Review

CLINICAL INVESTIGATION

Angiokinase inhibitors in non-small-cell lung cancer

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Angiogenesis is an essential component of tumor growth and metastasis. To date, an anti-VEGF antibody, bevacizumab, in combination with paclitaxel and carboplatin in the first-line setting is the only approved antiangiogenic treatment in non-small-cell lung cancer (NSCLC). Angiokinase inhibitors are oral small-molecule agents. They not only inhibit the VEGF pathway, but also target other important signaling pathways contributing to angiogenesis: the PDGF and FGF pathways. Several angiokinase inhibitors have been studied or are in investigations for the treatment of NSCLC, and we review the current developmental status and future perspectives of these inhibitors (including sorafenib, sunitinib, motesanib and nintedanib) in NSCLC.

Keywords: angiokinase inhibitors • antiangiogenesis • non-small-cell lung cancer • predictive biomarker • tyrosine kinase inhibitors

Lung cancer is the leading cause of death from cancer worldwide [1]. Non-small-cell lung cancer (NSCLC) accounts for more than 80% of lung cancers [2], and many patients with advanced or metastatic disease have poor survival. First-line chemotherapy with platinum-doublet therapy has been shown to improve survival in patients without driver mutations [3]. Currently approved second-line treatments in patients with no/unknown driver mutations are monotherapy with docetaxel [4], erlotinib [5] or pemetrexed [6]. However, Phase III trials showed low response rates (RRs; less than 10%) and modest survival benefits with these agents. The overall survival (OS) was only 6–9 months. There is an unmet medical need for more effective treatments for patients with NSCLC.

Angiogenesis is a key process for tumor growth and metastases. Among the factors involved in tumor angiogenesis, VEGF has been the most extensively studied [7]. VEGF, the ligand of VEGFR, is the central mediator of angiogenesis, and overexpression of VEGF has been shown to be associated with poor prognosis in NSCLC patients [8–11]. Thus, targeting angiogenesis may be a promising therapy for patients with NSCLC. Figure 1 summarizes the anticancer effects of such antiangiogenic agents.

Generally, a balance of proangiogenic and antiangiogenic signals maintains an organized and efficient vasculature and blood supply in tissues. Tumors may produce proangiogenic factors that cause abnormal vasculature and inefficient blood supply. As a result, chemotherapeutic agents cannot penetrate into the tumor because of poor blood supply and a 'high interstitial fluid pressure'. When an antiangiogenic agent is administered, the therapy can achieve 'vascular normalization' and enhance drug delivery. Finally, the vascular network may be completely destroyed via potent and persistant antiangiogenesis. This 'starves' the tumor [12–15]. Furthermore, since a high VEGF level is linked to cancer-associated systemic syndrome, which may present with cachexia or paraneoplastic syndrome, anti-VEGF therapy may prolong survival via 'off-tumor target' effects. Some preclinical and clinical evidence suggests the potential benefits (relieving cancer-associated systemic syndrome) and harms (endocrinopathy) of

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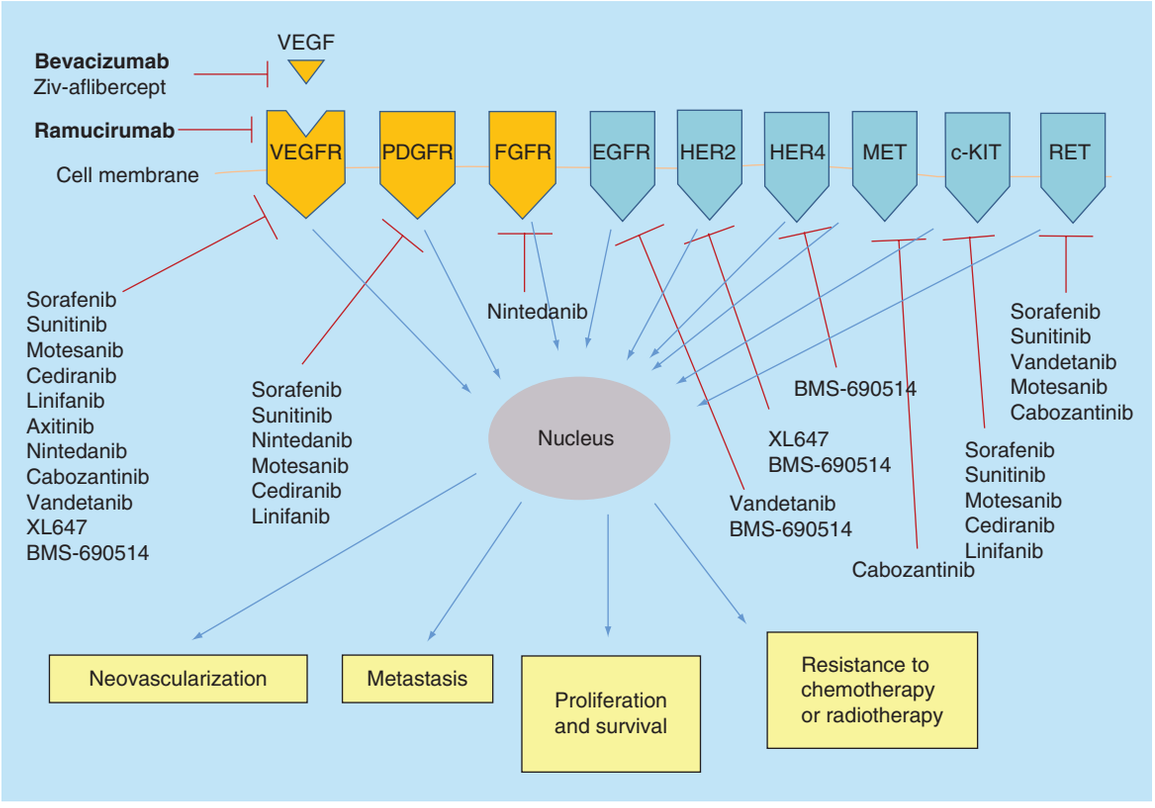

Figure 1. Antiangiogenic agents that interfere with tumor formation. Antiangiogenic tyrosine kinase inhibitors, monoclonal antibodies or recombinant fusion proteins inhibit the signal transduction involved in angiogenesis, proliferation, survival, metastasis or resistance to therapy. The key pathways of angiogenesis are the VEGFR, FGFR and PDGFR pathways.

the 'off-tumor target' effects of antiangiogenic therapy [15–17]. These are some of the postulated mechanisms of antiangiogenic therapy.

Bevacizumab is an anti-VEGF monoclonal antibody and it has documented survival benefit in combination with first-line paclitaxel and carboplatin for advanced non-squamous NSCLC patients. According to a Phase III trial (E4599), patients received bevacizumab in addition to chemotherapy (paclitaxel and carboplatin) have a median OS of 12.3 months, compared with 10.3 months in those receiving chemotherapy alone (hazard ratio [HR] for death: 0.79; p = 0.003) [18]. However, another Phase III trial (AVAiL) did not show a significant OS benefit when adding bevacizumab to gemcitabine and cisplatin in patients with advanced NSCLC [19,20]. An open-label, Phase II Japanese study (J025567) randomized 154 advanced or recurrent chemotherapy-naive nonsquamous NSCLC patients with activating *EGFR* mutations to bevacizumab–erlotinib or erlotinib alone. Compared with erlotinib alone, progression-free survival (PFS) was significantly prolonged by adding bevacizumab to erlotinib (16.0 vs 9.7 months; HR: 0.54; p = 0.0015). The OS data were not mature [21].

Ziv-aflibercept is a recombinant fusion protein that also targets VEGF. Improved RRs and PFS but not OS of docetaxel plus ziv-aflibercept over docetaxel alone have been demonstrated in platinum-pretreated nonsquamous NSCLC patients [22].

Recently, ramucirumab, a human IgG1 monoclonal antibody against VEGFR2, was to have an OS benefit (10.5 vs 9.1 months; HR: 0.857; p = 0.0235) in the second-line setting in combination with docetaxel versus docetaxel alone [23]. Ramucirumab is the first agent to improve OS of NSCLC patients in the second-line setting compared with chemotherapy alone. Table 1 summarizes the results of Phase III studies of antiangiogenic antibodies and fusion protein in NSCLC. Recombinant human endostatin (endostar) is an agent made in China that inhibits tumor endothelial cell proliferation, angiogenesis and tumor growth. A Phase III study showed the combination of this agent with vinorelbine–cisplatin provided longer times to tumor progression and RRs as compared with vinorelbine–cisplatin alone for advanced NSCLC patients [24]. It is routinely used in combination with chemotherapy in China.

In addition to VEGF, PDGF and FGF are important factors of neovascularization. Upregulation of the

PDGFR and FGFR pathways may provide resistance to anti-VEGF therapy [25–27]. Therefore, targeting multiple angiokinases (e.g., blocking the VEGF, PDGF and FGF pathways through tyrosine kinase) is a reasonable therapeutic approach rather than targeting a single VEGF pathway. Exploration of new compounds that inhibit multiple angiokinase pathways is important to provide therapeutic efficacy with reasonable safety and tolerability.

This article will summarize recent advances and the clinical development of angiokinase inhibitors (Table 2) for the treatment of advanced NSCLC.

Multitargeted angiokinase inhibitors in NSCLC

Sorafenib

Sorafenib (Nexavar®, BAY 43-9006; Bayer Pharmaceuticals Corp., CT, USA) is a small-molecule tyrosine kinase inhibitor (TKI) of VEGFR1, 2 and 3, Raf, PDGFR-β, c-KIT, FLT-3 and RET [28]. Sorafenib was approved for the treatment of advanced renal cell carcinoma, hepatocellular carcinoma and differentiated thyroid cancer based on the results of three large Phase III trials: TARGET [29], SHARP [30] and DECISION [31]. Common side effects are hand–foot syndrome, diarrhea, rash, alopecia and nausea.

For advanced NSCLC, two Phase III trials of first-line chemotherapy (paclitaxel–carboplatin in ESCAPE and gemcitabine/cisplatin in NExUS) alone or in combination with sorafenib did not demonstrate an OS benefit. Furthermore, shorter OS was found in squamous NSCLC with the combination treatment in the ESCAPE trial, so patients with squamous histology were excluded in NExUS and subsequent trials [32,33].

For previously treated patients (two or more prior therapies), E2501, a Phase II double-blind randomized discontinuation trial, demonstrated a better 2-month disease control rate (DCR) in the sorafenib group after randomization (54 and 23% for patients initially receiving sorafenib and placebo, respectively, p = 0.005; HR for progression: 0.51; 95% CI: 0.30–0.87; p = 0.014). A trend towards better OS

Table 1. Results of Phase III studies of antiangiogenic antibodies and fusion protein in non-small-cell lung cancer.

Agent, study name	Mode of action	Study design	Primary end point	RR	PFS	OS
Bevacizumab, E4599 [18]	VEGF-A monoclonal antibody	Stage IIIb/IV nonsquamous NSCLC patients randomized to: paclitaxel–carboplatin–bevacizumab (15 mg/kg; n = 434) or paclitaxel–carboplatin (n = 444)	OS	35 vs 15% (p < 0.001)	6.2 vs 4.5 months (HR: 0.66; p < 0.001)	12.3 vs 10.3 months (HR: 0.79; p < 0.003)
Bevacizumab, AVAiL [19,20]	VEGF-A monoclonal antibody	Stage IIIb/IV nonsquamous NSCLC patients randomized to: gemcitabine–cisplatin–placebo (n = 347) or gemcitabine–cisplatin–bevacizumab (7.5 mg/kg; n = 345) or gemcitabine–cisplatin–bevacizumab (15 mg/kg; n = 341)	PFS	20.1 vs 34.1 vs 30.4% (p < 0.0001 and p = 0.0023, respectively)	6.1 vs 6.7 vs 6.5 months (HR: 0.75, p = 0.003 and HR: 0.82, p = 0.03, respectively)	13.1 vs 13.6 vs 13.4 months (HR: 0.92, p = 0.420 and HR: 1.03, p = 0.761, respectively)
Ramucirumab, REVEL [23]	VEGFR2 IgG1 monoclonal antibody	Advanced squamous or nonsquamous NSCLC patients who had progressed during or after first-line platinum-based chemotherapy randomized to: ramucirumab–docetaxel (n = 628) or placebo–docetaxel (n = 625)	OS	23 vs 14% (p < 0.0001)	4.5 vs 3.0 months (HR: 0.76; p < 0.0001	10.5 vs 9.1 months (HR: 0.86; p = 0.023)
Ziv-aflibercept, VITAL [22]	Recombinant fusion protein that targets VEGF ('VEGF trap') and PGF	Advanced nonsquamous NSCLC patients who had progressed during or after first-line platinum-based chemotherapy randomized to: ziv-aflibercept–docetaxel (n = 456) or placebo–docetaxel (n = 457)	OS	23.3 vs 8.9% (p < 0.001)	5.2 vs 4.1 months (HR: 0.82; p = 0.0035)	10.1 vs 10.4 months (HR: 1.01; p = 0.9)

HR: Hazard ratio; NSCLC: Non-small-cell lung cancer; OS: Overall survival; PFS: Progression-free survival; RR: Response rate.

Table 2. Angiokinase inhibitors and their targets.

Agent	VEGFR1	VEGFR2	VEGFR3	PDGFR	FGFR	KIT	EGFR	Other targets
Sorafenib	•	•	•	•	–	•	–	FLT-3, RET, RAF
Sunitinib	•	•	•	•	–	•	–	FLT-3, RET, CSF-1R
Motesanib	•	•	•	•	–	•	–	RET
Cediranib	•	•	•	•	–	•	–	–
Linifanib	•	•	•	•	–	•	–	FLT-3
Axitinib	•	•	•	–	–	–	–	–
Nintedanib	•	•	•	•	•	–	–	–
Cabozantinib	–	•	–	–	–	–	–	MET, RET, KIT, FLT-3
Vandetanib	–	•	•	–	–	–	•	RET
XL647	–	•	–	–	–	–	•	HER-2, EphB4
BMS-690514	•	•	•	–	–	–	•	HER-2, HER-4

The dots represent inhibitors that have those targets. The dash line represents inhibitors that do not have those targets.

with sorafenib was also observed (13.7 vs 9.0 months; HR: 0.67; 95% CI: 0.40–1.11).

Sorafenib in combination with EGFR TKIs may overcome resistance to EGFR TKIs. A Phase II randomized US study in 168 patients with advanced NSCLC (two or more prior therapies) showed a higher DCR (54 vs 38%; p = 0.056) in the sorafenib/erlotinib arm. In 67 patients with wild-type *EGFR*, median PFS was 3.38 months for the combination arm versus 1.77 months for the control arm (p = 0.018). Median OS was 8 months for the combination arm versus 4.5 months for the control arm (p = 0.019) with wild-type *EGFR* [34].

Third- or fourth-line treatment with sorafenib alone has been evaluated in a Phase III trial (MISSION). This trial enrolled 703 patients with advanced nonsquamous NSCLC (two or three prior treatments). Although improved PFS and RRs were demonstrated, the primary end point (OS improvement) was not met (248 vs 253 days; p = 0.4687) [35].

Sunitinib

Sunitinib (Sutent®, SU11248; Pfizer, Inc., NY, USA) is a TKI of VEGFR1, 2 and 3, PDGFR, c-KIT, FLT-3, RET and CSF-1R [36]. Sunitinib was approved for the treatment of advanced renal cell carcinoma [37], imatinib-resistant or -intolerant gastrointestinal stromal tumors [38] and advanced pancreatic neuroendocrine tumors according to Phase III trials [39]. Common side effects are diarrhea, fatigue, nausea, hypertension, hand–foot syndrome, neutropenia, thrombocytopenia and anemia.

In a Phase II study of 63 patients with advanced NSCLC who were pretreated with platinum-based chemotherapy, 50 mg/day of sunitinib was used for 4 weeks followed by 2 weeks off. An overall RR of 11.1% and 28.6% stable disease (SD) were achieved. The median PFS was 12 weeks and median OS was 23.4 weeks. Fatigue (29%), pain/myalgia (17%), nausea/vomiting (10%) and dyspnea (11%) were commonly reported grade 3 or 4 adverse events (AEs) [40]. In another Phase II study, of 47 patients with pretreated NSCLC received continuous doses of sunitinib of 37.5 mg/day, only one demonstrated a partial response (PR) and 11 had SD (23.4%). The median PFS was 11.9 weeks and median OS was 37.1 weeks. Grade 3 or 4 AEs included fatigue (17.0%), hypertension (8.5%) and dyspnea (6.4%) [41].

In the Phase II CALGB30704 trial, 130 patients with progressive NSCLC after first-line treatment were randomized to pemetrexed, sunitinib or the combination. The 18-week PFS rates (the primary end point) in the pemetrexed, sunitinib and combination arms were 54% (95% CI: 40–71), 37% (95% CI: 25–54) and 48% (95% CI: 35–66), respectively (p = 0.25). The pemetrexed arm showed a longer median OS (pemetrexed: 10.5 months; sunitinib: 8.0 months; and combination: 6.7 months; p = 0.03), as well as a better toxicity profile [42]. SUN1087 is a Phase III trial of sunitinib 37.5 mg/day plus erlotinib 150 mg/day in comparison with erlotinib alone. It enrolled 960 relapsed NSCLC patients and the primary end point of OS. Statistically significant improvements in PFS (3.6 vs 2.0 months; p = 0.0023) were shown, but there was only a trend in OS benefit (9.0 vs 8.5 months; p = 0.1388). The combination treatment arm had more grade 3 or 4 toxicities [43].

Motesanib

Motesanib (AMG 706; Amgen, CA, USA) is a VEGFR1, 2 and 3, PDGFR, KIT and RET inhibitor [44]. A Phase Ib study of motesanib plus

carboplatin–paclitaxel with or without panitumumab for advanced NSCLC enrolled 31 patients with untreated disease and 14 patients with prior chemotherapy. The maximum tolerated dose (MTD) was 125 mg once daily. The dose-limiting toxicities were grade 4 pulmonary embolism and grade 3 deep vein thrombosis. Common AEs related to motesanib were fatigue (60%), diarrhea (53%), hypertension (38%), anorexia (27%) and nausea (22%). The objective RR of motedanib in combination with chemotherapy with or without panitumumab was 17% [45].

A Phase II trial randomized 186 patients with advanced nonsquamous NSCLC to paclitaxel–carboplatin plus motesanib 125 mg every day (arm A), motesanib 75 mg twice daily for 5 days on/2 days off (arm B) or bevacizumab 15 mg/kg every 3 weeks (arm C). The primary end point was objective RR. Objective RRs in the three arms were as follows: arm A, 30% (95% CI: 18–43); arm B, 23% (95% CI: 13–36); and arm C, 37% (95% CI: 25–50). The median PFS in arm A was 7.7 months, arm B was 5.8 months and arm C was 8.3 months; the median OS for arm A was 14.0 months, arm B was 12.8 months and arm C was 14.0 months. The incidence of AEs was greater in arms A and B than in arm C. More grade 5 AEs not attributable to progressive disease occurred in arm B (n = 10) than in arm A (n = 4) and arm C (n = 4). The efficacy of motesanib 125 mg every day or bevacizumab plus paclitaxel–carboplatin was comparable [46].

The Phase III MONET-1 trial compared motesanib 125 mg/day plus paclitaxel–carboplatin with chemotherapy alone in untreated patients. Because of a higher early mortality and gross hemoptysis in patients with squamous cell carcinoma, the study was halted temporarily and restarted in order to enroll only patients with nonsquamous histology. A total of 1090 patients (890 patients with adenocarcinoma) were randomized, and 448 patients received motesanib–paclitaxel–carboplatin. The combination arm did not have significantly longer OS (13.5 vs 11.0 months; HR: 0.88; 95% CI: 0.75–1.03; p = 0.11) [47]. Nevertheless, in the preplanned subset analysis, Asian patients has superior median PFS (7 vs 5.3 months; p = 0.0004) and OS (20.9 vs 14.5 months; p = 0.0004) in the motesanib–paclitaxel–carboplatin arm in comparison to the placebo–paclitaxel–carboplatin arm, as well as a higher objective RR (62 vs 27%; p < 0.0001) [48]. Based on these promising results, another Phase III study with a similar design in Asian patients is ongoing (MONET-A study; JPRN-JapicCTI-121887).

Cediranib

Cediranib (Recentin®, AZD2171; AstraZeneca Pharmaceuticals, DE, USA) is a VEGFR1, 2 and 3, PDGFR and c-KIT inhibitor [49]. In a Phase I trial, 30 or 45 mg of cediranib was used in combination with paclitaxel and carboplatin in 20 previously untreated NSCLC patients. Common AEs of the combination included fatigue, diarrhea, anorexia, neutropenia and manageable hypertension. In the 20 evaluable patients, there were nine (45%) confirmed responses. The 30-mg dose of cediranib was selected in subsequent Phase II trials [50].

A randomized Phase II trial (BR24) assessed the efficacy and safety of cediranib with paclitaxel and carboplatin as a first-line therapy. Of the 296 NSCLC patients enrolled, the first 45 received cediranib 45 mg and the following 251 received cediranib 30 mg. In the primary Phase II analysis (30-mg cohort), the adjusted HR for PFS was 0.77 with a higher RR for cediranib (38 vs 16%; p < 0.0001). In spite of this efficacy, the addition of 30-mg cediranib to paclitaxel–carboplatin was not tolerable. Cediranib toxicity appeared to be dose related, with 30 mg being more tolerable than 45 mg. In addition, 37% of patients required dose modification to 20 mg [51]. Therefore, a subsequent Phase III trial (BR29) used cediranib 20 mg daily in combination with paclitaxel–carboplatin. The trial was halted for futility at the interim analysis (HR for PFS: 0.89; 95% CI: 0.66–1.20; p = 0.45). The addition of cediranib increased RR (52 vs 34%; p = 0.001), but did not significantly improve PFS or OS [52].

A study of second-line cediranib and pemetrexed showed promising activity in 38 recurrent NSCLC patients, with a RR of 35%, PFS of 5.7 months and OS of 11.5 months in nonsquamous histology. Grade 3 or 4 AEs included neutropenia, febrile neutropenia, fatigue, diarrhea and infection [53].

Linifanib

Linifanib (ABT869; Abbvie, IL, USA) is a TKI that inhibits VEGFR1, 2 and 3, PDGFR, c-KIT and FLT-3 [54]. In a Phase I trial, confirmed PRs were observed with single-agent linifanib in patients with metastatic NSCLC. The dose levels in the Phase II trial were chosen based on results from this Phase I trial, which identified the recommended Phase II high dose as 0.25 mg/kg. As activity was also observed at 0.10 mg/kg, this lower dose was also evaluated in the Phase II trial [55]. A Phase II trial evaluated linifanib monotherapy (0.1 or 0.25 mg/kg) in NSCLC patients with one to two prior lines of systemic therapy. In 139 patients with advanced NSCLC, linifanib showed modest clinical activity, with a RR of 5%, PFS of 3.6 months and OS of 9.0 months. The most common drug-related grade 3 or 4 AE was hypertension (14%) [56].

A randomized, three-arm Phase II trial assessed linifanib 7.5 mg, linifanib 12.5 mg or placebo with

paclitaxel–carboplatin as a first-line therapy for patients with advanced nonsquamous NSCLC. A total of 138 patients were randomized. The addition of linifanib to chemotherapy resulted in a significant improvement in PFS in the 7.5-mg arm versus placebo (8.3 vs 5.4 months; p = 0.022) and a trend toward an OS improvement in the 12.5-mg arm versus placebo (13.0 vs 11.3 months; p = 0.650). The combination therapy was tolerable. Thrombocytopenia was the only grade 3/4 AE that was significantly higher in linifanib (7.5 mg: 16.7%; 12.5 mg: 29.8%) versus placebo (2.1%). Other AEs related to the dose of linifanib were diarrhea, hypertension, weight loss, palmar–plantar erythrodysesthesia and hypothyroidism [57].

Axitinib

Axitinib (Inlyta®, AG-013736; Pfizer) is a selective TKI of VEGFR1, 2 and 3. It is approved as a second-line treatment for advanced renal cell carcinoma because the Phase III AXIS study demonstrated longer PFS with axitinib than with sorafenib [58].

Based on the antitumor effect (cavitation of lung lesions) in two NSCLC patients in a Phase I trial in advanced solid tumors [59], a Phase II trial of axitinib 5 mg monotherapy twice daily was conducted. Thirty-two patients with advanced NSCLC were enrolled and 23 had prior chemotherapy for metastatic disease. The major histologic type was adenocarcinoma (75%). Three patients (9%) had a confirmed PR, and the DCR was 41%. The median PFS and median OS were 4.9 and 14.8 months, respectively. Axitinib was well tolerated, and grade 3 AEs were fatigue (22%), hypertension (9%) and hyponatremia (9%) [60].

A randomized Phase II trial compared first-line axitinib–paclitaxel/carboplatin with bevacizumab–paclitaxel–carboplatin in advanced nonsquamous NSCLC. The trial was discontinued after the preliminary analysis because the axitinib arm did not demonstrate improved efficacy but had more toxicities [61]. Another randomized Phase II trial combining axitinib with first-line cisplatin–pemetrexed did not demonstrate significant survival benefits [62].

Nintedanib

In contrast to the above agents, nintedanib (BIBF 1120; Boehringer Ingelheim, Germany) is a 'triple-angiokinase inhibitor' that simultaneously acts on three key pathways involved in angiogenesis via VEGFRs, PDGFRs and FGFRs [63]. Theoretically, by inhibiting PDGFR/FGFR, nintedanib may overcome the antiangiogenic resistance developed by VEGFR inhibition.

In a Phase I study of advanced NSCLC patients after one prior platinum-based chemotherapy, the MTD of nintedanib plus pemetrexed was 200 mg twice daily. One patient who received 100 mg twice daily of nintedanib and pemetrexed had a complete response for more than 3.5 years [64]. Another Phase I study also showed that the MTD was 200 mg twice daily in combination with paclitaxel–carboplatin in untreated patients. Among the 26 patients, seven (26.9%) had a confirmed PR and ten (38.5%) had SD [65].

A Phase II trial evaluated the efficacy of nintedanib (150 or 250 mg twice daily) in NSCLC patients in whom first- or second-line platinum-based chemotherapy had failed. The median PFS was 6.9 weeks, with no significant difference between treatment arms. The median OS was 21.9 weeks. Tumor stabilization was achieved in 46% of patients (Eastern Cooperative Oncology Group [ECOG] performance status 0–1 patients: 59%), with one confirmed PR (250 mg twice daily). Three patients had a clinical benefit for more than 1 year, and one (on 250 mg twice daily) had a 74% reduction in tumor size (PR) for up to 9 months. The most commonly reported drug-related AEs were nausea (57.5%), diarrhea (47.9%), vomiting (42.5%), anorexia (28.8%), abdominal pain (13.7%) and reversible liver enzyme elevation (~10%). Patients with ECOG performance statuses of 0 or 1 had a median PFS and OS of 2.7 and 8.7 months, respectively [66].

The Phase III LUME-Lung 1 study enrolled 1314 patients with recurrent NSCLC (adenocarcinoma: 50%; squamous cell carcinoma: 42%) who had received one prior chemotherapy. Patients were randomized to receive nintedanib–docetaxel or placebo–docetaxel. The study met its primary end point (i.e., PFS). PFS was significantly improved in the nintedanib–docetaxel group compared with the active control group (median: 3.4 months [95% CI: 2.9–3.9] vs 2.7 months [95% CI: 2.6–2.8]; HR: 0.79 [95% CI: 0.68–0.92]; p = 0·0019). In a predefined analysis, OS was significantly longer for patients with adenocarcinoma who progressed within 9 months after initiation of the first-line treatment in the nintedanib–docetaxel group (median OS: 10.9 months [95% CI: 8.5–12.6] vs 7.9 months [95% CI: 6.7–9.1]; HR: 0.75 [95% CI: 0.60–0.92]; p = 0.0073). Similar results were noted for all patients with adenocarcinoma (median OS: 12.6 months [95% CI: 10.6–15.1] vs 10.3 months [95% CI: 8.6–12.2]; HR: 0.83 [95% CI: 0.70–0.99]; p = 0.0359), but not significant in the total study population. Common grade 3 or worse AEs in the combination group were diarrhea (6.6%) and an increase of liver enzymes (<10%) [67]. To date, LUME-Lung 1 study is the first trial in the second-line setting combining a targeted agent with chemotherapy in order to show an OS benefit. Since patients with relatively chemotherapy-refractory adenocarcinoma benefit

more from nintedanib–docetaxel, future study is warranted in order to investigate the predictive biomarkers of nintedanib use.

The Phase III LUME-Lung 2 trial evaluated the addition of nintedanib to pemetrexed for the second-line treatment of nonsquamous NSCLC. The study was halted prematurely after an interim futility analysis, although the primary end point of PFS favored the nintedanib arm (4.4 vs 3.6 months; HR: 0.83; p = 0.04). There was no difference in OS or RR [68].

Cabozantinib

Cabozantinib (Cometriq®, XL184; Exelixis, CA, USA) is an inhibitor of VEGFR2, MET, RET, KIT and FLT-3 [69]. As vandetanib, cabozantinib is approved for the treatment of medullary thyroid cancer according to a Phase III study [70]. MET is the only known receptor of HGF, and HGF and VEGF may synergistically promote angiogenesis. The HGF/MET pathway has a role in the development of resistance to VEGF pathway-targeted therapy. Therefore, cabozantinib, which simultaneously inhibits MET and VEGFR2, has the potential to overcome MET-driven resistance to agents targeting the VEGF pathway.

A Phase II randomized discontinuation trial evaluated cabozantinib in NSCLC patients who had received prior EGFR and VEGF pathway-targeted therapy. Antitumor activity with a PFS of 4.2 months and a RR of 10% was observed [71].

A California Cancer Consortium Phase II trial (NCI9303) showed that cabozantinib may overcome resistance to EGFR TKIs by inhibiting the VEGFR and MET pathways. In this study, patients with known *EGFR* mutations and progression on an EGFR TKI were enrolled. Thirty-five patients received daily erlotinib 150 mg plus cabozantinib 40 mg. There were four patients with PRs (two confirmed and two unconfirmed). Correlative studies are ongoing in order to determine the correlation of response with *MET* amplification and T790M mutations.

Vandetanib

Vandetanib (Zactima®, ZD6474; AstraZeneca, UK) is a TKI of VEGFR2 and 3, EGFR and RET, although the difference in the 50% inhibitory concentration for VEGFR and EGFR translates into the more potent inhibition of VEGFR [72]. It is approved for the treatment of advanced medullary thyroid cancer according to the results of the Phase III ZETA trial [73].

In the Phase III ZODIAC trial, patients with advanced NSCLC progressing after first-line chemotherapy were randomized to docetaxel plus vandetanib or docetaxel plus placebo. The primary end point was PFS. The combination arm showed a significant improvement in PFS (4 vs 3.2 months; HR: 0.79; p < 0.0001). The median OS rates of docetaxel plus vandetanib and of docetaxel plus placebo were 10.6 and 10.0 months, respectively (HR: 0.91; p = 0.196). Grade 3 or worse AEs (rash, neutropenia, leukopenia and febrile neutropenia) were more common with the combination treatment [74]. Another Phase III trial (ZEAL) used a similar design in order to evaluate the efficacy of pemetrexed plus vandetanib versus pemetrexed plus placebo. There was no significant difference in PFS or OS between the treatment arms [75].

The Phase III ZEST trial was conducted in order to assess the efficacy of vandetanib versus erlotinib in unselected NSCLC patients after one to two prior chemotherapy regimens, but vandetanib did not demonstrate an advantage of efficacy compared with erlotinib. More AEs were noted in the vandetanib arm [76]. In addition, for patients pretreated with EGFR TKIs and one or two chemotherapy regimens, vandetanib did not show significantly superior OS to placebo in the ZEPHYR study [77]. A Phase II study from the BATTLE trial reported an 8-week DCR of 33% [78].

In summary, only one Phase III trial of vandetanib showed a PFS advantage. However, vandetanib is not available for salvage therapy (crossover to vandetanib is not allowed on disease progression). Clinically significant improvements in PFS should be accompanied by improvements without undue treatment-associated toxic effects. However, in the case of vandetanib, such improvements are associated with more grade 3 or worse AEs. No OS benefit was demonstrated in all four Phase III trials of vandetanib. As a result, vandetanib is no longer in development in NSCLC.

XL647

XL647 (Exelixis) is an orally bioavailable small-molecule receptor TKI that inhibits VEGFR2, EGFR, HER2 and EphB4 [79]. In a Phase II trial of 55 treatment-naive patients mostly with minimal or no smoking history, 41 were treated with XL647 350 mg on a 5 days on/9 days off schedule and 14 were treated on a daily-dosing schedule. The RR and PFS for the two schedules combined were 20% and 5.3 months (90% CI: 3.7–6.7), respectively. Thirty-eight patients (69%) had material available for mutation testing, and 14 *EGFR*-sensitizing mutations were detected. The RR and PFS for *EGFR* mutation-positive patients were 57% and 9.3 months (90% CI: 5.5–11.7), respectively. The toxicities were comparable between the two schedules, with the most common AEs being diarrhea, nausea and fatigue [80]. In another Phase II trial of 33 evaluable patients with relapsed or recurrent advanced NSCLC who progressed after at least 12 weeks of SD or response to erlotinib or gefitinib and/or those patients

with a documented *EGFR* T790M mutation, XL647 300 mg was administered once daily. One PR was observed (RR: 3%; 90% CI: 0–14). The 3% RR that was observed did not meet the prespecified threshold to recommend further study of XL647 in patients who develop acquired resistance to erlotinib or gefitinib [81].

BMS-690514

BMS-690514 (Bristol-Myers Squibb, NJ, USA) is an inhibitor of EGFR, HER2, HER4 and VEGFR1, 2 and 3. Similarly to vandetanib, BMS-690514 inhibits both the HER and VEGFR families, offering activity of targeting tumor growth and angiogenesis in a single agent [82]. A Phase I/IIa study in patients with advanced solid tumors showed antitumor activity in patients with NSCLC. Six out of 21 (29%, including one PR) NSCLC patients with wild-type *EGFR* achieved disease control versus seven out of ten (70%, including one PR) patients with *EGFR* mutations (including T790M). The most frequent drug-related AEs were diarrhea and acneiform rash [83].

Predictive biomarkers

Unlike EGFR TKIs (e.g., erlotinib, gefitinib and afatinib) or anaplastic lymphoma kinase inhibitors (e.g., crizotinib and ceritinib) in advanced NSCLC, there are no validated biomarkers that are consistently predictive of benefit from antiangiogenic therapy. Current patient selection for antiangiogenic therapy is largely based on exclusion for side effects.

Antagonism of VEGF decreases the production of nitric oxide and leads to increased hypertension, a common AE during antiangiogenic therapy. In a retrospective analysis of the E4599 study (paclitaxel and carboplatin with or without bevacizumab), the development of hypertension may have been associated with better outcomes [84]. However, current evidence does not suggest hypertension as a marker for the efficacy of antiangiogenic therapy in advanced NSCLC.

In contrast to the driver mutations identified in NSCLC, angiogenesis is not specific to lung cancer formation. Therefore, almost all biomarkers related to angiogenesis are not unique to lung cancer. Commonly used biomarkers such as VEGF-A, VEGFR1, E-selectin and ICAM-1 are measured by immunohistochemistry staining on tissues or ELISA in plasma. In contrast to the gene mutation status (i.e., exists or does not exist), the levels of expression of these biomarkers are difficult define (i.e., high, low or intermediate), so comparisons between studies are difficult to perform. In addition, these arbitrary definitions may not be accurate for the dynamic process of angiogenesis. Nevertheless, in the E4599 study, patients with a low baseline soluble ICAM level had a higher RR and better OS than those with high ICAM, regardless of the treatment arm. Patients with high VEGF levels were more likely to be responsive to bevacizumab plus chemotherapy compared with chemotherapy alone, but this was not predictive of survival [85]. Exploratory analyses of samples from BR24 suggest that low baseline angiotensin-converting enzyme levels [86] and low soluble VEGFR3 [87] might be predictive biomarkers in NSCLC patients who receive cediranib with paclitaxel–carboplatin.

Why doesthe VEGF-A level not serve as a reliable predictive biomarker in the antiangiogenic treatment of cancer? First, the heterogeneity in methods of measuring plasma and tumor VEGF-A levels prevents meaningful comparisons between studies. Second, the angiogenic potential of a tumor is not determined by a single cytokine, but rather is determined by the sum of proangiogenic and antiangiogenic factors. Third, bevacizumab is able to sequester plasma VEGF-A after use, regardless of the pretreatment levels [88,89].

In summary, no reliable predictive biomarkers have so far been found that can be used routinely. Investigating this area will help to identify patients who can benefit most from antiangiogenic treatments and avoid unnecessary toxicities as well as costs in patients who cannot benefit from them.

Conclusion & future perspective

Angiogenesis is essential for the growth of tumors and has been studied as a target of anticancer treatments for decades. Bevacizumab, an anti-VEGF monoclonal antibody, in combination with first-line paclitaxel–carboplatin is the only antiangiogenic agent that is approved by the US FDA for the treatment of nonsquamous NSCLC. Ramucirumab, a VEGFR2 monoclonal antibody, was recently reported to show an OS benefit in the second-line setting in combination with docetaxel over docetaxel alone.

Angiokinase inhibitors that target multiple proangiogenic pathways (e.g., VEGFR, PDGFR and FGFR, among others) may theoretically provide therapeutic advantages over agents with single targets, such as bevacizumab. However, most trials of angiokinase inhibitors failed to demonstrate an OS benefit. Nintedanib is an unique 'triple-angiokinase inhibitor'. The Phase III LUME-Lung 1 study (nintedanib plus docetaxel) met its primary end point in terms of PFS, but an OS benefit was not found in the study population. The subgroup analysis showed an OS benefit in patients with adenocarcinoma [67]. A subgroup analysis of the Phase III MONET-1 study (motesanib plus paclitaxel–carboplatin) demonstrated significantly superior RR, PFS and OS in Asian patients [48].

Antiangiogenic therpy facilitates the drug delivery of chemotherapy [12–14]. In addition, antiangiogenic

agents can enhance the tolerance to chemotoxicity and prolong survival in animal models [90]. To date, antiangiogenic agents with OS benefits to have been demonstrated in Phase III trials were all administered in combination with chemotherapy. More studies are needed in order to determine the efficacy of monotherapy, the capacity of overcoming resistance to EGFR TKIs or anaplastic lymphoma kinase inhibitors and the appropriate dosing schedule to decrease toxicities. In patients with activating *EGFR* mutation, the imbalance of postprogression use of EGFR TKIs may significantly influence OS. In the era of personalized medicine in NSCLC, the stratification and selection of patient populations for the trials of angiokinase inhibitors should be carefully planned. Finally, in order to select an appropriate patient population, reliable predictive biomarkers are urgently needed.

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Executive summary

Background

- Patients with advanced or metastatic non-small-cell lung cancer (NSCLC) generally have poor survival.
- First-line chemotherapy with platinum-doublet therapy has been shown to modestly improve survival.
- Targeting angiogenesis may improve the outcomes of advanced NSCLC.

Current status & evidence of antiangiogenic therapy in NSCLC

- Bevacizumab in combination with first-line paclitaxel–carboplatin is the only antiangiogenic agent approved by the US FDA for the treatment of nonsquamous NSCLC.
- Ramucirumab, a human IgG1 monoclonal antibody that targets the extracellular domain of VEGFR2, has an overall survival (OS) benefit in the second-line treatment setting with docetaxel.

Multitargeted angiokinase inhibitors in NSCLC

- In addition to the VEGF pathway, the PDGF and FGFR pathways are important pathways of angiogenesis. Upregulations of these pathways may contribute to the resistance to anti-VEGF therapy.
- Angiokinase inhibitors with multiple targets (e.g., VEGFR, PDGFR and FGFR, among others) may provide a therapeutic advantage.
- Sorafenib, sunitinib, vandetanib, nintedanib, axitinib, motesanib, cabozantinib, cediranib, linifanib, XL647 and BMS-690514 are angiokinase inhibitors that have been studied in the treatment of NSCLC.
- OS benefits have been demonstrated in subgroup analyses of Phase III studies.
- OS was significantly longer for patients with adenocarcinoma who progressed within 9 months after the initiation of first-line treatment in the nintedanib–docetaxel group of the second-line LUME-Lung 1 study.
- A subgroup analysis of the Phase III MONET-1 study assessing the efficacy of first-line paclitaxel–carboplatin with or without motesanib in NSCLC showed a promising response rate and survival benefits in Asian patients with nonsquamous histology.

Predictive biomarkers

- In contrast to the driver mutations identified in NSCLC, angiogenesis is not specific to lung cancer formation. Therefore, almost all biomarkers related to angiogenesis are not unique to lung cancer.
- No reliable predictive biomarkers have so far been found that can be used routinely.

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