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Emerging Options for the Management of Non-Small Cell Lung Cancer

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Abstract: Lung cancer is one of the leading causes of death in industrialized and developing countries. Approximately 80% of patients are diagnosed with non-small cell histology. Although a multidisciplinary approach is necessary for the treatment of patients at early or locally-advanced stages of the disease, further successes in the treatment of patients with advanced disease will largely rely on improved systemic tumor control. Although therapies directed against the epidermal growth factor receptor (EGFR) have been incorporated into daily clinical practice, the value of other treatments remains to be elucidated. The current review highlights the most important driver mutations in non-small cell lung cancer (NSCLC) and describes recent study results and the status of EGFR-directed therapy, anaplastic lymphoma kinase (ALK)-directed agents, antiangiogenic therapy, and mesenchymal-epithelial transition factor (MET) inhibitors. However, many other agents with different modes of action are being examined in clinical research.

Keywords: lung cancer, NSCLC, chemotherapy, targeted therapy

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Introduction

Lung cancer is one of the most frequent malignant tumors in Europe¹ and the United States² and is associated with a relatively older age at initial diagnosis, high mortality, and low cure rates.^{2,3}

The majority of patients are diagnosed at a locally-advanced or metastatic stage, making systemic therapies the mainstay for treatment. However, the disease control achieved with classical doublet chemotherapy in advanced or metastatic non-small cell lung cancer (NSCLC) is usually restricted to only a few months.⁴⁻⁶ Improved patient selection for existing therapies and the introduction of novel agents are integral to an optimized treatment outcome.

Several novel drugs were developed over the last few years and tested in phase I, II, and III studies. A few drugs were approved (erlotinib, gefitinib, bevacizumab, and crizotinib) or are awaiting approval (afatinib), whereas other drugs missed their statistical targets in phase III trials (eg, small-molecule angiogenesis inhibitors) or were withdrawn due to insufficient study results (cetuximab). In recent years, with growing insight into molecular alterations in lung cancer, tremendous efforts have been made to identify and develop new agents. The present review focuses on known driver mutations in NSCLC, epidermal growth factor receptor (EGFR)-directed therapy, anaplastic lymphoma kinase (ALK) inhibitors, mesenchymal-epithelial transition factor (MET)-inhibitors, and angiogenesis inhibitors. However, other pathways may stimulate interest and different agents may soon enter clinical research.

Driver Mutations in NSCLC

Since the first attempts to systemically treat advanced lung cancer with drugs, the substances have had molecular targets. Certain traditional chemotherapy agents interfere with DNA replication and repair (eg, platinum compounds, topoisomerase inhibitors, and antifolates) or mitotic cell division (taxanes and vinca alkaloids). However, the term “targeted therapy” has been increasingly used in recent years to describe novel, more specific agents that modulate signal transduction from the cell surface (or other locations within the cell) to the nucleus. The term usually indicates a favorable relationship between toxicity and efficacy because the therapy is specific to the target. Ideally, a certain diagnostic procedure should allow the separation of responders from

non-responders before treatment. However, today, the majority of targeted therapies for NSCLC are prescribed without the detection of the necessary target of the substance (eg, second-line erlotinib in patients without activating EGFR mutations) or without a reliable predictive test or biomarker (eg, bevacizumab). Therefore, outcomes in such patient populations remain modest. The term “targeted therapy” is currently widely used but was recently critically judged.⁷ Exciting insights into novel pathways and drugs should be combined with efforts to find predictive tests for agents that are already approved.

The most recent classifications of lung tumors, the 1999 World Health Organization (WHO) classification⁸ and the 2011 Classification of Adenocarcinoma,⁹ are based on the light microscopy-related differentiation of different types of NSCLC. To date, beyond tumor stage, these classifications have served as the basis of our treatment decisions. However, genomic alterations have increasingly gained attention as a powerful tool to select specific treatments for patients. Several somatic mutations (and other alterations) have been revealed, which are prevalent in genes that encode transmembrane or intracellular signaling elements important for proliferation and apoptosis. Recent trials demonstrated that driver mutations possess crucial therapeutic relevance.

Approximately 60% of all primary pulmonary adenocarcinomas exhibit a specific mutation, gene arrangement, or amplification that is responsible for the malignant phenotype.¹⁰ The Lung Cancer Mutation Consortium (LCMC) represents the largest initiative in the United States that prospectively collects and tests tumor tissue from lung cancer patients (<http://www.golcmc.com>). The causative role of these changes in the development of malignancy is corroborated by the fact that the changes are mutually exclusive in most cases.¹¹ For instance, if a V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) mutation is detected in a pulmonary adenocarcinoma, an activating epidermal growth factor (EGF) receptor mutation can be excluded, and sequencing is unnecessary.¹² In patients without a known driver mutation, other yet-unknown or complex genomic alterations may be responsible for the malignant phenotype.¹³ Mutations in the EGF receptor gene were one of the first changes detected, facilitated by the relatively frequent occurrence of this alteration. Table 1 gives an overview of the most important findings in NSCLC.

**Table 1.**

	Frequency, histology, prognosis	References
EGF receptor mutations, exons 18–21; EGF receptor amplification	0%–50% depending on smoking history and ethnicity, highest in never-smoking pts. with AC, higher in Asians than in Caucasians, very rare in squamous cell histology or large-cell carcinoma. Various different activating and resistance mutations known, majority of pts. have mutations in exons 19 and 21, activating mutations associated with long PFS with EGF receptor tyrosine kinase inhibitors, EGFR copy number closely linked to mutation but rarely available and used	10–19
KRAS mutation, exon 1 (codons 12 and 13) or exon 2 (codon 61)	0%–43% depending on histology, 16% in a mixed NSCLC population, 25% among pts. with AC, 2%–5% in never-smokers, 43% in former/current smokers with AC, rare in squamous cell histology. Pts. with mutation have poor survival and rarely respond to chemotherapy	11,13–15,20,21
ALK rearrangements	1%–13% among NSCLC pts., depending on histology, smoking habits and age; more commonly found in light- or never-smokers and younger pts. with AC; more frequently found in male pts.; up to 12% in never-smokers with AC. Presence of rearrangement associated with resistance to EGFR tyrosine kinase inhibitors	10,13,14,21–25
BRAF mutations, exons 11 and 15	2%–3% among AC pts., more frequently found in current or former smokers, not found in SCC	10,11,14,15
HER2 mutation, exon 20	1%–10% among AC pts., appears to be more common in never-smokers, infrequent in SCC	10,11,15,21,26
MET amplification/mutations	Amplification in up to 21% of NSCLC pts. Contributes to primary and acquired resistance to EGFR TKIs, detectable in AC and SCC, somatic MET mutations rare	10,14,27–30
PIK3CA mutations	Detectable in 1%–5% of AC and 7% of SCC. Therapeutic relevance unclear	10,11,14,15
AKT1 mutations	Up to 1% in SCC, not found in AC	10,15,28
PTEN mutations	2%–11%, more frequently found in smokers and SCC	11,14,31

Others: DDR2, FGFR1, RET, ROS1.

Abbreviations: pts., patients; AC, adenocarcinoma; SCC, squamous cell carcinoma.

Targeting the EGF Receptor Gefitinib and erlotinib

In 2002 and 2003, several large phase III studies demonstrated that a platinum-based doublet combination treatment, regardless of whether the platinum agent is combined with gemcitabine, vinorelbine, docetaxel, or paclitaxel, is unable to prolong progression-free and overall survival by more than 3.4–5.75 months (mo.) and 7.4–11.3 mo., respectively.^{4–6} Numerous attempts with dose and protocol alterations, including triplet and alternating regimens, could not define a new standard. Gefitinib and erlotinib, two small-molecule tyrosine kinase inhibitors directed against the EGFR (synonymous with (syn.) ErbB1 and HER1) yielded the first clinical study data. Both gefitinib and erlotinib inhibit the EGFR tyrosine kinase by binding to the adenosine triphosphate (ATP)-binding site located within the kinase domain. Without ATP binding, autophosphorylation and downstream signaling are suppressed.³²

In the last decade, studies began to test the clinical activities of erlotinib and gefitinib in patients with platinum-pretreated advanced NSCLC. In the landmark BR21 study, erlotinib was tested against a placebo in patients with one or two prior chemotherapy regimens.³³ The study revealed a small benefit in progression-free survival in favor of erlotinib (median 2.2 versus (vs.) 1.8 mo., hazard ratio (HR)=0.61, $P < 0.001$) and overall survival (median 6.7 vs. 4.7 mo., HR = 0.70, $P < 0.001$) and led to the approval of erlotinib as a second-line treatment by the Federal Drug Association (FDA) and the European authorities. In contrast, the Iressa Survival Evaluation in Lung Cancer (ISEL) study failed to show a benefit for NSCLC patients pretreated with 1 or 2 chemotherapy regimens and randomized to receive gefitinib or a placebo.³⁴ The median survival (primary endpoint) was not superior for gefitinib (5.6 mo. for gefitinib vs. 5.1 mo. for the placebo, HR = 0.89, $P = 0.087$; median time to treatment failure 3.0 mo. for gefitinib vs. 2.6 mo. for the placebo, HR = 0.82, $P = 0.0006$).



In unselected populations of untreated patients with advanced or metastatic NSCLC, gefitinib was tested as a third agent in combination with platinum-based doublet combination therapy in the 3-arm INTACT 1 and INTACT 2 studies. INTACT 1 used cisplatin and gemcitabine in combination with either gefitinib or a placebo in 1093 patients and failed to detect a benefit for gefitinib in progression-free survival (PFS) or survival.³⁵ Similarly, the INTACT 2 study was based on a regimen of carboplatin/paclitaxel, and gefitinib added no benefit compared with a placebo.³⁶ With a comparable study design, erlotinib did not exhibit an additional benefit as a third combination partner in the TRIBUTE study (phase III; combination with carboplatin and paclitaxel)³⁷ or TALENT study (combination with cisplatin and gemcitabine).³⁸

A new era in the treatment of lung cancer began in 2004, with the first insight that treatment with gefitinib is associated with superior efficacy in patients with NSCLC and alterations in the EGFR gene. Lynch¹⁶ and Paez¹⁹ demonstrated that the tumors of patients responding to gefitinib had activating mutations in the EGFR tyrosine kinase domain. Pao and coworkers found that many of the responders were never-smokers and had adenocarcinoma and concluded that such tumors form a distinct subtype of lung cancer.¹⁷ Nearly 90% of activating EGFR mutations are exon 19 in-frame deletions of amino acids 746–750 or exon 21L858R substitutions,^{39,40} whereas exon 19 deletions confer a superior response compared with other mutations.⁴⁰ Patients with exon 18 or 20 mutations less frequently respond to an EGFR tyrosine kinase inhibitor (TKI) or are resistant to these agents. The frequency of activating EGFR mutations is highly dependent on sex, former smoking habits, and ethnicity. Patients of Asian ethnicity possess EGFR mutations more frequently.^{19,41} The frequency approaches 50%–60% in East Asian never-smokers and is 0%–10% in Caucasian current smokers, whereas mutations are rarely found in patients with squamous cell histology.^{10–12,39,42} The EGF receptor copy number, as assessed by fluorescence in situ hybridization (FISH), is closely linked to EGFR mutations^{18,43} but may be of less predictive value in patients treated with an EGFR TKI.⁴³ A strong cutaneous rash or the absence of any cutaneous toxicity during treatment with erlotinib defines the favorably and poorly responding patient subgroups, respectively.^{44,45}

Recent pivotal studies that only recruited patients with activating EGFR mutations clarified that treatment with an EGFR-directed tyrosine kinase inhibitor is superior to standard doublet chemotherapy in terms of response rate and PFS. However, longer survival was not shown, most likely because many patients received an EGFR TKI as a second-line therapy. EURTAC, OPTIMAL, WJTOG-3405, and NEJ002 each randomized EGFR-mutated patients to receive either chemotherapy or an EGFR TKI (see Table 2), and the median PFS in EGFR-mutated patients reached an impressive 9.2–13.1 mo.

Resistance to gefitinib and erlotinib

Although long PFS can be achieved in the subpopulation of patients with activating EGFR mutations, every patient will ultimately experience disease progression. The development of secondary resistance to erlotinib and gefitinib has led to significant research efforts. From recent publications, we know that certain patients develop a secondary EGFR mutation with gefitinib or erlotinib that is clinically associated with resistance to first-generation TKIs. The T790M mutation in exon 20 of the kinase domain is relatively rare in untreated patients but occurs in up to 50% of patients with acquired resistance to erlotinib or gefitinib.⁵¹ Moreover, many patients exhibiting secondary resistance are known to have an amplification of MET, a member of the insulin receptor tyrosine kinase family. MET amplification has been detected in up to 20% of EGFR TKI-resistant tumors.^{51,52} Other mechanisms of acquired resistance to erlotinib and gefitinib include mutations of KRAS, PIK3CA mutations and more complex cellular transformations, including epithelial-to-mesenchymal transformation and transformation into a small-cell type.⁵¹

Second-generation tyrosine kinase inhibitors

Afatinib (BIBW2992) is an oral, selective, irreversible ErbB family blocker of the EGFR, HER2, and ErbB4 and is one of the most promising novel agents. Afatinib was already submitted for approval in Europe in September 2012 for the treatment of NSCLC and has priority review status at the FDA. The submission is based on the pivotal LUX-Lung study program. In the LUX-Lung 3 study, untreated patients with advanced or metastatic NSCLC and activating EGFR muta-

Table 2.

	Region of accrual	TKI	Chemotherapy	N (TKI/chemotherapy)	ORR (TKI/chemotherapy)	Median PFS (TKI/chemotherapy)	Median survival (TKI/chemotherapy)	Dropouts due to intolerance (TKI/chemotherapy)
EURTAC ⁴⁶	Europe	Erlotinib	Platinum doublet	86/87	58/15%	9.7/5.2 (HR = 0.37, $P < 0.001$)	19.3/19.5 (n.s.)	13/23%
OPTIMAL ⁴⁷	China	Erlotinib	Carboplatin Gemcitabine	83/82	83/36%	13.1/4.6 (HR = 0.16, $P < 0.001$)	n.r.	1/6%
WJTOG-3405 study ⁴⁸	Japan	Gefitinib	Cisplatin Docetaxel	88/89	62/32%	9.2/6.3 (HR = 0.49, $P < 0.001$)	n.r.	16/12%
NEJ002 study ^{49,50}	Japan	Gefitinib	Carboplatin Paclitaxel	114/114	74/31%	10.8/5.4 (HR = 0.30, $P < 0.001$)	27.7/26.6 (n.s.)	n.r.

Abbreviations: TKI, tyrosine kinase inhibitor; ORR, overall response rate; PFS, progression-free survival.

tions were randomized to receive afatinib or cisplatin/pemetrexed for comparison.⁵³ For the primary endpoint, PFS, treatment with afatinib was associated with 11.1 mo., compared with 6.9 mo. for the other treatment (HR = 0.58, $P < 0.0004$), but the survival data are still pending. For 2 symptoms, cough and dyspnea, a statistically significant delay in deterioration was reported for afatinib compared with chemotherapy. Whether afatinib is effective in patients with acquired resistance to gefitinib or erlotinib was the focus of the LUX-Lung 1 study.⁵⁴ In this study, 585 patients who had received 1 or 2 previous chemotherapy regimens and had disease progression after at least 12 weeks of treatment with erlotinib or gefitinib were treated with afatinib or a placebo. The median overall survival (OS) (primary endpoint) was 10.8 mo. for afatinib and 12.0 mo. for the placebo group (HR = 1.08, $P = 0.74$). The median PFS was longer for afatinib (3.3 vs. 1.1 mo., HR = 0.38, $P < 0.0001$). The authors concluded that the lack of a benefit in OS was due to treatments given after the study and that the difference in PFS indicates a degree of efficacy. In a different publication, the investigators reported significantly improved symptoms (cough, dyspnea, pain, fatigue, and effects on physical functioning and quality of life [QOL]) in patients treated with afatinib.⁵⁵

Dacomitinib (PF00299804) is a novel irreversible, second-generation TKI of the EGFR, HER2, and HER4. In a randomized phase II study, 188 patients who received 1 or 2 prior treatment regimens but no previous EGFR-directed therapy were allocated to dacomitinib or erlotinib treatment.⁵⁶ The median PFS (primary endpoint) was 2.9 mo. for patients treated with dacomitinib and 1.9 mo. for erlotinib (HR = 0.66, $P = 0.012$). Dacomitinib resulted in a clinically meaningful HR of 0.55 ($P = 0.006$) in a subpopulation of patients with KRAS-wild type tumors, whereas KRAS/EGFR-wild type patients had an HR of 0.61 ($P = 0.043$). This small but statistically significant advantage should be confirmed in a phase III study with a similar study design (ARCHER 1009 study, NCT01360554), in which a subpopulation of KRAS-wild type tumors will again be analyzed. Other trials using the agent are underway.

EGFR-directed antibodies

Although a variety of EGFR-directed small-molecule TKIs are approved or are in clinical development,



another way of interfering with EGF receptor function is the use of monoclonal antibodies. These antibodies specifically bind to the extracellular domain of the EGFR and block the binding of ligands. The complexes are internalized, and receptors are subsequently downregulated [reviewed in].⁵⁷

Cetuximab is a chimeric human-murine monoclonal IgG1 antibody. Based on the results of the FLEX study, cetuximab was a recent candidate for approval. However, the application was withdrawn in 2012, when the authorities demanded additional study evidence. The FLEX study tested whether the addition of cetuximab to a platinum-based doublet regimen (cisplatin/vinorelbine) is associated with a benefit in patients with advanced or metastatic NSCLC.⁵⁸ In total, 1125 patients were randomized to receive chemotherapy plus cetuximab or a placebo. The median OS for cetuximab was 11.3 mo. compared with 10.1 mo. for the placebo (HR = 0.87, $P = 0.044$). No significant differences were noted in the QOL between the treatments. An acne-like skin rash and diarrhea were the most frequent side effects attributable to cetuximab. Tumor tissue was collected in the study, and molecular markers were reported in a subsequent publication. O'Byrne and coworkers could not demonstrate that activating EGFR mutations or KRAS status were predictive markers for therapeutic success with cetuximab.⁵⁹ The patients who developed a skin rash early in the treatment with cetuximab had a favorable outcome.⁶⁰ Identifying another predictive marker was the subject of a subsequent publication by Pirker and colleagues,⁶¹ which used the tissue samples and data set of the FLEX study. Based on the immunohistochemical detection of the EGFR in the tumor tissue, the patients were divided into subgroups with high or low EGFR expression (99.6% of the FLEX patients had sufficient tumor tissue, and 31% and 69% had a high and low expression, respectively). The group found that a survival benefit was restricted to patients with high EGFR expression, whereas patients with low expression had no benefit with the addition of cetuximab.

Other EGFR-directed monoclonal antibodies being researched include panitumumab, necitumumab, and matuzumab. Necitumumab is a fully human monoclonal IgG1 antibody targeting EGFR. 2 large phase III studies addressed the efficacy of the agent in advanced or metastatic NSCLC. The INSPIRE

study (NCT00982111) recruited only patients with non-squamous histology and tested whether necitumumab is associated with a benefit when added to cisplatin/pemetrexed chemotherapy. Due to concerns about thromboembolic side effects, the study was terminated in 2011. SQUIRE (NCT00981058) is testing whether necitumumab added to cisplatin/gemcitabine results in a benefit in overall survival.

Panitumumab is another fully human anti-EGFR monoclonal IgG2 antibody. It is currently in phase II of clinical testing. Matuzumab, a humanized anti-EGFR monoclonal IgG1 antibody with a prolonged half-life, was tested as a second-line treatment for NSCLC in a randomized phase II study.⁶² In this 3-arm study, pretreated patients with advanced NSCLC were randomized to receive pemetrexed alone or in combination with one of 2 schedules with matuzumab (weekly or every 3 weeks). The study showed a statistically not significant trend in improvement in the objective response and overall survival for pemetrexed plus weekly matuzumab compared with pemetrexed alone. As for cetuximab, Schittenhelm and coworkers demonstrated that strong immunohistochemical staining of EGFR is associated with a superior response compared with the response in patients with low expression.⁶³ Until now, matuzumab has not proceeded to phase III development.

ALK Inhibition

In 2007, the exciting observation that ALK gene rearrangements are detectable in the tumor tissue of a small number of patients suffering from advanced NSCLC was published.²⁵ Inversions within chromosome 2 resulted in a novel fusion oncogene, known as echinoderm microtubule-associated protein-like 4 (EML4)-ALK. The presence of ALK rearrangements or mutations results in the activation of ALK and its downstream signaling pathways. As a consequence, cellular proliferation and survival are no longer controlled (reviewed in).⁶⁴ FISH, immunohistochemistry (IHC), and reverse transcription polymerase chain reaction (RT-PCR) have been applied to detect rearrangements, although the optimal assay remains to be elucidated. Depending on clinical characteristics and smoking history, ALK rearrangements were detected in 1%–12% of patients with NSCLC,^{10,13,14,21,24,25,65} although the alteration is most frequently detected in relatively young male patients with adenocarcinoma



who are light- or never-smokers. In the majority of patients, ALK translocations and EGFR mutations are mutually exclusive.⁶⁶ When treated with conventional platinum-based chemotherapy, patients with ALK rearrangements, compared with wild type patients, have similar response rates and overall survival.²²

Crizotinib is an oral small-molecule inhibitor of the receptor tyrosine kinases ALK and c-MET. In a recent extended phase I study, 149 ALK-positive patients with advanced or metastatic NSCLC received 250 mg crizotinib twice daily.⁶⁷ Most of the patients had previously completed chemotherapy, and 143 patients were included in the response-evaluable population. In total, 87 of the patients (60.8%) achieved an objective response. The median duration of the response was 49 weeks, the median PFS was 9.7 mo. (95% CI: 7.7–12.8), and the 1-year-survival 74.8% (95% CI: 66.4–81.5).

Updated efficacy and safety data from a globally ongoing, open-label, single-arm phase II study was presented at the ASCO 2012 meeting (Profile 1005 study).⁶⁸ More than 900 patients with advanced ALK-positive NSCLC who progressed after at least one course of chemotherapy were enrolled at that time. Among the 255 subjects evaluable for efficacy, the overall response rate (ORR) was reported to be 53%, and the median PFS was 8.5 mo. (95% CI: 6.2–9.9). A statistically significant and clinically meaningful improvement in patient-reported symptoms (pain, pain in chest, cough, dyspnea, insomnia, fatigue, and decreased global QOL) from the baseline values was observed. The most common reported side effects were visual disturbances and gastrointestinal symptoms (nausea, vomiting, and diarrhea), most of which were grade 1 or 2. Cases of severe, life-threatening, or fatal drug-related hepatotoxicity and pneumonitis were reported (see also).⁶⁹

Based on the response rates in the phase I and II studies, crizotinib was approved by the FDA in August 2011. The Committee for Medicinal Products for Human Use (CHMP) at the European Medicines Agency (EMA) concluded that the beneficial effect of treatment with crizotinib is greater than the treatment's risks, and thus, crizotinib has been given conditional approval.

The Profile 1007 study was a global phase III study that compared crizotinib with single-agent pemetrexed or docetaxel as a second-line treatment in ALK-positive patients with advanced or metastatic NSCLC.

Interim results were published at the 2012 ESMO meeting,⁷⁰ and the full-text publication of the final results is expected soon. The study accrued 347 patients. Crizotinib significantly improved PFS compared with chemotherapy (primary endpoint, median 7.7 vs. 3.0 mo., HR = 0.49, $P < 0.0001$). Crizotinib tripled the overall response rate, from 20% to 65% ($P < 0.0001$). The interim analysis of overall survival revealed no statistically significant difference between crizotinib and chemotherapy (median 20.3 vs. 22.8 mo., HR = 1.02, $P = 0.54$). However, 62% of the chemotherapy patients crossed over to crizotinib after progression. QOL parameters were not reported in the abstract.

According to the current NSCLC guidelines of the National Comprehensive Cancer Network (NCCN), all diagnosed cases of advanced adenocarcinoma of the lung, beyond being tested for EGFR mutations, should be tested for rearrangements of ALK (<http://www.nccn.org>). The guidelines recommend crizotinib as a first-line therapy in patients with advanced ALK-positive NSCLC. Despite the notable antitumor activity of crizotinib in ALK-positive NSCLC, every patient eventually acquires resistance to this therapy. Next-generation ALK inhibitors are currently under investigation in early-phase studies. At the ASCO 2012 annual meeting, preliminary results for LDK378 were presented. In a population of ALK-positive patients with lung cancer, the investigators reported objective responses in patients already pretreated with crizotinib.⁷¹

MET Inhibitors

MET is a tyrosine kinase receptor for hepatocyte growth factor (HGF) that is primarily expressed on epithelial cells. The activation of MET induces several pathways controlling the development and growth of different types of cancers (reviewed in).⁷² In a recent study comprising 380 surgically resected patients with NSCLC, the investigators found that an increased MET copy number (assessed by FISH) and MET overexpression (assessed by IHC) are negative prognostic factors for survival.³⁰ MET amplification is a mechanism of resistance to gefitinib and erlotinib in patients with activating EGFR mutations.^{51,52} This fact supports the dual inhibition of MET and the EGFR, which is applied in current studies of tivantinib and onartuzumab.



MET is a promising target for anticancer treatment, and several MET inhibitors are under clinical study for the treatment of NSCLC. Tivantinib (ARQ197) is a selective small-molecule tyrosine kinase inhibitor with high specificity for c-MET. In a randomized phase II study published in 2011, the combination of tivantinib and erlotinib was compared with a placebo and erlotinib.⁷³ Of the 167 randomly assigned patients, all had been previously treated with chemotherapy for advanced NSCLC, but none had undergone EGFR TKI therapy. The primary endpoint was PFS. Tumor tissue was examined for EGFR and KRAS mutations, and the incidence of EGFR mutations was 15%. The median PFS was not significantly different between the treatments (3.8 mo. for tivantinib vs. 2.3 mo. for the placebo, HR = 0.81, $P = 0.24$). Interestingly, the investigators found an HR of 0.18 ($P = 0.006$) for PFS in the small subpopulation with KRAS-mutated tumors. The side effects were typical of EGFR-directed therapy (rash, mucosal toxicity, and diarrhea) and were not significantly increased in the tivantinib group. The patients in the tivantinib plus erlotinib arm, and especially patients with non-squamous histology, had a significantly longer time until the development of new metastases. Based on the results of the study, tivantinib entered a phase III clinical trial. The MARQUEE study (NCT01244191)⁷⁴ repeated the design of the randomized phase II study but limited the recruitment to non-squamous histology. In a recent press release, the company announced that the independent data-monitoring committee of the study recommended that the trial be terminated early (<http://www.daiichisankyo.com/news/detail/004480.html>). A planned interim analysis revealed that the study did not meet the primary endpoint of improved overall survival. A randomized phase II study comparing erlotinib/tivantinib versus single-agent chemotherapy in previously treated patients with advanced NSCLC and a KRAS mutation is currently underway (NCT01395758).

Onartuzumab (Met-MAb) is another agent in current clinical development. This compound is a humanized monovalent (1-armed) antibody fragment that specifically binds to the MET receptor. Consequently, the binding of the receptor to its ligand, HGF, and its signaling pathways are inhibited. A recent phase II study compared the efficacy of the combination of onartuzumab and erlotinib with a placebo and erlotinib in

NSCLC patients previously treated with intravenous chemotherapy.⁷⁵ Among the 128 randomized patients, 54% had c-MET-positive tumors, as assessed by IHC. In this subpopulation, the addition of onartuzumab resulted in superior PFS (primary endpoint, median 3.0 vs. 1.5 mo., HR = 0.47, $P = 0.01$). In patients with c-MET-negative tumors, onartuzumab had a detrimental effect on overall survival. The patients were also tested for EGFR and KRAS mutations and by MET-FISH. The results of the study should be confirmed by the MetLung study (NCT01456325), a randomized phase III study that is currently recruiting. This study will test whether a combination of onartuzumab plus erlotinib is superior to a placebo plus erlotinib in chemotherapy-pretreated patients with MET-positive NSCLC.

Crizotinib, which was recently approved for the treatment of ALK-rearranged NSCLC, is also a potent MET inhibitor. A durable response in a patient with MET-amplified NSCLC but no ALK rearrangement has been reported.⁷⁶

Angiogenesis Inhibitors

The formation of blood vessels is a crucial process in the development and growth of any malignant tumor.⁷⁷ The restriction of vessel growth to control tumor growth represents one of the most extensively studied pathways in oncology. Therapeutic targets mainly involve circulating cytokines and growth factors (vascular endothelial growth factor [VEGF], platelet-derived growth factor [PDGF], and fibroblast growth factor [FGF]) and their transmembrane receptors. In NSCLC, one antiangiogenic agent is currently approved (bevacizumab). However, numerous other agents could not fulfill early hopes. Several of the antiangiogenic tyrosine kinase inhibitors studied were approved for other indications (eg, sorafenib and sunitinib in renal cell carcinoma) but failed or are in danger of failing in NSCLC. Currently, no biomarker or surrogate marker is established for treatment with bevacizumab. Thus, adequate patient selection with the power to improve outcomes is lacking. Angiogenesis seems to be a complex mechanism with several parallel signaling pathways that are highly adaptable.⁷⁸

Bevacizumab represents the first substance used in lung cancer that specifically targets tumor angiogenesis. Based on the results of the pivotal



ECOG 4599 and AVAiL studies, this humanized monoclonal antibody against VEGF-A was approved by the European authorities in 2005 and the FDA in 2006 for combination treatment of NSCLC. In the ECOG 4599 study,⁷⁹ 878 patients with untreated advanced NSCLC (only non-squamous histology allowed) were randomly assigned to either carboplatin/paclitaxel or carboplatin/paclitaxel/bevacizumab. The patients additionally treated with bevacizumab had superior overall survival (primary endpoint, 12.3 vs. 10.3 mo., HR = 0.79, $P = 0.003$) and progression-free survival (6.2 vs. 4.5 mo., $P < 0.001$). The response rate for bevacizumab was 35% compared with an unexpectedly low rate (15%) for the standard treatment. QOL was not assessed. In the experimental arm, five patients died from severe pulmonary hemorrhage (none in the standard arm). The advantage of bevacizumab could not be confirmed in the AVAiL study.^{80,81} Here, 1043 patients were randomized to cisplatin/gemcitabine/placebo or cisplatin/gemcitabine plus 1 of 2 doses of bevacizumab (3-arm design). The primary endpoint of the study was changed from survival to progression-free survival while the study was running. The median PFS was reported as 6.7/6.5 mo. (for 7.5/15 mg/kg bevacizumab, respectively) in the experimental arms compared with 6.1 mo. for the control population (HR = 0.75/0.82, $P = 0.003/0.03$). The median OS was not significantly different across the groups: 13.6/13.4 for bevacizumab compared with 13.1 mo. for the placebo. QOL parameters were not reported.

Patients with squamous-cell carcinoma were excluded from treatment at an early stage because of concerns about hemoptysis. Recently, an international consensus panel of specialists additionally recommended withholding bevacizumab from patients with a history of grade ≥ 2 hemoptysis.⁸² Major blood vessel infiltration, encasement, and abutting can predict hemoptysis. However, standardization by means of radiological criteria remains difficult. Because pemetrexed is one of the most effective partners used along with platinum agents in the treatment of non-squamous NSCLC, a triplet combination comprising platinum, pemetrexed, and bevacizumab has gained increasing attention. In the recent AVAPERL study,⁸³ patients treated with cisplatin, pemetrexed, and bevacizumab, with maintenance treatment with pemetrexed and bevacizumab, achieved a median

PFS of 10.2 mo. The data were too premature to allow a definitive analysis of OS.

Another antibody is currently in an advanced stage of clinical development. Ramucirumab is a fully human antibody targeting VEGF receptor 2. This antibody functions as a receptor antagonist and blocks the binding of VEGF. The results of randomized phase II studies were recently presented, and a phase III clinical study program is ongoing. In a NSCLC population stratified by histology (the data for adenocarcinoma have been presented, and squamous cell carcinomas are still being recruited in 2 other arms), 140 patients were randomized to receive a platinum agent and (in adenocarcinoma patients) pemetrexed, with ramucirumab in one arm.⁸⁴ The median PFS (primary endpoint) was 6.3 mo. with ramucirumab compared with 4.3 mo. without ramucirumab (HR = 0.48; 90% CI: 0.31–0.74). Survival results are not yet reported. The disease control rate at the first staging interval was 87% compared with 72%. Another single-arm phase II study (SCC not primarily excluded) reported a median PFS of 7.85 mo. and a DCR of 90% with a combination of carboplatin, paclitaxel, and ramucirumab.⁸⁵ Although the investigators of the first study did not report adverse bleeding events, Camidge and coworkers specified that 23% of subjects suffered from epistaxis.⁸⁵

Aflibercept is a recombinant fusion protein comprising different VEGF receptor domains and binding to VEGF-A and -B with a much higher affinity than bevacizumab. Moreover, this drug specifically binds to placenta growth factor (PlGF). In a recent large phase III study in patients with advanced or metastatic non-squamous NSCLC pretreated with a platinum agent, 913 patients were randomized to receive docetaxel plus aflibercept or docetaxel plus a placebo.⁸⁶ The primary endpoint was overall survival. The median overall survival was not superior with aflibercept/docetaxel (median 10.1 vs. 10.4 mo. for docetaxel/placebo, $P = 0.90$). A small benefit in progression-free survival (median 5.2 vs. 4.1 mo., $P = 0.0035$) and the objective response rate (23 vs. 9%, $P < 0.001$) was reported by the authors. Given the relatively poor results, it is currently unclear whether aflibercept will be further developed for the treatment of NSCLC.

Several VEGF receptor-directed tyrosine kinase inhibitors have been studied over the last few years.



However, none of these TKIs is currently approved for the indication of NSCLC. Sunitinib is a receptor tyrosine kinase inhibitor with multiple targets. In addition to VEGF receptors 1, 2, and 3, this drug inhibits PDGF receptors α and β and KIT. In 2 smaller phase II studies in which sunitinib was administered as a monotherapy to patients who were pretreated with NSCLC, the substance yielded response rates of 2/11% and median PFS of 12/12 weeks, respectively.^{87,88} However, a phase III study published in 2012 could not confirm the earlier efficacy data. In a study conducted by Scagliotti and colleagues, pretreated patients with disease progression after one or two prior chemotherapy regimens were 1:1-randomized to receive erlotinib plus sunitinib or erlotinib plus a placebo.⁸⁹ The primary endpoint was overall survival and the combination was not superior to erlotinib alone (9.0 vs. 8.5 mo., HR = 0.92, $P = 0.14$). However, patients treated with erlotinib and sunitinib had longer PFS (3.6 vs. 2.0 mo., HR = 0.807, $P = 0.0023$).

Sorafenib is a small-molecule tyrosine kinase inhibitor with multiple targets. This agent is an inhibitor of VEGFR and PDGFR and targets the Raf/Mek/Erk pathway. In unselected patients with advanced NSCLC, sorafenib was tested in 2 large phase III studies. One study sought to elucidate whether a combination of carboplatin, paclitaxel, and sorafenib is superior to a standard treatment with carboplatin and paclitaxel plus a placebo.⁹⁰ The study randomized 926 patients. However, the study was terminated prematurely, when an interim evaluation revealed that the experimental arm could not reach statistical significance. Moreover, patients with squamous cell histology were found to have higher mortality with sorafenib. Among all of the treated patients, the median OS for the treatment with sorafenib was 10.7 compared with 10.6 mo. (HR = 1.15, $P = 0.92$). Another study with a comparable phase III design used cisplatin and gemcitabine as the chemotherapy backbone, and the patients were randomized to receive additional sorafenib or a placebo.⁹¹ Because of concerns caused by the other study, patients with squamous cell carcinoma were excluded at a certain point. However, the primary study endpoint of overall survival was not significantly different between the sorafenib and placebo treatments (12.4 vs. 12.5 mo., HR = 0.98, $P = 0.40$). An analysis of progression events revealed a minimal advantage for the experimental arm (6.0 vs. 5.5 mo.,

HR = 0.83, $P = 0.008$). Another group selected only pretreated KRAS-mutated patients for treatment with sorafenib,⁹² and 59 patients were included. The authors reported a median PFS of 2.3 mo. and a median OS of 5.3 mo. in this poor-prognosis subpopulation.

Vandetanib (ZD6474) is another oral receptor tyrosine kinase inhibitor that inhibits KDR/VEGFR2, VEGFR3, EGFR, and RET signaling. The substance revealed an attractive preclinical efficacy profile. However, after a series of clinical studies in pretreated patients with NSCLC, the results did not meet expectations, and the company decided to withdraw any application for approval for the treatment of NSCLC. For instance, in the ZODIAC study, 1391 pretreated patients with NSCLC were randomized to receive docetaxel plus vandetanib or docetaxel plus a placebo.⁹³ Among the patients treated with vandetanib, PFS was slightly longer (4.0 vs. 3.1 mo., HR = 0.79, $P < 0.0001$). The ZEAL,⁹⁴ ZETA,⁹⁵ and ZEPHYR⁹⁶ studies each addressed the population of platinum-pretreated patients and compared vandetanib with a placebo, pemetrexed, or vandetanib in combination with pemetrexed. However, the results were mainly negative.

Other tyrosine kinase inhibitors with antiangiogenic effects include motesanib, pazopanib, axitinib, and nintedanib. Phase III study results are currently available or awaited for motesanib and nintedanib. For nintedanib (BIBF 1120), a potent small-molecule inhibitor of VEGFR1, VEGFR2, VEGFR3, FGFR-1, FGFR-2, FGFR-3, and PDGFR- α/β , 2 phase III studies will be presented this year (LUME-Lung 1 and 2 studies). The studies address the role of nintedanib added to docetaxel (LUME-Lung 1) or pemetrexed (LUME-Lung 2) in pretreated NSCLC patients. Motesanib (AMG 706) is a selective oral inhibitor of VEGF receptors 1, 2, and 3; the PDGF receptor; KIT; and RET. Recently, the results of the MONET1 study have been published.⁹⁷ The study randomized 1090 patients with advanced or metastatic non-squamous NSCLC to receive carboplatin and paclitaxel with daily oral motesanib or a placebo. The study was negative for the primary endpoint of overall survival (median 13.0 vs. 11.0 mo., respectively, HR = 0.90; $P = 0.14$). The median PFS was 5.6 mo. for motesanib compared with 5.4 mo. for the placebo ($P < 0.001$). The company developing the treatment will continue to conduct a phase III study in East Asian patients.



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Competing Interests

DB has held consultant or advisory roles with Eli Lilly and Boehringer, received honoraria from Eli Lilly, Boehringer and Sanofi Aventis, received research funding from Sanofi Aventis, and received reimbursement for travel expenses from Eli Lilly, Boehringer, Sanofi Aventis, Roche and Pierre Fabre. KH has received an honorarium for lectures from Amgen, and reimbursement for travel expenses from Amgen and Roche.

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As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests. Provenance: the authors were invited to submit this paper.

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