# Therapeutic options targeting angiogenesis in nonsmall cell lung cancer

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ABSTRACT   There is a major unmet medical need for effective and well-tolerated treatment options for patients with advanced nonsmall cell lung cancer (NSCLC), in both first-line and relapsed/refractory settings. Experimental evidence has validated signalling pathways that regulate tumour angiogenesis, including the vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF) pathways, as valid anti-cancer drug targets. However, to date, bevacizumab (an anti-VEGF monoclonal antibody) is the only antiangiogenic agent to be approved for the treatment of NSCLC. Many other agents, including antibodies, small-molecule tyrosine kinase inhibitors and vascular disrupting agents, have been assessed in phase III trials but have generally failed to demonstrate clinically meaningful benefits. This lack of success probably reflects the redundancy of proangiogenic pathways and the molecular and clinical heterogeneity of NSCLC.

In this review we summarise recently completed and ongoing randomised clinical trials of emerging antiangiogenic agents in patients with NSCLC. We highlight recent promising data with agents that simultaneously inhibit multiple proangiogenic pathways, including the PDGF and FGF pathways, as well as the VEGF pathway. Finally, we discuss the outlook for antiangiogenic agents in NSCLC, emphasising the need for clinically validated prognostic and predictive biomarkers to identify patients most likely to respond to therapy.

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## Introduction

Most patients with nonsmall cell lung cancer (NSCLC) present with advanced inoperable disease; the prognosis for these patients is extremely poor. Indeed, 5-year survival rates for patients diagnosed with stage IIIB or IV NSCLC are only 5% and 1%, respectively [1]. The standard first-line therapy for advanced NSCLC comprises platinum-based combination therapy, which prolongs survival, controls symptoms and improves quality of life, *versus* best supportive care in patients with good performance status [2]. A minority of patients may receive "personalised" first-line therapy according to the identification of "druggable" genetic alterations in tumour tissue. For example, patients with activating mutations in the epidermal growth factor receptor (*EGFR*) gene should receive an EGFR small-molecule inhibitor such as erlotinib (Tarceva; Hoffmann-La Roche Ltd, Basel, Switzerland), gefitinib (Iressa; AstraZeneca, London, UK) or afatinib (Giotrif; Boehringer Ingelheim, Ingelheim, Germany). Patients with rearrangements of the anaplastic lymphoma kinase (*ALK*) gene may receive the ALK inhibitor crizotinib (Xalkori; Pfizer, New York, NY, USA).

Regardless of the first-line treatment used, clinical outcomes in patients with IIIB/IV NSCLC are generally poor. Most patients with stage IIIB/IV NSCLC experience disease progression within 4–6 months of discontinuing first-line chemotherapy [3]; those who receive EGFR inhibitors generally become resistant to therapy within 10–14 months [4]. Few effective second-line treatment options are available to patients who progress after first-line therapy. Treatment guidelines recommend docetaxel or pemetrexed (the latter in patients with non-squamous histology only) [2]. Erlotinib may be a further option as second- or third-line treatment [2]. However, survival benefits with available second-line agents are modest [5–7]. Furthermore, approximately 50% of patients who fail first-line therapy go on to receive second-line chemotherapy [8]. Hence, there is an urgent need for effective and well-tolerated treatment options for NSCLC in both first-line and relapsed/refractory settings.

In many cancers, including NSCLC, proangiogenic pathways have been established as important and effective therapeutic targets because they are essential for tumour growth, progression and metastasis [9]. Tumour angiogenesis is essential for the development and progression of malignant tumours; it is a highly complex process involving a network of autocrine and paracrine signalling pathways within the tumour and surrounding stromal cells. A key driver of tumour angiogenesis is hypoxia, which stimulates the overproduction of proangiogenic factors relative to antiangiogenic factors (fig. 1) [10, 11].

One of the best characterised proangiogenic pathways is the vascular endothelial growth factor (VEGF) signalling pathway. This comprises six growth factors (VEGFA to E and placental growth factor) and three VEGF receptors (VEGFR1 to 3). Interactions between VEGF ligands and VEGFRs stimulate several downstream signalling cascades that coordinate endothelial cell proliferation, differentiation, permeability and migration in order to stimulate the generation of new blood vessels [12]. The prominent role of the VEGF signalling pathway in tumour angiogenesis prompted the clinical development of angiogenesis inhibitors for the treatment of various cancers, including NSCLC. In general, this has involved two main approaches: 1) high molecular weight, injectable, monoclonal antibodies that block the function of VEGF ligands or receptors; and 2) small-molecule, orally administered tyrosine kinase inhibitors (TKIs) that directly inhibit VEGFRs and their signalling pathways [13]. The proof of principle for VEGF inhibition in NSCLC has been demonstrated in clinical trials of bevacizumab (Avastin; Hoffmann-La Roche Ltd), an anti-VEGF monoclonal antibody. Bevacizumab, in combination with platinum-based chemotherapy, has been shown to improve survival *versus* chemotherapy alone in a first-line setting in patients with non-squamous NSCLC [14].

Unfortunately, NSCLC tumours often acquire resistance to antiangiogenic agents because proangiogenic pathways have substantial redundancy, allowing adaptation to bypass the inhibition of a single pathway. Acquired resistance involves a complex myriad of interactions between the tumour cells themselves and cells within the tumour microenvironment, *e.g.* pericytes, smooth muscle cells, fibroblasts and endothelial cells [15]. Recent intensive research has led to insights into the biology of acquired resistance that may ultimately lead to the development of more effective antiangiogenic agents. Emerging evidence has implicated two key signalling pathways, the fibroblast growth factor (FGF) and platelet-derived growth factor (PDGF) signalling pathways, in adaptive resistance to VEGF therapy [15].

The FGF family includes 22 ligands and five receptors with diverse biological functions, including angiogenesis [16, 17]. FGF receptors (FGFRs) are known to be overexpressed in many cancer types and, in some cases, have been identified as oncogenes to which tumour cells are addicted [17]. FGFRs have been identified as among the most commonly mutated kinase genes in human cancers, with mutations in FGFR2 and FGFR3 being the most prevalent [17]. Two FGFRs, FGFR1 and 2, are expressed in endothelial cells and activate proangiogenic intracellular signalling pathways, including the phosphatidylinositol 3-kinase and mitogen-activated protein kinase pathways. Like the FGF signalling pathway, the PDGF pathway is integral to the regulation of angiogenesis. Enhanced PDGF expression has been associated with tumourigenesis and angiogenesis [18]. Five dimeric PDGF ligands are released from platelets in response to vascular damage and bind to two PDGF receptors (PDGFRs) (α and β) expressed on endothelial cells, pericytes and vascular smooth muscle cells [19, 20]. This activates intracellular signalling cascades (which overlap with the VEGF signalling system) to promote vascular integrity, development and stabilisation.

In this review, we provide an overview of recent advances in the development of antiangiogenic agents for the treatment of NSCLC in both first-line and relapsed/refractory settings focusing on ongoing or recently completed phase III studies of TKIs that simultaneously inhibit multiple proangiogenic pathways.

## Antiangiogenic agents in the first-line setting
### Bevacizumab
To date, bevacizumab is the only antiangiogenic agent approved for the first-line treatment of NSCLC. Its use is restricted to patients with tumours with a non-squamous histology (~70% of patients with NSCLC).
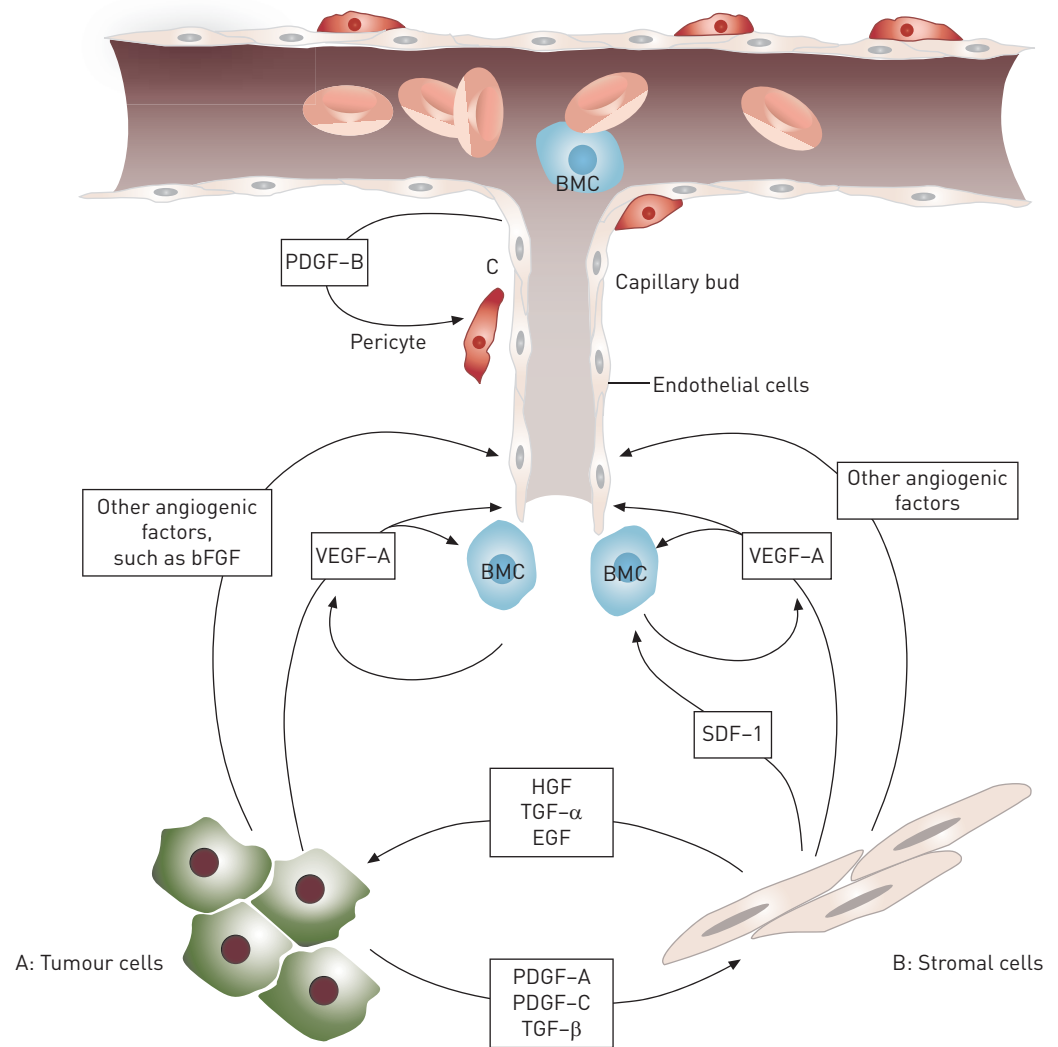
FIGURE 1 Molecular pathways underlying angiogenesis. A: Tumour cells produce vascular endothelial growth factor (VEGF)-A and other angiogenic factors, such as basic fibroblast growth factor (bFGF), angiopoietins, interleukin-8, placental growth factor and VEGF-C. These stimulate resident endothelial cells to proliferate and migrate. B: An additional source of angiogenic factors is the stroma. This is a heterogeneous compartment, comprising fibroblastic, inflammatory and immune cells. Recent studies indicate that tumour-associated fibroblasts produce chemokines, such as stromal cell-derived factor (SDF)-1, which may recruit bone-marrow-derived angiogenic cells (BMC). VEGF-A or placental growth factor may also recruit BMC. Tumour cells may also release stromal cell-recruitment factors, such as platelet-derived growth factor (PDGF)-A, PDGF-C or transforming growth factor (TGF)-β. A well-established function of tumour-associated fibroblasts is the production of growth/survival factor for tumour cells, such as epidermal growth factor (EGF) receptor ligands, hepatocyte growth factor and heregulin. C: Endothelial cells produce PDGF-B, which promotes recruitment of pericytes in the microvasculature after activation of PDGF receptor-β. HGF: hepatocyte growth factor. Reproduced from [10] with permission.

Bevacizumab was approved based on two seminal phase III trials (table 1) [14, 21]. In the ECOG (Eastern Cooperative Oncology Group) 4599 trial, 878 patients with non-squamous NSCLC were randomised to receive carboplatin/paclitaxel with or without bevacizumab (15 mg·kg$^{-1}$ intravenously) [14]. In this trial, bevacizumab was associated with significant prolongation of both overall survival (12.3 months *versus* 10.3 months, hazard ratio (HR) for death: 0.79; p=0.003) and progression-free survival (PFS) (6.2 months *versus* 4.5 months, HR 0.66; p<0.001) *versus* placebo. However, in a retrospective sub-analysis of elderly patients (aged ⩾70 years), there was no significant improvement in overall survival or PFS [29]. Grade ⩾3 adverse events were significantly higher in the bevacizumab arm and included a number of toxicities that are often associated with VEGF inhibition including neutropenia, febrile neutropenia, bleeding events, hypertension and proteinuria. In the AVAiL (Avastin in Lung Cancer) trial, 1043 patients with non-squamous NSCLC were randomised to receive cisplatin/gemcitabine with or without bevacizumab

(7.5 mg·kg$^{-1}$ or 15 mg·kg$^{-1}$) [21]. As with ECOG 4599, bevacizumab was associated with improvement in PFS (at both doses) *versus* placebo (7.5 mg·kg$^{-1}$: 6.7 months *versus* 6.1 months, p=0.003; 15 mg·kg$^{-1}$: 6.5 months *versus* 6.1 months, p=0.03). In contrast to ECOG 4599, improved PFS was observed in elderly patients [30]. However, there was no significant difference in overall survival between treatment arms [22]. The most common grade ⩾3 adverse events were myelosuppression events.

TABLE 1 Recent phase III trials assessing antiangiogenic agents in a first-line setting

| Agent and study name [ref.] | Target (s) | Study design | Overall response rate | Progression-free survival | Overall survival |
|---|---|---|---|---|---|
| **Monoclonal antibodies** | | | | | |
| Bevacizumab; ECOG 4599 [14] | VEGF | Stage IIIB/IV non-squamous NSCLC Patients randomised to: carboplatin/paclitaxel (n=444) or carboplatin/paclitaxel + bevacizumab (15 mg·kg$^{-1}$; n=434) Primary end-point: overall survival | Carboplatin/paclitaxel: 15% Carboplatin/paclitaxel + bevacizumab: 35% (p<0.001) | Carboplatin/paclitaxel: 4.5 months Carboplatin/paclitaxel + bevacizumab: 6.2 months HR 0.66 (95% CI 0.57–0.77); p<0.001 | Carboplatin/paclitaxel: 10.3 months Carboplatin/paclitaxel + bevacizumab: 12.3 months HR 0.79 (95% CI 0.67–0.92); p=0.003 |
| Bevacizumab; AVAiL [21, 22] | VEGF | Stage IIIB/IV non-squamous NSCLC Patients randomised to: cisplatin/gemcitabine (n=347), cisplatin/gemcitabine + bevacizumab (7.5 mg·kg$^{-1}$; n=345) or cisplatin/gemcitabine + bevacizumab (15 mg·kg$^{-1}$; n=351) Primary end-point: progression-free survival | Cisplatin/gemcitabine: 20.1% Cisplatin/gemcitabine + bevacizumab (7.5 mg·kg$^{-1}$): 34.1% Cisplatin/gemcitabine + bevacizumab (15 mg·kg$^{-1}$): 30.4% (p<0.0001 and p=0.0023, respectively) | Cisplatin/gemcitabine: 6.1 months Cisplatin/gemcitabine + bevacizumab (7.5 mg·kg$^{-1}$): 6.7 months Cisplatin/gemcitabine + bevacizumab (15 mg·kg$^{-1}$): 6.5 months HR 0.75 (95% CI 0.62–0.91); p=0.003 and HR 0.92 (95% CI 0.68–0.98); p=0.03, respectively | Cisplatin/gemcitabine: 13.1 months Cisplatin/gemcitabine + bevacizumab (7.5 mg·kg$^{-1}$): 13.6 months Cisplatin/gemcitabine + bevacizumab (15 mg·kg$^{-1}$): 13.4 months HR 0.92 (95% CI 0.78–1.11); p=0.420 and HR 1.03 (95% CI 0.86–1.23); p=0.761, respectively |
| **Multi-targeted antiangiogenic orally administered TKIs** | | | | | |
| Cediranib; BR24 [23] | VEGFR-1–3, PDGFR-β, FGFR-1 and c-kit | Stage IIIB/IV NSCLC all histologies Patients randomised to: carboplatin/paclitaxel (n=125) or carboplatin/paclitaxel + cediranib (30 mg·day$^{-1}$; n=126) Primary end-point: progression-free survival | Carboplatin/paclitaxel: 16% Carboplatin/paclitaxel + cediranib: 38% (p<0.0001) | Carboplatin/paclitaxel: 5.0 months Carboplatin/paclitaxel + cediranib: 5.6 months HR 0.77 (95% CI 0.56–1.08); p=0.13 | Carboplatin/paclitaxel: 10.1 months Carboplatin/paclitaxel + cediranib: 10.5 months HR 0.78 (95% CI 0.57–1.06); p=0.11 |
| Cediranib; BR29 [24] | VEGFR-1–3, PDGFR-β, FGFR-1 and c-kit | Stage IIIB/IV NSCLC all histologies Patients randomised to: carboplatin/paclitaxel or carboplatin/paclitaxel + cediranib (20 mg·day$^{-1}$) Primary end-point: overall survival | Carboplatin/paclitaxel: 34% Carboplatin/paclitaxel + cediranib: 52% (p=0.001) | Carboplatin/paclitaxel: 5.5 months Carboplatin/paclitaxel + cediranib: 5.5 months HR 0.91 (95% CI 0.71–1.18); p=0.5 | Carboplatin/paclitaxel: 12.1 months Carboplatin/paclitaxel + cediranib: 12.2 months HR 0.95 (95% CI 0.69–1.30); p=0.74 |
| Sorafenib; ESCAPE [25] | VEGFR-2–3, PDGFR-β, c-kit, Raf and flt-3 | Stage IIIB/IV NSCLC all histologies Patients randomised to: carboplatin/paclitaxel (n=462) or carboplatin/paclitaxel + sorafenib (400 mg; n=464) Primary end-point: overall survival | Carboplatin/paclitaxel: 27% Carboplatin/paclitaxel + sorafenib: 24% (p=0.102) | Carboplatin/paclitaxel: 5.4 months Carboplatin/paclitaxel + sorafenib: 4.6 months HR 0.99 (95% CI 0.84–1.16); p=0.433 | Carboplatin/paclitaxel: 10.6 months Carboplatin/paclitaxel + sorafenib: 10.7 months HR 1.15 (95% CI 0.94–1.41); p=0.915 |
| Sorafenib; NExUS [26] | VEGFR-2–3, PDGFR-β, c-kit, Raf and flt-3 | Stage IIIB/IV non-squamous NSCLC Patients randomised to: gemcitabine/cisplatin (n=387) or gemcitabine/cisplatin + sorafenib (400 mg; n=385) Primary end-point: overall survival | Gemcitabine/cisplatin: 26% Gemcitabine/cisplatin + sorafenib: 28% (p=0.27) | Gemcitabine/cisplatin: 5.5 months Gemcitabine/cisplatin + sorafenib: 6.0 months HR 0.83 (95% CI 0.71–0.97); p=0.008 | Gemcitabine/cisplatin: 12.5 months Gemcitabine/cisplatin + sorafenib: 12.4 months HR 0.98 (65% CI 0.83–1.16); p=0.401 |
| Motesanib; MONET1 [27] | VEGFR-1–3, PDGFR-β, c-kit and RET | Stage IIIB/IV non-squamous NSCLC Patients randomised to: carboplatin/paclitaxel (n=549) or carboplatin/paclitaxel + motesanib (125 mg; n=541) Primary end-point: overall survival | Carboplatin/paclitaxel: 26% Carboplatin/paclitaxel + motesanib: 40% (p<0.001) | Carboplatin/paclitaxel: 5.4 months Carboplatin/paclitaxel + motesanib: 5.6 months HR 0.79 (95% CI 0.61–0.98); p<0.001 | Carboplatin/paclitaxel: 11.0 months Carboplatin/paclitaxel + motesanib: 13.0 months HR 0.90 (95% CI 0.78–1.04); p=0.14 |
| **Vascular disrupting agents** | | | | | |
| Vadimezan; ATTRACT-1 [28] | | Stage IIIB/IV NSCLC all histologies Patients randomised to: carboplatin/paclitaxel (n=650) or carboplatin/paclitaxel + vadimezan (1800 mg·m$^{-2}$; n=649) Primary end-point: overall survival | Carboplatin/paclitaxel: 25% Carboplatin/paclitaxel + vadimezan: 25% (p=1.0) | Carboplatin/paclitaxel: 5.5 months Carboplatin/paclitaxel + vadimezan: 5.5 months HR 1.04 (95% CI 0.91–1.19); p=0.727 | Carboplatin/paclitaxel: 12.7 months Carboplatin/paclitaxel + vadimezan: 13.4 months HR 1.01 (95% CI 0.85–1.19); p=0.535 |

ECOG: Eastern Cooperative Oncology Group; AVAiL: Avastin in Lung Cancer; TKI: tyrosine kinase inhibitor; ESCAPE: Evaluation of Sorafenib, Carboplatin and Paclitaxel Efficacy in NSCLC; NExUS: NSCLC research Experience Utilising Sorafenib; MONET1: Motesanib NSCLC Efficacy and Tolerability Study; ATTRACT-1: Antivascular Targeted Therapy: Researching ASA404 in Cancer Treatment; VEGF: vascular endothelial growth factor; VEGFR: VEGF receptor; PDGFR: platelet-derived growth factor receptor; FGFR: fibroblast growth factor receptor; RET: Rearranged during Transfection; NSCLC: nonsmall cell lung cancer; HR: hazard ratio.

Based on these trials, bevacizumab was approved by the US Food and Drug Administration in 2006 and the European Medicines Agency in 2009 for first-line treatment of advanced NSCLC in combination with chemotherapy. It has been reported that bevacizumab may increase the risk of haemorrhage [31]. However, a recent phase IV study of 2212 patients with non-squamous NSCLC indicated that first-line bevacizumab plus chemotherapy has a manageable safety profile with a low incidence of grade $\geqslant 3$ bleeding events (4%) [32].

Following the approval of bevacizumab for first-line treatment of non-squamous NSCLC, trials are ongoing to define its role in maintenance beyond progression and in adjuvant settings. In the ongoing ECOG 5508 trial, patients receiving induction therapy of carboplatin/paclitaxel/bevacizumab were randomised to receive maintenance therapy with bevacizumab, pemetrexed or bevacizumab plus pemetrexed [33]. The phase III AvaALL trial, with overall survival as its primary end-point, is currently randomising patients with advanced non-squamous NSCLC who have progressed following bevacizumab plus platinum-based chemotherapy to standard second-line therapy (pemetrexed, docetaxel or erlotinib) with or without bevacizumab [34].

The ECOG E1505 study is currently assessing the impact of adding bevacizumab to adjuvant chemotherapy in patients with completely resected stage IB–IIIA NSCLC [35].

### Recently completed randomised trials

Following the approval of bevacizumab for the first-line treatment of non-squamous NSCLC, intense efforts are underway to develop other anti-VEGF agents (antibodies and small-molecule TKIs). However, recently reported phase III trials have failed to demonstrate a survival advantage compared with standard therapy (table 1) [23–27]. Some recently assessed TKIs and vascular disrupting agents are detailed below.

### Multi-targeted antiangiogenic orally administered TKIs

#### Cediranib

Cediranib (Recentin; AstraZeneca, London, UK) is an orally administered TKI that inhibits VEGFR1–3, PDGFR-$\alpha/\beta$, FGFR1 and c-kit [36]. In a phase II/III trial (n=251), interim analysis indicated a trend towards improved PFS in patients with advanced NSCLC treated with first-line cediranib (30 mg per day) plus carboplatin/paclitaxel versus chemotherapy alone (5.6 months versus 5.0 months; p=0.13); however, the study was halted due to safety concerns [23]. In a subsequent phase III study, cediranib (20 mg per day) plus carboplatin/paclitaxel did not confer a survival advantage versus chemotherapy alone and increased toxicity; grade >3 hypertension (15% versus 3%, p=0.0002), anorexia (7% versus 1%, p=0.02) and diarrhoea (16% versus 1%, p<0.0001) were all significantly increased, hence the trial was halted [24].

#### Sorafenib

Sorafenib (Nexavar; Bayer, Pittsburgh, PA, USA) inhibits VEGFR2–3, PDGFR-$\beta$, c-kit, Raf and flt-3 [37]. A phase III trial (ESCAPE (Evaluation of Sorafenib, Carboplatin and Paclitaxel Efficacy in NSCLC); n=926) assessed sorafenib plus carboplatin/paclitaxel versus chemotherapy alone in patients with advanced untreated NSCLC [25]. There was no significant improvement in PFS (4.6 months versus 5.4 months; p=0.43) or overall survival (10.7 months versus 10.6 months; p=0.13). Furthermore, a high mortality rate was noted in patients with tumours showing a squamous histology. A second phase III trial (NExUS (NSCLC research Experience Utilising Sorafenib); n=772) showed a PFS improvement, but not an overall survival improvement, for sorafenib plus gemcitabine/cisplatin versus chemotherapy alone in a first-line setting [26].

#### Motesanib

Motesanib (Amgen, Thousand Oaks, CA, USA) inhibits VEGFR1–3, PDGFR, c-kit and RET [38]. A phase III trial (MONET1 (Motesanib NSCLC Efficacy and Tolerability Study); n=1090) assessed motesanib plus carboplatin/paclitaxel versus chemotherapy alone in advanced non-squamous NSCLC. Motesanib conferred significant improvements in PFS (5.6 months versus 5.4 months; p<0.001) and response rate (40% versus 26%; p<0.001), but there was no significant improvement in the primary end-point, overall survival (13.0 months versus 11.0 months; p=0.14) [27]. Moreover, the incidence of grade $\geqslant 3$ adverse events (73% versus 59%) and grade 5 adverse events (14% versus 9%) were higher with motesanib treatment.

#### Axitinib

Axitinib (Inlyta; Pfizer) inhibits VEGFR1–3, PDGFR-$\beta$ and c-kit [39]. An initial single-arm phase II study (n=32) assessed the single-agent axitinib in patients with NSCLC (first and second line). The results of this study were promising, with a reported disease control rate (partial response plus stable disease) of 41%, median PFS of 4.9 months and median overall survival of 14.8 months [40]. However, subsequent phase II clinical trial results have been disappointing. In a randomised study, axitinib plus carboplatin/paclitaxel did

not improve PFS or overall survival *versus* bevacizumab plus carboplatin/paclitaxel [41]. In another study, axitinib plus pemetrexed/cisplatin did not improve overall survival or PFS *versus* chemotherapy alone [42].

### Vascular disrupting agents
#### Vadimezan
Vadimezan is a fused tricyclic analogue of flavone acetic acid that acts as a vascular disrupting agent. In contrast to antiangiogenic agents that inhibit proliferation of new blood vessels, vadimezan induces an acute and largely irreversible collapse in existing tumour vascular supply [43]. In a phase III trial (ATTRACT-1 (Antivascular Targeted Therapy: Researching ASA404 in Cancer Treatment); n=1299) the addition of intravenous vadimezan to carboplatin/paclitaxel chemotherapy failed to improve either overall survival (13.4 months *versus* 12.7 months; p=0.54) or PFS (5.5 *versus* 5.5 months; p=0.73) in patients with advanced stage IIIB/IV NSCLC [28]. Grade 4 neutropenia (27% *versus* 19%) and infusion site pain (10% *versus* 0.5%) were reported more frequently in the ASA404 arm.

## Antiangiogenic agents in a relapsed/refractory setting
### Recently completed randomised trials
There is a major unmet need for new treatment options in patients with relapsed/refractory NSCLC. Unfortunately, to date, no antiangiogenic agents have been approved for the treatment of relapsed/refractory NSCLC. The results from the majority of phase III trials that have assessed antiangiogenic agents in a second-line setting have been disappointing (table 2) [44–53]. However, there has been recent progress with agents that simultaneously target multiple signalling pathways.

### Multi-targeted antiangiogenic orally administered TKIs
#### Nintedanib
Nintedanib is an orally administered, small-molecule triple angiokinase inhibitor of VEGF1–3, PDGF-α and β, and FGFR1–3 that has demonstrated substantial anti-tumour and antiangiogenic activity in pre-clinical experiments [54, 55] and in clinical phase I/II trials in patients with NSCLC [56–58]. Nintedanib is the first antiangiogenic agent to demonstrate a survival benefit in the second-line treatment of patients with adenocarcinoma NSCLC *versus* an active comparator [44].

Two independent, multicentre, phase III studies have assessed nintedanib combined with either docetaxel or pemetrexed in patients with advanced or recurrent NSCLC for whom first-line chemotherapy had failed (table 2). The LUME-Lung 1 study (n=1314) assessed nintedanib (200 mg twice daily; day 2–21) plus docetaxel (75 mg·m$^{-2}$ every 21 days) *versus* docetaxel alone in patients with stage III/IV or recurrent NSCLC with any histology [44]. Nintedanib plus docetaxel significantly improved PFS *versus* docetaxel alone regardless of histology (HR 0.79, 95% CI 0.68–92; 3.4 months *versus* 2.7 months; p=0.002). In the hierarchical testing for the key secondary end-point, overall survival, there was a significant improvement in patients with adenocarcinoma (HR 0.83, 95% CI 0.70–99; 12.6 months *versus* 10.3 months; p=0.036) with the greatest improvement observed in patients who started nintedanib <9 months after initiation of first-line therapy (HR 0.75, 95% CI 0.60–92; 10.9 months *versus* 7.9 months; p=0.036). In addition, there was a trend towards increased overall survival in all histologies (10.1 months *versus* 9.1 months; p=0.272). Incidence of grade ⩾3 adverse events was 71.3% *versus* 64.3%. The most common adverse events were diarrhoea (42.3% *versus* 21.8%) and reversible alanine aminotransferase elevations (28.5% *versus* 8.4%). LUME-Lung 2 (n=713) assessed nintedanib (200 mg twice daily; day 2–21) plus pemetrexed (500 mg·m$^{-2}$ every 21 days) *versus* pemetrexed alone in patients with non-squamous NSCLC [45]. In this study, recruitment was halted early based on a pre-planned futility analysis of investigator-assessed PFS by an independent data monitoring committee. The data monitoring committee concluded that the likelihood of meeting the primary end-point (centrally reviewed PFS) was low, although no safety concerns were raised. Following the futility analysis, patients were unblinded and followed up per protocol. Interestingly, subsequent analysis (n=713; planned enrolment was n=1111) demonstrated that the primary end-point of centrally reviewed PFS was met even though the study was stopped prematurely. Nintedanib plus pemetrexed significantly improved PFS (HR 0.83, 95% CI 0.70–99; 4.4 months *versus* 3.6 months; p=0.04), but not overall survival, *versus* pemetrexed alone. Notably, the incidence of grade ⩾3 hypertension, bleeding and thromboembolism was similar between treatment arms [44, 45].

#### Vandetanib
Vandetanib (Zactima; AstraZeneca) is an orally administered TKI that inhibits VEGFR2 and 3, RET and EGFR [59]. Based on a large phase III programme comprising four randomised trials in patients with advanced disease, development of vandetanib in NSCLC has been discontinued. The ZODIAC (Zactima in Combination with Docetaxel in NSCLC) trial assessed second-line docetaxel plus vandetanib *versus*

**TABLE 2** Recent phase III trials assessing antiangiogenic agents in a second- or third-line setting

| Agent and study name [ref.] | Target (s) | Study design | Overall response rate | Progression-free survival | Overall survival |
|---|---|---|---|---|---|
| **Multi-targeted antiangiogenic orally administered TKIs** | | | | | |
| Nintedanib; LUME-Lung 1 [44] | VEGF-1–3, PDGF-α and β, and FGFR-1–3 | Stage IIIB/IV NSCLC all histologies. Patients randomised to: docetaxel (n=659) or docetaxel + nintedanib (200 mg twice daily; n=655). Primary end-point: progression-free survival | Overall response rate not reported. DCR was significantly greater in the docetaxel + nintedanib arm in patients with adenocarcinoma (p<0.0001) | Docetaxel: 2.7 months. Docetaxel + nintedanib: 3.4 months. HR 0.79 (CI 0.68–0.92); p=0.002 | In patients with adenocarcinoma: Docetaxel: 10.3 months. Docetaxel + nintedanib: 12.6 months. HR 0.83; p=0.036. In overall population: Docetaxel: 9.1 months. Docetaxel + nintedanib: 10.1 months. HR 0.94; p=0.272 |
| Nintedanib; LUME-Lung 2 [45] | VEGF-1–3, PDGF-α and β, and FGFR-1–3 | Stage IIIB/IV non-squamous NSCLC. Patients randomised to: pemetrexed (n=360) or pemetrexed + nintedanib (200 mg twice daily; n=353). Primary end-point: progression-free survival | No difference in overall response rate between pemetrexed and pemetrexed + nintedanib (9%). Pemetrexed: DCR 53%. Pemetrexed + nintedanib: DCR 61% (p=0.039) | Pemetrexed: 3.6 months. Pemetrexed + nintedanib: 4.4 months. HR 0.83 (95% CI 0.7–0.99); p=0.04 | No significant difference (median values NR) |
| Vandetanib; ZODIAC [46] | VEGFR-1 and -2, RET and EGFR | Stage IIIB/IV NSCLC all histologies. Patients randomised to docetaxel (n=697) or docetaxel + vandetanib (100 mg·day⁻¹; n=694). Primary end-point: progression-free survival | Docetaxel: 10%. Docetaxel + vandetanib: 17% (p=0.0001) | Docetaxel: 3.2 months. Docetaxel + vandetanib: 4.0 months. HR 0.79 (97.6% CI 0.70–0.90); p<0.0001 | Docetaxel: 10.0 months. Docetaxel + vandetanib: 10.6 months. HR 0.91 (97.5% CI 0.78–1.07); p=0.196 |
| Vandetanib; ZEAL [47] | VEGFR-1 and -2, RET and EGFR | Stage IIIB/IV NSCLC all histologies. Patients randomised to: pemetrexed (n=278) or pemetrexed + vandetanib (100 mg·day⁻¹; n=256). Primary end-point: progression-free survival | Pemetrexed: 8%. Pemetrexed + vandetanib: 19% (p<0.001) | Pemetrexed: 11.9 weeks. Pemetrexed + vandetanib: 17.6 weeks. HR 0.86 (97.6% CI 0.69–1.06); p=0.108 | Pemetrexed: 9.2 months. Pemetrexed + vandetanib: 10.5 months. HR 0.86 (97.5% CI 0.65–1.13); p=0.219 |
| Vandetanib; ZEPHYR [48] | VEGFR-1 and -2, RET and EGFR | Stage IIIB/IV NSCLC all histologies. Pre-treated with EGFR inhibitor and one or two chemotherapy regimens. Patients randomised to: placebo (n=307) or vandetanib (300 mg·day⁻¹; n=617). Primary end-point: overall survival | Placebo: 0.7%. Vandetanib: 2.6% (p=0.028) | Placebo: 1.8 months. Vandetanib: 1.9 months. HR 0.63 (95.2% CI 0.54–0.74); p<0.001 | Placebo: 7.8 months. Vandetanib: 8.5 months. HR 0.95 (95.2% CI 0.81–1.11); p=0.527 |
| Vandetanib; ZEST [49] | VEGFR-1 and -2, RET and EGFR | Stage IIIB/IV NSCLC all histologies. Patients randomised to: erlotinib (150 mg·day⁻¹; n=617) or vandetanib (300 mg·day⁻¹; n=623). Primary end-point: progression-free survival | Erlotinib: 12%. Vandetanib: 12% (p=0.98) | Erlotinib: 2.0 months. Vandetanib: 2.6 months. HR 0.98 (95.2% CI 0.87–1.10); p=0.721 | Erlotinib: 7.8 months. Vandetanib: 6.9 months. HR 1.01 (95.1% CI 0.89–1.16); p=0.830 |
| Sorafenib; MISSION [50] | VEGFR-2–3, PDGFR-β, c-kit, Raf and flt-3 | Stage IIIB/IV non-squamous NSCLC. Patients randomised to: placebo (n=353) or sorafenib (400 mg twice daily; n=350). Primary end-point: overall survival | Placebo: 0.9%. Sorafenib: 4.9% (p<0.001) | Placebo: 43 days. Sorafenib: 84 days. HR 0.61; p<0.0001 | Placebo: 253 days. Sorafenib: 248 days. HR 0.99; p=0.4687 |
| Sunitinib [51] | VEGF-1–3, PDGFR-α and β, and RET | Stage IIIB/IV NSCLC all histologies. Patients randomised to: erlotinib (150 mg·day⁻¹; n=480) or erlotinib + sunitinib (37.5 mg·day⁻¹; n=480). Primary end-point: overall survival | Erlotinib: 6.9%. Erlotinib + sunitinib: 10.6% (p=0.048) | Erlotinib: 2.0 months. Erlotinib + sunitinib: 3.6 months. HR 0.81 (95% CI 0.70–0.94); p=0.0023 | Erlotinib: 8.5 months. Erlotinib + sunitinib: 9.0 months. HR 0.92 (95% CI 0.80–1.07); p=0.139 |
| **Monoclonal antibodies, decoy receptors** | | | | | |
| Bevacizumab; BeTa [52] | VEGF | Stage IIIB/IV NSCLC all histologies. Patients randomised to: erlotinib (150 mg·day⁻¹; n=317) or erlotinib + bevacizumab (n=319). Primary end-point: progression-free survival | Erlotinib: 6%. Erlotinib + bevacizumab: 13% (p-value NR) | Erlotinib: 1.7 months. Erlotinib + bevacizumab: 3.4 months. HR 0.62 (95% CI 0.52–0.75); p-value NR | Erlotinib: 9.2 months. Erlotinib + bevacizumab: 9.3 months. HR 0.97 (95% CI 0.80–1.18); p=0.758 |
| Aflibercept; VITAL [53] | VEGF | Non-squamous NSCLC. Patients randomised to: docetaxel (n=457) or docetaxel + aflibercept (6 mg·day⁻¹; n=456). Primary end-point: overall survival | Docetaxel: 8.9%. Docetaxel + aflibercept: 23.3% (p<0.001) | Docetaxel: 4.1 months. Docetaxel + aflibercept: 5.2 months. HR 0.82 (95% CI 0.72–0.94); p=0.0035 | Docetaxel: 10.4 months. Docetaxel + aflibercept: 10.1 months. HR 1.01 (95% CI 0.87–1.17); p=0.9 |

TKI: tyrosine kinase inhibitor; ZODIAC: Zactima in Combination with Docetaxel in NSCLC; ZEAL : Zactima Efficacy with Alimta in Lung Cancer; ZEPHYR: Zactima Efficacy Trial for NSCLC Patients with a History of EGFR-TKI and Chemoresistance; ZEST: Zactima Efficacy Study *versus* Tarceva; VEGF: vascular endothelial growth factor; PDGF: platelet-derived growth factor; FGFR: fibroblast growth factor receptor; VEGFR: VEGF receptor; EGFR: epidermal growth factor receptor; PDGFR: PDGF receptor; NSCLC: nonsmall cell lung cancer; NR: not reported; DCR: disease control rate; HR: hazard ratio.

docetaxel alone [46]. A significant improvement in median PFS was observed in the combination arm (HR 0.83, 95% CI 0.70–99; 4.0 months *versus* 3.2 months; p<0.0001), but there was no significant improvement in overall survival (HR 0.91, 97.5% CI 0.78–1.07; 10.6 months *versus* 10.0 months; p=0.196). The ZEAL (Zactima Efficacy with Alimta in Lung Cancer) trial assessed second-line pemetrexed plus vandetanib *versus* pemetrexed alone [47]. In this trial there was no significant improvement in either PFS (HR 0.86, 95% CI 0.69–1.06; 17.6 weeks *versus* 11.9 weeks; p=0.108) or overall survival (HR 0.86, 95% CI 0.65–1.13; 10.5 months *versus* 9.2 months; p=0.219). Similarly, in the ZEST (Zactima Efficacy Study *versus* Tarceva) trial, the use of vandetanib instead of erlotinib did not confer any survival advantage [49]. Vandetanib was also assessed in a third-line setting in the ZEPHYR (Zactima Efficacy Trial for NSCLC Patients with a History of EGFR-TKI and Chemoresistance) trial [48]. In this study, vandetanib conferred a small but significant improvement in PFS (HR 0.63, 95% CI 0.54–0.74; 1.9 months *versus* 1.8 months; p<0.001), but no improvement in overall survival *versus* placebo (HR 0.95, 95% CI 0.81–1.11; 8.5 months *versus* 7.8 months; p=0.527). The adverse event profile of vandetanib was consistent across studies; rates of diarrhoea, rash and hypertension were higher than observed in control arms.

### Sorafenib

A recent phase III study assessed third-line sorafenib monotherapy *versus* placebo in patients with non-squamous NSCLC (the MISSION trial) [50]. Sorafenib conferred a significant improvement in median PFS (HR 0.61; 84 days *versus* 43 days; p<0.0001), but not overall survival, *versus* placebo (HR 0.99; 248 days *versus* 253 days; p=0.469). Rates of all (99% *versus* 91%) and serious adverse events (39% *versus* 32%) were higher in the sorafenib group. A phase II trial has assessed sorafenib plus pemetrexed in a second-line setting in a phase II trial with disappointing results [60]. Neither overall survival nor PFS were improved in patients given sorafenib plus pemetrexed *versus* pemetrexed alone, although *post hoc* analysis suggested a marginal PFS benefit with the combination in patients who had previously received bevacizumab.

### Sunitinib

Sunitinib (Sutent; Pfizer) is a TKI that inhibits VEGF1–3, PDGFR-α and β, and RET [61]. A recent phase III study assessed second-line sunitinib plus erlotinib *versus* erlotinib alone in patients with advanced NSCLC [51]. Median PFS (HR 0.81, 95% CI 0.70–0.94; 3.6 months *versus* 2.0 months; p=0.0023) but not median overall survival (HR 0.92, 95% CI 0.80–1.07; 9.0 months *versus* 8.5 months; p=0.139) was significantly improved in the sunitinib plus erlotinib arm *versus* erlotinib alone. Grade ⩾3 treatment related adverse events that were more common in the sunitinib arm included rash/dermatitis (17.4% *versus* 9.6%), diarrhoea (15.8% *versus* 2.9%) and asthenia/fatigue (8.0% *versus* 3.3%). A phase II study demonstrated that the addition of sunitinib to pemetrexed did not improve survival outcomes *versus* pemetrexed alone; indeed, sunitinib had a detrimental impact on overall survival and tolerability [62].

### *Monoclonal antibodies/decoy receptors*
### Bevacizumab

A recent phase III study assessed bevacizumab with or without erlotinib in a second-line setting [52]. Although median PFS was greater in the bevacizumab arm (HR 0.62, 95% CI 0.52–0.75; 3.4 months *versus* 1.7 months), the trial did not achieve its primary end-point of improved median overall survival (HR 0.97, 95% CI 0.80–1.18; 9.3 months *versus* 9.2 months). In the bevacizumab arm, 42% of patients had a serious adverse event compared with 36% of controls. There were 20 (6%) grade 5 adverse events, including two arterial thromboembolic events in the bevacizumab arm, and 14 (4%) in the control arm. Ongoing studies are assessing the feasibility of combining bevacizumab with pemetrexed or docetaxel in a second-line setting.

### Aflibercept

Disappointing results have also been obtained with agents other than TKIs. Aflibercept is a novel recombinant protein designed to act as soluble decoy receptor for VEGF, thus preventing it from binding to its receptors. A recent phase III trial assessed aflibercept plus docetaxel *versus* docetaxel alone in 913 patients with advanced NSCLC who had progressed following first-line chemotherapy [53]. Aflibercept improved median PFS (HR 0.82, 95% CI 0.72–0.94; 5.2 months *versus* 4.1 months; p=0.004) but not median overall survival (HR 1.01, 95% CI 0.87–1.17; 10.1 months *versus* 10.4 months; p=0.9) and it was associated with increased adverse events. Grade ⩾3 adverse events that occurred more frequently in the aflibercept arm *versus* the placebo arm were neutropenia (28% *versus* 21%), fatigue (11% *versus* 4%), stomatitis (9% *versus* <1%) and hypertension (7% *versus* <1%).

*Vascular disrupting agents*
Vadimezan

A phase III trial assessed docetaxel with or without vadimezan in a second-line setting in patients with advanced NSCLC; the trial was terminated based on an interim analysis that showed no increase in overall survival benefit [63].

## Other investigational antiangiogenic agents in NSCLC

Despite recent failures, the major unmet clinical need for additional treatment in NSCLC continues to drive the clinical development of novel antiangiogenic agents in both first-line and relapsed/refractory settings. Several agents currently being assessed in clinical trials are described below.

### Ramucirumab

Ramucirumab is a monoclonal antibody that specifically binds VEGFR2 [64]. Preliminary data from a phase II trial that assessed ramucirumab plus carboplatin/paclitaxel in a first-line setting were encouraging, with a 67% response rate reported [65]. In this study, two patients reported serious adverse events possibly related to ramucirumab: grade 4 febrile neutropenia and grade 2 pneumothorax. Another phase II trial to assess ramucirumab in a first-line setting in combination with four different chemotherapy regimens is currently recruiting patients [66]. In addition, the ongoing phase III trial REVEL (Randomized Evaluation of the Effects of Anacetrapib Through Lipid-modification) is assessing ramucirumab plus docetaxel *versus* docetaxel alone in patients who have progressed following platinum chemotherapy [67].

### Cediranib

Cediranib in combination with pemetrexed has recently been assessed in a phase II trial of patients with relapsed/refractory NSCLC (who may or may not have been treated with bevacizumab). A promising response rate of 35%, PFS of 5.6 months and overall survival of 11.5 months was observed in patients with non-squamous histology [68]. Grade 3/4 toxicities included neutropenia (14%), febrile neutropenia (5%), fatigue (22%), diarrhoea (14%) and infection (8%). One patient each developed a pulmonary haemorrhage, cardiac ischaemia and a cerebrovascular event.

### Pazopanib

Pazopanib (Votrient; GlaxoSmithKline) is a TKI with activity against VEGFR1–3, PDGFR-$\alpha$/$\beta$ and c-kit [69]. A number of phase II trials are ongoing in patients with NSCLC including: first-line therapy plus paclitaxel, second-line therapy plus pemetrexed and maintenance therapy [70–72]. An early clinical trial demonstrated that pazopanib (800 mg per day) plus pemetrexed had preliminary activity in patients with advanced NSCLC [73]. The most common adverse events included fatigue, neutropenia, diarrhoea and thrombocytopenia. The rates of all grade and grade 4 haematological toxicities were higher with the combination regimen than with either monotherapy. A phase III trial assessed pazopanib monotherapy (800 mg per day) in patients with resectable stage I/II NSCLC (n=35) [74]. Three partial responses (8.6%) and 30 cases of stable disease (88.6%) were observed.

### Linifanib

Linifanib is a TKI that inhibits VEGFR1–3, PDGFR-$\beta$, c-Kit and FLT-3 [75]. A phase II study assessed linifanib monotherapy (two dose regimens) in a second-/third-line setting in 139 patients with advanced NSCLC; linifanib displayed modest clinical activity with an overall response rate of 5%, PFS of 3.6 months and overall survival of 9.0 months [76]. In this study, the most common linifanib-related adverse events were fatigue (42%), decreased appetite (38%), hypertension (37%), diarrhoea (32%), nausea (27%), palmar–plantar erythrodysesthesia (24%) and proteinuria (22%). These events were more common in the high-dose group. The most common linifanib-related grade 3 or 4 adverse event was hypertension (14%).

Another phase II study assessed paclitaxel/carboplatin with or without linifanib (7.5 mg or 12.5 mg) in previously untreated patients with advanced non-squamous NSCLC [77]. The addition of linifanib to chemotherapy was tolerable at the doses tested and resulted in a significant improvement in PFS (7.5 mg group: 8.3 months *versus* 5.4 months, p=0.022) and a modest trend towards survival improvement in the 12.5 mg group (13.0 months *versus* 11.3 months; p=nonsignificant) *versus* placebo.

## Outlook for antiangiogenic therapy in NSCLC

Some antiangiogenic agents have demonstrated efficacy in clinical trials. The approval of bevacizumab in combination with platinum chemotherapy has shown that antiangiogenic agents can improve outcomes in a first-line setting. Moreover, recent data indicate that nintedanib, a triple kinase inhibitor, can improve survival when added to docetaxel as a second-line treatment of patients with lung adenocarcinoma [44, 45].

To date, no other antiangiogenic agents have emerged to supplement the current armamentarium available for patients with advanced NSCLC, although several are in development. Thus, there remains a substantial requirement to identify new treatment options for these patients.

Given the biological rationale for targeting angiogenesis, and the clinical precedent of bevacizumab, why has there been such a high failure rate of trials that have assessed antiangiogenic agents in NSCLC? There are several possible explanations for this observation. First, agents may not effectively combat the redundancy of angiogenic pathways. Owing to the structural similarities of tyrosine kinases most small-molecule TKIs have inhibitory activity over a range of receptors. However, other than nintedanib, no agents with inhibitory potency over all subtypes of VEGFR, PDGFR and FGFR have been tested in a phase III trial. Secondly, the TKIs tested to date may not completely inhibit signalling *via* their target receptors [9]. It is possible that agents with more favourable pharmacological profiles may be effective at completely abrogating, rather than downregulating, signalling *via* proangiogenic pathways. Finally, owing to the highly heterogeneous nature of NSCLC, it is probable that certain patients are more likely to respond to antiangiogenic agents than others. In several diseases, validated biomarkers have been identified for specific subgroups of patients who have a high probability of responding to a particular agent. Clinical experience with EGFR inhibitors suggests that antiangiogenic agents will be most effective against tumours with specific molecular characteristics. In recent years, significant progress has been made in identifying disease variants according to histological subtype or genetic characterisation of tumours [78, 79]. Drugs have been identified that work effectively in a subset of patients defined by genetic variants, *e.g.* afatinib, erlotinib and gefitinib in patients with activating EGFR mutations. Biomarkers are urgently required for antiangiogenic agents and are a focus of intensive research.

Another important consideration for the development and application of antiangiogenic agents in NSCLC is their characteristic adverse event profiles [80]. Generally, targeted agents are much better tolerated than chemotherapy and are associated with lower incidences of cytopenia. However, most antiangiogenic agents may be associated with class-specific adverse events such as hypertension, haemorrhage or venous thromboembolism. The risk of such events may preclude treatment in some patients. Therefore, it is important that accumulated safety data are considered for emerging agents and factors that predict the risk of adverse events are identified.

## Conclusions

Available treatment options for advanced NSCLC have limited efficacy, with few advances in clinical trials over the past decade leaving a substantial unmet medical need for new treatment options. There is a biological and clinical rationale for targeting angiogenesis in patients with advanced NSCLC, as demonstrated by the approval of bevacizumab and recent encouraging phase III data with nintedanib. Future priorities for the development of antiangiogenic agents in NSCLC include the development of drugs that effectively and potently inhibit a network of proangiogenic signals. Further biological studies are required to understand the pathogenesis of NSCLC in order to facilitate the identification of prognostic and predictive biomarkers that could be routinely applied in clinical practice.

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