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Lung Cancer (HA Wakelee, Section Editor)

The Role of Angiogenesis Inhibitors in the Era of Immune Checkpoint Inhibitors and Targeted Therapy in Metastatic Non-Small Cell Lung Cancer

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Opinion statement

The treatment of advanced non-small cell lung cancer (NSCLC) has evolved to include targeted therapy, immunotherapy as well as chemotherapy for selected patients in the first-line setting. Angiogenesis inhibitors have been used in combination with chemotherapy in the first-line and maintenance settings providing improved progression-free survival (PFS) and objective response rate (ORR), as well as overall survival (OS) in selected studies. Biologic rationale exists for combining anti-angiogenic agents with immunotherapy and targeted kinase inhibitors (TKIs). A recent study has demonstrated improved survival when anti-PD-L1 therapy was added to chemotherapy plus bevacizumab. Subgroup analysis of patients with mutations in the epidermal growth factor receptor (EGFR) gene and rearrangements in the anaplastic lymphoma kinase (ALK) gene also demonstrated benefit with combined anti-PD-L1, bevacizumab, and platinum chemotherapy.

Further investigation into combination therapy is warranted in the *EGFR*- and *ALK*-positive population given this signal. Anti-angiogenics combined with EGFR-targeted treatment in the wild-type population have shown modest PFS benefit with no OS benefit, and their routine use has not been adopted. The combination of EGFR inhibitors plus vascular endothelial growth factor (VEGF) inhibitors in the *EGFR* mutation-positive population has demonstrated substantial improvements in response and PFS; however, given the higher toxicity and lack of survival benefit to date, combination therapy in this group should be used with caution. At the present time, use of bevacizumab can be recommended with atezolizumab and chemotherapy for the first-line treatment of non-squamous NSCLC patients. Data with other checkpoint inhibitors and anti-angiogenics are too early to make firm recommendations regarding their use.

Introduction

Systemic treatment options for patients with metastatic NSCLC have substantially improved in the past decade. Current first-line treatment options in stage IV disease depend largely on the molecular characteristics of the tumor, and *EGFR/ALK/ROS1/BRAF* and PD-L1 testing for these patients is routine [1]. In patients with molecular drivers (*EGFR/ALK/ROS1/BRAF*), first-line treatment consists of targeted therapy. For patients with *EGFR* mutant advanced lung cancer, first-line therapy options consist of gefitinib, erlotinib, afatinib, dacomitinib, or osimertinib, based on improved progression-free survival and tolerability when compared to chemotherapy [2–5].

In patients without a molecular driver or intermediate/low PD-L1 expression, platinum doublet chemotherapy plus or minus anti-PD-1 therapy (pembrolizumab) remains the backbone of treatment. The addition of anti-angiogenic therapies to chemotherapy, specifically VEGF inhibitors, has consistently shown improvement in PFS and ORR but data on OS benefit are conflicting. First-line trials with bevacizumab [6, 7], and second-line trials with ramucirumab (REVEL) and nintedanib (LUME-Lung1) have shown improved OS, most commonly in those with lung adenocarcinoma [8, 9]. These trials have led to the approval of bevacizumab in combination with chemotherapy in the first-line setting in non-squamous NSCLC, ramucirumab in combination with docetaxel in any pathologic subtype, and nintedanib in combination with docetaxel in the second-line setting for patients with adenocarcinoma. Data from meta-analyses have consistently revealed PFS and ORR benefit with the addition of anti-VEGF agents to chemotherapy but OS benefit has not been consistent [10–12].

Immunotherapy has become a cornerstone of treatment of advanced NSCLC. In the Keynote 024 study, patients with PD-L1 tumor proportion score (TPS) ≥ 50%, (by 22C3 assay, *EGFR* and *ALK* wild type) had improved OS (30.0 months with pembrolizumab v. 14.2 months with chemotherapy, HR 0.63; 95% CI 0.47, 0.86) with reduced toxicity [13]. Pembrolizumab has consequently replaced chemotherapy as the first-line treatment choice in this patient population. Second-line trials of nivolumab and atezolizumab in pre-treated but otherwise unselected advanced NSCLC patients as well as pembrolizumab in those with PD-L1 TPS-positive tumors (≥ 1%) have all shown improved OS compared to docetaxel chemotherapy [14–17]. Recently, combinations of chemotherapy plus anti-PD-1 agents in squamous and non-squamous NSCLC patients have shown OS benefit in the driver mutation-negative population regardless of PD-L1 status and are emerging as standard in those with low or negative PD-L1 tumors [18, 19].

To date, there are few trials of combination angiogenesis inhibitors with TKIs or immunotherapy. The mostly widely studied agent in combination with TKIs and/or immunotherapy is bevacizumab; however, other monoclonal antibodies such as ramucirumab and multi-targeted kinase inhibitors such as nintedatinib have also been studied in early phase trials. This article will explore the role of angiogenesis inhibitors in the context of immunotherapy and targeted therapy in metastatic NSCLC.

Rationale for combining angiogenesis inhibitors and anti-PD-1/PD-L1 immunotherapy

Immunotherapy in the form of checkpoint inhibition is a highly effective anti-cancer treatment; however, it is not active in all patients. PD-1 and PD-L1 inhibitors do not have direct cytotoxic effects, but rather exert their therapeutic effect through disruption of the interaction between programed death receptor on T effector cells and programed death ligand on tumor cells. Blocking this pathway releases the inhibition of T effector cells and promotes immune-mediated anti-tumor activity. Immune activity in tumor cells is not solely regulated by PD-1/PD-L1 interaction, and angiogenic factors play a direct and indirect role in immune suppression [20••].

In order for checkpoint inhibition to have an anti-cancer effect, T cells must have access to and be functional in the tumor microenvironment. It has been extensively described that tumor cells upregulate vascular endothelial growth factor (VEGF) expression in order to promote neovascularization. This process, however, results in the formation of abnormal vessels and induces a hypoxic and acidic environment [20••]. This contributes to the immunosuppressive effect of the tumor microenvironment, and in vitro and in vivo mouse models, hypoxia enhances the activity of suppressor T regulatory cells and inhibits effector T cell function [21]. Also, hypoxic conditions have been found to lead to PD-L1 upregulation in tumor-bearing mice [22].

Expression of VEGF and basic fibroblast growth factor (bFGF) has been shown to have negative regulatory effects on leukocyte adhesion in nude mice models harboring colon carcinomas and melanomas [23]. This results in decreased trafficking of immune cells into the tumor microenvironment [20••]. VEGF also plays a role in dendritic cell maturation, and increased levels of VEGF have been shown to block development of dendritic cells, as well as other hematopoietic stem cells [24].

In preclinical models, VEGF and vascular endothelial growth factor receptor (VEGFR) inhibitors can improve immune cell differentiation, translocation, and function through manipulation of the tumor microenvironment [25]. These data have led to the hypothesis that angiogenesis inhibitors and immune checkpoint inhibitors may be synergistic. In vitro studies of combination VEGF/PD-L1 blockade revealed improved anti-PD-L1 efficacy by enhancing the translocation and activity of T effector cells into the tumor microenvironment [25]. These preclinical data have led to the hypothesis that interruption of the VEGF pathway may allow augmentation of the effect of PD-1/PD-L1 blockade and has led to the development of clinical trials of combination therapy.

Rationale for combining VEGF inhibitors with EGFR TKIs

VEGF and EGFR signal transduction have many overlapping and parallel downstream pathways [26]. EGFR-mediated signaling has been associated with an increase in the production of small molecular stimulators of angiogenesis such as IL-8, VEGF, and angiopoietin 1 and 2 among others [27]. There is also evidence to suggest that blocking VEGF signaling in vitro can result in

downregulation of EGFR autocrine signaling via decreased phosphorylation of the EGFR signaling pathway [28].

As such, there is biological rationale for dual inhibition of these pathways. In preclinical mouse xenograft models, dual inhibition of VEGF and EGFR has been shown to have additive [29], and in some studies synergistic [30], effects on tumor inhibition. This potential synergy of dual blockade has been especially interesting in *EGFR* oncogene driven cancers. Acquired EGFR TKI resistance may be in part related to increase VEGF signaling. In a xenograft model of human squamous cell carcinoma, tumors with acquired EGFR TKI resistance demonstrated significant upregulation of VEGF expression, postulating this as a potential resistance mechanism [31]. In *EGFR* mutant NSCLC xenograft models, in tumors initially sensitive to an EGFR TKI (erlotinib), VEGF expression was suppressed in the erlotinib-sensitive phase and restored in the erlotinib-refractory phase [32]. This preclinical groundwork has led to interest in combining VEGF inhibitors with EGFR inhibitors in the clinical realm.

Immunotherapy and bevacizumab: clinical data

Bevacizumab is the most extensively studied anti-angiogenic agent with checkpoint inhibitors. Bevacizumab is a monoclonal antibody targeting VEGF and has been approved for the use in metastatic non-squamous NSCLC in combination with first-line chemotherapy. Sandler et al. reported a median improvement in OS by 2 months (HR 0.79, $p = 0.003$) with bevacizumab combined with carboplatin/paclitaxel chemotherapy [6]. Other trials of combination chemotherapy plus bevacizumab have shown mixed results. Meta-analyses consistently reveal PFS and ORR benefit, but less certainty in OS benefit [10–12].

IMpower150 was a 3-arm trial of patients with driver mutation-negative non-squamous NSCLC (or driver mutation positive-post-progression on approved TKIs), in which they were randomized to receive bevacizumab/carboplatin/paclitaxel (BCP), atezolizumab/carboplatin/paclitaxel (ACP), or atezolizumab/bevacizumab/carboplatin/paclitaxel (ABCP) [33••]. The statistical analysis plan prespecified comparison of the BCP arm versus the ACP arm if the ABCP arm revealed improved OS when compared to the BCP arm. Only an indirect comparison could be made between the ABCP and ACP arm. In the driver mutation-negative population, median PFS was longer in the ABCP vs the BCP arm (8.3 months vs. 6.8 months, HR 0.62, 95% CI 0.52, 0.74), and median OS was longer in the ABCP arm versus the BCP arm (19.2 months vs. 14.7 months, HR 0.78, 95% CI 0.64, 0.96). When ACP and BCP were compared, there was no statistically significant improvement in OS (HR 0.88, 95% CI 0.72, 1.08, $p = 0.204$) [34••]. No direct comparison was made between ACP and ABCP outcomes and although both arms had similar median OS results (19.4 months vs. 19.2 months), only the HR for the ABCP group was significant when compared to the BCP group [34••]. Therefore, it is reasonable to wonder if the addition of bevacizumab to the ACP regimen was the key factor responsible for the improved survival outcome.

Interestingly, in the *EGFR*/*ALK*-positive prespecified subgroup analysis, the ABCP group had improved PFS compared to the BCP group (median, 9.7 months vs. 6.1 months; HR 0.59, 95% CI 0.37, 0.94) [31]. In this subgroup,

OS improvement was also seen, although not statistically significant (median OS NR vs. 17.5 months; HR 0.54, 95% CI 0.29, 1.03) [34••]. This signal is worth exploring further, as in many prior anti-PD-L1/PD-1 trials, there has been little benefit to the addition of checkpoint inhibitors in this subgroup.

Bevacizumab has also been studied in the maintenance setting with or without nivolumab in patients post-platinum doublet chemotherapy [35]. This phase I study has only been published in abstract form and was conducted to assess safety and tolerability. There were no new safety signals recognized, but promising median PFS was observed in non-squamous patients of 37.1 weeks with nivolumab and bevacizumab ($N = 12$), and 21.4 weeks with nivolumab monotherapy ($N = 13$), although numbers were small.

Pembrolizumab has also been combined with bevacizumab in the Keynote 021 study (cohort B, non-squamous patients only) [18]. Each individual within the cohort was randomized to pembrolizumab 2 or 10 mg/kg q3weekly. Preliminary data have been presented from cohort A ($N = 25$) (pembrolizumab/carboplatin/paclitaxel + pembrolizumab maintenance), cohort B ($N = 25$) (pembrolizumab/carboplatin/paclitaxel/bevacizumab, + pembrolizumab/bevacizumab maintenance) (non-squamous), and cohort C ($N = 24$) (carboplatin/pemetrexed/pembrolizumab+ pemetrexed/pembrolizumab maintenance). Median PFS in cohort A (no bevacizumab) was 10 months (95% CI 4, NR), not reached for cohort B (95% CI 4.1, NR) and 10 months in cohort C (no bevacizumab) (95% CI 6, 15). Survival data were not yet mature, and given the small numbers, no inferences regarding efficacy can be made. There were no new safety issues identified.

Studies are ongoing to investigate the combinations of bevacizumab with checkpoint inhibitors and chemotherapy; however, most are in their infancy and have not reported preliminary results. The IMpower150 trial revealed improved OS with atezolizumab added to bevacizumab/carboplatin/paclitaxel, including in an exploratory subgroup of patients with *EGFR*/*ALK*-positive lung cancer. More data are necessary to confirm this finding in the subgroup analysis, and in future trials, direct comparisons of immunotherapy with or without bevacizumab will be important.

Immunotherapy and ramucirumab: clinical data

Ramucirumab is a monoclonal antibody that targets the VEGF receptor 2 (VEGFR2). Contrary to bevacizumab which binds VEGF-A, ramucirumab blocks the VEGF receptor preventing binding of VEGF and downstream signaling. In the REVEL trial, ramucirumab was evaluated in combination with docetaxel in the second-line setting for NSCLC patients that progressed after first-line platinum doublet chemotherapy [9]. Median OS was 10.5 months in the ramucirumab plus docetaxel arm and 9.1 months in the placebo plus docetaxel arm (HR 0.86, 95% CI 0.75, 0.98). This study led to the US Food and Drug Administration (FDA) approval of ramucirumab in combination with docetaxel post-progression after platinum doublet chemotherapy.

Keynote 098 is a phase 1a/b clinical trial assessing a combination of ramucirumab with pembrolizumab in multiple tumor types (NSCLC, gastric/gastroesophageal junction, urothelial carcinoma, biliary tract cancer) post-progression on systemic therapy [36, 37]. Currently, only the interim safety and

clinical activity report is available in abstract form [38]. Twenty-seven patients were included in the NSCLC cohort (78% adenocarcinoma, 15% squamous cell carcinoma) and received ramucirumab (10 mg/kg on day 1) with pembrolizumab (200 mg on day 1) on a q3 weekly cycle. Thirty percent of patients had an objective response, and 85% experienced disease control. Median PFS was not reached, and median duration of treatment is 6.8 months or longer. All subgroups of PD-L1 status exhibited response. There were no new safety signals. In a heavily pretreated population (59% ≥ 2 lines of therapy), these results are encouraging; however, small numbers limit inference of effectiveness of this combination. The data on combination ramucirumab and immunotherapy is sparse, and we await the results of multiple ongoing trials (see "Future Directions") prior to making any definitive conclusions about its role with checkpoint inhibitors in NSCLC.

Anti-angiogenesis and anti-EGFR therapy: clinical data in the *EGFR* wild-type population

There have been multiple studies of combination EGFR inhibitors and anti-angiogenesis inhibitors in an unselected population. Many of these trials have shown modest improvements in PFS and ORR, but little OS impact and have not changed practice. Zhao et al. published a meta-analysis that included 7109 patients from 16 different phase II/III RCTs [39•]. ORR and PFS were found to be significantly improved in the patients who received combined therapy compared to those that received EGFR inhibitor monotherapy (odds ratio for ORR = 1.39, 95% CI 1.12, 1.74, PFS HR 0.73, 95% CI 0.67, 0.81). OS analysis comparing those that received combination therapy compared to controls, however, did not show a statistically significant benefit with combination therapy (HR 0.98, 95% CI 0.92, 1.04, $p = 0.41$). The most widely studied combination therapy has been with bevacizumab and erlotinib. A systematic review and meta-analysis of combination bevacizumab and erlotinib that included 10 studies with a total of 2802 participants did not find an OS (95% CI, 0.87, 1.12; $p = 0.825$) or ORR (95% CI 0.69, 1.67, $p = 0.758$) benefit when bevacizumab was added to erlotinib [40•]. There was no statistically significant difference in PFS (5.6 months vs. 4.7 months, 95% CI 0.63, 1.15, $p = 0.297$). Subgroup analysis, however, showed improved OS (95% CI 0.29, 0.69, $p < 0.001$) in the *EGFR* mutant subpopulation.

On the individual trial level, the combination of erlotinib and bevacizumab has been compared to erlotinib alone in non-squamous, unselected, NSCLC patients in the second-line [41]. OS did not differ between placebo and bevacizumab group (HR 0.97, 95% CI 0.80, 1.18); however, PFS was longer in the bevacizumab group (3.4 months vs. 1.7 months, HR 0.62, 95% CI 0.52, 0.75). Bevacizumab combined with erlotinib versus placebo as a maintenance therapy post-first-line platinum doublet chemotherapy also revealed combination bevacizumab/erlotinib compared with bevacizumab/placebo improved PFS (4.8 months vs. 3.7 months, HR 0.71, 95% CI 0.58, 0.86) with no OS benefit (14.4 months vs. 13.3 months HR, 0.92, 95% CI 0.70, 1.21) [42]. Other phase II trials have compared efficacy of bevacizumab/erlotinib versus bevacizumab/chemotherapy (cisplatin/gemcitabine or carboplatin/paclitaxel)

in the front line setting in stage IV non-squamous patients. This trial was halted prematurely at an interim analysis which showed median PFS in the bevacizumab/erlotinib arm was 18.4 weeks compared to 25.0 weeks in the bevacizumab/chemotherapy arm (HR 2.05, $p = 0.0183$) [43].

Bevacizumab has also been studied in combination with cetuximab, a monoclonal antibody to EGFR in stage IV non-squamous NSCLC patients undergoing first-line platinum doublet chemotherapy (carboplatin/paclitaxel) [44]. This was first studied in a phase II trial to assess safety as the primary endpoint. There were no new safety signals. The median PFS was 7 months (95% CI 6, 8 months) and median OS was 15 months (95% CI 11, 21 months). Given these findings, a phase 3 trial was conducted in non-squamous NSCLC, and patients were randomized to paclitaxel plus carboplatin or carboplatin plus paclitaxel and bevacizumab (15 mg/kg, q21 days), either with cetuximab or without [45]. The primary endpoint was a co-primary endpoint of OS in the entire study population, and PFS in the *EGFR* FISH-positive subgroup. The median follow-up was 35.2 months (IQR 22.9, 39.9). In the *EGFR* FISH-positive subgroup, there was no statistically significant difference in PFS or OS. Median PFS was 5.4 months versus 4.8 months (HR 0.92, 95% CI 0.75, 1.12) and median OS in the entire study population was 10.9 months in the cetuximab group versus 9.2 months in the control group (HR 0.93, 95% CI 0.83, 1.04). Bevacizumab treatment was not associated with improved OS, PFS, or ORR in either the whole population or when patients were stratified by *EGFR* FISH status.

Although bevacizumab has been the most widely studied anti-angiogenic in the *EGFR* wild-type population, there have been other combination studies with erlotinib and small molecule anti-angiogenics. A phase III trial of sunitinib (37.5 mg/m2 daily) in combination with erlotinib versus placebo in combination with erlotinib in the second- or third-line setting revealed median OS of 9.0 months for sunitinib plus erlotinib versus 8.5 months for placebo plus erlotinib (HR 0.92, 95% CI 0.79, 1.07) [46]. There was improvement in PFS (in the sunitinib arm 3.6 months vs. 2.0 months in the placebo arm, HR 0.81, 95% CI 0.70, 0.94), and ORR (ORR 10.6% vs. 6.9%, two-sided stratified log-rank $p = 0.047$).

Overall, evidence for use of anti-angiogenesis inhibitors in combination with EGFR inhibitors in an unselected patient population has consistently had modest PFS, and RR improvement, but there has been little impact on OS. Given these data, there has not been wide uptake of combination therapy in an unselected population.

Anti-VEGF therapy and anti-EGFR therapy: clinical data in the *EGFR* mutant NSCLC population

The most intriguing data with combination EGFR inhibitors and anti-VEGF treatments have been in the *EGFR* mutated "oncogene addicted" tumors. Seto et al. published a phase II randomized control trial of erlotinib plus bevacizumab or erlotinib alone as first-line therapy in stage IIIB/IV non-squamous NSCLC patients with activating *EGFR* mutations [47•]. The primary endpoint was PFS, and final analysis showed median PFS was 16.0 months with erlotinib plus bevacizumab (95% CI 13.9, 18.1) and 9.7 months with erlotinib alone (95% CI 5.7, 11.1) (HR 0.54, 95% CI 0.36, 0.79). The improved PFS, however, did not

translate to OS benefit. OS was 47.0 months for the erlotinib/bevacizumab group and 47.4 months for the erlotinib group (HR 0.81, 95% CI 0.53, 1.23, $p = 0.3267$) [48••]. A subsequent phase III trial has been published in abstract form, comparing bevacizumab/erlotinib to erlotinib monotherapy in the first-line setting for non-squamous *EGFR* mutation-positive disease [49••]. PFS was the primary endpoint and it was met at the interim analysis; however, the combination therapy had more grade 3 or higher adverse events, with 29% of patients in the bevacizumab/erlotinib arm discontinuing the study medication compared to 15% in the erlotinib monotherapy arm. PFS was 16.9 months (95% CI 14.2, 21.0) in the bevacizumab/erlotinib group and 13.3 months (95% CI 11.1, 15.3) with erlotinib monotherapy (HR 0.61, 95% CI 0.42, 0.88). OS data is not yet mature, and it will be interesting to see if the PFS benefit is maintained, given the negative OS benefit in the phase II study.

A similar single-arm phase II study was conducted in eight European countries, the BELIEF trial [50•]. Patients in this single-arm study received erlotinib and bevacizumab with the primary endpoint of PFS. Pretreatment *EGFR* T790M mutation status was centrally determined with a high sensitivity assay and was present in 34% of patients. Median PFS was 13.2 months (95% CI 10.3, 15.5) which did not meet the prespecified endpoint of 18 months. The primary endpoint was met in the prespecified subgroup of T790M mutation-positive patients. In this group, median PFS was 16.0 months (95% CI 12.7, NR), with a 12 month PFS of 68% (95% CI 50, 81), whereas in the T790M-negative group, median PFS was 10.5 months (95% CI 9.4, 14.2), with a 12 month PFS of 48% (95% CI 36, 59).

The IMpower150 study (discussed above) prespecified a subgroup analysis of the *EGFR*/*ALK*-positive population [33••]. Patients with driver mutation (*EGFR*/*ALK*)-positive disease were allowed on study post-progression on approved TKIs. They were randomized to therapy with BCP, ACP, and ABCP. When comparing the ABCP and BCP groups, there was an improved PFS in the ABCP group (median 9.7 months vs. 6.1 months, HR 0.59, 95% CI 0.37, 0.94). This trend was also seen in the updated survival analysis (median OS ABCP group NR and 17.5 months in the BCP group HR 0.54, 95% CI 0.29, 1.03) [34••]. This signal has not been seen in this subgroup in prior trials and warrants further investigation into the potential synergistic effect of anti-angiogenic agents and immune checkpoint inhibitors in the *EGFR* mutation-positive population. Although details of this subgroup analysis are limited, patients with *ALK*-rearranged lung cancer and are an important group for further study also.

In the *EGFR* activating mutation population, bevacizumab in combination with EGFR TKIs, or in combination with checkpoint inhibitors, has yielded an interesting signal. There may be enhanced benefit in this population and further trials of combination therapies are warranted to further evaluate the potential synergy of these drugs in this group of patients.

Future directions

Anti-angiogenics—specifically VEGF/R inhibitors—and checkpoint inhibitors have strong biological and preclinical rationale for their combination. Combination therapy is now a treatment option in the first line for

Table 1. Trials of immunotherapyz combined with anti-angiogenics (clinicaltrials.gov)

Clinical trial number	Population	Intervention	Phase	Status
NCT01633970	Advanced solid tumors	Atezolizumab + Bevacizumab	I	Active, not recruiting
NCT02443324	Advanced solid tumors (for NSCLC 0–3 prior lines of therapy)	Ramucirumab + embrolizumab (cohort C)	I	Active, not recruiting
NCT02572687	Stage IV GI or thoracic malignancies, NSCLC arm 1–3 prior lines of therapy, no prior anti-PD-1/PD-L1 therapy	Ramucirumab + durvalumab (NSCLC arm)	I	Active, not recruiting
NCT01454102/ Checkmate 012	Stage IIIB/IV NSCLC, first or subsequent line of therapy	Nivolumab + bevacizumab maintenance (arm D)	I	Active, not recruiting
NCT02574078/ Checkmate 370	Stage IV NSCLC	Nivolumab and bevacizumab maintenance (arm A)	I/II	Active, not recruiting
NCT03377023	Stage IV NSCLC, first or subsequent lines of therapy	Ipilimumab + nivolumab + nintedanib	I/II	Active, recruiting
NCT03713944	Stage IV non-squamous NSCLC, first line	Carboplatin, pemetrexed, atezolizumab, bevacizumab	II	Not yet recruiting
NCT03689855	Stage IV, NSCLC, post-progression on checkpoint inhibitor therapy (monotherapy or combined with chemotherapy)	Ramucirumab + atezolizumab	II	Not yet recruiting
NCT03647956	Stage IV NSCLC with *EGFR* activating mutations progressed post-EGFR TKIs	Atezolizumab, bevacizumab, carboplatin, pemetrexed	II	Recruiting
NCT03527108	Stage IV NSCLC post-progression on EGFR TKIs, chemotherapy or other IO agent (monotherapy or combined with chemotherapy)	Nivolumab + ramucirumab	II	Not yet recruiting
NCT02681549	Stage IV NSCLC + melanoma with one untreated brain metastases, no prior anti-PD-1/PD-L1 therapy	Pembrolizumab + bevacizumab	II	Recruiting
NCT03117049	Stage IIIB/IV non-squamous NSCLC, first line	Nivolumab + bevacizumab + carboplatin + paclitaxel	III	Recruiting

metastatic non-squamous NSCLC patients after IMpower150 showed that the addition of bevacizumab to chemotherapy and atezolizumab improved survival when compared to bevacizumab and chemotherapy

Table 2. Trials of anti-EGFR therapy combined with anti-angiogenics (clinicaltrials.gov)

Clinical trial number	Population	Intervention	Phase	Status
NCT03766490	Stage IV NSCLC, *EGFRmut*, second-line post-progression on TKI T790M (−)	Gefitinib/icotinib + anlotinib	N/A	Not yet recruiting
NCT02789345	Stage IV NSCLC, *EGFRmut* T790M (+) post-first-line TKI	Ramucirumab + Osimertinib	I	Active, not recruiting
NCT01454102/Checkmate 012	Stage IIIB/IV NSCLC, first or subsequent line of therapy	Erlotinib + bevacizumab maintenance (arm E)	I	Active, not recruiting
NCT02803203	Stage IV, *EGF-Rmut* positive, no prior TKI therapy	Osimertinib + bevacizumab	I/II	Recruiting
NCT02574078/Checkmate 370	Stage IV NSCLC	Nivolumab + Erlotinib maintenance (Arm E)	I/II	Active, not recruiting
NCT02039674/Keynote 021	Stage IV NSCLC, *EGFRmut* positive	Pembrolizumab and erlotinib (arm E) pembrolizumab + gefitinib (arm F)	I/II	Active, not recruiting
NCT03133546	Stage IV NSCLC, *EGFRmut* T790M (+), post-first-line EGFR TKI	Osimertinib + bevacizumab	II	Recruiting
NCT03126799	Stage IV NSCLC *EGFRmut* positive, first-line	Erlotinib + bevacizumab	II	Recruiting
NCT02971501	Stage IV NSCLC, *EGFRmut* positive, post-progression on EGFR TKI (T790M ±) with brain metastases	Osimertinib + bevacizumab (arm I)	II	Recruiting
NCT02655536	Stage IV, *EGFRmut* positive + asymptomatic brain metastases, first-line	Erlotinib + bevacizumab	II	Recruiting
NCT02411448	Stage IV NSCLC, *EGFRmut* positive (exon 19 del, L858R), first-line	Erlotinib + ramucirumab (Part A) Gefitinib or osimertinib + ramucirumab (part C)	III	Active, not recruiting

alone. In this trial, there was also PFS and non-statistically significant OS benefit from combination atezolizumab, bevacizumab, and chemotherapy in the *EGFR/ALK* mutation-positive subgroup. In *EGFR/ALK*-

positive patients, this signal has not been seen in other trials with checkpoint inhibitors, and warrants further investigation prior to adoption. Although there are promising data for combined anti-PD-L1/PD-1 and anti-VEGF/R with other agents, data are too early for routine recommendation of these combinations into treatment algorithms. There are ongoing phase I–III clinical trials (Table 1) of combination therapy which will help answer whether anti-angiogenics play a role in multiple settings by perpetuating checkpoint inhibitor response.

There is a larger body of clinical evidence for combination anti-angiogenics and EGFR inhibitors. In unselected patients, although combination therapy has managed to improve PFS and ORR in some trials, benefits have been modest and have not lead to improved OS; therefore, widespread use has not been routinely adopted. In the subgroup of *EGFR* activating mutants, data for treatment with combination EGFR inhibitors and anti-angiogenics has been the most promising, but increased toxicity of combination therapy and lack of OS improvement has limited routine use. Ongoing phase I–III trials of combination anti-angiogenics and EGFR inhibitors are now overwhelmingly in the *EGFR* activating mutation population (Table 2). There are, however, ongoing maintenance trials of anti-EGFR/anti-angiogenic therapy in the wild-type population (Table 2). Hopefully, we will be able to evaluate whether the addition of anti-angiogenics in patients with *EGFR* activating mutations improves the benefit from EGFR TKIs, without significantly increasing toxicity, as was seen in earlier trials.

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Compliance with Ethical Standards

Conflict of Interest

Kirstin Perdrizet declares that she has no conflict of interest.

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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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References and Recommended Reading

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

- • Of importance
- •• Of major importance

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