds to about 600 to 700 mg/d of gefitinib. The fact that the IDEAL studies did not discern differences in outcome between gefitinib at 250 and 500 mg/d may have to do with the small sample size of these randomized phase II studies, which does preclude conclusions on survival.

**Cetuximab**-Cetuximab (Erbitux) is an IgG1 human/mouse chimeric antibody binding EGFR that competitively inhibits activation of the EGF receptor kinase activity. There is limited experience with cetuximab in advanced NSCLC at this point. Only one single-agent study has been performed in advanced NSCLC,[25] but results are still preliminary. In this study of 29 patients who failed after one or more regimens, there were two partial responses. Cetuximab is administered at a starting dose of 400 mg/m$^2$, followed by 250-mg/m$^2$ weekly doses thereafter. The main side effects of cetuximab are skin rash and acneiform skin toxicity, and
up to 4% hypersensitivity reactions.[26] Interestingly, diarrhea is not a common side effect of monoclonal therapy, in contrast to TKI treatment.

### Other EGFR Inhibitors
A phase II study of pertuzumab as a single agent has concluded accrual in patients with advanced NSCLC. Pertuzumab is an ErbB2 monoclonal antibody, with a different epitope than trastuzumab (Herceptin), which as its main action prevents homo- and heterodimerization of the receptor.[27,28] In doing so it also blocks the EGFR pathway. A number of TKIs have been developed that have a broader inhibitory spectrum on other tyrosine kinases of the Erb family or other receptor families. CI-1033, a pan-HER inhibitor (inhibitor of all ErbB members), has recently completed a randomized phase II study of three different schedules of administration. The results are awaited. Toxicities of this agent appear similar to EGFR inhibitors (skin rash and diarrhea), although some other side effects have been described (thrombocytopenia and allergy).[29] A randomized phase II study of lapatinib has recently been completed. Lapatinib inhibits both EGFR and ErbB2 with similar potency. The study randomized untreated NSCLC patients to receive two different doses of lapatinib. However, the study was later amended to only include patients who were never smokers or had adenocarcinomas with bronchoalveolar carcinoma features or pure bronchoalveolar carcinoma and allowed one line of prior chemotherapy. Given the important issue of patient selection, based on molecular markers for EGFR action (eg, EGFR mutations), the combination of inhibitory activities on other tyrosine kinases may increase the number of patients who may benefit from the treatment. Inhibitors of EGFR and VEGFR2[30] are being developed in advanced NSCLC. ZD6474 is undergoing large randomized phase II studies in advanced NSCLC, some of which have recently completed accrual.[31] Phase I studies with AEE788 inhibiting both EGFR/ErbB2 and the vascular endothelial receptor 2 (VEGFR2)[32,33] are running.

### Combinations With Chemotherapy
The oral EGFR targeting the TKIs gefitinib and erlotinib have both been tested in several large randomized controlled trials in combination with platinum doublet chemotherapy combinations. These studies all failed to show a benefit of the concomitant use of these agents in over 4,000 patients with advanced NSCLC.[34-37] In none of these studies were patients selected based on EGFR expression or any other marker of efficacy; this lack of patient selection may have caused the lack of positive outcome. Interestingly, however, the time to progression and survival curves suggest that maintenance EGFR inhibition may be of help after termination of chemotherapy. In the initial part of the survival curves, the EGFR TKI arms of all these studies do worse than the placebo arms. This is unlikely due to toxicity, as even the higher doses of these drugs are relatively well tolerated in combination with chemotherapy. EGFR inhibitors act mainly by reducing proliferation in wild-type EGFR tumor cells; proliferating tumor cells are those most affected by chemotherapy, therefore an antagonistic effect between EGFR TKIs and chemotherapy is plausible. Based on these considerations, sequential studies of EGFR TKIs (both gefitinib and erlotinib) following chemotherapy have been planned or are presently accruing; these studies investigate whether a TKI may increase outcome in patients who were not progressing on chemotherapy. Cetuximab given at 400 mg/m² on day 1 and at 250 mg/m² weekly thereafter has been combined with cisplatin at 80 mg/m² on day 1 and vinorelbine at 25 mg/m² on day 1 and 8, in a randomized phase II study.[38] A total of 101 patients whose tumors expressed EGFR were included. At a preliminary assessment the response rate was 31.7% in the cetuximab arm and 20% in the chemotherapy alone arm. Based on these results, a large phase III randomized study has recently been launched to compare cisplatin/vinorelbine to the same chemotherapy in combination with cetuximab. Furthermore, there are two ongoing randomized phase II studies in the US that use the chemotherapy regimens carboplatin/paclitaxel and cisplatin/gemcitabine with or without cetuximab. In a phase I/II trial of advanced NSCLC patients treated with one prior regimen were given erlotinib and bevacizumab (Avastin), a recombinant anti-VEGF monoclonal antibody.[39] Both agents could be given at the full dose of 150 mg/d of erlotinib and 15 mg/kg of bevacizumab every 3 weeks. In the 40 patients enrolled, response rate was 17.5% and median survival was 9.3 months. These results appear promising and have stimulated further studies of this combination in first- and second-line treatment of advanced NSCLC.

### Selection of Patients for EGFR Inhibitors
Patient characteristics and several molecular markers of the tumor have been described as candidate markers to select patients for treatment with EGFR inhibitors. From multivariate analysis in the randomized trials, particular patient characteristics such as female gender, adenocarcinoma, bronchiolar histology, never-smoking status, and Asian race have been related to drug sensitivity to
EGFR inhibitors.

Strikingly, in these patient groups a higher incidence of EGFR mutations in the ATP binding site domain has also been detected, sensitizing for treatment with gefitinib or erlotinib but not for cetuximab. Immunohistochemical staining of the extracellular domain of the EGFR receptor was not correlated with response to gefitinib or erlotinib in NSCLC patients. Amplification of the EGFR gene detected with FISH and the activity of molecules downstream of EGFR, such as p-Akt, and mutations of K-ras may play a role in sensitivity to EGFR inhibitors. The presence of K-ras mutations, detected in approximately 30% of NSCLC patients, is likely to constitute a useful marker to select those patients that will not benefit from anti-EGFR therapy. However, in a large randomized study of chemotherapy with or without erlotinib as first-line therapy in advanced NSCLC patients, EGFR mutations, detected in 13% of tumors, were associated with longer survival, irrespective of treatment. K-ras mutations, detected in 21% of tumors, were associated with significantly decreased time to progression and survival in patients treated with erlotinib plus chemotherapy. These results suggest that EGFR mutations may be a positive prognostic factor for survival that is independent of treatment with erlotinib, and that the combination of EGFR inhibitors and chemotherapy should be avoided in patients with K-ras mutations. Patient characteristics, amplification of the EGFR gene, the presence of EGFR mutations, and the absence of K-ras mutation are all candidates for inclusion in treatment algorithms for individualized treatment with EGFR inhibitors in NSCLC patients. However, the beneficial effects observed in the positive trials cannot be ascribed to the small population of responding patients only. To date, it is too early to exclude patients solely on the basis of one of these characteristics, as none have been validated in prospective clinical trials.

Conclusions

The introduction of EGFR inhibitors into the treatment of NSCLC is an important development. The side effects are generally less than with chemotherapy. While there is a general effect on symptom control and survival in some studies, limited subgroups of patients particularly benefit from this treatment. The discovery of EGFR mutations in the tyrosine kinase domain may present the possibility of patient selection and novel strategies. Although patient selection based on EGFR mutations only may not be sufficient, this knowledge will stimulate a more rational use of these agents in the future. Also newer drugs with broader activity on multiple pathways are being investigated, which may increase the number of patients who benefit.

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