Angiogenesis inhibition as a therapeutic strategy in non-small cell lung cancer (NSCLC)

Richard D. Hall[1], Tri M. Le[1], Daniel E. Haggstrom[2], Ryan D. Gentzler[1]

[1]Division of Hematology/Oncology, University of Virginia School of Medicine, Charlottesville, VA 22908, USA; [2]Levine Cancer Institute, Carolinas Healthcare System, Charlotte, NC, USA

Contributions: (I) Conception and design: RD Hall, TM Le, RD Gentzler; (II) Administrative support: None; (III) Provision of study materials or patients: RD Hall, TM Le, RD Gentzler; (IV) Collection and assembly of data: RD Hall, TM Le, DE Haggstrom, RD Gentzler; (V) Data analysis and interpretation: RD Hall, TM Le, DE Haggstrom, RD Gentzler; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Ryan D. Gentzler. Division of Hematology/Oncology, University of Virginia School of Medicine, Charlottesville, VA 22908, USA. Email: ryan.gentzler@virginia.edu.

Abstract: In many cancers, including non-small cell lung cancer (NSCLC), tumor angiogenesis pathways have been identified as important therapeutic targets. Angiogenesis is essential in the process of primary tumor growth, proliferation and metastasis. One of the best characterized group of protein factors for angiogenesis include the members of the vascular endothelial growth factor (VEGF) family, consisting of VEGF-(A-D), and placenta growth factor (PIGF). Targeting tumor angiogenesis has been approached through two primary methods, monoclonal antibodies that block VEGF-vascular endothelial growth factor receptor (VEGFR) binding or small molecule tyrosine kinase inhibitors (TKIs) that inhibit the downstream VEGFR mediated signaling. Many TKIs inhibit multiple pro-angiogenic and pro-proliferative pathways such as the mitogen activated protein (MAP) kinase pathway. Bevacizumab and ramucirumab, monoclonal antibodies targeting VEGF and the VEGFR, respectively, have each led to improvements in overall survival (OS) for NSCLC when added to standard first and second line chemotherapy, respectively. Small incremental gains seen with both bevacizumab and ramucirumab may be further improved upon by incorporating novel agents and treatment strategies, and many additional trials are ongoing.

Keywords: Lung cancer; non-small cell lung cancer (NSCLC); angiogenesis; vascular endothelial growth factor (VEGF); targeted therapy

Submitted Jun 14, 2015. Accepted for publication Jun 21, 2015.
doi: 10.3978/j.issn.2218-6751.2015.06.09
View this article at: http://dx.doi.org/10.3978/j.issn.2218-6751.2015.06.09

Introduction

Lung cancer is the leading cause of cancer related mortality in the United States with more deaths directly attributable to the disease than breast, prostate, and colorectal cancer combined. It is estimated that 158,040 Americans will die from lung cancer in 2015 (1). Despite recent advances in the treatment of non-small cell lung cancer (NSCLC), including the discovery of oncogene driver mutations and subsequent targeting of *EGFR* mutations and *ALK* rearrangements through tyrosine kinase inhibitors (TKIs), significant work remains to reduce morbidity and improve survival for NSCLC patients (2-6).

In many cancers, including NSCLC, tumor angiogenesis pathways have been identified as important therapeutic targets. Angiogenesis is essential in the process of primary tumor growth, proliferation and metastasis (7,8). A key stimulant of intratumoral angiogenesis is tissue hypoxia, which leads to overproduction of pro-angiogenic factors. One of the best characterized and vital groups of protein factors include the members of the vascular endothelial growth factor (VEGF) family, consisting of VEGF-(A-D),

Table 1 Key clinical trials for bevacizumab and ramucirumab

Trial	Additional agents combined with VEGF monoclonal antibodies	PFS (or TTP)	OS	RR	Notes
Bev					
Johnson *et al*., phase II (19)	Carbo, paclitaxel ± bev	7.4 *vs*. 4.2 months (P=0.023)	17.7 *vs*. 14.9 months (P=0.63)	31.5% *vs*. 18.8%	PFS benefit, not powered for OS
ECOG 4599 (20)	Carbo, paclitaxel ± bev	6.2 *vs*. 4.5 months (P<0.001)	12.3 *vs*. 10.3 months (P=0.003)	35% *vs*. 15% (P<0.001)	OS benefit of 2 months
AVAiL (21,22)	Cisplatin, gemcitabine ± bev	6.7/6.5 *vs*. 6.1 months (P=0.003, 0.03)	13.6/13.4 *vs*. 13.1 months (P=0.420, 0.761)	34%/30.4% *vs*. 20.1% (P<0.0001, 0.0023)	No OS benefit, not powered for OS
AVAPERL (23,24)	Maintenance: pem/bev *vs*. pem (no bev)	7.4 *vs*. 3.7 months (P<0.001)	17.1 *vs*. 13.2 months (P=0.29)	55.5% *vs*. 50.0%	Not powered for OS
POINTBREAK (25)	Carbo/pem *vs*. carbo/paclitaxel	6.0 *vs*. 5.6 months (P=0.012)	12.6 *vs*. 13.4 months (P=0.949)	34.1% *vs*. 33.0%	Maintenance trial included bev in both arms
PRONOUNCE (26)	Carbo/pem (no bev) *vs*. carbo/paclitaxel/bev	4.4 *vs*. 5.49 months (P=0.610)	10.5 *vs*. 11.7 months (P=0.615)	23.6% *vs*. 27.4% (P=0.414)	Not powered for PFS or OS
Ram					
Camidge *et al*., phase II (27)	Carbo, paclitaxel + ram	7.85 months	16.85 months	55%	–
REVEL (28)	Docetaxel (no ram) *vs*. docetaxel/ram		10.5 *vs*. 9.1 months (P<0.0001)		OS benefit of 1.4 months

VEGF, vascular endothelial growth factor; PFS, progression free survival; TTP, time to progression; OS, overall survival; RR, response rate; bev, bevacizumab; carbo, carboplatin; ECOG, Eastern Cooperative Oncology Group; pem, pemetrexed; ram, ramucirumab.

and placenta growth factor (PIGF). Of these, VEGF-A (subsequently referred to as VEGF) is principally responsible for vessel formation in adult tissues (9,10). VEGF binds to a family of transmembrane receptor tyrosine kinases (RTKs) called VEGF receptors (VEGFRs) {VEGFR with three isoforms VEGFR-[1-3]} (11-13). VEGF binds with higher affinity to VEGFR-1, however, its primary effects on angiogenesis are mediated by VEGFR-2, the primary receptor involved in endothelial cell proliferation and migration (10,14). VEGF binding to VEGFR-2 stimulates downstream signal transduction leading to endothelial proliferation, differentiation, permeability, migration and the generation of new blood vessels (15). Tumor angiogenesis is characterized by the formation of abnormal, tortuous, and poorly organized vessels with altered permeability (13,16). These features lead to erratic tumor growth and decreased drug delivery due to changes in the permeability of the tumor vasculature (17).

Targeting tumor angiogenesis has been approached through two primary methods, monoclonal antibodies that block VEGF-VEGFR binding or small molecule TKIs that inhibit the downstream VEGFR mediated signaling. Many TKIs inhibit multiple pro-angiogenic and pro-proliferative pathways such as the mitogen activated protein (MAP) kinase pathway (18). The first anti-angiogenic agent approved for use in NSCLC was bevacizumab (approved in 2006; Avastin®; Genentech Inc., San Francisco, CA, USA). Due to the success of bevacizumab, multiple antibodies and small molecule TKI's targeting angiogenesis have been studied.

In this review, we will provide an overview of the recent advances in the use of anti-angiogenic agents in the treatment of NSCLC. We will review bevacizumab and ramucirumab (*Table 1*), two U.S. Food and Drug Administration (FDA)

Table 2 Summary of TKIs with anti-angiogenesis properties and their targets

Medication	Molecular targets	Notable clinical response
Sorafenib (29)	VEGFR-2, VEGFR-3, PDGFR, KIT, FLT3, RAF	Improved PFS and TTP
Pazopanib (30)	VEGFR-1, VEGFR-2, VEGFR-3, PDGFR, KIT	No difference when added to standard cisplatin/pemetrexed
Sunitinib (31)	VEGFR-1, VEGFR-2, VEGFR-3, PDGFR, KIT, FLT3, RET	Improved PFS/ORR, no change in OS
Cediranib (32)	VEGFR-1, VEGFR-2, VEGFR-3	No change in PFS or OS
Motesanib (33)	VEGFR-1, VEGFR-2, VEGFR-3, PDGFR, KIT	Improved PFS, no change in OS
Linifanib (34)	VEGFR-1, VEGFR-2, VEGFR-3, PDGFR	Improved PFS and OS
Vandetanib (35)	VEGFR-2, VEGFR-3, EGFR, RET	Improved PFS
Nintedanib (36)	VEGFR-1, VEGFR-2, VEGFR-3, PDGFR, FGFR	Improved PFS

TKIs, tyrosine kinase inhibitors; VEGFR, vascular endothelial growth factor receptor; PDGFR, platelet derived growth factor receptors; PFS, progression free survival; TTP, time to progression; ORR, overall response rate; OS, overall survival; FGFR, fibroblast growth factor receptor.

approved monoclonal antibodies with specific indications in NSCLC and highlight recent data suggesting new uses for these medications. We will also review data using anti-angiogenic TKI therapy, often in combination with chemotherapy (*Table 2*), a largely unsuccessful endeavor to date due to increased toxicity and lack of meaningful clinical benefit with one recent exception (nintedanib).

Monoclonal antibodies

Bevacizumab

Bevacizumab, the first monoclonal antibody approved by the FDA, is a recombinant, humanized IgG1 monoclonal antibody that binds to VEGF, inhibiting binding to VEGFR-1 and VEGFR-2 (12,37,38). In 2004, a randomized phase II trial was published and compared two doses of bevacizumab combined with a standard chemotherapy doublet (19). Bevacizumab 7.5 mg/kg or 15 mg/kg were added to carboplatin and paclitaxel and compared to chemotherapy alone. Patients who received the higher dose of bevacizumab had a higher response rate (RR) (31.5% *vs.* 18.8%) and longer median time to progression (TTP) (7.4 *vs.* 4.2 months, P=0.023) compared to chemotherapy alone. There were no statistically significant differences in overall survival (OS) between groups. Higher rates of life-threatening hemoptysis were observed in the bevacizumab groups, which in subset analyses were attributed to distinct clinical features including centrally located tumors close to major blood vessels, cavitary tumors, and squamous histology. These clinical features remain contraindications for use and have been excluded from subsequent trials with bevacizumab.

Based on the success of the phase II bevacizumab study, the Eastern Cooperative Oncology Group (ECOG) conducted a large randomized, phase III trial (ECOG 4599) comparing carboplatin and paclitaxel alone or with bevacizumab 15 mg/kg (20). Bevacizumab was continued until progression or intolerance. OS was significantly improved in the bevacizumab group (12.3 *vs.* 10.3 months, P=0.003), and both the response rate (RR) (35% *vs.* 15%, P<0.001) and progression free survival (PFS) (6.2 *vs.* 4.5 months, P<0.001) were significantly improved as well. The experimental regimen was well tolerated overall, but higher rates of Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or greater bleeding events (4.4% *vs.* 0.7%, P<0.001) were observed in the bevacizumab group. Bevacizumab gained FDA approval in combination with first-line chemotherapy for advanced NSCLC in 2006 following publication of ECOG 4599. A second randomized, phase III study (AVAiL) compared another chemotherapy doublet, cisplatin and gemcitabine, with bevacizumab at two different doses, 7.5 mg/kg and 15 mg/kg (21,22). PFS was significantly prolonged with both the high dose of bevacizumab *vs.* chemo alone (6.5 *vs.* 6.1 months, P=0.03) and the low dose bevacizumab *vs.* chemo alone (6.7 *vs.* 6.1, P=0.003). There was no statistically significant improvement in OS in either of the bevacizumab groups, however, the study was not powered to assess for difference in OS because the study was amended after publication of ECOG 4599.

The optimal duration of bevacizumab is unknown.

Bevacizumab was continued until progression or unacceptable toxicity in ECOG 4599. Several studies, including AVAPERL, POINTBREAK, and PRONOUNCE, have evaluated maintenance chemotherapy in non-squamous NSCLC using pemetrexed combined with bevacizumab (23-26). It is unclear whether the benefit of maintenance therapy in these trials is largely attributed to cytotoxic chemotherapy or whether bevacizumab provides additional benefit. The ECOG 5508 trial, a randomized phase III trial with three arms (carboplatin, paclitaxel, and bevacizumab followed by either bevacizumab alone, pemetrexed alone, or bevacizumab and pemetrexed) recently completed accrual. It is hoped that this trial will provide insight into the additional utility of bevacizumab continuation maintenance beyond 4-6 cycles of chemotherapy. The AvaALL study (NCT01351415) randomized patients with progressive disease after first line chemotherapy and bevacizumab to continued bevacizumab with second line chemotherapy or chemotherapy alone (39). This study completed accrual in early 2015, and results are awaited to determine the benefits of bevacizumab beyond progression. Bevacizumab has also been studied in the adjuvant setting in combination with chemotherapy for patients with stage IB-IIIA NSCLC. The ECOG 1505 study (NCT00324805) randomized patients to chemotherapy alone or chemotherapy plus bevacizumab (40). This trial has completed accrual and results are expected in the near future.

One new area of promise for bevacizumab is among patients with *EGFR* mutant NSCLC. A phase II trial for patients with treatment-naïve metastatic *EGFR*-mutant lung cancer randomized 154 patients to standard erlotinib or erlotinib plus bevacizumab (41). The addition of bevacizumab in this setting resulted in a significantly improved PFS (16.0 *vs*. 9.7 months, HR 0.54, P=0.0015]. Survival data was not mature at the time of publication, but the study was not powered to show a difference in OS. The improvement in PFS was impressive, and it is possible that bevacizumab may have a greater magnitude of benefit is the *EGFR*-mutant population than in the wild-type population. Two ongoing trials, BELIEF (NCT01562028) and ACCRU (NCT01532089) are evaluating erlotinib and bevacizumab in this patient population in Europe and the United States, respectively.

In carefully selected non-squamous NSCLC patients, the addition of bevacizumab to platinum doublet chemotherapy has prolonged OS at the expense of increased rates of clinically significant bleeding. It is important to recognize that adding bevacizumab to platinum doublet chemotherapy should not be used as a standard therapy for all patients with non-squamous NSCLC due to increased risk of complications with relatively modest clinical benefit. There is an ongoing need to identify biomarkers to guide selection of patients who are most likely to benefit from bevacizumab (42). Although baseline VEGF levels have been identified as a potentially useful biomarker that correlates with PFS and OS for patients receiving bevacizumab, this biomarker has not been evaluated prospectively to determine if it is predictive of OS improvement (43).

Ramucirumab

Ramucirumab, a fully human IgG1 monoclonal antibody targeting the extracellular domain of VEGFR-2, gained FDA approval for the second line treatment of NSCLC in 2014. It was first FDA-approved for the treatment of gastric cancer in the second line setting based on results of the REGARD trial resulting in improved OS when compared to best supportive care and placebo (44). Ramucirumab is also approved in the second line setting in combination with paclitaxel for gastric cancer and FOLFIRI for colorectal cancer based on data from the RAINBOW (45) and RAISE (46) studies, respectively. When bound to VEGFR-2, ramucirumab prevents VEGF from binding and activating VEGFR-2, inhibiting formation, proliferation, and migration of new blood vessels (47). This differs from bevacizumab, which targets VEGF. The addition of ramucirumab to standard chemotherapy has been evaluated in both the first-line and second-line settings.

Ramucirumab was first evaluated in NSCLC in an open-label, single-arm phase II trial combined with paclitaxel and carboplatin in 40 patients with untreated, advanced (stage IIIB/IV) NSCLC (27). Ramucirumab (10 mg/kg) was given with paclitaxel and carboplatin in 21-day cycle, and continued for up to 6 cycles. In the absence of withdrawal criteria (disease progression or intolerable toxicity), patients were allowed to continue on ramucirumab monotherapy every 21 days. The 6-month PFS rate was 59.0% and ORR was 55.0%, comparing favorably to historical controls. Another phase II, randomized, open-label trial evaluated the use of ramucirumab in combination with pemetrexed and platinum chemotherapy as first-line therapy in advanced, non-squamous NSCLC (48). Patients were randomized 1:1 to receive pemetrexed and platinum chemotherapy alone or with ramucirumab for 4-6 cycles followed by maintenance therapy with pemetrexed alone or pemetrexed

plus ramucirumab. This study failed to meet its primary endpoint [PFS, 5.6 months in the pemetrexed-platinum arm *vs*. 7.2 months in the ramucirumab-pemetrexed-platinum arm (P=0.132)]. Subsequent development of ramucirumab has focused on second line therapy as a result of these studies.

The REVEL trial was a multi-center, randomized, phase III trial that compared docetaxel alone to docetaxel plus ramucirumab in patients who progressed after platinum doublet chemotherapy (28). Patients previously treated with bevacizumab (14-15%) and both squamous and non-squamous histology patients were included. A total of 1,253 patients were enrolled and randomized to treatment. Median OS in the docetaxel plus ramucirumab arm was 10.5 *vs*. 9.1 months in the docetaxel plus placebo arm (HR 0.76, P<0.0001). The most common severe (CTCAE grade 3 or greater) adverse events (AEs) were neutropenia, febrile neutropenia, fatigue, leukopenia, and hypertension. Interestingly, rates of grade 3 or greater pulmonary hemorrhage and grade 5 AEs were not different between the two groups, despite inclusion of patients with squamous histology. Based on this study, ramucirumab was approved by the United States FDA in combination with docetaxel for patients with squamous or non-squamous histology after first line platinum-based chemotherapy.

Tyrosine kinase inhibitors (TKIs)

TKIs are attractive treatment options for patients with advanced cancer due to their oral bioavailability and relatively favorable toxicity profile compared to cytotoxic chemotherapy. Numerous TKIs with anti-angiogenic activity (most inhibit VEGFR-1 and/or VEGFR-2) have additional RTKs targets (*Table 2*). Many TKIs have been studied in a variety of combinations and lines of therapy for patients with lung cancer. A number of these drugs are effective as single agents in other advanced cancers, such as renal cell carcinoma and soft tissue sarcomas. Unfortunately, the development of anti-angiogenic TKIs has failed to yield an indication for use in lung cancer due to lack of efficacy or increased cumulative toxicity when combined with chemotherapy. We briefly summarize the more well studied TKIs and highlight challenges with anti-angiogenic TKIs.

One of the first TKIs studied in NSCLC was sorafenib. Unfortunately, in two large, phase III trials evaluating the additional benefit of sorafenib to platinum doublet chemotherapy for the first line treatment of NSCLC did not improve OS when compared to platinum doublet chemotherapy alone (29,49). Sorafenib may have a role in treating advanced KRAS mutant NSCLC following first line therapy and appears to have efficacy in *EGFR* wild-type tumors based on a sorafenib sensitivity signature analysis, but this remains to be tested in a randomized trial (50,51). Pazopanib was studied in a multicenter, randomized, phase II trial combined with cisplatin and pemetrexed chemotherapy. Unfortunately this combination had an unacceptable toxicity profile compared with cisplatin and pemetrexed alone (30). A phase I trial of pazopanib combined with vinorelbine proved to be too toxic as well (52). Sunitinib was studied in combination with erlotinib *vs*. erlotinib alone in a phase III, randomized study in *EGFR* wild-type patients after first line platinum doublet chemotherapy (31). No OS difference was observed but PFS and ORR were improved with the combination (31). A recent randomized, phase II study comparing pemetrexed alone to the combination of pemetrexed with sunitinib (CALGB 30704) failed to show a benefit with statistically superior OS in the pemetrexed only arm compared to the two combination arms (53).

Cediranib is a multi-kinase inhibitor that has been studied in the first-line setting for advanced NSCLC. In a phase II/III trial, cediranib 30 mg daily was compared with placebo in addition to chemotherapy with carboplatin and paclitaxel (54). Interim analysis indicated a trend towards increased PFS, however the study was halted due to safety concerns (increased mortality in the cediranib containing arm). A subsequent phase III study using a 20 mg dose and similar design was conducted (32). This trial was halted at an interim analysis due to significantly higher rates grade 3 or greater hypertension, anorexia, and diarrhea without statistically significant increases in PFS or OS. Motesanib showed promise in an early phase II trial, where two arms of motesanib at low and high doses were compared with bevacizumab in a three-arm trial in combination with carboplatin and paclitaxel for first-line therapy in patients with advanced NSCLC (55). Results from this trial estimated that the efficacy of motesanib 125 mg bid was comparable to bevacizumab. A phase III trial (MONET1) was performed assessing motesanib plus chemotherapy (carboplatin and paclitaxel) *vs*. chemotherapy alone in patients with advanced non-squamous NSCLC (33). While the study found a significant increase in PFS for patients receiving motesanib (5.6 *vs*. 5.4 months, P<0.001), there was no significant improvement in the primary endpoint of OS (13.0 *vs*. 11.0 months, P=0.14). Although there were no specific high grade toxicities attributed to motesanib, the incidence of

grade 3 or higher AEs and the incidence of grade 5 AEs were significantly higher in the motesanib group.

Linifanib showed modest activity in a phase II study in 139 patients with relapsed/refractory NSCLC setting (56). Patients received linifanib monotherapy at two different doses with an ORR 5%, with PFS of 3.6 months and OS of 9.0 months. A recent phase II study evaluated the efficacy of carboplatin and paclitaxel with or without linifanib in treatment naïve patients (34). Addition of linifanib 7.5 mg to carboplatin and paclitaxel was associated with a significantly improved PFS compared to placebo (8.3 *vs.* 5.4 months, P=0.022). Addition of linifanib 12.5 mg showed no significant increase in OS *vs.* placebo (13.0 *vs.* 11.3 months, P=0.65). Unfortunately both dose arms of linifanib were associated with increased toxicity compared with platinum doublet chemotherapy alone. Vandetanib is an oral multi-kinase inhibitor that has been studied in four phase III trials. The ZODIAC trial assessed docetaxel plus vandetanib *vs.* docetaxel alone following platinum-based therapy and showed that the combination was associated with a significantly increased PFS over docetaxel alone but with increased grade 3 or greater AEs (35). The ZEAL trial assessed pemetrexed plus vandetanib *vs.* pemetrexed alone following platinum-based therapy for advanced NSCLC (57). There was no significant difference in the pemetrexed plus vandetanib *vs.* pemetrexed alone in either PFS or OS, and the addition of vandetanib to pemetrexed increased the incidence of some AEs. A third study by Natale *et al.* compared single agent vandetanib to erlotinib in unselected patients with advanced NSCLC after treatment failure with one to two prior cytotoxic regimens (58). There were no significant differences in either PFS or OS between the vandetanib and erlotinib arms. A fourth study (ZEPHYR) compared vandetanib to placebo in advanced NSCLC after at least one prior cytotoxic regimen and one EGFR TKI line of therapy and detected a small difference in PFS *vs.* placebo but no significant difference in OS (59).

Nintedanib, a potent TKI with anti-VEGFR-2 as well as fibroblast growth factor receptor (FGFR) and platelet derived growth factor receptors (PDGFR) α and β activity has produced promising results in a large trial of NSCLC. The LUME-Lung 1 study, a randomized, phase III, double-blind, placebo controlled trial of 1,314 NSCLC patients compared nintedanib plus docetaxel to placebo plus docetaxel (36). PFS was improved in the nintedanib plus docetaxel arm [3.4 (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 pre-specified sub-group analysis, patients with adenocarcinoma histology had improved OS with the combination compared to docetaxel alone [12.6 (95% CI, 10.6-15.1) *vs.* 10.3 months (95% CI, 8.6=12.2); HR 0.83 (95% CI, 0.70-0.099), P=0.0359]. The LUME Columbus study (NCT02231164) is an active phase III study that is evaluating the combination of nintedanib plus docetaxel *vs.* docetaxel alone in non-squamous NSCLC after first line platinum doublet chemotherapy.

Conclusions

Angiogenesis inhibition continues to be an attractive therapeutic strategy for patients with NSCLC. To date, small molecule inhibitors of angiogenesis have largely failed to produce meaningful improvements in OS. One exception may be nintedanib, which showed promise in the LUME Lung 1 study and is the subject of an ongoing phase III study (LUME Columbus) (36). If nintedanib ultimately shows a clinically significant benefit in second line therapy, it will have to compete with ramucirumab, which was approved by the FDA in 2014 and is not limited to non-squamous histology.

Bevacizumab and ramucirumab have both led to improvements in OS when added to standard first and second line chemotherapy, respectively. Small incremental gains seen with both bevacizumab and ramucirumab may be further improved upon by incorporating novel agents and treatment strategies. One example of this strategy can be seen with the promising results of adding bevacizumab to erlotinib for *EGFR*-mutant cancers that led to a greater than 6 month improvement in PFS (41). In addition to the BELIEF (NCT01562028) and ACCRU (NCT01532089) studies, the RELAY study (NCT02411448) is studying ramucirumab in combination with erlotinib in first line *EGFR* mutant NSCLC. With the dawn of immunotherapy treatment in lung cancer, it remains to be seen whether angiogenesis inhibitors (either anti-angiogenic TKIs or monoclonal antibodies) when combined with checkpoint inhibitors may have additive effects. Although gains in OS have been small, many other drugs have failed to improve OS in the NSCLC patient population. The improvements in OS seen with both bevacizumab and ramucirumab can be clinically meaningful for patients who have a significantly shortened lifespan.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin 2015;65:5-29.
2. Kris MG, Johnson BE, Berry LD, et al. Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. JAMA 2014;311:1998-2006.
3. Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2012;13:239-46.
4. Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol 2013;31:3327-34.
5. Shaw AT, Kim DW, Mehra R, et al. Ceritinib in ALK-rearranged non-small-cell lung cancer. N Engl J Med 2014;370:1189-97.
6. Shaw AT, Kim DW, Nakagawa K, et al, Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med 2013;368:2385-94.
7. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;144:646-74.
8. Aggarwal C, Somaiah N, Simon G. Antiangiogenic agents in the management of non-small cell lung cancer: where do we stand now and where are we headed? Cancer Biol Ther 2012;13:247-63.
9. Giaccone G. The potential of antiangiogenic therapy in non-small cell lung cancer. Clin Cancer Res 2007;13:1961-70.
10. Lohela M, Bry M, Tammela T, et al. VEGFs and receptors involved in angiogenesis versus lymphangiogenesis. Curr Opin Cell Biol 2009;21:154-65.
11. Ferrara N. Pathways mediating VEGF-independent tumor angiogenesis. Cytokine Growth Factor Rev 2010;21:21-6.
12. Ferrara N, Gerber HP, LeCouter J. The biology of VEGF and its receptors. Nat Med 2003;9:669-76.
13. Folkman J. Angiogenesis: an organizing principle for drug discovery? Nat Rev Drug Discov 2007;6:273-86.
14. Alevizakos M, Kaltsas S, Syrigos KN. The VEGF pathway in lung cancer. Cancer Chemother Pharmacol 2013;72:1169-81.
15. Hicklin DJ, Ellis LM. Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis. J Clin Oncol 2005;23:1011-27.
16. Ferrara N, Kerbel RS. Angiogenesis as a therapeutic target. Nature 2005;438:967-74.
17. Jain RK. Normalizing tumor vasculature with anti-angiogenic therapy: a new paradigm for combination therapy. Nat Med 2001;7:987-9.
18. Imai K, Takaoka A. Comparing antibody and small-molecule therapies for cancer. Nat Rev Cancer 2006;6:714-27.
19. Johnson DH, Fehrenbacher L, Novotny WF, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol 2004;22:2184-91.
20. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 2006;355:2542-50.
21. Reck M, von Pawel J, Zatloukal P, et al. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAil. J Clin Oncol 2009;27:1227-34.
22. Reck M, von Pawel J, Zatloukal P, et al. Overall survival with cisplatin-gemcitabine and bevacizumab or placebo as first-line therapy for nonsquamous non-small-cell lung cancer: results from a randomised phase III trial (AVAiL). Ann Oncol 2010;21:1804-9.
23. Barlesi F, Scherpereel A, Rittmeyer A, et al. Randomized phase III trial of maintenance bevacizumab with or without pemetrexed after first-line induction with bevacizumab, cisplatin, and pemetrexed in advanced nonsquamous non-small-cell lung cancer: AVAPERL (MO22089). J Clin Oncol 2013;31:3004-11.
24. Barlesi F, Scherpereel A, Gorbunova V, et al. Maintenance bevacizumab-pemetrexed after first-line cisplatin-pemetrexed-bevacizumab for advanced nonsquamous nonsmall-cell lung cancer: updated survival analysis of the AVAPERL (MO22089) randomized phase III trial. Ann Oncol 2014;25:1044-52.
25. Patel JD, Socinski MA, Garon EB, et al. PointBreak: a randomized phase III study of pemetrexed plus carboplatin and bevacizumab followed by maintenance pemetrexed and bevacizumab versus paclitaxel plus carboplatin and bevacizumab followed by maintenance bevacizumab in

patients with stage IIIB or IV nonsquamous non-small-cell lung cancer. J Clin Oncol 2013;31:4349-57.
26. Zinner RG, Obasaju CK, Spigel DR, et al. PRONOUNCE: randomized, open-label, phase III study of first-line pemetrexed + carboplatin followed by maintenance pemetrexed versus paclitaxel + carboplatin + bevacizumab followed by maintenance bevacizumab in patients ith advanced nonsquamous non-small-cell lung cancer. J Thorac Oncol 2015;10:134-42.
27. Camidge DR, Berge EM, Doebele RC, et al. A phase II, open-label study of ramucirumab in combination with paclitaxel and carboplatin as first-line therapy in patients with stage IIIB/IV non-small-cell lung cancer. J Thorac Oncol 2014;9:1532-9.
28. Garon EB, Ciuleanu TE, Arrieta O, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. Lancet 2014;384:665-73.
29. Paz-Ares LG, Biesma B, Heigener D, et al. Phase III, randomized, double-blind, placebo-controlled trial of gemcitabine/cisplatin alone or with sorafenib for the first-line treatment of advanced, nonsquamous non-small-cell lung cancer. J Clin Oncol 2012;30:3084-92.
30. Scagliotti GV, Felip E, Besse B, et al. An open-label, multicenter, randomized, phase II study of pazopanib in combination with pemetrexed in first-line treatment of patients with advanced-stage non-small-cell lung cancer. J Thorac Oncol 2013;8:1529-37.
31. Scagliotti GV, Krzakowski M, Szczesna A, et al. Sunitinib plus erlotinib versus placebo plus erlotinib in patients with previously treated advanced non-small-cell lung cancer: a phase III trial. J Clin Oncol 2012;30:2070-8.
32. Laurie SA, Solomon BJ, Seymour L, et al. Randomised, double-blind trial of carboplatin and paclitaxel with daily oral cediranib or placebo in patients with advanced non-small cell lung cancer: NCIC Clinical Trials Group study BR29. Eur J Cancer 2014;50:706-12.
33. Scagliotti GV, Vynnychenko I, Park K, et al. International, randomized, placebo-controlled, double-blind phase III study of motesanib plus carboplatin/paclitaxel in patients with advanced nonsquamous non-small-cell lung cancer: MONET1. J Clin Oncol 2012;30:2829-36.
34. Ramalingam SS, Shtivelband M, Soo RA, et al. Randomized Phase II Study of Carboplatin and Paclitaxel With Either Linifanib or Placebo for Advanced Nonsquamous Non-Small-Cell Lung Cancer. J Clin Oncol 2015;33:433-41.
35. Herbst RS, Sun Y, Eberhardt WE, et al. Vandetanib plus docetaxel versus docetaxel as second-line treatment for patients with advanced non-small-cell lung cancer (ZODIAC): a double-blind, randomised, phase 3 trial. Lancet Oncol 2010;11:619-26.
36. Reck M, Kaiser R, Mellemgaard A, et al. Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): a phase 3, double-blind, randomised controlled trial. Lancet Oncol 2014;15:143-55.
37. Vasudev NS, Reynolds AR. Anti-angiogenic therapy for cancer: current progress, unresolved questions and future directions. Angiogenesis 2014;17:471-94.
38. Presta LG, Chen H, O'Connor SJ, et al. Humanization of an anti-vascular endothelial growth factor monoclonal antibody for the therapy of solid tumors and other disorders. Cancer Res 1997;57:4593-9.
39. Gridelli C, Bennouna J, De Castro J, et al. AvaALL: Open-label randomized phase IIIb trial evaluating the efficacy and safety of standard of care with or without continuous bevacizumab (BV) treatment beyond disease progression in patients (pts) with advanced nonsquamous non-small cell lung cancer (NSCLC) after first-line (1L) treatment with BV plus platinum-doublet chemotherapy (CT). 2012 ASCO Annual Meeting. Chicago, Illinois, USA, 2012.
40. Wakelee HA, Schiller JH, Gandara DR. Current status of adjuvant chemotherapy for stage IB non-small-cell lung cancer: implications for the New Intergroup Trial. Clin Lung Cancer 2006;8:18-21.
41. Seto T, Kato T, Nishio M, et al. Erlotinib alone or with bevacizumab as first-line therapy in patients with advanced non-squamous non-small-cell lung cancer harbouring EGFR mutations (JO25567): an open-label, randomised, multicentre, phase 2 study. Lancet Oncol 2014;15:1236-44.
42. Gentzler RD, Yentz SE, Johnson ML, et al. The changing landscape of phase II/III metastatic NSCLC clinical trials and the importance of biomarker selection criteria. Cancer 2014;120:3853-8.
43. Mok T, Gorbunova V, Juhasz E, et al. A correlative biomarker analysis of the combination of bevacizumab and carboplatin-based chemotherapy for advanced nonsquamous non-small-cell lung cancer: results of the phase II randomized ABIGAIL study (BO21015). J Thorac Oncol 2014;9:848-55.
44. Fuchs CS, Tomasek J, Yong CJ, et al. Ramucirumab monotherapy for previously treated advanced gastric or

gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet 2014;383:31-9.
45. Wilke H, Muro K, Van Cutsem E, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol 2014;15:1224-35.
46. Tabernero J, Yoshino T, Cohn AL, et al. Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study. Lancet Oncol 2015;16:499-508.
47. Spratlin JL, Cohen RB, Eadens M, et al. Phase I pharmacologic and biologic study of ramucirumab (IMC-1121B), a fully human immunoglobulin G1 monoclonal antibody targeting the vascular endothelial growth factor receptor-2. J Clin Oncol 2010;28:780-7.
48. Doebele RC, Spigel D, Tehfe M, et al. Phase 2, randomized, open-label study of ramucirumab in combination with first-line pemetrexed and platinum chemotherapy in patients with nonsquamous, advanced/metastatic non-small cell lung cancer. Cancer 2015;121:883-92.
49. Scagliotti G, Novello S, von Pawel J, et al. Phase III study of carboplatin and paclitaxel alone or with sorafenib in advanced non-small-cell lung cancer. J Clin Oncol 2010;28:1835-42.
50. Blumenschein GR Jr, Saintigny P, Liu S, et al. Comprehensive biomarker analysis and final efficacy results of sorafenib in the BATTLE trial. Clin Cancer Res 2013;19:6967-75.
51. Dingemans AM, Mellema WW, Groen HJ, et al. A phase II study of sorafenib in patients with platinum-pretreated, advanced (Stage IIIb or IV) non-small cell lung cancer with a KRAS mutation. Clin Cancer Res 2013;19:743-51.
52. Gentzler RD, Kaklamani VG, Worden R, et al. Phase (Ph) I study of pazopanib (P) in combination with vinorelbine (V) in patients with metastatic non-small cell lung cancer (mNSCLC) and breast cancer (mBC). 2013 ASCO Annual Meeting. Chicago, Illinois, USA, 2013.
53. Heist RS, Wang X, Hodgson L, et al. CALGB 30704 (Alliance): A randomized phase II study to assess the efficacy of pemetrexed or sunitinib or pemetrexed plus sunitinib in the second-line treatment of advanced non-small-cell lung cancer. J Thorac Oncol 2014;9:214-21.
54. Goss GD, Arnold A, Shepherd FA, et al. Randomized, double-blind trial of carboplatin and paclitaxel with either daily oral cediranib or placebo in advanced non-small-cell lung cancer: NCIC clinical trials group BR24 study. J Clin Oncol 2010;28:49-55.
55. Blumenschein GR Jr, Kabbinavar F, Menon H, et al. A phase II, multicenter, open-label randomized study of motesanib or bevacizumab in combination with paclitaxel and carboplatin for advanced nonsquamous non-small-cell lung cancer. Ann Oncol 2011;22:2057-67.
56. Tan EH, Goss GD, Salgia R, et al. Phase 2 trial of Linifanib (ABT-869) in patients with advanced non-small cell lung cancer. J Thorac Oncol 2011;6:1418-25.
57. de Boer RH, Arrieta O, Yang CH, et al. Vandetanib plus pemetrexed for the second-line treatment of advanced non-small-cell lung cancer: a randomized, double-blind phase III trial. J Clin Oncol 2011;29:1067-74.
58. Natale RB, Thongprasert S, Greco FA, et al. Phase III trial of vandetanib compared with erlotinib in patients with previously treated advanced non-small-cell lung cancer. J Clin Oncol 2011;29:1059-66.
59. Lee JS, Hirsh V, Park K, et al. Vandetanib Versus placebo in patients with advanced non-small-cell lung cancer after prior therapy with an epidermal growth factor receptor tyrosine kinase inhibitor: a randomized, double-blind phase III trial (ZEPHYR). J Clin Oncol 2012;30:1114-21.

Cite this article as: Hall RD, Le TM, Haggstrom DE, Gentzler RD. Angiogenesis inhibition as a therapeutic strategy in non-small cell lung cancer (NSCLC). Transl Lung Cancer Res 2015;4(5):515-523. doi: 10.3978/j.issn.2218-6751.2015.06.09

