Potential role of multi-targeted tyrosine kinase inhibitors in non-small-cell lung cancer

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Treatment outcomes for patients with metastatic non-small-cell lung cancer (NSCLC) are poor with chemotherapy. In recent years, novel agents that target specific, aberrant molecular pathways in NSCLC have been under evaluation in clinical trials. To date, just two targeted agents have impacted the natural history of the disease—erlotinib and bevacizumab—each of which targets a single molecule in a signalling pathway involved in NSCLC. While modest, the activity of these single-target agents results in improved clinical outcomes, highlighting the potential of agents that target biological pathways in patients with NSCLC. However, as NSCLC is a highly heterogeneous disease, it is likely that agents with multiple targets (e.g. sunitinib, sorafenib, ZD6474, AZD2171 and AMG 706) may have greater activity than those with single-target activity through inhibition of other pathways that may act as salvage or escape mechanisms for malignant cells. New multi-targeted therapeutic agents currently undergoing clinical evaluation have shown promise as single agents, and preclinical studies have indicated that this efficacy may be due at least in part to the inhibition of multiple pathways that may result in a synergistic antitumour effect.

Key words: angiogenesis, non-small-cell lung cancer, sunitinib, tyrosine kinase inhibitor, vascular endothelial growth factor receptor

Introduction

Lung cancer is the leading cause of cancer mortality worldwide and is responsible for more deaths annually in western countries than breast, colorectal and prostate cancers combined [1]. Approximately 85% of lung cancers are non-small-cell lung cancer (NSCLC) and the majority (>50%) of patients are diagnosed at the advanced/metastatic stage of the disease. Treatment options for these patients remain limited (Table 1), with the focus on improving patients’ disease-related symptoms and health-related quality of life. The disease tends to be diagnosed predominantly in older patients, with many new diagnoses occurring in individuals >75 years of age, and is among the leading causes of death in both males and females between the ages of 60 and 79 [1]. Long-term survival for patients with advanced/metastatic disease is typically <1 year.

current standard of care

Patients who present with a malignant effusion from NSCLC or metastatic disease are rarely candidates for curative therapy. Patients with performance status (PS) of zero to two are typically eligible for systemic chemotherapy, consisting primarily of platinum-based doublets for patients with PS of zero to one and single-agent chemotherapy for patients with PS of two. However, in patients with poor PS (3–4), chemotherapy is not indicated.

Currently, platinum-based chemotherapy regimens are the standard of care for first-line treatment of patients with NSCLC [2], with combination regimens providing comparable efficacy (Table 1). More than 10 years ago a meta-analysis indicated that cisplatin-based chemotherapy achieves a modest but significant improvement in prolonging survival compared with best supportive care [3], and a recently presented individual patient meta-analysis has confirmed statistically superior efficacy of cisplatin over carboplatin in advanced NSCLC [4]. Despite this difference, the benefit is modest, and both agents remain standard depending upon the combination and the individual patient’s comorbidities. Although these treatments improve survival, there appears to be a plateau in efficacy in advanced NSCLC, despite several trials of various doublet or even triplet combinations.

Recently, the anti-vascular endothelial growth factor (VEGF) monoclonal antibody (mAb) bevacizumab in combination with paclitaxel/carboplatin chemotherapy has been approved for first-line use in specific clinically defined patient populations [5]. The addition of targeted agents to standard chemotherapy represents a significant step towards improving outcomes for patients with NSCLC.

In the second-line setting, docetaxel and pemetrexed are currently recommended by the National Comprehensive Cancer Network. Docetaxel significantly improved the 1-year survival rate (21% to 32%) and lengthened median survival...
(up to 6.6 months) when compared against best supportive care [6]. Pemetrexed showed comparable improvements, with a slightly improved side-effect profile compared with docetaxel [7]. The epidermal growth factor receptor (EGFR) small-molecule inhibitor, erlotinib, is also approved for use in the second-line setting. A phase III study showed erlotinib treatment improved overall survival (OS) from 4.7 to 6.7 months in patients with NSCLC who had previously received first- or second-line chemotherapy [hazard ratio (HR), 0.70; P < 0.001]. The response rate was 8.9% with erlotinib compared with <1% in the placebo group (P < 0.001). Five per cent of patients discontinued erlotinib because of toxic effects [8]. A summary of the efficacy of currently approved and developmental targeted agents is shown in Table 2 and is discussed below.

**current controversies in treating NSCLC**

Despite active chemotherapeutic agents for NSCLC, the prognosis of metastatic NSCLC remains poor when compared with that observed for other solid tumour types, such as breast or colorectal cancer. Some regimens that contain cisplatin (and a non-cisplatin combination with gemcitabine or paclitaxel) have yielded objective response rates in the range of 20%–40%, but duration of response is usually <6 months, with median OS <1 year (10 months) and 1-year survival ~30%–35% [15, 16]. The modest survival benefit and increased toxicity associated with platinum-based therapy have resulted in the investigation of non-platinum-containing regimens. In a study by Georgoulias et al. [17] overall response rates were similar among patients who received gemcitabine plus docetaxel (n = 219) and those who received cisplatin plus docetaxel (n = 222): 34.6% [95% CI (confidence interval) 26.2% to 38.6%] versus 33.3% (95% CI 24.1% to 36.2%), respectively. There was no significant difference in terms of median duration of response, time to progression (TTP) or OS. This study and others raise the possibility that doublets of newer agents that do not include a platinum agent might be as effective as those that do.

In contrast, Gridelli et al. [18] reported that patients receiving platinum-based therapy (either cisplatin/vinorelbine or cisplatin/gemcitabine) achieved significantly longer progression-free survival (PFS) than those patients who received non-platinum-based therapy (gemcitabine/vinorelbine) (median PFS of 23 versus 17 weeks, HR, 1.29; 90% CI 1.11–1.52, P = 0.004). Median survival was also better in patients who received platinum-based therapy, but the difference was not statistically significant (38 versus 32 weeks, HR, 1.15; 90% CI 0.96–1.37; P = 0.08). With inconclusive data regarding the optimal doublet combination and whether that doublet should include a platinum agent, clinicians must consider the benefits of platinum-containing regimens against the treatment-related toxicity associated with such treatment approaches.

**biomarkers to predict sensitivity to current treatment options**

Although the benefits of chemotherapy in general are modest, survival can vary significantly, from weeks to years, among individual patients. These considerable differences in prognosis...
and probable differences in response to treatment have led researchers to investigate biomarkers that may identify factors that predict response to chemotherapy.

Recent studies indicate that cisplatin resistance is associated with the increased expression of the excision repair cross-complementing 1 (ERCC1) and ribonucleotide reductase M1 (RRM1) genes [19, 20]. Median OS was significantly longer in patients with low ERCC1 expression (17.3 versus 10.9 months, \( P = 0.0032 \)) and in patients with low RRM1 expression (13.9 versus 10.9 months, \( P = 0.0390 \)), compared with those with higher expression. In addition, among patients who were treated with cisplatin, lower ERCC1 expression was highly predictive of improved survival (23.0 versus 12.4 months, \( P = 0.0001 \)). Furthermore, BRCA1, which is a well-characterised gene from the breast cancer cell line MCF5, is a component of several DNA repair pathways and has been found to be overexpressed in cisplatin-resistant breast and ovarian cell lines [21]. The expression of BRCA1 mRNA was shown to correlate with that of ERCC1 and therefore may be a predictor of cisplatin sensitivity in patients with NSCLC [22].

EGFR, which is overexpressed in a wide variety of tumour cell lines, including lung cancer, is the target of many new therapies. However, its value as a biomarker as assessed through immunohistochemistry has been limited by ambiguous results that stem from a lack of pathology and scoring standardisation [23]. In addition, EGFR expression does not necessarily correlate with prediction of response. In summary, the predictive value of biomarkers in this setting is promising but requires further investigation (see DePrimo’s and Bello’s article in this supplement for an in-depth discussion on the role of biomarkers).

**rationale for novel therapies and their targets**

Several components of cell-signalling pathways regulating normal cell growth and function are frequently altered in malignant lung cancer cells. Many of these components are being explored as potential therapeutic targets. Preclinical studies have indicated that some targeted agents yield additive or synergistic activity when combined with chemotherapy [24, 25]. This activity, in conjunction with the potential for less toxicity, has led to the exploration of novel rationally designed targeted therapies (Table 3).

Modulation of molecular targets that control normal cell-cycle pathways and apoptosis may influence angiogenesis, the process by which tumours develop new vasculature. It is likely that to achieve improved patient outcomes, strategies that target multiple pathways including angiogenesis, apoptosis and other cell-cycle control pathways will be required. Various strategies have been investigated, including ligand blockade by mAbs or inhibition of receptor signalling by tyrosine kinase inhibitors (TKIs). This article will review various molecular targets, the preclinical rationale for targeting them, and the clinical data supporting the use of targeted therapies.

**receptor tyrosine kinase KIT**

KIT is a receptor tyrosine kinase structurally similar to other receptors such as platelet-derived growth factor receptor (PDGFR), macrophage colony-stimulating factor-1, c-FMS and FMS-like receptor tyrosine kinase (Flt3) [26, 27]. Steel factor (also known as stem-cell factor) is the ligand for the KIT receptor. Functional activity of KIT is necessary for normal development of haematopoietic progenitor cells, mast cells, germ cells and the interstitial cells of Cajal [28, 29]. Dysregulation of KIT kinase activity has been identified in several malignancies including NSCLC. In addition, KIT inhibitors may potentially play an adjunctive role in small-cell lung cancer in which KIT activation is secondary to ligand binding rather than an acquired mutation [30]. Although a small phase II study which investigated imatinib as second-line treatment in SCLC failed to show significant activity [31], inhibition of KIT in combination with other signalling pathways has not been studied in the clinical setting.

**the human epidermal growth factor receptor family**

The human epidermal growth factor receptor (HER) family is implicated in various cellular processes, including cellular proliferation, migration and inhibition of apoptosis and is pivotal in tumourigenesis and disease progression [32, 33]. The HER family consists of HER1/EGFR (ErbB1), HER2/neu (ErbB2),

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**Table 3.** Targeted therapies approved or in development in NSCLC (completed trials)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Class</th>
<th>Highest development stage in NSCLC</th>
</tr>
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<tbody>
<tr>
<td>Bevacizumab</td>
<td>VEGF</td>
<td>mAb</td>
<td>Approved (in combination with paclitaxel/carboplatin)</td>
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<td>EGFR</td>
<td>TKI</td>
<td>Approved</td>
</tr>
<tr>
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<td>EGFR</td>
<td>TKI</td>
<td>Approved in Japan</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>EGFR</td>
<td>MAb</td>
<td>III</td>
</tr>
<tr>
<td>ZD6474 (vandetanib)</td>
<td>VEGFR, EGFR, RET</td>
<td>TKI</td>
<td>III</td>
</tr>
<tr>
<td>AZD2171 (cediranib)</td>
<td>VEGFR, PDGFR, KIT</td>
<td>TKI</td>
<td>II/III</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>VEGFR, PDGFR, KIT, RET, FLT3, CSF-1R</td>
<td>TKI</td>
<td>II</td>
</tr>
<tr>
<td>AMG 706 (motesanib)</td>
<td>VEGFR/PDGFR/KIT, RET</td>
<td>TKI</td>
<td>I</td>
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</tbody>
</table>

EGFR, epidermal growth factor receptor; mAb, monoclonal antibody; NSCLC, non-small-cell lung cancer; PDGFR, platelet-derived growth factor receptor; TKI, tyrosine kinase inhibitor; VEGF(R), vascular endothelial growth factor (receptor).
HER3 (ErbB3) and HER4 (ErbB4) [34]. Various ligands can bind HER1/EGFR, HER3 and HER4, inducing homo- or heterodimerization. HER2 does not bind to any known ligand but is the preferred dimerisation partner for each of the HER receptors including itself [35]. The most widely studied members of the HER family are HER1/EGFR and HER2, both of which are overexpressed or dysregulated in many tumour types, including NSCLC.

HER1/EGFR. The overexpression of EGFR in NSCLC generally correlates with advanced disease stage and poor prognosis [36]. Upon binding of ligand, epidermal growth factor, the receptor dimersises and activates its tyrosine kinase domain, triggering pathways involved in tumour growth and progression, including cell proliferation, inhibition of apoptosis, metastasis and upregulation of angiogenesis. Several agents that inhibit EGFR and its activation have been developed as potential therapies for NSCLC. The two most extensively studied TKIs are erlotinib and gefitinib, which have been initially approved for use as second-line therapy of NSCLC in the USA [37, 38], although gefitinib was subsequently withdrawn from this indication because of negative outcomes reported from subsequent clinical studies. Due to the synergy of these agents with chemotherapy shown in preclinical models, results from large phase III trials of the first-line use of erlotinib and gefitinib in combination with chemotherapy were highly anticipated. Unfortunately, the combination of either of these agents with chemotherapy failed to produce a survival advantage over chemotherapy alone [39–42].

Selection of patients, based on molecular markers and patient characteristics, has become an important issue for the further development of these drugs, given that the activity might be limited to a relatively small group of patients with NSCLC [43]. A retrospective analysis comparing the outcomes of patients with and without EGFR mutations treated with EGFR inhibitors demonstrated that patients with EGFR mutations have higher response rates and longer OS than those without mutations [43]. For example, a response rate of 65% versus 14% and a median survival of 30.5 versus 6.6 months were observed with gefitinib in patients with and without EGFR mutations, respectively [44]. Additional clinical characteristics associated with an increased likelihood of a clinical or radiographic response to EGFR inhibitors include female sex, never smokers, adenocarcinomas and Asian ethnicity [43].

Currently, clinical data supporting the use of monoclonal antibodies targeted against EGFR (e.g. cetuximab and panitumumab) in NSCLC are limited [45] and insufficient to define the role of such agents in NSCLC treatment. A phase III study testing the addition of cetuximab to cisplatin/vinorelbine in advanced NSCLC has completed accrual, and results are expected at the beginning of 2008.

HER2/neu. HER2 is overexpressed in 10%–30% of NSCLC cases and is associated with poor prognosis [46]. To date, trials of HER2-targeted therapies, such as trastuzumab, have been insufficiently powered to determine whether NSCLC patients with HER2 gene amplification benefit from such agents. In a phase II study, 52 patients with HER2+ NSCLC received weekly trastuzumab plus paclitaxel/carboplatin chemotherapy. Overall response rate was 25% with 1-year survival of 42% [47]. In another report, of 21 patients with HER2+ NSCLC who received weekly trastuzumab plus gemcitabine and cisplatin, eight patients had a partial response (PR), and the median TTP was 36 weeks [48]. The frequency of HER2 mutations in NSCLC may be too low to develop feasible, prospective clinical trials in this patient group.

Lapatinib, a dual-targeted TKI of both EGFR and HER2, has shown limited activity in NSCLC in a phase I trial [49] and is not currently being investigated in NSCLC. Multi-targeted agents will be discussed in further detail in sections below.

angiogenesis activators

The process of neovascularisation is an important mechanism by which tumours maintain their continued growth and metastatic potential. The angiogenic process is complex and is controlled by various local factors with proangiogenic and antiangiogenic activities. Such factors are logical and attractive therapeutic targets.

VEGF, the prototypical proangiogenic molecule, has been implicated in several steps throughout the angiogenesis process [50]. Its importance is highlighted by studies that have shown VEGF mRNA levels correlate with tumour angiogenesis, patient survival and postoperative relapse in patients with NSCLC [51]. A systematic review of the literature evaluating VEGF or its receptors in NSCLC has corroborated its status as an unfavourable prognostic factor (HR = 1.48; 95% CI 1.27–1.72) [52]. The VEGF family consists of six growth factors (VEGF-A, -B, -C, -D, -E and placental growth factor) and three receptors (VEGFR-1, -2 and -3). The best-characterised growth factor, VEGF-A, induces vascular permeability. Enhanced permeability can lead to the accumulation of fibrin, which acts as a scaffold for new blood vessels and other cells that generate mature vascularised stroma [53].

Other factors that mediate the process of angiogenesis include the PDGF family of receptors, which is structurally related to the VEGF family and has been shown to have significant angiogenic properties [54]. In addition, cyclooxygenase 2 (COX-2), an enzyme involved in the arachidonic acid cascade, is upregulated and overexpressed in many tumours, including lung cancer. COX-2 is expressed in newly formed tumour blood vessels and is associated with a poor prognosis [55]. Other identified angiogenic factors include fibroblast growth factor (FGF), angiogenin, interleukin-8 and -12, angiotropin, transforming growth factor (TGF)-β, tumour necrosis factor-α, Tie-2 and nitric oxide synthase [56–58].

Various inhibitors of the angiogenic cascade are under study for malignancies, including NSCLC [59]. The following section provides a brief overview of the antiangiogenic agents in an advanced stage of clinical development. Recently reported clinical trial data will be reviewed, and ongoing (or planned) studies of these therapies in the NSCLC setting will be highlighted.
Effects of bevacizumab include hypertension and proteinuria. Currently, it is not known whether this is an antiangiogenic concern for bleeding in the central nervous system. Patients with brain metastases were also excluded because of the presence of cavitations in pretreatment radiographs [61].

Frequent events associated with bevacizumab and associated with the review of patient risk factors, early onset haemorrhage was found to be related to bevacizumab and associated with the addition of bevacizumab (35% versus 15% P < 0.001).

This study represents the first in which a targeted antiangiogenic therapy combined with chemotherapy has demonstrated superior efficacy compared with chemotherapy alone in the first-line treatment of NSCLC. Notably, patients with squamous cell histology were excluded from this trial because of previously reported pulmonary bleeding safety concerns in this subset of patients [12]. In a retrospective review of patient risk factors, early onset haemorrhage was found to be related to bevacizumab and associated with the presence of cavitations in pretreatment radiographs [61]. Patients with brain metastases were also excluded because of the concern for bleeding in the central nervous system. Currently, it is not known whether this is an antiangiogenic class effect or specific to bevacizumab. Other major adverse effects of bevacizumab include hypertension and proteinuria.

**multi-targeted agents**

As NSCLC is a heterogeneous disease with a multi-factorial pathobiology, a single-targeted agent may not be the optimal choice for this patient population. There have been several failures in clinical trials of targeted therapies in lung cancer. It is believed that there is multi-level cross-stimulation among targets along several pathways of signal transduction that lead to malignancy in this tumour type. By blocking only one of these pathways, as most first-generation targeted agents do, it allows other pathways to act as salvage or escape mechanisms for cancer cells [62]. Therefore, a logical approach would involve a single agent with multiple targets, which in combination with chemotherapy may provide a more complete therapeutic benefit. Such agents include a number of small-molecule TKIs that target several receptor TKs associated with NSCLC and activated vascular endothelial cells.

The advantages of multi-targeted TKIs over single-targeted agents include convenience of multi-activity in single agent, higher likelihood of single-agent activity, direct targeting of both tumour and blood vessels and potentially lower costs. These benefits must be weighted against potential disadvantages; for instance, the inhibition of each target may not be equally effective at the relevant dose used in patients, and the potential exists for different toxicity profiles for multi-targeted agents, compared with single-targeted agents.

ZD6474 (vandetanib) is an oral, multi-targeted TKI that prevents both the development of the tumour’s blood supply through inhibition of VEGFR-2 (antiangiogenesis) and the growth and survival of the tumour itself through inhibition of EGFR [63, 64]. ZD6474 also inhibits glial-cell-line-derived neurotrophic factor (rearranged during transfection; RET). Inhibition of EGFR signalling has been shown to inhibit the secretion of VEGF as well as other proangiogenic factors such as FGF and TGF. Preclinical studies have shown ZD6474 to be active in a wide range of models, including lung tumours [24]. In a randomised phase II trial of 168 patients with advanced NSCLC who had failed at least one prior platinum-based chemotherapy regimen, patients receiving ZD6474 (300 mg once daily) had a median PFS of 11.0 weeks compared with 8.1 weeks for patients receiving gefitinib (250 mg once daily) (HR = 0.69, P = 0.025) [9]. The difference in OS did not reach statistical significance, but there was a trend in favour of initial gefitinib use compared with initial ZD6474 use (7.4 versus 6.1 months) (patients in either arm were allowed to cross-over to the alternative agent upon progression of disease). Adverse events associated with ZD6474 included QTc-related events (21%), diarrhoea (8.4%) and rash (4.8%). There was no unexpected safety finding with gefitinib-treated patients. In a second phase II randomised trial, 127 patients with advanced NSCLC and failure of prior platinum-based chemotherapy were treated with docetaxel (75 mg/m² every 3 weeks) plus either ZD6474 (100 or 300 mg once daily) or placebo [65]. At both doses of ZD6474, PFS was prolonged (19 and 17 weeks, respectively, versus 12 weeks for docetaxel alone). Common adverse events included rash, diarrhoea and asymptomatic QTc prolongation. Several clinical trials of ZD6474 are currently ongoing.

Sunitinib (SU11248) is an oral, multi-targeted receptor TKI with direct antiproliferative effects and antiangiogenic properties. It targets VEGFR-1, -2 and -3, PDGFR-α and -β, KIT (stem-cell factor receptor), RET, colony-stimulating factor receptor (CSF-1R) and FMS-like receptor tyrosine kinase (FLT3) [66–68]. Sunitinib may prove particularly active against NSCLC because, in preclinical studies, it exhibited broad and potent antitumour activity, causing regression, growth arrest or substantially reduced growth of established xenografts derived from human or rat tumour cell lines [68] including in H226 NSCLC models [69]. More importantly, in a study designed to evaluate the specific contribution of VEGF- and PDGF-pathway inhibition to antitumour activity, results in all but one tumour model showed that inhibition of both pathways resulted in superior activity than inhibition of either one alone. The antitumour efficacy of sunitinib was equivalent to the combining of two single pathway inhibitors [69]. The efficacy of sunitinib in models of different signalling pathways supports the hypothesis that multi-targeted inhibitors have the additive antitumour efficacy of combined single-targeted agents.

Preliminary results from a multicentre, phase II trial show that single-agent sunitinib demonstrates activity and acceptable tolerability in previously treated advanced NSCLC patients.
Sixty-three patients were recruited on the 4/2 schedule [4 weeks on sunitinib (50 mg/day) followed by 2 weeks off]. Eligibility criteria included confirmed diagnosis of NSCLC, ECOG PS of zero to one, no recent gross hemoptysis, no brain metastases, patients previously treated with one or two chemotherapy regimens (at least one of which was platinum-based) and adequate end-organ function. Based on RECIST criteria, 9.3% had a confirmed objective tumour response rate. The mean duration of response was 12.2 weeks with a median PFS of 11.3 weeks. Median OS for patients on sunitinib was 23.9 weeks (95% CI 17.0–28.3) [10]. The majority of patients showed some reduction in target lesion measurements (Figure 1A). The drug was well tolerated and most side-effects were mild to moderate; grade 3/4 adverse events included fatigue (22%/9%), pain/myalgia (14%/3%), dyspnoea (13%/0%) and nausea/vomiting (10%/0%). The majority of non-haematologic adverse events were reported as either grade 1 or 2. There was a 5% incidence of grade 3/4 neutropenia and a 5% incidence of grade 3/4 thrombocytopenia. The response rate with single-agent sunitinib in this study population compares favourably with other agents approved in the second-line setting; thus, further investigations are underway in first- and second-line therapy of NSCLC. A phase III trial with sunitinib in combination with cisplatin and gemcitabine in the first line and a phase II trial in combination with erlotinib in patients who have received previous treatment with a platinum-based regimen are planned. Sorafenib (BAY 43-9006), which was initially developed as a Raf-specific inhibitor, also inhibits VEGFR-2 and -3 and PDGFGR-β [70]. In preclinical models of colon cancer, breast cancer and NSCLC, sorafenib significantly inhibited tumour angiogenesis as measured by anti-CD31 immunostaining [71]. In a multicentre, uncontrolled phase II trial, 54 patients with relapsed or refractory NSCLC received single-agent sorafenib (400 mg twice daily) [11]. Of the 52 assessable patients, no objective responses were reported, and stable disease (SD) was reported at 59%. Median PFS was 2.7 months and median OS was 6.7 months. Tumour shrinkage was observed in 29% of patients (Figure 1B). Adverse events were predictable; the most frequent drug-related adverse effects were diarrhoea (40%), hand–foot syndrome (HFS) (37%), fatigue (27%) and nausea (25%). Frequent drug-related adverse events grade ≥3 included HFS [n = 5 (10%)] and hypertension [n = 2 (4%)]. Three patients discontinued due to adverse events (HFS, elevated lipase and myocardial infarction).

**Figure 1.** (A) Maximum percentage change of target lesions by patient on sunitinib on the 4/2 schedule. Patients with partial response are highlighted [10]. (B) Maximum percentage reduction of target lesions by patient on sorafenib [11].
In a two-stage design phase II trial, patients with recurrent NSCLC with measurable disease who had received only one prior chemotherapy regimen were evaluated by dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) for their response to sorafenib (400 mg twice daily) on a 28-day cycle [72]. Five patients were assessable for response and six for toxicity. Best responses included one PR (41% tumour reduction at week 8, with PR until week 28) and one unconfirmed PR at week 3. Two had SD (16 and 19 weeks) and one had progressive disease after 8 weeks of treatment. Common skin toxic effects (rash, HFS, keratoacanthoma, vasculitis) were all grade 1 or 2. Grade 3 toxic effects included anaemia (n = 1), hyponatraemia (n = 2) and nausea (n = 1). DCE-MRI of one patient showed decrease in permeability parameters and tumour size. Two other patients showed no decrease in the permeability parameters [72]. A phase III first-line study randomising patients to paclitaxel/carboplatin or paclitaxel/carboplatin/sorafenib is underway.

PTK787 (vatalanib) is an oral TKI that targets VEGFR-1, -2 and -3 primarily, but also targetsPDGFR-β and KIT. A prospective, single-arm, multicentre, proof-of-principle phase II study is being conducted to investigate both the efficacy and safety of PTK787 in patients with stage III/IV NSCLC who received first-line treatment with a platinum-based chemotherapy regimen. Of the 56 patients enrolled to date, 48 are assessable for response: one (2%) with a PR (for >20 weeks), 27 (56%) with SD and 20 (42%) with progressive disease. The most common side-effects are nausea and vomiting [73]. One patient developed interstitial lung disease and one patient with a tracheal stent had a fatal pulmonary bleed.

AZD2171 (cediranib) is a TKI of VEGFR-1, -2 and -3, as well as PDGFR-β and KIT, with broad-spectrum activity in preclinical models [74]. Preliminary results from a phase I study of AZD2171 (30 or 45 mg) in combination with paclitaxel/carboplatin in patients with advanced NSCLC showed the regimen to be associated with predictable and manageable toxic effects. Dose reductions were required in six patients in the 30-mg group due to a dose-related toxicity (hypertension grade ≥2) [75]. One patient in each dose group had a dose-limiting toxicity: grade 3 alanine aminotransferase elevation in the 30-mg group and grade 3 febrile neutropenia with grade 3 mucositis in the 45-mg group. Other common toxic effects included fatigue, anorexia, mucositis and diarrhoea. No hemoptysis was observed [75]. Of the 15 patients assessable for response, six had a PR, eight had SD and one had progressive disease. Many of the patients with SD had evidence of tumour shrinkage, including central cavitation. A phase II/III trial of paclitaxel/carboplatin and AZD2171 or placebo is currently underway.

AMG 706 (motesanib) is a multi-kinase inhibitor with antiangiogenic and antitumour activity achieved by selectively targeting the VEGF, PDGF, KIT and RET receptors. Preliminary results indicate that AMG 706 can be combined safely with paclitaxel/carboplatin and/or the investigational EGFR-targeted agent, panitumumab, in patients with advanced NSCLC. Treatment-related adverse events were generally mild to moderate in severity [76]. Grade 3 events were fatigue (n = 10), hypertension (n = 6), dyspnoea (n = 2) and sinusitis (n = 2). Two patients had a grade 4 pulmonary embolism.

Table 4. Ongoing and future trials of targeted therapies in NSCLC

<table>
<thead>
<tr>
<th>Agent</th>
<th>Phase</th>
<th>Design</th>
<th>Planned N</th>
<th>Primary endpoint</th>
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<tbody>
<tr>
<td>First-line setting</td>
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<tr>
<td>ZD6474 (vandetanib)</td>
<td>II</td>
<td>Carboplatin/paclitaxel</td>
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<td>Carboplatin/paclitaxel</td>
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<td>PFS</td>
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<td>Docetaxel + placebo</td>
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<td></td>
</tr>
<tr>
<td>ZD6474 (vandetanib)</td>
<td>III</td>
<td>Erlotinib</td>
<td>1150</td>
<td>PFS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ZD6474</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sunitinib</td>
<td>II</td>
<td>Erlotinib + sunitinib</td>
<td>136</td>
<td>PFS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Erlotinib + placebo</td>
<td></td>
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</tr>
</tbody>
</table>

OS, overall survival; PFS, progression-free survival; RR, response rate; TtP, time to progression.
conclusions
The success of multi-targeted antiangiogenic therapies in other cancers has increased optimism that these therapies can provide a benefit in the treatment of NSCLC as well (Table 2). As shown in Table 4, numerous trials are underway to determine whether improved survival and/or response rates can be achieved by simultaneously inhibiting various angiogenic factors, and some of the newly developed agents that have been described are beginning to show evidence of clinical activity. Given the possibility that multi-targeted therapies may provide an advantage over single-targeted therapies, there appears to be a trend against using a single highly specific agent. Other pathways need to be targeted in NSCLC. However, as NSCLC is a highly heterogeneous disease, the observed benefit of inhibiting one pathway versus another may be only incrementally better. Combination therapy approaches may be more likely to succeed.

Current data support the likelihood that multi-targeted agents will be used in combination regimens, both with traditional therapies such as cytotoxic chemotherapy, radiation therapy and surgery, as well as with specific single-targeted agents. Given the number of pathways that can be inhibited, the focus of future clinical trials will be the determination of the most effective therapeutic combinations. Many agents that have shown promising activity in the relapsed setting are now being examined as first- and second-line treatment options (Table 4). Future treatment decisions will focus on patient selection, and be on the basis of individual characteristics, such as comorbidity profiles, compliance factors, patient wishes and socioeconomic factors, as well as evidence-based guidelines.

disclosures
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