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The Role of Anti-angiogenesis in Non-small-cell Lung Cancer: an Update

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Abstract

Recognition of the vascular endothelial growth factor (VEGF) pathway as a key mediator of angiogenesis has led to the clinical study of several VEGF and VEGF receptor (VEGFR) targeted therapies in non-small-cell lung cancer (NSCLC). These targeted therapies include neutralizing antibodies to VEGF (bevacizumab and aflibercept) and VEGFR-2 (ramucirumab) and tyrosine kinase inhibitors (TKIs) with selectivity for the VEGFRs. Bevacizumab and ramucirumab are associated with survival advantages in the treatment of advanced NSCLC: bevacizumab in the first-line setting in combination with carboplatin/paclitaxel and ramucirumab in combination with docetaxel in the second-line setting. The VEGFR-2 TKIs have been associated with responses and improved progression-free survival in selected NSCLC settings; however, this level of activity has thus far been insufficient to confer significant survival advantages. This review will focus on the current state of VEGF targeted therapies in NSCLC.

Keywords

Anti-angiogenesis; VEGF; Lung cancer; Bevacizumab; Ramucirumab; Tyrosine kinase inhibitors

Introduction

Lung cancer is the leading cause of cancer mortality in the USA and worldwide [1]. An estimated 224,210 new cases of lung cancer will be diagnosed in 2014 in the USA alone, and 159,260 lung cancer deaths are estimated to occur [1]. Historically, palliative chemotherapy in the metastatic non-small-cell lung cancer (NSCLC) setting resulted in modest survival prolongation and preservation of quality of life. [2–6] A series of large randomized controlled phase 3 clinical trials established platinum-based doublets as the standard of care in the treatment of metastatic NSCLC with response rates of 20 to 30 % and a median survival of 8 to 11 months [7–11].

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Compliance with Ethics Guidelines

Conflict of Interest Liza C. Villaruz and Mark A. Socinski declare that they have no conflict of interest.

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Overexpression of vascular endothelial growth factor (VEGF) has been found in most human tumors, including NSCLC, and is associated with increased tumor recurrence, metastasis, and death [12–16]. The angiogenic phenotype is considered a hallmark of the malignant process whereby proangiogenic mechanisms overwhelm or circumvent the negative regulators of angiogenesis [17]. The VEGF/VEGF-receptor (VEGFR) pathway plays a pivotal role in normal and pathologic angiogenesis [18]. VEGF pathway activation leads to endothelial cell survival, mitogenesis, migration, differentiation, and mobilization of endothelial progenitor cells from the bone marrow into the peripheral circulation [18].

The VEGF-related gene family is composed of six secreted glycoproteins referred to as VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placenta growth factor (PlGF) -1 and -2 [19–21]. VEGF-A (commonly referred to as VEGF) is an endothelial specific mitogen with a diverse range of angiogenic activities [22]. *VEGF-A* undergoes alternate splicing to yield isoforms of 121, 165, 189, and 206 amino acids, which have distinct tissue-specific expression patterns, suggesting defined roles in vasculogenesis and tumor angiogenesis [20, 21, 23–25]. The VEGF ligands mediate their effect through several receptor tyrosine kinases (Fig. 1 [18]). All isoforms of VEGF bind to VEGFR-1 and VEGFR-2, whereas PlGF-1 and -2 and VEGF-B specifically bind and activate VEGFR-1 [26–28]. While VEGFR-1 is critical for physiologic and developmental angiogenesis, the precise function of VEGFR-1 in angiogenesis is unclear [18]. The majority of the effects of VEGF are mediated through binding of VEGF R-2, which leads to microvascular permeability, invasion, migration, and survival [29–31]. Other mediators of the VEGF ligands include VEGFR-3, which may be involved in cardiovascular development and vascular remodeling during embryogenesis and lymphangiogenesis in the adult, and NRP-1 and NRP-2, which are likely to serve as co-receptors for VEGF [18].

Recognition of the VEGF pathway as a key mediator of angiogenesis has led to the clinical study of several VEGF targeted therapies in lung cancer. These targeted therapies include neutralizing antibodies to VEGF (bevacizumab, currently the only FDA-approved anti-angiogenic therapy in NSCLC, and aflibercept) and VEGFR-2 (ramucirumab) and receptor tyrosine kinase inhibitors (TKIs) with preferential selectivity for the VEGFRs. This review will focus on the current state of VEGF targeted therapies in advanced lung cancer with a particular focus on bevacizumab.

Monoclonal Antibodies

Bevacizumab

Bevacizumab is the recombinant humanized version of the murine anti-human VEGF monoclonal antibody A4.6.1 [32]. A phase Ib clinical trial demonstrated bevacizumab in combination with cytotoxic chemotherapy to be a well-tolerated regimen with no exacerbation of the expected toxicities of chemotherapy [33]. A subsequent phase II clinical trial of bevacizumab at doses of 7.5 mg/kg (low dose) and 15 mg/kg (high dose) in combination with carboplatin/paclitaxel in chemotherapy-naïve advanced NSCLC demonstrated a response rate (RR) of 31.5 % with high-dose bevacizumab in combination with carboplatin/paclitaxel compared with 18.8 % with carboplatin/paclitaxel alone, a longer time to progression (7.4 vs 4.2 months, respectively), and a modest increase in overall

survival (OS) to 17.7 months from 14.9 months, respectively [34]. In this phase II clinical trial, bleeding was the most prominent adverse event manifesting in two distinct clinical patterns: minor mucocutaneous bleeding and major hemoptysis. None of the cases of mucocutaneous bleeding, most commonly epistaxis, required change in bevacizumab administration. Six of the 66 patients (9 %) treated with bevacizumab on this phase II trial experienced major bleeding described as hemoptysis or hematemesis, four events of which were fatal. These patients were noted to have centrally located tumors close to major blood vessels; five patients were noted to have cavitation or necrosis of tumors, either at baseline or developing during bevacizumab therapy, and four patients were noted to have squamous cell histology. This phase II clinical trial was a critical step in the development of bevacizumab as it identified a signal of efficacy with regard to survival and, more importantly, a signal of toxicity in the squamous cell population, which influenced the design of subsequent phase III clinical trials.

The intergroup trials E4599 and AVAiL are two large randomized phase III clinical trials evaluating the addition of bevacizumab to platinum-based doublet chemotherapy in patients with advanced non-squamous NSCLC in the first-line setting. Both clinical trials excluded patients with squamous cell histology, patients with hemoptysis (one-half teaspoon of bright red blood per event), or intracranial metastases, and patients on therapeutic anticoagulation or aspirin at doses more than 325 mg/day [35, 36]. E4599 met its primary endpoint demonstrating that the addition of bevacizumab 15 mg/kg to carboplatin/paclitaxel significantly improved median OS in patients with advanced non-squamous NSCLC compared with chemotherapy alone (12.3 vs 10.3 months, hazard ratio (HR) 0.79, $P=0.003$; Table 1 and Fig. 1a [35]). The addition of bevacizumab significantly improved RRs from 15 % with chemotherapy alone to 35 % with the addition of bevacizumab ($P<0.001$; Table 1) and prolonged median progression-free survival (PFS) from 4.5 to 6.2 months ($P<0.001$; Table 1 and Fig. 1b), respectively. The corresponding rates of clinically significant bleeding were 4.4 and 0.7 %, respectively ($P<0.001$). The addition of bevacizumab was associated with an increase in hematologic toxicity compared with carboplatin/paclitaxel alone, resulting in higher rates of neutropenia, febrile neutropenia, and thrombocytopenia. The European counterpart, AVAiL, evaluated the addition of bevacizumab (7.5 or 15 mg/kg) to cisplatin/gemcitabine versus chemotherapy alone in patients with advanced non-squamous NSCLC. This trial met its primary endpoint with a significant prolongation in PFS from 6.1 to 6.7 months in the low-dose bevacizumab group (HR 0.75, $P=0.003$; Table 1) and from 6.1 to 6.5 months in the high-dose bevacizumab group (HR 0.82, $P=0.03$; Table 1 [36]). The update of AVAiL failed to demonstrate an OS advantage with bevacizumab (13.1, 13.4, and 13.6 months for the placebo, high-dose bevacizumab, and low dose-bevacizumab groups, respectively, HR 1.03, $P=0.761$; Table 1), although more than 60 % patients with progression of their disease went on to receive second-line therapy [37]. The survival results of AVAiL should be considered with caution as the statistical plan was altered after the initiation of the trial. Originally intended to be a two-stage adaptive design in which one of the bevacizumab groups would be dropped resulting in a two-arm study, the study was amended to proceed with three arms for the duration. In addition, the primary endpoint originally intended to be OS was changed to PFS after the results of E4599 became available. Lastly, the interval at which disease status was assessed differed between the trials

(every 6 weeks in E4599 vs every 9 weeks in AVAiL), introducing interval censoring into the PFS endpoint.

While squamous cell histology is a contraindication to bevacizumab therapy, it is important to note that the BRIDGE clinical trial, an open-label phase II study, assessed the addition of bevacizumab to carboplatin/paclitaxel chemotherapy with cycle 3 of chemotherapy in patients with previously untreated advanced predominantly squamous cell histology NSCLC [38]. The BRIDGE clinical trial had strict patient selection criteria and excluded patients with untreated brain metastases, tumor cavitation, gross hemoptysis within 3 months, major surgical procedures or trauma within 28 days, evidence of bleeding diathesis or coagulopathy, or major blood vessel tumor impingement or invasion. In this study, bevacizumab was associated with grade 3 pulmonary hemorrhage in 1 of 31 patients (3.2 %) with no other serious bleeding events. While this rate of pulmonary hemorrhage in patients with squamous cell NSCLC was lower than what would be expected from the prior phase II trial of bevacizumab with chemotherapy in the first-line setting, the BRIDGE clinical trial was small, and the use of bevacizumab in patients with predominantly squamous NSCLC outside of a clinical trial is not recommended.

In both E4599 and AVAiL, bevacizumab was given as maintenance therapy after the completion of six cycles of platinum doublet chemotherapy/bevacizumab. Although data specifically assessing the role of bevacizumab in the maintenance setting are limited, a retrospective analysis of patients with non-progressive disease after induction therapy on E4599 demonstrated a superior PFS (4.4 vs 2.8 months, respectively, HR 0.64, $P<0.001$) and OS (12.8 vs 11.4 months, respectively, HR 0.75, $P=0.03$) in patients receiving bevacizumab maintenance compared with patients who did not [39]. The ATLAS clinical trial randomized patients with advanced NSCLC without disease progression or significant toxicity after four cycles of chemotherapy/bevacizumab to maintenance therapy with either bevacizumab/placebo or bevacizumab/erlotinib [40]. Bevacizumab/placebo maintenance was associated with a PFS of 3.7 months, compared with 4.8 months with bevacizumab/erlotinib (HR 0.71, $P<0.001$; Table 1). E5508 is a randomized phase III clinical trial of maintenance therapy with bevacizumab, pemetrexed, or the combination following carboplatin, paclitaxel, and bevacizumab induction therapy in advanced non-squamous NSCLC patients. This trial is currently ongoing and will further inform upon the role bevacizumab maintenance following bevacizumab-containing induction therapy.

With the emergence of histology as an important predictor of benefit from pemetrexed-based therapy, the POINTBREAK clinical trial aimed to establish which platinum doublet is best paired with bevacizumab in the non-squamous setting: carboplatin/paclitaxel vs carboplatin/pemetrexed. This study failed to demonstrate an OS advantage of a pemetrexed-based platinum doublet compared with a paclitaxel-based platinum doublet in combination with bevacizumab (12.6 vs 13.4 months, respectively, HR 1, $P=0.949$; Table 1 [41]). Both regimens demonstrated tolerability, although the toxicity profiles differed; carboplatin/pemetrexed/bevacizumab compared with carboplatin/paclitaxel/bevacizumab was associated with significantly more study drug-related grade 3 or 4 anemia (14.5 vs 2.7 %, respectively), thrombocytopenia (23.3 vs 5.6 %, respectively), and fatigue (10.9 vs 5.0 %, respectively), whereas carboplatin/paclitaxel/bevacizumab compared with carboplatin/pemetrexed/

bevacizumab was associated with significantly more grade 3 or 4 neutropenia (40.6 vs 25.8 %, respectively), febrile neutropenia (4.1 vs 1.4 %, respectively), sensory neuropathy (4.1 vs 0 %, respectively), and alopecia (grade 1 or 2; 36.8 vs 6.6 %, respectively). Given these data, the decision of which platinum doublet to be paired with bevacizumab is often based on the respective toxicity profiles of pemetrexed-based therapy compared with paclitaxel-based therapy.

The BeTa trial assessed the role of bevacizumab/erlotinib versus erlotinib/placebo in patients with advanced NSCLC who have progressed after first-line therapy. This trial failed to meet its primary endpoint of OS (9.3 vs 9.2 months, respectively, HR 0.97, $P=0.7583$; Table 1) for patients treated with bevacizumab/erlotinib versus erlotinib alone [42]. While there seemed to be an improvement in PFS (3.4 vs 1.7 months, respectively, HR 0.62, 95 % confidence interval (CI) 0.52–0.75; Table 1) and RR in the bevacizumab containing arm, these secondary endpoint differences were not defined as significant based on the statistical design of this study. AvaALL is an open-label randomized phase IIIb trial evaluating the role of continuation of bevacizumab therapy in patients who have progressed after first-line treatment with a bevacizumab-containing platinum doublet and at least two cycles of bevacizumab maintenance. In this clinical trial, patients randomized to the experimental arm continue to receive bevacizumab with second line and subsequent lines of treatment. While there is currently limited evidence to support the use of bevacizumab beyond the first-line setting, AvaLL may help to further delineate the role of bevacizumab therapy beyond progression.

In a post hoc analysis of the BeTa clinical trial, PFS was substantially longer in the subset of patients with *EGFR* mutant lung cancers treated with bevacizumab/erlotinib compared with erlotinib alone [43]. The role of bevacizumab in the *EGFR* mutant population was specifically addressed in a randomized clinical trial comparing erlotinib/bevacizumab with erlotinib alone in the first-line setting. This trial demonstrated a significant PFS benefit with the addition of bevacizumab to erlotinib compared with erlotinib alone in patients with *EGFR* mutant lung cancers (16 vs 9.7 months, respectively, HR 0.54, $P=0.0015$; Table 1) and in the subset of patients with *EGFR* exon 19 deletions (18.0 vs 10.3 months, respectively, HR 0.41, $P=0.0011$) and a numerically longer PFS in patients with *EGFR* L858R mutations (13.9 vs 7.1 months, respectively, HR 0.67, $P=0.1653$ [44]). Two clinical trials, BELIEF (NCT01562028) and ACCRU RC1126 (NCT01532089), are ongoing to further evaluate the efficacy of this regimen in the *EGFR* mutant population.

In order to further assess the safety of bevacizumab in combination with chemotherapy in the first-line treatment of advanced non-squamous NSCLC, an open-label, single group, phase 4 clinical trial (SAiL) enrolled 2212 patients treated with bevacizumab in whom the incidence of thromboembolism was 8 %, of hypertension 6 %, of bleeding 4 %, of proteinuria 3 %, and of pulmonary hemorrhage 1 %; 3 % of patients died because of these adverse events, which were most commonly thromboembolism (1 %) and bleeding (1 % [45]). In reviewing the body of safety data with bevacizumab, an expert panel of oncologists, radiologists, and pulmonologists concluded that NSCLC patients are inherently at increased risk of pulmonary hemorrhage owing to their underlying disease process and that the only absolute contra-indications to bevacizumab therapy are squamous cell histology and the

presence of grade 2 hemoptysis (2.5 ml/event [46]). This panel concluded that no clinical or radiological features (including cavitation and central tumor location) reliably predict severe pulmonary hemorrhage in bevacizumab-treated patients [46]. While major blood vessel infiltration, encasement, and abutting may predict for pulmonary hemorrhage, standardized radiological criteria for defining infiltration have not been established [46].

ARIES was a prospective observational cohort study which evaluated outcomes in a large community-based population of NSCLC patients receiving bevacizumab in the first-line setting [47•] and was critical in delineating the safety of bevacizumab in patients receiving anticoagulation, a patient population who had been excluded from the pivotal E4599 and AVAiL clinical trials. Among 1967 patients enrolled on ARIES, 8 % had brain metastases and 7 % had a history of hemoptysis; among 1290 patients on concomitant medications, 13 % were receiving anticoagulation (76 prophylactic /92 therapeutic) and 35 % were receiving antiplatelet therapy. In this observational cohort, the rate of grade 3 bevacizumab-associated events was similar to those seen in E4599 and AVAiL; 1.2 % patients developed severe pulmonary hemorrhage, and 0.2 % had grade 3 to 5 CNS hemorrhage, with a trend for bevacizumab-related adverse events occurring more frequently in the first 6 months of bevacizumab therapy. These data would indicate that eligibility for bevacizumab should not be influenced by concomitant anticoagulation or antiplatelet therapy.

Brain metastases are a common complication of NSCLC, and few randomized phase III clinical trials have included patients with brain metastases. In a recent phase III trial enrolling patients with chemotherapy-naïve NSCLC with or without brain metastases, 17 % of patients had brain metastases (7 % patients with squamous cell histology and 19 % patients with adenocarcinoma histology) which underscores the importance of characterizing the safety of bevacizumab in patients with metastatic disease to the brain [48]. The PASSPORT clinical trial specifically assessed the safety of bevacizumab in patients with non-squamous NSCLC and treated brain metastases with the primary endpoint of grade 2 intracranial hemorrhage. In 106 safety evaluable patients who had completed therapy for their intracranial disease (radiation 4 weeks and/or neurosurgery 3 months prior to bevacizumab treatment), bevacizumab either in the first- or second-line setting was associated with no episodes of grade 2 intracranial hemorrhage [49•]. This trial concluded that bevacizumab in patients with NSCLC and treated brain metastases seems to be safe and is associated with a low incidence of CNS hemorrhage.

Selection of patients that are most likely to benefit from chemotherapy plus bevacizumab is limited by the lack of a validated biomarker of response to VEGF therapy. In an embedded substudy of E4599, the onset of hypertension with bevacizumab portended better OS and PFS, relative to patients who did not have onset of hypertension, although this clinical biomarker is of limited prospective utility [50]. In a planned prospective biomarker assessment of VEGF, basic fibroblast growth factor (bFGF), intercellular adhesion molecule (ICAM), and E-selectin within E4599, baseline ICAM levels were associated with response and survival in patients irrespective of treatment arm [51]. Patients with low baseline ICAM levels had a higher RR (32 vs 14 %; $P=0.02$) and better overall survival ($P=0.00005$) than those with high ICAM levels, respectively, regardless of treatment arm. Patients with high

VEGF levels were more likely to respond to carboplatin/paclitaxel/bevacizumab compared with carboplatin/paclitaxel, but this was not predictive of survival.

Ramucirumab

Ramucirumab is a fully human IgG1 monoclonal antibody that specifically binds to the VEGFR-2 extracellular domain with high affinity, preventing binding of all VEGF ligands and receptor activation and signaling [52]. Two phase II clinical trials have assessed the addition of ramucirumab to platinum doublet chemotherapy in the first-line setting. Camidge et al. enrolled squamous and non-squamous patients on a single-arm trial of carboplatin/paclitaxel/ramucirumab and demonstrated tolerability of this regimen, a RR of 55 %, a median PFS of 7.9 months and OS of 17.9 months [53]. Of interest in this single-arm trial is that the single-nucleotide polymorphism (SNP) rs2981582 on the *FGFR-2* gene had significant associations with improved overall survival, PFS, and best overall response. Doebele et al. randomized patients with non-squamous NSCLC to either platinum/pemetrexed or platinum/pemetrexed/ramucirumab and demonstrated no statistically significant improvements in PFS (5.6 vs 7.2 months, respectively, HR 0.75, $P=0.132$), OS (10.4 vs 13.9 months, HR 1.03, $P=0.892$), and RR (38.0 and 49.3 %, respectively, $P=0.180$) and no new or unexpected safety findings [54].

The REVEL clinical trial is a randomized phase III clinical trial which assessed the addition of ramucirumab to docetaxel compared with docetaxel/placebo in patients with squamous or non-squamous advanced NSCLC after platinum-based chemotherapy. This trial met its primary endpoint demonstrating an OS advantage with the addition of ramucirumab (9.1 months with docetaxel/ramucirumab vs 10.5 months with docetaxel/placebo, HR 0.86, $P=0.023$; Table 1 and Fig. 2a), in addition to a PFS prolongation (4.5 vs 3.0 months, respectively, HR 0.76, $P<0.0001$; Table 1 and Fig. 2b) and improvement in RR (23 vs 14 %, respectively, OR 1.89, $P<0.0001$; Table 1 [55•]). Although this study was not powered for subgroup analyses, most subgroups of patients had numerically longer survival with the addition of ramucirumab compared with docetaxel/placebo, including patients with non-squamous disease (11.1 vs 9.7 months, respectively, HR 0.83, 95 % CI 0.71–0.97), patients with squamous disease (9.5 vs 8.2 months, HR 0.88, 95 % CI 0.69–1.13), and responders to first-line platinum therapy (11.2 vs 10.3 months, HR 0.84, 95 % CI 0.71–0.99). The most common grade 3 or worse adverse events were neutropenia (49 % patients in the ramucirumab group vs 40 % in the placebo group), febrile neutropenia (16 vs 10 %), fatigue (14 vs 10 %), leukopenia (14 vs 12 %), and hypertension (6 vs 2 %). The numbers of deaths from adverse events (5 vs 6 %) and grade 3 or worse pulmonary hemorrhage (1 vs 1 %) did not differ between the treatment groups. The efficacy of ramucirumab in combination with docetaxel across NSCLC histologies and the safety with regard to the risk of pulmonary hemorrhage make ramucirumab of particular interest in patients with squamous cell NSCLC.

Aflibercept

VEGF trap or aflibercept is a recombinant fusion protein, consisting of human VEGFR-1 extracellular domain 2 and VEGFR-2 extracellular domain 3, fused to the hinge region of the human IgG1 Fc domain. Aflibercept has high affinity VEGF binding (approximately

1000-fold greater than bevacizumab), the ability to bind VEGF-B, as well as PIGF-1 and -2, and a longer half-life [56]. In a single-arm clinical trial assessing the safety and efficacy of single-agent aflibercept in patients with erlotinib- and platinum-resistant advanced lung adenocarcinomas, aflibercept was well tolerated but had little single-agent activity; the overall RR was 2.0 % (95 % CI, 0.2–7.2 %), median PFS 2.7 months, and OS 6.2 months (Table 1) [57]. In the second-line setting, the VITAL clinical trial randomized patients with non-squamous NSCLC to docetaxel/aflibercept or docetaxel/placebo and failed to meet its primary endpoint of improvement in OS with the addition aflibercept (10.1 vs 10.4 months, respectively, HR 1.01, $P=0.90$; Table 1 [58]). In exploratory analyses, median PFS was 5.2 versus 4.1 months, respectively (HR 0.82, $P=0.0035$; Table 1) and RR was 23.3 versus 8.9 %, respectively ($P<0.001$; Table 1). Grade 3 adverse events occurred more frequently with docetaxel/aflibercept compared with docetaxel/placebo and were neutropenia (28.0 vs 21.1 %, respectively), fatigue (11.1 vs 4.2 %, respectively), stomatitis (8.8 vs 0.7 %, respectively), and hypertension (7.3 vs 0.9 %, respectively).

Tyrosine Kinase Inhibitors

The role of anti-angiogenic TKIs in the treatment of advanced NSCLC has been the subject of multiple phase II and III clinical trials. Multi-targeted TKIs with activity against VEGFR-2—sorafenib, sunitinib, nintedanib, cediranib, motesanib, pazopanib, axitinib, and vandetanib—have been studied as single agents and in combination with erlotinib or chemotherapy in patients with treatment-naïve and previously treated NSCLC (Table 2 [59–83]). As single agents and in combination with chemotherapy, these multi-targeted TKIs have been associated with improvement in RRs and PFS in selected trials (Table 2). However, these improvements in RRs and PFS have not translated to gains in OS, suggesting a level of activity in patients with unselected NSCLC that is unlikely sufficient to drive OS.

LUME Lung 1 was a randomized phase III clinical trial assessing the addition of nintedanib to docetaxel in patients with advanced NSCLC with progressive disease after first-line therapy. In this clinical trial, PFS was significantly improved with docetaxel/nintedanib compared with docetaxel/placebo group (3.4 vs 2.7 months, respectively, HR 0.79, $P=0.0019$; Table 2 [66]), while OS was not significantly impacted (10.1 vs 9.1 months, respectively, HR 0.94, $P=0.2720$). OS was significantly improved for patients with adenocarcinoma histology who progressed within 9 months after start of first-line treatment with docetaxel/nintedanib compared with docetaxel/placebo group (10.9 vs 7.9 months, respectively, HR 0.75, $P=0.0073$) and for all patients with adenocarcinoma histology (12.6 vs 10.3 months, respectively, HR 0.83, $P=0.0359$), suggesting a histology-specific benefit. Based on these results, LUME Columbus is an ongoing randomized, double-blind, phase III trial assessing the efficacy and safety of nintedanib plus docetaxel versus placebo plus docetaxel in patients with advanced adenocarcinoma of the lung after failure of first-line therapy.

CALBG 30607 evaluated the role of switch maintenance sunitinib versus placebo in patients with advanced NSCLC following 4 cycles of induction therapy with the primary endpoint of PFS. This trial crossed the superiority boundary on the primary endpoint at an interim analysis demonstrating a median PFS of 4.3 months with sunitinib versus 2.8 months with

placebo (HR 0.59, $P=0.0008$; Table 2) with improvements in both the squamous (4.3 vs 2.4 months, respectively, HR 0.55, $P=0.02$) and non-squamous histologic subsets (4.3 vs 2.8 months, respectively, HR 0.64, $P=0.02[62\bullet]$). There was no significant difference in OS between the treatment arms (Table 2), and the rate of subsequent therapy was 61 % on the sunitinib arm and 74 % on the placebo arm ($P=0.049$). These data would suggest a therapeutic niche for sunitinib in the maintenance setting after first-line therapy.

Nikolinakos et al. conducted profiling of cytokine and angiogenic factors (CAFs) to investigate the relationship between baseline CAF levels, CAF changes during treatment, and tumor shrinkage in early-stage NSCLC patients treated with pazopanib [84]. Pazopanib therapy was associated with significant changes of eight CAFs, with the largest changes being in sVEGFR2 and placental growth factor. Post-treatment changes in plasma sVEGFR2 and interleukin (IL)-4 and baseline levels of 11 CAFs significantly correlated with tumor shrinkage. This study identified a baseline CAF signature consisting of hepatocyte growth factor and IL-12 which was associated with tumor response to pazopanib. Furthermore, CAF profiling in a randomized phase II clinical trial evaluating vandetanib monotherapy, vandetanib in combination with carboplatin/paclitaxel, or carboplatin/paclitaxel alone in previously untreated patients with advanced NSCLC demonstrated distinct patterns in plasma CAFs between the treatment arms [85]. While these results indicate that CAF profiling may provide insight into the biologic effects of treatment with VEGFR TKIs, these candidate biomarkers have not been prospectively validated as predictive of outcome.

Anti-angiogenic Agents in the Treatment of Local or Locally Advanced NSCLC

The survival benefit of bevacizumab in patients with advanced NSCLC seen in E4599 led to the development of E1505 which is assessing the addition of bevacizumab to cisplatin-based chemotherapy in patients with resected stage IB to IIIA NSCLC. This trial has completed accrual; in an interim safety analysis, there were no unexpected toxicities with bevacizumab. Adjuvant bevacizumab was associated with increased grade 3/4 hypertension, proteinuria, and abdominal pain with only one case each of fatal hemoptysis and non-fatal bronchopleural fistula [86].

A phase I/II clinical trial assessed the safety and efficacy of the incorporation of bevacizumab and erlotinib into concurrent chemoradiotherapy in stage III NSCLC [87]. Forty-five eligible patients received induction chemotherapy with carboplatin/paclitaxel/bevacizumab followed by concurrent chemotherapy with bevacizumab and thoracic conformal radiation therapy to 74 Gy with or without erlotinib, followed by consolidation therapy with bevacizumab and erlotinib. This approach was associated with an induction response rate and overall response rate of 39 and 60 %, respectively, a PFS of 10.2 months, and an OS of 18.4 months. This approach was associated with significant grade 3/4 esophagitis with one patient developing a grade 3 tracheoesophageal fistula. Based on these results, the incorporation of bevacizumab into concurrent chemoradiotherapy in the treatment of stage III NSCLC is associated with excess toxicity and not currently recommend.

Conclusions

The recognition of the VEGF pathway as a key regulator of angiogenesis in NSCLC has led to the study of several anti-angiogenic agents, including monoclonal antibodies to VEGF and VEGFR-2 and VEGFR TKIs. To date, only bevacizumab and ramucirumab have demonstrated a level of activity that drives overall survival in the treatment of advanced NSCLC: bevacizumab in the first-line setting in combination with carboplatin/paclitaxel and ramucirumab in combination with docetaxel in the second-line setting. Given these findings, the use of anti-angiogenic agents in combination with chemotherapy represents a standard of care in eligible patients. Caution should be exercised regarding patient selection criteria as the addition of anti-angiogenic agents in selected patient populations can increase the risk of certain toxicities. VEGFR-2 TKIs are associated with a level of activity that may drive responses and PFS in selected NSCLC settings; however, this level of activity has thus far been insufficient to confer significant survival advantages. Finally, the development of biomarkers of response to anti-angiogenic therapies may help identify patient populations most likely to respond to these targeted agents.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance

1. Howlader, N.; Noone, AM.; Krapcho, M.; Garshell, J.; Neyman, N.; Altekruse, SF., et al. SEER cancer statistic review. 2014. p. 1975-2011. http://seer.cancer.gov/csr/1975_2011/
2. Hopwood P, Stephens RJ. Symptoms at presentation for treatment in patients with lung cancer: implications for the evaluation of palliative treatment. The medical research council (MRC) lung cancer working party. *Br J Cancer*. 1995; 71:633–6. [PubMed: 7533520]
3. Burdett S, Stephens R, Stewart L, Tierney J, Auperin A, Le Chevalier T, et al. Chemotherapy in addition to supportive care improves survival in advanced non-small-cell lung cancer: a systematic review and meta-analysis of individual patient data from 16 randomized controlled trials. *J Clin Oncol*. 2008; 26:4617–25. [PubMed: 18678835]
4. Burdett S, Stewart L, Pignon J-P. Chemotherapy in non-small cell lung cancer: an update of an individual patient data-based meta-analysis. *J Thorac Cardiovasc Surg*. 2005; 129:1205–6. [PubMed: 15867822]
5. Rapp E, Pater JL, Willan A, Cormier Y, Murray N, Evans WK, et al. Chemotherapy can prolong survival in patients with advanced non-small-cell lung cancer—report of a Canadian multicenter randomized trial. *J Clin Oncol*. 1988; 6:633–41. [PubMed: 2833577]
6. Non-small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. *Br Med J*. 1995; 311:899–909. [PubMed: 7580546]
7. Fossella F, Pereira JR, von Pawel J, Pluzanska A, Gorbounova V, Kaukel E, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. *J Clin Oncol*. 2003; 21:3016–24. [PubMed: 12837811]
8. Kelly K, Crowley J, Bunn PA Jr, Presant CA, Grevstad PK, Moinpour CM, et al. Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non-small-cell lung cancer: a southwest oncology group trial. *J Clin Oncol*. 2001; 19:3210–8. [PubMed: 11432888]
9. Scagliotti GV, De Marinis F, Rinaldi M, Crino L, Gridelli C, Ricci S, et al. Phase III randomized trial comparing three platinum-based doublets in advanced non-small-cell lung cancer. *J Clin Oncol*. 2002; 20:4285–91. [PubMed: 12409326]

10. Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med*. 2002; 346:92–8. [PubMed: 11784875]
11. Zatloukal P, Petruzelka L, Zemanova M, Kolek V, Skrickova J, Pesek M, et al. Gemcitabine plus cisplatin vs. gemcitabine plus carboplatin in stage IIIb and IV non-small cell lung cancer: a phase III randomized trial. *Lung Cancer*. 2003; 41:321–31. [PubMed: 12928123]
12. Ferrara N. The role of vascular endothelial growth factor in pathological angiogenesis. *Breast Cancer Res Treat*. 1995; 36:127–37. [PubMed: 8534862]
13. Mattern J, Koomagi R, Volm M. Association of vascular endothelial growth factor expression with intratumoral microvessel density and tumour cell proliferation in human epidermoid lung carcinoma. *Br J Cancer*. 1996; 73:931–4. [PubMed: 8611409]
14. Brown LF, Berse B, Jackman RW, Tognazzi K, Manseau EJ, Senger DR, et al. Expression of vascular permeability factor (vascular endothelial growth factor) and its receptors in adenocarcinomas of the gastrointestinal tract. *Cancer Res*. 1993; 53:4727–35. [PubMed: 8402650]
15. Brown LF, Berse B, Jackman RW, Tognazzi K, Guidi AJ, Dvorak HF, et al. Expression of vascular permeability factor (vascular endothelial growth factor) and its receptors in breast cancer. *Hum Pathol*. 1995; 26:86–91. [PubMed: 7821921]
16. Seto T, Higashiyama M, Funai H, Imamura F, Uematsu K, Seki N, et al. Prognostic value of expression of vascular endothelial growth factor and its flt-1 and KDR receptors in stage I non-small-cell lung cancer. *Lung Cancer*. 2006; 53:91–6. [PubMed: 16697074]
17. Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell*. 2000; 100:57–70. [PubMed: 10647931]
18. Hicklin DJ, Ellis LM. Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis. *J Clin Oncol*. 2005; 23:1011–27. [PubMed: 15585754]
19. Ferrara N, Gerber HP, LeCouter J. The biology of VEGF and its receptors. *Nat Med*. 2003; 9:669–76. [PubMed: 12778165]
20. Houck KA, Ferrara N, Winer J, Cachianes G, Li B, Leung DW. The vascular endothelial growth factor family: identification of a fourth molecular species and characterization of alternative splicing of RNA. *Mol Endocrinol*. 1991; 5:1806–14. [PubMed: 1791831]
21. Tischer E, Mitchell R, Hartman T, Silva M, Gospodarowicz D, Fiddes JC, et al. The human gene for vascular endothelial growth factor. Multiple protein forms are encoded through alternative exon splicing. *J Biol Chem*. 1991; 266:11947–54. [PubMed: 1711045]
22. Leung DW, Cachianes G, Kuang WJ, Goeddel DV, Ferrara N. Vascular endothelial growth factor is a secreted angiogenic mitogen. *Science*. 1989; 246:1306–9. [PubMed: 2479986]
23. Ferrara N. Molecular and biological properties of vascular endothelial growth factor. *J Mol Med (Berl)*. 1999; 77:527–43. [PubMed: 10494799]
24. Ferrara N. Vascular endothelial growth factor and the regulation of angiogenesis. *Recent Prog Horm Res*. 2000; 55:15–35. discussion 35–16. [PubMed: 11036931]
25. Cross MJ, Dixelius J, Matsumoto T, Claesson-Welsh L. VEGF-receptor signal transduction. *Trends Biochem Sci*. 2003; 28:488–94. [PubMed: 13678960]
26. Park JE, Chen HH, Winer J, Houck KA, Ferrara N. Placenta growth factor. Potentiation of vascular endothelial growth factor bioactivity, in vitro and in vivo, and high affinity binding to Flt-1 but not to Flk-1/KDR. *J Biol Chem*. 1994; 269:25646–54. [PubMed: 7929268]
27. Olofsson B, Korpelainen E, Pepper MS, Mandriota SJ, Aase K, Kumar V, et al. Vascular endothelial growth factor B (VEGF-B) binds to VEGF receptor-1 and regulates plasminogen activator activity in endothelial cells. *Proc Natl Acad Sci U S A*. 1998; 95:11709–14. [PubMed: 9751730]
28. Silvestre JS, Tamarat R, Ebrahimian TG, Le-Roux A, Clergue M, Emmanuel F, et al. Vascular endothelial growth factor-B promotes in vivo angiogenesis. *Circ Res*. 2003; 93:114–23. [PubMed: 12805240]
29. Dvorak HF. Vascular permeability factor/vascular endothelial growth factor: a critical cytokine in tumor angiogenesis and a potential target for diagnosis and therapy. *J Clin Oncol*. 2002; 20:4368–80. [PubMed: 12409337]
30. Zeng H, Dvorak HF, Mukhopadhyay D. Vascular permeability factor (VPF)/vascular endothelial growth factor (VEGF) peceptor-1 down-modulates VPF/VEGF receptor-2-mediated endothelial

cell proliferation, but not migration, through phosphatidylinositol 3-kinase-dependent pathways. *J Biol Chem.* 2001; 276:26969–79. [PubMed: 11350975]

31. Millauer B, Witzigmann-Voos S, Schnurch H, Martinez R, Moller NP, Risau W, et al. High affinity VEGF binding and developmental expression suggest Flk-1 as a major regulator of vasculogenesis and angiogenesis. *Cell.* 1993; 72:835–46. [PubMed: 7681362]
32. Presta LG, Chen H, O'Connor SJ, Chisholm V, Meng YG, Krummen L, 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. [PubMed: 9377574]
33. Margolin K, Gordon MS, Holmgren E, Gaudreault J, Novotny W, Fyfe G, et al. Phase Ib trial of intravenous recombinant humanized monoclonal antibody to vascular endothelial growth factor in combination with chemotherapy in patients with advanced cancer: pharmacologic and long-term safety data. *J Clin Oncol.* 2001; 19:851–6. [PubMed: 11157039]
34. Johnson DH, Fehrenbacher L, Novotny WF, Herbst RS, Nemunaitis JJ, Jablons DM, 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. [PubMed: 15169807]
35. Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med.* 2006; 355:2542–50. This randomized phase III clinical trial demonstrated an improvement in overall survival with bevacizumab in combination with platinum-based chemotherapy compared with chemotherapy alone in the 1st-line treatment of patients with non-squamous NSCLC. [PubMed: 17167137]
36. Reck M, von Pawel J, Zatloukal P, Ramlau R, Gorbounova V, Hirsh V, 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. [PubMed: 19188680]
37. Reck M, von Pawel J, Zatloukal P, Ramlau R, Gorbounova V, Hirsh V, 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. [PubMed: 20150572]
38. Hainsworth JD, Fang L, Huang JE, Karlin D, Russell K, Faoro L, et al. BRIDGE: an open-label phase II trial evaluating the safety of bevacizumab+carboplatin/paclitaxel as first-line treatment for patients with advanced, previously untreated, squamous non-small cell lung cancer. *J Thorac Oncol.* 2011; 6:109–14. [PubMed: 21107290]
39. Lopez-Chavez A, Young T, Fages S, Leon L, Schiller JH, Dowlati A, et al. Bevacizumab maintenance in patients with advanced non-small-cell lung cancer, clinical patterns, and outcomes in the eastern cooperative oncology group 4599 study: results of an exploratory analysis. *J Thorac Oncol.* 2012; 7:1707–12. [PubMed: 23059774]
40. Johnson BE, Kabbinavar F, Fehrenbacher L, Hainsworth J, Kasubhai S, Kressel B, et al. ATLAS: randomized, double-blind, placebo-controlled, phase IIIB trial comparing bevacizumab therapy with or without erlotinib, after completion of chemotherapy, with bevacizumab for first-line treatment of advanced non-small-cell lung cancer. *J Clin Oncol.* 2013; 31:3926–34. [PubMed: 24101054]
41. Patel JD, Socinski MA, Garon EB, Reynolds CH, Spigel DR, Olsen MR, 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. [PubMed: 24145346]
42. Herbst RS, Ansari R, Bustin F, Flynn P, Hart L, Otterson GA, et al. Efficacy of bevacizumab plus erlotinib versus erlotinib alone in advanced non-small-cell lung cancer after failure of standard first-line chemotherapy (BeTa): a double-blind, placebo-controlled, phase 3 trial. *Lancet.* 2011; 377:1846–54. [PubMed: 21621716]
43. Herbst R, Stern HM, Amler LC. Biomarker evaluation in the phase III, placebo-controlled, randomized BeTa trial of bevacizumab and erlotinib for patients with advanced non-small cell lung cancer (NSCLC) after failure of standard 1st-line chemotherapy: correlation with treatment outcomes. *J Thorac Oncol.* 2009; 4:S323.

44. Seto T, Kato T, Nishio M, Goto K, Atagi S, Hosomi Y, 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. [PubMed: 25175099]
45. Crino L, Dansin E, Garrido P, Griesinger F, Laskin J, Pavlakakis N, et al. Safety and efficacy of first-line bevacizumab-based therapy in advanced non-squamous non-small-cell lung cancer (SAiL, MO19390): a phase 4 study. *Lancet Oncol.* 2010; 11:733–40. [PubMed: 20650686]
46. Reck M, Barlesi F, Crino L, Henschke CI, Isla D, Stiebler S, et al. Predicting and managing the risk of pulmonary haemorrhage in patients with NSCLC treated with bevacizumab: a consensus report from a panel of experts. *Ann Oncol.* 2012; 23:1111–20. [PubMed: 22056855]
47. Lynch TJ Jr, Spigel DR, Brahmer J, Fischbach N, Garst J, Jahanzeb M, et al. Safety and effectiveness of bevacizumab-containing treatment for non-small-cell lung cancer: final results of the ARIES observational cohort study. *J Thorac Oncol.* 2014; 9:1332–39. ARIES was a prospective observational cohort study which evaluated outcomes in a large community-based population of NSCLC patients receiving bevacizumab in the 1st-line setting and was critical in delineating the safety of bevacizumab in patients receiving anticoagulation, a patient population who had been excluded from the pivotal E4599 and AVAiL clinical trials. [PubMed: 25122429]
48. Edelman MJ, Belani CP, Socinski MA, Ansari RH, Obasaju CK, Chen R, et al. Outcomes associated with brain metastases in a three-arm phase III trial of gemcitabine-containing regimens versus paclitaxel plus carboplatin for advanced non-small cell lung cancer. *J Thorac Oncol.* 2010; 5:110–6. [PubMed: 20035187]
49. Socinski MA, Langer CJ, Huang JE, Kolb MM, Compton P, Wang L, et al. Safety of bevacizumab in patients with non-small-cell lung cancer and brain metastases. *J Clin Oncol.* 2009; 27:5255–61. The PASSPORT clinical trial specifically assessed the safety of bevacizumab in patients with non-squamous NSCLC and treated brain metastases. In this clinical trial, there were no episodes of grade 2 intracranial hemorrhage, suggesting that bevacizumab in patients with NSCLC and treated brain metastases is safe and associated with a low incidence of CNS hemorrhage. [PubMed: 19738122]
50. Dahlberg SE, Sandler AB, Brahmer JR, Schiller JH, Johnson DH. Clinical course of advanced non-small-cell lung cancer patients experiencing hypertension during treatment with bevacizumab in combination with carboplatin and paclitaxel on ECOG 4599. *J Clin Oncol.* 2010; 28:949–54. [PubMed: 20085937]
51. Dowlati A, Gray R, Sandler AB, Schiller JH, Johnson DH. Cell adhesion molecules, vascular endothelial growth factor, and basic fibroblast growth factor in patients with non-small cell lung cancer treated with chemotherapy with or without bevacizumab—an eastern cooperative oncology group study. *Clin Cancer Res.* 2008; 14:1407–12. [PubMed: 18316562]
52. Youssoufian H, Hicklin DJ, Rowinsky EK. Review: monoclonal antibodies to the vascular endothelial growth factor receptor-2 in cancer therapy. *Clin Cancer Res.* 2007; 13:5544s–48s. [PubMed: 17875787]
53. Camidge DR, Berge EM, Doebele RC, Ballas MS, Jahan T, Haigentz M Jr, 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
54. Doebele RC, Spigel D, Tehfe M, Thomas S, Reck M, Verma S, 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.* 2014
55. Garon EB, Ciuleanu TE, Arrieta O, Prabhaskar K, Syrigos KN, Goksel T, 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. This randomized phase III clinical trial demonstrated an overall survival advantage of docetaxel/ramucirumab compared with docetaxel/placebo in the second line treatment of NSCLC. [PubMed: 24933332]
56. Aflibercept (AVE0005) Investigator's Brochure. 8. Apr 22. 2008
57. Leighl NB, Raez LE, Besse B, Rosen PJ, Barlesi F, Massarelli E, et al. A multicenter, phase 2 study of vascular endothelial growth factor trap (Aflibercept) in platinum- and erlotinib-resistant adenocarcinoma of the lung. *J Thorac Oncol.* 2010; 5:1054–9. [PubMed: 20593550]

58. Ramlau R, Gorbunova V, Ciuleanu TE, Novello S, Ozguroglu M, Goksel T, et al. Aflibercept and docetaxel versus docetaxel alone after platinum failure in patients with advanced or metastatic non-small-cell lung cancer: a randomized, controlled phase III trial. *J Clin Oncol.* 2012; 30:3640–7. [PubMed: 22965962]
59. Scagliotti G, Novello S, von Pawel J, Reck M, Pereira JR, Thomas M, 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. [PubMed: 20212250]
60. Paz-Ares LG, Biesma B, Heigener D, von Pawel J, Eisen T, Bennouna J, 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. [PubMed: 22851564]
61. Paz-Ares L, Hirsch V, Zhang L, De Marinis F, Yang JC-H, Wakelee HA, et al. Monotherapy administration of sorafenib in patients with non-small cell lung cancer: phase III, randomized, double-blind, placebo-controlled mission trial. *Ann Oncol.*
62. Socinski MA, Wang XF, Baggstrom MQ, Gu L, Stinchcombe TE, Edelman MJ, et al. Sunitinib (S) switch maintenance in advanced non-small cell lung cancer (NSCLC): An ALLIANCE (CALGB 30607), randomized, placebo-controlled phase III trial. *J Clin Oncol.* 2014; 32:5s. This phase III clinical trial established a progression-free survival benefit with switch maintenance therapy with sunitinib compared with placebo after 1st line therapy in advanced NSCLC.
63. Socinski MA, Novello S, Brahmer JR, Rosell R, Sanchez JM, Belani CP, et al. Multicenter, phase II trial of sunitinib in previously treated, advanced non-small-cell lung cancer. *J Clin Oncol.* 2008; 26:650–6. [PubMed: 18235126]
64. Novello S, Scagliotti GV, Rosell R, Socinski MA, Brahmer J, Atkins J, et al. Phase II study of continuous daily sunitinib dosing in patients with previously treated advanced non-small cell lung cancer. *Br J Cancer.* 2009; 101:1543–8. [PubMed: 19826424]
65. Scagliotti GV, Krzakowski M, Szczesna A, Strausz J, Makhson A, Reck M, 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. [PubMed: 22564989]
66. Reck M, Kaiser R, Eschbach C, Stefanic M, Love J, Gatzemeier U, et al. A phase II double-blind study to investigate efficacy and safety of two doses of the triple angiokinase inhibitor BIBF 1120 in patients with relapsed advanced non-small-cell lung cancer. *Ann Oncol.* 2011; 22:1374–81. [PubMed: 21212157]
67. Reck M, Kaiser R, Mellemaard A, Douillard JY, Orlov S, Krzakowski M, 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. [PubMed: 24411639]
68. Hanna NH, Kaiser R, Sullivan RN, Aren O, Ahn MJ, Tiangco B, et al. Lume-lung 2: A multicenter, randomized, double-blind, phase III study of nintedanib plus pemetrexed versus placebo plus pemetrexed in patients with advanced nonsquamous non-small cell lung cancer (SNCLC) after failure of first-line chemotherapy. *J Clin Oncol.* 2013; 31(suppl):abstr 8034.
69. Goss GD, Arnold A, Shepherd FA, Dediu M, Ciuleanu TE, Fenton D, 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. [PubMed: 19917841]
70. Gadgeel SM, Ruckdeschel JC, Wozniak AJ, Chen W, Hackstock D, Galasso C, et al. Cediranib, a VEGF receptor 1, 2, and 3 inhibitor, and pemetrexed in patients (pts) with recurrent non-small cell lung cancer (NSCLC). *J Clin Oncol.* 2011; 29(suppl):abstr 7564.
71. Blumenschein GR Jr, Kabbavar F, Menon H, Mok TS, Stephenson J, Beck JT, 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. [PubMed: 21321086]
72. Scagliotti GV, Vynnychenko I, Park K, Ichinose Y, Kubota K, Blackhall F, 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. [PubMed: 22753922]

73. Weiss JM, Villaruz LC, Socinski MA, Ivanova A, Grilley-Olson J, Dhruva N, et al. A single-arm phase II trial of pazopanib in patients with advanced non-small cell lung cancer with non-squamous histology with disease progression on bevacizumab containing therapy. *Lung Cancer*. 2014
74. Spigel D, Burris HA 3rd, Greco FA, Shih KC, Lipman AJ, Flora DB, et al. A Randomized phase II study of pazopanib or placebo in combination with erlotinib in patients with advanced non-small cell lung cancer. *J Thorac Oncol*. 2012; 7 Suppl(9):abstr 13.
75. Belani CP, Yamamoto N, Bondarenko IM, Poltoratskiy A, Novello S, Tang J, et al. Randomized phase II study of pemetrexed/cisplatin with or without axitinib for non-squamous non-small-cell lung cancer. *BMC Cancer*. 2014; 14:290. [PubMed: 24766732]
76. Twelves C, Chmielowska E, Havel L, Popat S, Swieboda-Sadlej A, Sawrycki P, et al. Randomised phase II study of axitinib or bevacizumab combined with paclitaxel/carboplatin as first-line therapy for patients with advanced non-small-cell lung cancer. *Ann Oncol*. 2014; 25:132–8. [PubMed: 24356624]
77. Schiller JH, Larson T, Ou SH, Limentani S, Sandler A, Vokes E, et al. Efficacy and safety of axitinib in patients with advanced non-small-cell lung cancer: results from a phase II study. *J Clin Oncol*. 2009; 27:3836–41. [PubMed: 19597027]
78. Heymach JV, Paz-Ares L, De Braud F, Sebastian M, Stewart DJ, Eberhardt WE, et al. Randomized phase II study of vandetanib alone or with paclitaxel and carboplatin as first-line treatment for advanced non-small-cell lung cancer. *J Clin Oncol*. 2008; 26:5407–15. [PubMed: 18936474]
79. de Boer RH, Arrieta O, Yang CH, Gottfried M, Chan V, Raats J, 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. [PubMed: 21282537]
80. Herbst RS, Sun Y, Eberhardt WE, Germonpre P, Saijo N, Zhou C, 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. [PubMed: 20570559]
81. Natale RB, Thongprasert S, Greco FA, Thomas M, Tsai CM, Sunpaweravong P, 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. [PubMed: 21282542]
82. Lee JS, Hirsh V, Park K, Qin S, Blajman CR, Perng RP, 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. [PubMed: 22370318]
83. Tan EH, Goss GD, Salgia R, Besse B, Gandara DR, Hanna NH, 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. [PubMed: 21597387]
84. Nikolinakos PG, Altorki N, Yankelovitz D, Tran HT, Yan S, Rajagopalan D, et al. Plasma cytokine and angiogenic factor profiling identifies markers associated with tumor shrinkage in early-stage non-small cell lung cancer patients treated with pazopanib. *Cancer Res*. 2010; 70:2171–9. [PubMed: 20215520]
85. Hanrahan EO, Lin HY, Kim ES, Yan S, Du DZ, McKee KS, et al. Distinct patterns of cytokine and angiogenic factor modulation and markers of benefit for vandetanib and/or chemotherapy in patients with non-small-cell lung cancer. *J Clin Oncol*. 2010; 28:193–201. [PubMed: 19949019]
86. Wakelee HA, Dahlberg SE, Keller SM, Gandara DR, Graziano SL, Leighl NB, et al. Interim report of on-study demographics and toxicity from E1505, a phase III randomized trial of adjuvant (adj) chemotherapy (chemo) with or without bevacizumab (B) for completely resected early-stage non-small cell lung cancer (NSCLC). *ASCO Meet Abstr*. 2011; 29:7013.
87. Socinski MA, Stinchcombe TE, Moore DT, Gettinger SN, Decker RH, Petty WJ, et al. Incorporating bevacizumab and erlotinib in the combined-modality treatment of stage III non-small-cell lung cancer: results of a phase I/II trial. *J Clin Oncol*. 2012; 30:3953–9. [PubMed: 23045594]

Fig. 1.

Kaplan–Meier estimates of **a** overall survival and **b** progression-free survival of carboplatin/paclitaxel/bevacizumab (BPC) and carboplatin/paclitaxel (PC) in E4599. From Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med* 355: 2542–2550. Copyright ©2006 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society

Fig. 2.

Kaplan–Meier estimates of **a** overall survival and **b** progression-free survival of ramucirumab/docetaxel and placebo/docetaxel in REVEL. Reprinted from The Lancet, Vol. 384, Garon EB, Ciuleanu TE, Arrieta O, Prabhaskar K, Syrigos KN, Goksel T, 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. Pages 665–673, Copyright ©2014, with permission from Elsevier

Table 1

Selected clinical trials evaluating anti-angiogenic monoclonal antibodies in advanced NSCLC

Study	Setting	Study arms	No. of patients	RR (%)	PFS (mos)	OS (mos)
<i>Bevacizumab</i>						
ECOG 4599 [35]	1st line	Carboplatin/paclitaxel	444	15	4.5	10.3
		Carboplatin/paclitaxel/bevacizumab	434	35*	6.2*	12.3*
AVAiL [36, 37]	1st line	Cisplatin/gemcitabine/placebo	347	20.1	6.1	13.1
		Cisplatin/Gemcitabine/Bevacizumab 7.5 mg/kg	345	34.1*	6.7*	13.6
POINTBREAK [41]	1st line	Cisplatin/Gemcitabine/Bevacizumab 15 mg/kg	351	30.4*	6.5*	13.4
		Carboplatin/paclitaxel/bevacizumab	467	33.0	5.6	13.4
Kato et al [44]	1st line	Carboplatin/pemetrexed/bevacizumab	472	34.1	6.0*	12.6
		Erlotinib	77	63.6	9.7	NR
ATLAS [39]	<i>EGFR</i> mutant	Erlotinib/bevacizumab	77	69.3	16*	
	Erlotinib Maintenance	Bevacizumab/placebo	373		3.7	13.3
BeTa [42]		Bevacizumab/erlotinib	370		4.8*	14.4
	2nd line	Erlotinib/placebo	317	6	1.7	9.2
<i>Ramucirumab</i>		Erlotinib/bevacizumab	319	13	3.4	9.3
Camidge et al [53]	1st line	Carboplatin/paclitaxel/ramucirumab	40	55	7.9	17.9
Doebele et al [54]	1st line	Platinum/pemetrexed	71	38	5.6	10.5
		Platinum/pemetrexed/ramucirumab	69	49.3	7.2	13.9
REVEL [55]	2nd line	Docetaxel/placebo	625	14	3.0	9.1
		Docetaxel/ramucirumab	628	23*	4.5*	10.5*
<i>Aflibercept</i>						
Leight et al [57]	3rd line and beyond	Platinum and erlotinib resistant Aflibercept	98	2	2.7	6.2
VITAL [58]	2nd line	Docetaxel/placebo	457	8.9	4.1	10.4
		Docetaxel/aflibercept	456	23.3*	5.2*	10.1

mos months, RR response rate, PFS progression-free survival, OS overall survival, NR not reported, TKI tyrosine kinase inhibitor

* $P < 0.05$

Table 2

Selected clinical trials evaluating anti-angiogenic tyrosine kinase inhibitors in NSCLC

Study	Setting	Study arms	No. of patients	RR (%)	PFS (mos)	OS (mos)
<i>Sorafenib</i>						
ESCAPE [59]	1st line	Carboplatin/paclitaxel/placebo	462	24	5.4	10.6
		Carboplatin/paclitaxel/sorafenib	464	27.4	4.6	10.7
NEXUS [60]	1st line	Cisplatin/gemcitabine/placebo	387	26	5.5	12.5
		Cisplatin/gemcitabine/sorafenib	385	28	6.0*	12.4
MISSION [61]	3rd/4th line	Placebo/BSC	353	0.9	1.4	8.4
		Sorafenib/BSC	350	4.9*	2.8*	8.3
<i>Sunitinib</i>						
CALGB 30607 [62]	Switch maintenance	Placebo	104	5.8	2.8	11.2
		Sunitinib	106	11	4.3*	11.2
Socinski et al [63]	2nd/3rd line	Sunitinib	63	11.1	3.0	9.3
Novello et al [64]	2nd/3rd line	Docetaxel/placebo	47	2.1	3.0	9.1
		Docetaxel/ramucirumab				10.5
Scagliotti et al [65]	2nd/3rd line	Erlotinib/placebo	480	6.9	2.0	8.5
		Erlotinib/sunitinib	480	10.6*	3.6*	9.0
<i>Nintedanib</i>						
Reck et al [66]	2nd line and beyond	Nintedanib	73	1.4	1.7	5.6
LUME Lung 1 [67]	2nd line	Docetaxel/placebo	659	2.7	3.3	9.1
		Docetaxel/nintedanib	655	3.4*	4.4	10.1
LUME Lung 2 [68]	2nd line	Pemetrexed/placebo	360	8.3	3.6	12.7
		Pemetrexed /nintedanib	353	9.1	4.4*	12.2
<i>Cediranib</i>						
BR24 [69]	1st line	Carboplatin/paclitaxel/placebo	125	16	5.0	10.1
		Carboplatin/paclitaxel/cediranib	126	38*	5.6	10.5 ^a
Gadgeel et al [70]	2nd/3rd line No prior bevacizumab	Pemetrexed/cediranib	38	29	5.6	11
<i>Motesanib</i>						
Bleumenshein et al [71]	1st line	Carboplatin/paclitaxel/bevacizumab	63	37	8.3	14

Study	Setting	Study arms	No. of patients	RR (%)	PFS (mos)	OS (mos)
MONET1 [72]	1st line	Carboplatin/Paclitaxel/Motesanib 125 mg qd	61	30	7.7	14
		Carboplatin/Paclitaxel/Motesanib 75 mg bid	62	23	5.8	12.8
		Carboplatin/paclitaxel/placebo	549	26	5.4	11
		Carboplatin/paclitaxel/motesanib	541	40*	5.6*	13
<i>Pazopanib</i>						
Weiss et al [73]	Progression of bevacizumab	Pazopanib	15	0	2.3	6.0
Spigel et al [74]	2nd/3rd line	Erlotinib/placebo	65	5	1.8	6.7
		Erlotinib/pazopanib	127	10	2.6*	6.8
<i>Axitinib</i>						
Belani et al [75]	1st line	Cisplatin/pemetrexed	57	26.3	7.1	15.9
		Cisplatin/Pemetrexed/Axitinib daily	55	45.5	8.0	17
		Cisplatin/Pemetrexed/Axitinib days 2–19	58	39.7	7.9	14.7
		Carboplatin/paclitaxel/placebo	60	43.3	6.1	13.3
Twelves et al [76]	1st line	Carboplatin/paclitaxel/axitinib	58	29.3	5.7	10.6
Schiller et al [77]	1st/2nd line	Axitinib	32	9	4.9	14.8
<i>Vandetanib</i>						
Heymach et al [78]	1st line	Carboplatin/paclitaxel	52	25	5.6	12.6
		Carboplatin/paclitaxel/vandetanib	56	32	6.0	10.2
		Vandetanib	73	7*	2.9	10.2
		Pemetrexed/placebo	278	8	3.0	9.2
ZEAL [79]	2nd line	Pemetrexed/vandetanib	256	19*	4.4	10.5
		Docetaxel/placebo	697	10	3.2	9.9
		Docetaxel/vandetanib	694	17*	4.0*	10.3
		Erlotinib	617	12	2.0	7.8
ZEST [81]	2nd/3rd line	Vandetanib	623	12	2.6	6.9
		Placebo	307	0.7	1.8	7.8
		Vandetanib	617	2.6*	1.9*	8.5
<i>Linifanib</i>						
Tan et al [83]	2nd/3rd line	Linifanib	139	5.0	3.6	9.0

mos months, *RR* response rate, *PFS* progression-free survival, *OS* overall survival, *NR* not reported, *TKI* tyrosine kinase inhibitor, *BSC* best supportive care, *qd* daily, *bid* twice daily

Survival in 296 randomly assigned patients

$P<0.05$ *

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