Abstract. Advanced or metastatic non-small cell lung cancer (NSCLC) is characterised by a poor prognosis and few second- or third-line treatments. First-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibition has paved the way for targeted therapies in lung cancer. Although these drugs result in excellent responses [and significantly improved progression-free survival (PFS)] in patients with activating EGFR mutations, only few studies revealed improved overall survival (OS), and resistance often develops. Bevacizumab, a monoclonal antibody which targets vascular endothelium growth factor (VEGF), has been fully developed in NSCLC, and small-molecule tyrosin kinase inhibitors (TKIs) have been approved as first-line therapy for patients with advanced and metastatic NSCLC harbouring EGFR mutations. In addition, crizotinib, a novel inhibitor of the anaplastic lymphoma kinase, has been approved for second-line treatment of NSCLC. Several new drugs targeting not only the EGFR pathways, but also signal transduction cascades involved in angiogenesis and the mitogene-activated extracellular signal-regulated kinase pathways are currently evaluated in phase III clinical trials. Experimental monoclonal antibodies are also currently undergoing phase III clinical trials and have shown promising activity which might help to improve the therapeutic landscape of NSCLC. However, many other drugs prolonged PFS, but failed to demonstrate a significant improvement of OS. PFS is often used as a predictor for improved OS since it is independent of subsequent treatment, but OS is acknowledged as the key clinical outcome in the treatment of advanced NSCLC. Furthermore, since there are only very few trials that have shown a benefit from the addition of TKIs to chemotherapy, additional studies using this unselected approach are not recommended. Therefore, there is a definite need for an improved understanding of the complex mechanisms that are involved in TKI-mediated pathways, and for the development of validated predictive markers to allow a better treatment decision on the basis of the probability of response. This would certainly help to avoid the unnecessary use of potential toxic drugs in patients with known resistance and would facilitate the discovery of new targets and drugs on the basis of resistance mechanisms.

Non-small-cell lung cancer (NSCLC) accounts for approximately 80-85% of all cases of lung cancer, and is the most common cause of death in men and second only to breast cancer in women (1). Treatment of NSCLC is guided by disease stage, histology, and mutation status. Surgery is the treatment of choice for early-stage localized disease, whereas multimodality therapy remains the norm for patients with locally advanced disease. Patients with advanced metastatic disease may derive a benefit from palliative chemotherapy. About 40% of patients with NSCLC present with metastatic or locally advanced disease, which underscores the importance of identifying therapeutic schemes that may benefit this large patient population. Combination chemotherapy, usually platinum-based, is currently the first-line therapy of choice (2-4). Based on these studies, doublet regimens containing cisplatin or carboplatin with paclitaxel, gemcitabine, docetaxel, vinorelbine or irinotecan are administered. Although these studies showed no differences in outcomes among combinations between platinum and third-generation chemotherapeutics, there is evidence that cisplatin and pemetrexed should be recommended as a first-line chemotherapy for non-squamous NSCLC (3).

The prognosis for patients with advanced NSCLC is poor. Recent, large, randomised phase III trials have demonstrated that platinum-based chemotherapy combinations yield a median survival time of 8-11 months, a 1-year survival rate of 30-45% and a 2-year survival rate of 10-20% (4). The treatment of NSCLC is therefore a major unmet need and
new therapies focusing on the molecular mechanisms that mediate the growth of lung cancer cells are urgently needed.

Targeted Therapies: Approved Drugs

In patients with advanced or metastatic NSCLC carrying epidermal growth factor receptor (EGFR) mutations, the use of EGFR tyrosine kinase inhibitors (TKIs) improved overall survival (OS) and safety, when compared with standard chemotherapy. There are currently three different TKIs (gefitinib, erlotinib, afatinib) available for patients with EGFR mutation-positive NSCLC in the first-line setting, approved in Europe and USA and the survival rates with use of these drugs are very similar. In addition, these drugs are under clinical evaluation in second-line and adjuvant settings [reviewed in (5)]. Although these drugs showed different incidence of non-haematological toxicity, at this time there is no direct data that evaluate the response after a close and correct management. With regard to progression-free survival (PFS), a significant interaction according to ethnicity (Asian versus Caucasian versus mixed) and trial design (retrospective versus prospective EGFR analysis), was found in a meta-analysis (6) and a trend toward significance with regard to the type of drug (gefitinib versus erlotinib versus afatinib) was determined. However, no statistically significant differences in survival were observed. With regard to response, the authors reported a significant interaction according to ethnicity, trial design and type of drug. These data, together with a deeper characterisation of the molecular background sustaining the oncogenic process, may therefore contribute to create a predictive clinicopathological model, aimed at improving the magnitude of benefit expected from the use of targeted agents.

Gefitinib

Gefitinib (Iressa®, AstraZeneca, UK) is targeted against the tyrosine kinase activity of the EGFR pathway. Gefitinib has an interesting developmental history and has contributed greatly to our understanding of the biology of NSCLC and the role of the EGFR signalling pathways. During the phase II dose-finding studies (IDEAL studies 1 and 2) gefitinib showed activity as monotherapy in patients with advanced NSCLC who had received prior chemotherapy with overall response rates of 19% (IDEAL 1, Asian-European trial) and 10% (IDEAL 2, US trial) (4). Several phase III clinical trials with gefitinib (IPASS, NEJ002, First-SIGNAL, West Japan Thoracic Oncology Group Study) have demonstrated its activity in advanced or metastatic NSCLC harboring EGFR mutations (4-7).

The IPASS trial (IRESSA Pan-Asia Study), a phase III open-label, randomised, controlled trial conducted in 87 centres in East Asia which compared the use of first-line gefitinib with paclitaxel/carboplatin in 1217 patients with stage IIIB/IV pulmonary adenocarcinoma demonstrated that gefitinib is superior to carboplatin/paclitaxel in terms of PFS and objective response rate, as first-line treatment for pulmonary adenocarcinoma among never-smokers or former light smokers in East-Asias, with the presence of an EGFR mutation being a strong predictor of the greater effect of gefitinib compared with carboplatin/paclitaxel. In the overall population, PFS was significantly longer in patients treated with gefitinib than in those treated with paclitaxel/carboplatin (9.5 versus 6.3 months, HR=0.74, 95% CI=0.65-0.85; p<0.0001) (7). After the results of the IPASS trial, gefitinib was approved for advanced and metastatic mutation-positive NSCLC in all settings of treatment in Europe and Asia, but not in the USA since the Federal Drug Administration (FDA) withdrew the approval of the drug in 2012 after post-marketing studies failed to show an OS benefit of patients taking gefitinib.

Erlotinib

Erlotinib (Tarceva®, Roche, Switzerland) inhibits EGFR signalling by binding to the intracellular TK domain. Several phase I/II trials demonstrated activity of erlotinib in NSCLC patients [reviewed in (4)]. These data were confirmed by the results of the phase III trial BR.21 (8). In this trial relevant for the approval of erlotinib as second/third-line therapy of advanced NSCLC, 731 patients with stage IIIB/IV NSCLC (unselected for EGFR mutations) were randomized in a 2:1 ratio after failure of at least one chemotherapy and were treated with erlotinib (150 mg/day) or placebo with best supported care (BSC). The study met its primary endpoint with a significant improvement in median OS (6.7 months versus 4.7 months; HR=0.70; p<0.001). Erlotinib also improved the response rate (8.9% versus <1%; p<0.001) and median duration of response (7.9 months versus 3.7 months), as well as the median PFS (2.2 months versus 1.8 months; HR=0.61; p<0.001) (8). However, a recently published trial (first- and second-line treatment), has established the importance of selecting patients by EGFR mutation, and have indicated this as the gold standard therapy (9).

Recently, data from two phase III trials EURTAC (10) and OPTIMAL (11) have shown that erlotinib has also activity as front-line therapy in NSCLC, thus the drug was approved by FDA and the European Medicines Agency (EMA) in 2013 for first-line treatment in patients with NSCLC harbouring EGFR mutations. The approval was based on the results of a randomised, multicenter open-label trial comparing erlotinib (N=86) to platinum-based doublet chemotherapy (N=88) in patients with metastatic NSCLC whose tumours had EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. Eligible patients were randomly assigned (1:1) to receive erlotinib (150 mg/day orally), or platinum-based doublet...
chemotherapy. The trial’s primary endpoint was PFS; secondary endpoints included OS and objective response rate. The median PFS was 10.4 months in the erlotinib arm and 5.2 months in the platinum-based chemotherapy arm (HR=0.34; 95% CI=0.23-0.49, \( p<0.001 \)). The median OS was 22.9 months in the erlotinib arm and 19.5 months in the platinum-based chemotherapy arm (HR=0.93; 95% CI=0.64-1.35, \( p=0.6482 \)). The overall response rate was 65% in the erlotinib arm and 16% in the platinum-based chemotherapy arm (10, 11).

Subsequently, the results of the SATURN study also showed a significant prolongation of PFS and OS with maintenance erlotinib compared with placebo (for patients with stable disease) (12). Despite considerable controversy, maintenance therapy has become an acceptable treatment paradigm and erlotinib is also approved for maintenance therapy of patients with advanced NSCLC in Europe and the USA (13).

**Afatinib**

Multitargeted agents represent the next generation of targeted therapies for solid tumors. The benefits of individually targeting the EGFR and the vascular epithelium growth factor receptor (VEGFR) signalling pathways have been clinically validated in recent years for a number of solid tumor types including NSCLC. Given the heterogeneity of this tumour type and potential cross-talk between these key signalling pathways, multiple inhibitions have the potential to offer additional clinical benefits in NSCLC.

Afatinib (Giotrif®, Boehringer Ingelheim, Germany) is an oral irreversible TKI of all members of the EGFR family. The drug has shown promising activity as front-line therapy in patients with EGFR mutation positive (NSCLC) (e.g. del19, L858R) compared with standard chemotherapy (4). In the LUX-Lung 3 trial, patients with mutation-positive NSCLC were randomly assigned (2:1 ratio) to receive afatinib (40 mg/day) or chemotherapy with cisplatin and pemetrexed every three weeks. The results were a median PFS of 11.1 months on afatinib and 6.9 months on platinum-based chemotherapy arm (HR=0.59, CI= 0.45-0.77; \( p<0.001 \)).

The median OS was 22.9 months in the erlotinib arm and 19.5 months in the platinum-based chemotherapy arm (HR=0.93; 95% CI=0.64-1.35, \( p=0.6482 \)). The overall response rate was 65% in the erlotinib arm and 16% in the platinum-based chemotherapy arm (10, 11).

Subsequently, the results of the SATURN study also showed a significant prolongation of PFS and OS with maintenance erlotinib compared with placebo (for patients with stable disease) (12). Despite considerable controversy, maintenance therapy has become an acceptable treatment paradigm and erlotinib is also approved for maintenance therapy of patients with advanced NSCLC in Europe and the USA (13).

**Crizotinib**

Anaplastic lymphoma kinase (ALK) is a validated tyrosine kinase target in several types of cancer, including NSCLC, anaplastic large-cell lymphoma, and paediatric neuroblastoma. ALK rearrangements are found in approximately 3-5% of all cases of NSCLC and define a distinct molecular NSCLC subtype.

Crizotinib (Xalkori®, Pfizer, USA) is an oral small-molecule TKI targeting ALK, c-MET, and ROS1 (17). In two single-group studies, crizotinib showed marked antitumour activity in patients with ALK-positive NSCLC, with objective response rates of approximately 60% and a median PFS of 8.1-9.7 months (18, 19).

Due to these promising results, a phase III, open-labeled trial was conducted comparing crizotinib with chemotherapy in 347 patients with locally advanced or metastatic ALK-positive NSCLC who had received one prior platinum-based regimen. Patients were randomly assigned to receive oral treatment with crizotinib (250 mg \( b.i.d. \)) or intravenous chemotherapy with either pemetrexed (500 mg/m\(^2\)) or docetaxel (75 mg/m\(^2\)) every three weeks. Patients in the chemotherapy group who had disease progression were permitted to crossover to crizotinib. The primary endpoint was PFS. The response rates were 65% with crizotinib, as compared with 20% with chemotherapy \( (p<0.001) \). PFS was 7.7 months in the crizotinib group and 3.0 months in the chemotherapy group \( (p<0.001) \).

In addition, improved quality of life in the crizotinib-treated
patients was also noted. An interim analysis of OS showed no significant improvement with crizotinib as compared with chemotherapy \((p=0.54)\), however, the apparent lack of a survival benefit probably reflects the confounding effects of crossover, effects that have been observed in other randomised trials of molecularly targeted agents in patients with NSCLC.

Most recently, the results of a phase III trial (PROFIL 1014) comparing crizotinib \((N=172)\) with cisplatin (carboplatin) plus cetuximab \((N=171)\) as first-line treatment of advanced NSCLC were published (21). In this trial, crizotinib was found to significantly prolong PFS \((\text{median } 10.9 \text{ versus } 7.0 \text{ months}; \text{HR}=0.454; 95\% \text{ CI}=0.346-0.596; p<0.0001)\) in previously untreated patients with ALK-positive advanced non-squamous NSCLC compared with standard platinum-based chemotherapy and has demonstrated that as first-line treatment crizotinib is superior to standard chemotherapy doublet regimens in prolonging PFS for patients with ALK-positive advanced NSCLC. Based on these findings, the drug was fully approved by FDA and EMA at the end of 2013 as second-line therapy for ALK-positive advanced or metastatic NSCLC.

### Bevacizumab

Bevacizumab (Avastin®; Roche, Switzerland) is a monoclonal antibody with high affinity for VEGF. The drug is currently approved (FDA, EMA) for the treatment of advanced and metastatic non-squamous NSCLC in combination with paclitaxel and carboplatin. Completed phase III trials evaluating bevacizumab plus chemotherapy have shown prolonged PFS; however, not all trials showed significant improvement of OS \((22)\). Hence, several studies with bevacizumab plus chemotherapy in advanced or metastatic NSCLC are ongoing.

In the ECOG 5508 study \((NCT01107626)\), patients \((N=1282)\) will receive bevacizumab alone, pemetrexed alone, or bevacizumab and pemetrexed combined after induction therapy with carboplatin and paclitaxel plus bevacizumab. The primary endpoint is OS. The study is still recruiting patients.

In another study \((NCT00976456)\), elderly patients \((N=250)\) will receive bevacizumab plus pemetrexed or bevacizumab plus pemetrexed/carboplatin; the primary endpoint is non-inferiority of bevacizumab/pemetrexed compared with bevacizumab/pemetrexed/carboplatin based on PFS. The study is active, but no longer recruiting.

### Table I. Selected phase III targeted therapies trials in patients with advanced or metastatic non-small cell lung cancer (NSCLC).  

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>MONET-1:</td>
<td>Paclitaxel/carboplatin plus motesanib (versus) paclitaxel/carboplatin plus placebo</td>
<td>OS unchanged, toxicity increased</td>
<td>Scagliotti et al. (24)</td>
</tr>
<tr>
<td>(N=1090)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADVGO:</td>
<td>Paclitaxel/carboplatin plus figitumumab (versus) paclitaxel/carboplatin plus placebo</td>
<td>Serious adverse events in the figitumumab arm</td>
<td><a href="http://www.pfizer.com">www.pfizer.com</a></td>
</tr>
<tr>
<td>Recruiting stopped</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BR 26:</td>
<td>Second-line, dacomitinib (versus) placebo</td>
<td>PFS and OS unchanged</td>
<td><a href="http://www.pfizer.com">www.pfizer.com</a></td>
</tr>
<tr>
<td>(N=720)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARCHER-1009:</td>
<td>Second-third-line, dacomitinib (versus) erlotinib</td>
<td>PFS unchanged</td>
<td><a href="http://www.pfizer.com">www.pfizer.com</a></td>
</tr>
<tr>
<td>(N=800)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARCHER-1050:</td>
<td>Dacomitinib (versus) gefitinib</td>
<td>Results expected in 2015</td>
<td><a href="http://www.clinicaltrials.gov">www.clinicaltrials.gov</a></td>
</tr>
<tr>
<td>(N=440)</td>
<td>(patients with (EGFR) mutation)</td>
<td></td>
<td>(Study NCT01774721)</td>
</tr>
<tr>
<td>ATTRACT-1:</td>
<td>Paclitaxel/carboplatin (versus) placebo</td>
<td>PFS and OS unchanged</td>
<td>Lara et al. (25)</td>
</tr>
<tr>
<td>(N=1299)</td>
<td>plus ASA404</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATTRACT-2:</td>
<td>Docetaxel plus ASA404 (versus) docetaxel plus placebo</td>
<td>OS unchanged</td>
<td><a href="http://www.clinicaltrials.gov">www.clinicaltrials.gov</a></td>
</tr>
<tr>
<td>(N=900)</td>
<td></td>
<td></td>
<td>(Study NCT00738387)</td>
</tr>
<tr>
<td>VITAL:</td>
<td>Docetaxel plus aflibercept (versus) placebo</td>
<td>OS unchanged</td>
<td>Novello et al. (26)</td>
</tr>
<tr>
<td>(N=900)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ZODIAC:</td>
<td>Docetaxel plus vandetanib (versus) docetaxel plus placebo</td>
<td>PFS and OS unchanged</td>
<td>Herbst et al. (27)</td>
</tr>
<tr>
<td>(N=1391)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BR 29:</td>
<td>Paclitaxel/carboplatin plus cediranib (versus) paclitaxel/carboplatin plus placebo</td>
<td>Not reported yet</td>
<td>Aggarwal et al. (22)</td>
</tr>
<tr>
<td>(N=750)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESCAPE:</td>
<td>Paclitaxel/carboplatin plus sorafenib (versus) paclitaxel/carboplatin plus placebo</td>
<td>PFS and OS unchanged</td>
<td>Scagliotti et al. (28)</td>
</tr>
<tr>
<td>(N=926) (study halted)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FLEX:*</td>
<td>Cisplatin/vinorelbine plus cetuximab (versus) cisplatin/vinorelbine plus placebo</td>
<td>OS increased</td>
<td>Pirker et al. (29)</td>
</tr>
<tr>
<td>(N=1125)</td>
<td></td>
<td>(11.3 versus 10.1 months)</td>
<td></td>
</tr>
</tbody>
</table>

*Approval refused by the European Medicines Agency (EMA) due to contrary data from other studies. \(EGFR\): epidermal growth factor receptor.
The NCT00948675 trial (N=360) is evaluating chemotherapy with pemetrexed/cisplatin followed by maintenance therapy with pemetrexed compared with bevacizumab plus carboplatin/paclitaxel followed by maintenance therapy with bevacizumab. The primary endpoint is OS. The study is active, but no longer recruiting, results have not yet been reported.

In terms of adjuvant treatment with bevacizumab, the ECOG E1505 study (NCT00324805, N=1500) is currently recruiting patients with completely resected stage IB-IIIA NSCLC to evaluate OS in patients treated with an adjuvant chemotherapy regimen of vinorelbine/cisplatin, docetaxel/cisplatin, gemcitabine/cisplatin or pemetrexed/cisplatin with or without bevacizumab. The primary endpoint is OS. However, interim safety data showed significant toxicity (grade 3/4) with bevacizumab plus chemotherapy versus chemotherapy alone (23).

**Potential Drugs for Approval**

Several targeted therapies (small molecules and monoclonal antibodies) are currently in phase III clinical development for NSCLC. These agents have shown promising activity in phase I/II studies, however, many drugs failed to significantly improve OS when combined with chemotherapy (Table I). On the other hand, results form recently completed and ongoing phase III trials with newer targeted therapies will determine if these drugs will be incorporated into clinical practise.

**Tivantinib**

Tivantinib (ArQule, USA), a staurosporine derivative, is a small-molecule TKI selectively inhibiting c-MET. c-MET activity can have profound effects on cell growth, survival, motility, invasion and angiogenesis. Dysregulation of MET signalling has been shown to contribute to tumourigenesis in a number of malignancies. c-MET is also overexpressed in 60-80% of patients with NSCLC, whereas c-MET mutations are found in 20% of these patients (4).

In a recently published phase II study (N=176) with patients previously treated for NSCLC, the combination of tivantinib (360 mg b.i.d) plus erlotinib (150 mg/day) significantly improved PFS and OS compared with placebo plus erlotinib in the subset of patients with non-squamous histology, a population enriched for c-MET overexpression (30). Based on these results, a phase III, randomised, double-blind, placebo-controlled study (MARQUEE) of tivantinib plus erlotinib versus placebo plus erlotinib in previously treated patients with locally advanced or metastatic, non-squamous NSCLC was conducted. The primary endpoint of this trial was OS. However, although the interim analysis showed a statistically significant improvement in PFS in the intent-to-treat population, this benefit did not carry over to OS and the study was stopped subsequently (31).

In this regard, it is worth noting that a similar clinical phase III exploring the monoclonal antibody to c-MET, omartuzumab (Roche, Switzerland) (erlotinib plus omartuzumab versus erlotinib plus placebo) as second-line treatment for patients with c-MET mutation-positive NSCLC has been halted due to futility (32).

**Nintedanib**

Nintedanib (Vargatef®, Boehringer Ingelheim, Germany) is an angiokinase inhibitor targeting VEGFR1-3, fibroblast growth factor receptors 1-3 and platelet-derived growth factor receptor and has also activity against SCR and FLT-3. To date, phase I and II trials with nintedanib have been shown an improvement for survival of patients with advanced and metastatic NSCLC, and toxicity profiles seemed to be acceptable in these clinical trials (33).

In the LUME-Lung 1 phase III trial (N=1300) the combination of docetaxel (75 mg/m², day 1, every three weeks) plus nintedanib (200 mg b.i.d.) versus docetaxel plus placebo as second-line therapy in patients with advanced or metastatic NSCLC was evaluated. OS was found to be significantly prolonged in the nintedanib arm (12.6 versus 10.3 months) and was even more pronounced in patients with adenocarcinoma histology (34). Based on these clinical data the drug has been submitted for EMA approval (expected in 2015).

The LUME-Lung 2 phase III clinical trial (NCT00806819) (N=1302) has also been conducted to evaluate nintedanib plus pemetrexed versus pemetrexed plus placebo as second-line treatment for advanced or metastatic NSCLC. Preliminary data indicated no differences between PFS and OS between both arms (www.clinicaltrials.gov).

**Selumetinib**

Selumetinib (AstraZeneca, UK) is an inhibitor of MEK1,2 (mitogene-activated extracellular signalregulated kinase) downstream of KRAS, with preclinical evidence of synergistic activity with docetaxel in KRAS mutant carcinomas. Since currently no targeted therapies are available for KRAS-mutant NSCLC, selumetinib has been tested in this patient group. The results from a randomised phase II study (N=87) evaluating the combination of selumetinib with docetaxel against docetaxel alone in KRAS mutation-positive NSCLC patients have demonstrated a high and durable response rate of 37.2% versus 0 % (p<0.0001), translating into a statistically significant improvement in PFS of 5.3 versus 2.1 months (HR=0.58, p<0.014) (35).

Following these results, selumetinib is being evaluated as combination therapy (SELECT-1). This study is a...
randomised, double-blind, placebo-controlled trial (N=634) that will evaluate the safety and efficacy of selumetinib (75 mg b.i.d. orally) plus docetaxel (75 mg/m² intravenously, on day 1 of every 21 days) as a second-line therapy in locally advanced or metastatic KRAS mutation-positive NSCLC. The study is designed to evaluate PFS as the primary endpoint and OS as a secondary endpoint. This trial is currently enrolling patients (NTC01933932) and is to date the only study which evaluates targeted therapy in patients with NSCLC harbouring KRAS mutations.

Ramucirumab

Ramucirumab (Cyramza®; Lilly, USA) is an investigational monoclonal antibody that binds to VEGFR-2 and blocks ligand binding and activation. The drug has been tested in several phase II NSCLC clinical trials and has showed overall response rates up to 55% (36). Due to these encouraging results, an international, randomised, placebo-controlled, double-blinded phase III trial (REVEL, N=1242) has examined the efficacy and safety of ramucirumab treatment administered in combination with docetaxel, as compared with docetaxel administered with placebo, in patients with stage IIIB/IV NSCLC whose disease progressed during or after first-line platinum-based chemotherapy with or without maintenance treatment. The primary endpoint was OS; secondary endpoints included PFS, overall response rate, disease control rate, patient-reported outcomes, and assessment of safety and tolerability of ramucirumab. Eligible patients were randomized at a 1:1 ratio to receive either docetaxel (75 mg/m²) plus ramucirumab (10 mg/kg) or docetaxel (75 mg/m²) plus placebo. Recently published results from this study have shown that patients treated on the ramucirumab/docetaxel arm (N=628) achieved a median OS of 10.5 months compared to 9.1 months for patients on the ramucirumab/placebo arm (N=625). The OS HR for those treated of 10.5 months compared to 9.1 months for patients on the ramucirumab/docetaxel arm (N=628) achieved a median OS from this study have shown that patients treated on the docetaxel (75 mg/m²) plus placebo. Recently published results of a phase III trial (SQUIRE) (N=1093) of necitumumab in combination with gemcitabine and cisplatin versus gemcitabine and cisplatin plus placebo in squamous NSCLC have been reported (40). The study results showed that patients in the necitumumab plus chemotherapy arm had an improvement in OS (HR=0.84, p=0.012) with a median survival of 11.5 months compared to 9.9 months for patients treated in the chemotherapy-only arm. PFS and the disease control rate, defined as patients demonstrating either a complete or partial response or stable disease, were also significantly improved. Based on this study a regulatory submission of necitumumab is anticipated early next year as first-line therapy for patients with NSCLC (stage IIIB/IV) with squamous histology.

Ceritinib

Ceritinib (Zykadia®; Novartis, Switzerland) is a small molecule that targets ALK- and insulin-like growth factor (IGF) 1 receptor TKIs. NSCLCs harbouring ALK gene rearrangements are sensitive to the TKI crizotinib, but invariably develop resistance (41). Ceritinib is a novel, more potent ALK inhibitor than crizotinib, with significant antitumour activity in preclinical models (41). Moreover, the drug showed promising activity in patients with NSCLC harbouring ALK mutations (mainly the gatekeeper mutation L1196M). In a recently reported phase I trial ceritinib demonstrated a partial response rate of 56% (44/79) in patients with crizotinib-resistant advanced or metastatic NSCLC (42). The drug is even active in patients with brain metastasis from NSCLC.

Due to these encouraging results the drug is currently being evaluated in two phase III trials. In the first study (NCT 01828099), untreated patients with ALK-positive NSCLC (N=348) are randomised between ceritinib alone versus chemotherapy; the primary endpoint is PFS. In the second study (NCT01828112), patients with previously treated ALK-positive NSCLC (pretreated with platinum-doublet chemotherapy plus crizotinib) (N=236) are randomised between ceritinib alone versus chemotherapy. Again, the primary endpoint is PFS. Both studies are currently recruiting patients.

It should be noted that ceritinib (although already approved by the FDA) is not the only promising drug in patients with crizotinib-resistant disease CH5424802 (ALK inhibitor, Chugai), AP26113 (ALK inhibitor, Ariad) and the heat-shock protein 90 inhibitor AUY922 (Novartis) had demonstrated considerable activity in this cluster of patients in phase I/II studies and due to a more potent CNS penetration (43).

Further Considerations

Targeted therapies are currently being evaluated in a variety of treatment settings in NSCLC and novel strategies of disrupting tyrosine kinase-controlled pathways have been investigated.
However, many of the recently reported trials have failed to improve OS which might be due to several key reasons. Firstly, without a validated biomarker, specific subgroups of patients who are more likely to respond cannot be selected. Furthermore, the redundancy in tyrosine kinase-triggered pathways leads to primary and secondary resistance to an agent that targets a specific signal transduction cascade; as a result, agents that target multiple pathways are currently under investigation. Finally, it is unlikely that any TKI could achieve complete inhibition of its target(s), which may result in reduced but not completely abrogated signalling (22). A possible potential mechanism for the lack of synergy between these agents and chemotherapy may be the G1 phase cell-cycle arrest caused by TKIs, which then may interfere with the cell cycle-dependent cytotoxicity of chemotherapy (44). In addition, most of the TKIs are associated with significant additional toxicity suggesting that combination with chemotherapy might not be the best setting for the use of multitargeted TKIs.

Since there are only very few trials that have shown a benefit from the addition of TKIs to chemotherapy, additional studies using this unselected approach are not recommended. Therefore, there is a definite need for an improved understanding of the complex mechanisms that are involved in the TKI-mediated pathways, and for the development of validated predictive markers to allow a better treatment decision on the basis of the probability of response. This would certainly help to avoid the unnecessary use of potentially toxic drugs in patients with known resistance and would facilitate the discovery of new targets and drugs on the basis of resistance mechanisms (45).

To date, no perspective studies have yet compared gefitinib, erlotinib, and afatinib for adverse events (AEs) and efficacy, irrespective of \textit{EGFR} mutation status. However, some retrospective trials have been published suggesting that gefitinib does have the more favourable toxicity profile when compared with erlotinib and afatinib. One such study (46) compared AEs between gefitinib and erlotinib in patients with NSCLC. The authors found that the erlotinib-treated group had more AEs, including rash, fatigue, stomatitis, anorexia and constipation. On the other hand, liver dysfunction and nail changes were more frequent in the gefitinib-treated group. AEs of grade 2 or more, including rash, fatigue, and nausea, were again more frequent in the erlotinib-treated group (46). This group also showed more of a tendency to require dose reduction due to their AEs, suggesting that gefitinib may have a better toxicity profile than erlotinib.

A more recently published meta-analysis adds weight to this proposal. Haspinger \textit{et al.} performed a systematic review and meta-analysis in order to estimate through indirect comparison the relative risk benefit associated with gefitinib, erlotinib, and afatinib. Data extraction was performed by two independent reviewers ad focused on benefit (overall response rate, PFS) and selected harm outcomes (diarrhoea, rash, fatigue, nausea, anorexia and constipation). They found that all three TKIs had similar activity and efficacy (overall response rate, PFS) while the toxicity was less favourable for afatinib, with a significant higher risk of diarrhoea, rash, and nail disorders (47). Based on these safety results, the authors suggested that afatinib may not be the first choice for treatment of patients with NSCLC harbouring \textit{EFGR} mutations. In addition, these findings suggest a more favourable toxicity profile and quality of life with gefitinib.

### Table II: Overall survival (OS) benefits in patients with advanced or metastatic non-small cell lung cancer (NSCLC) following treatment with targeted therapies.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Study design</th>
<th>N</th>
<th>Median OS benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nindetanib</td>
<td>Docetaxel plus nindetanib versus docetaxel (second-line)</td>
<td>1341</td>
<td>2.1 Months (adenocarcinoma only) (34)</td>
</tr>
<tr>
<td>Tivantinib</td>
<td>Erlotinib plus tivantinib versus erlotinib (second-line)</td>
<td>176</td>
<td>3.4 Months (phase II trial) (30)</td>
</tr>
<tr>
<td>Necitumumab</td>
<td>Cisplatin/gemcitabine plus cisplatin/gemcitabine plus placebo (first-line)</td>
<td>1093</td>
<td>1.6 Months (squamous cell carcinoma only) (40)</td>
</tr>
<tr>
<td>Ramucirumab</td>
<td>Docetaxel plus ramucirumab versus docetaxel plus placebo (second-line)</td>
<td>1250</td>
<td>1.4 Months (37)</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Carboplatin/paclitaxel plus bevacizumab versus carboplatin/paclitaxel plus placebo (first-line)</td>
<td>878</td>
<td>2.0 Months (22)</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>Platinum-based doublet plus cetuximab versus platinum-based doublet plus placebo (first-line)</td>
<td>1125</td>
<td>1.2 Months (29)</td>
</tr>
</tbody>
</table>
The question remains whether the benefit of targeted therapy for NSCLC may be best defined by PFS since in this regard published are still unconvincing. Truly, PFS is regarded as a good predictor for improved OS (and is independent of subsequent treatment), but OS is acknowledged as the key clinical outcome in the treatment of advanced NSCLC. All large previous randomised phase III trials assessing first-line treatment demonstrated a significantly higher response rate and longer PFS in patients treated with first-generation EGFR-TKIs, including gefitinib and erlotinib, than in patients treated with standard platinum-based combination chemotherapy. Although these trials met their primary endpoint with significantly longer PFS, no significant difference was observed in terms of OS. However, no restrictions were imposed on treatment after the end of protocol therapy in any of these trials and the majority of patients in the control arm received EGFR-TKI therapy at least once.

None of these randomised trials has yet demonstrated a statistically significant improvement with these TKIs in terms of OS, which is of course the strongest endpoint for clinical research in oncology, in a condition of no effective treatment afterwards. When effective treatment is given as post therapy, it will be difficult to distinguish the treatment effect of original and subsequent treatments because differences in OS are potentially confounded by crossover, and a relevant number of patients assigned to chemotherapy arms received TKIS as second- or third-line treatment after disease progression. Intuitively, the high proportion of crossover may extend the benefit associated with the administration of TKIs to patients assigned to the control arm, and its ‘salvage’-effect may compensate for the relevant differences in PFS of first-line treatment consistently demonstrated in all TKI trials.

Nevertheless, future studies should clearly focus on OS as a primary endpoint for any type of targeted therapy in patients with NSCLC. Since published data for significant OS benefits in NSCLC are moderate (Table II), more meaningful results for patients are clearly needed. ASCO Guidelines recommend for advanced or metastatic NSCLC that clinical trials should aim to improve OS by 25% to 30%, with a minimal increase in toxicity (48). For squamous cell disease, that benefit should be 2.5 to 3.0 months (target HR=0.77-0.80); for non-squamous cell disease it should be 3.25-4.0 months (target HR=0.76-0.80). These recommendations, however, are not intended to set standards for regulatory approval or insurance coverage but rather to encourage patients and investigators to demand more from clinical trials.

In conclusion, personalised medicine for NSCLC patients is now a reality, and patients with *EGFR* mutations should be treated with the best available TKI. From all published data, gefitinib currently represents an ideal first-line treatment option for this molecularly selected subgroup of patients.

**Disclaimer**

The Author states there are no conflicts of interest in regard to this article.

**References**


Received December 9, 2014
Revised December 23, 2014
Accepted January 7, 2015