

Bevacizumab in the treatment of NSCLC: patient selection and perspectives

Alessia E Russo¹
Domenico Priolo¹
Giovanna Antonelli¹
Massimo Libra²
James A McCubrey³
Francesco Ferrà¹

¹Medical Oncology Department, San Vincenzo Hospital, Taormina (Messina), Italy; ²Laboratory of Translational Oncology & Functional Genomics, Department of Biomedical and Biotechnological Sciences, University of Catania, Catania, Italy; ³Department of Microbiology and Immunology, Brody School of Medicine at East Carolina University, Greenville, NC, USA

Abstract: Non-small-cell lung cancer (NSCLC) represents about 85% of all lung cancers, and more than half of NSCLCs are diagnosed at an advanced stage. Chemotherapy has reached a plateau in the overall survival curve of about 10 months. Therefore, in last decade novel targeted approaches have been developed to extend survival of these patients, including antiangiogenic treatment. Vascular endothelial growth factor (VEGF) signaling pathway plays a dominant role in stimulating angiogenesis, which is the main process promoting tumor growth and metastasis. Bevacizumab (bev; Avastin[®]) is a recombinant humanized monoclonal antibody that neutralizes VEGF's biologic activity through a steric blocking of its binding with VEGF receptor. Currently, bev is the only antiangiogenic agent approved for the first-line treatment of advanced or recurrent nonsquamous NSCLC in "bev-eligible" patients. The ineligibility to receive bev is related to its toxicity. In the pivotal trials of bev in NSCLC, fatal bleeding events including pulmonary hemorrhage were observed with rates higher in the chemotherapy-plus-bev group. Therefore, in order to reduce the incidence of severe pulmonary hemorrhage, numerous exclusion criteria have been characteristically applied for bev such as central tumor localization or tumor cavitation, use of anticoagulant therapy, presence of brain metastases, age of patients (elderly). Subsequent studies designed to evaluate the safety of bev have demonstrated that this agent is safe and well tolerated even in those patients subpopulations excluded from pivotal trials. This review outlines the current state-of-the-art on bev use in advanced NSCLC. It also describes patient selection and future perspectives on this antiangiogenic agent.

Keywords: bevacizumab, nonsquamous NSCLC, eligibility, safety, subpopulations

Introduction

Lung cancer is the most common cause of cancer-related mortality worldwide. Non-small-cell lung cancer (NSCLC) represents about 85% of all lung cancer cases;¹ the majority of NSCLC patients present with advanced-stage disease at diagnosis, and even if platinum-based doublet chemotherapy has improved the outcome of these patients, prognosis remains poor with a median survival time that does not exceed 10 months.² Therefore, in last decade novel targeted therapies have been developed. In 2015, two immune checkpoint inhibitors targeting programmed cell death-1 (PD-1), nivolumab and pembrolizumab, were approved for second-line therapy of NSCLC.³⁻⁶ In 2016, another checkpoint inhibitor targeting program death-ligand 1 (PD-L1), atezolizumab, was approved for the same indication.⁷ Moreover, pembrolizumab also received approval in 2016 for first-line NSCLC treatment in patients with high PD-L1-expressing tumors.⁸

Correspondence: Francesco Ferrà
Medical Oncology Department, San Vincenzo Hospital, Contrada Sirina,
98039 Taormina (ME), Italy
Tel +39 094 2579 282
Fax +39 094 2522 15
Email francescoferrau@tin.it

Angiogenesis inhibition is regarded another attractive therapeutic strategy for patients with NSCLC. In 1971, Folkman⁹ first suggested that tumor growth was dependent on angiogenesis, a complex process in which new blood vessels form out of preexisting capillaries; the development of hypoxic regions in the tumor promotes the production of proangiogenic factors. The vascular endothelial growth factor (VEGF) signaling pathway plays a dominant role in stimulating tumor angiogenesis.¹⁰ VEGF is overexpressed by most of solid tumors, and circulating levels of VEGF are elevated in many cancers, including lung cancer.¹¹ These findings have given rise to the development of agents that block the VEGF pathway to limit tumor angiogenesis. Bevacizumab (bev, Avastin) is a recombinant, humanized monoclonal antibody that blocks VEGF.¹² The Eastern Cooperative Oncology Group (ECOG) 4599 study compared the efficacy of carboplatin (carbo)/paclitaxel with or without bev in patients with advanced nonsquamous NSCLC.¹³ The addition of bev to paclitaxel and carbo has significantly improved the median overall and progression-free survival (PFS), marking the beginning of a new paradigm for the first-line treatment of advanced or metastatic NSCLC with nonsquamous cell histology in appropriately selected patients.

This review summarizes current data and future perspectives on bev in NSCLC. It also describes evidences of its good safety profile in patient subpopulations previously considered ineligible for bev, underlining that the selection of patients able to receive bev is currently based only on two valid eligibility criteria (NSCLC with nonsquamous histology and no history of clinically significant hemoptysis), considering the lack of valid biomarkers predictive of response to treatment with antiangiogenic therapy.

The role of tumor angiogenesis in NSCLC

Tumor growth and spread is dependent on the formation of new blood vessels out of preexisting capillaries;^{9,14} this process, termed tumor angiogenesis, is largely mediated by the hypoxia-inducible factor (HIF)-1 α which promotes transcription of proangiogenic genes encoding proteins such as VEGF, basic fibroblast growth factor, angiopoietins, interleukin-8, and placental growth factor, under hypoxic conditions.^{15,16} The overexpression of these proangiogenic factors stimulates resident endothelial cells to proliferate and migrate to form new capillary tubes.^{17,18} Bone-marrow-derived angiogenic cells are also recruited by tumor-associated stroma.¹⁹

The VEGF signaling pathway plays a dominant role in tumor angiogenesis. Its consists of five ligands (VEGF-A,

VEGF-B, VEGF-C, VEGF-D, and placental growth factor) and three VEGF tyrosine kinase receptors (VEGFR-1, VEGFR-2, and VEGFR-3). VEGFR-2 is the major mediator of VEGF-driven responses in endothelial cells.²⁰ VEGF is overexpressed by a majority of solid tumors, and circulating levels of VEGF are elevated in many cancer patients, including those with lung cancer.¹¹ It has been demonstrated that levels of VEGF correlate significantly with increased angiogenesis, poor prognosis, and lymph node metastasis in patients with NSCLC.^{21–25} Furthermore, Chen et al²⁶ have found that microvessel density, an indirect measure of angiogenesis, was higher in NSCLC tumor specimens from patients with advanced-stage than those with early-stage NSCLC, and it was also higher in patients with lymph node metastases than in those with no metastases. In addition, in a recent paper analyzing the role VEGFR2 expression in NSCLC cells lines, it has been shown that VEGF-dependent VEGFR2 activation was relevant in a subset of NSCLC cells and was associated with increased tumor cell proliferation.²⁷

Currently, the most established approach for limiting tumor angiogenesis is blockade of the VEGF pathway using monoclonal antibodies or tyrosine kinase inhibitors.

bev in the treatment of NSCLC

bev is a recombinant humanized monoclonal IgG1 antibody comprising amino acid sequences which are about 93% human and 7% murine. It has high affinity in binding with all VEGF-A isoforms circulating in blood and neutralizes VEGF's biologic activity through a steric blocking of its binding with VEGFR.

bev was approved for first-line treatment of bev-eligible patients with advanced nonsquamous NSCLC in combination with chemotherapy according to results of two Phase III trials (Table 1). In the randomized Phase III trial ECOG 4599, 878 patients with recurrent or advanced NSCLC (stage IIIB or IV) were randomized to receive carbo/paclitaxel with or without bev.¹³ Chemotherapy was administered every 3 weeks for six cycles and bev was administered at 15 mg/kg every 3 weeks until evidence of disease progression or unacceptable toxicity. Patients with squamous-cell tumors, brain metastases, clinically significant hemoptysis, or inadequate organ function or performance status ECOG >1 were excluded. Improvement of overall survival (OS), PFS and objective response rate (ORR) were observed for the combination of bev and chemotherapy. Specifically, the median survival was 12.3 months in patients treated with chemotherapy plus bev, as compared with 10.3 months in the chemotherapy-alone group (hazard ratio (HR) for death,

Table 1 Pivotal Phase III studies of bev in NSCLC: ECOG4599 and AVAiL

	ECOG 4599 ¹³	AVAiL ²⁸
Eligibility criteria		
Diagnoses	Stage IIIB, IV, or recurrent	Stage IIIB, IV, or recurrent
Histology	No predominantly squamous-cell cancer	Only nonsquamous NSCLC
Age	≥18 years	≥18 years
Performance Status	ECOG 0–I	ECOG 0–I
Main exclusion criteria		
	– Significant hemoptysis	– Significant hemoptysis
	– CNS metastases	– CNS metastases
	– Hemorrhagic diathesis	– History of thrombotic or hemorrhagic disorders
	– Coagulopathy	– Therapeutic anticoagulation
	– Therapeutic anticoagulation	– Use of aspirin
	– Use of aspirin	– Uncontrolled hypertension
	– Uncontrolled hypertension	– Tumors invading or abutting major blood vessels
Treatment arms		
	Arm 1: bev + carbo + pac	Arm 1: cis + gem + bev 7.5 mg/kg
	Arm 2: carbo + pac	Arm 2: cis + gem + bev 15 mg/kg
		Arm 3: cis + gem + placebo
Primary endpoint		
	OS	PFS
Results		
	Improvement in OS, PFS, ORR with bev	Improvement in PFS and ORR with both doses of bev
		No significant difference in OS

Abbreviations: bev, bevacizumab; carbo, carboplatin; cis, cisplatin; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; gem, gemcitabine; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; pac, paclitaxel; PFS, progression-free survival.

0.79; $p=0.003$). The median PFS in the two groups was 6.2 and 4.5 months, respectively (HR for disease progression, 0.66; $p<0.001$), with corresponding response rates of 35% and 15% ($p<0.001$). Rates of clinically significant bleeding were 4.4% and 0.7%, respectively ($p<0.001$). There were 15 treatment-related deaths in the chemotherapy-plus-bev group, including 5 from pulmonary hemorrhage.

In the randomized, placebo-controlled, Phase III trial Avastin in Lung Cancer (AVAiL), 1,043 patients with advanced (stage IIIB, with supraclavicular lymph node metastasis or malignant pleural or pericardial effusion, or stage IV) or recurrent nonsquamous NSCLC were randomized to receive cisplatin (cis) and gemcitabine (gem) for up to six cycles plus low-dose bev (7.5 mg/kg), high-dose bev (15 mg/kg), or placebo every 3 weeks until disease progression.²⁸ PFS was significantly prolonged with both doses of bev; the HRs for PFS were 0.75 (median PFS, 6.7 vs 6.1 months for placebo; $p=0.003$) in the low-dose group and 0.82 (median PFS, 6.5 vs 6.1 months for placebo; $p=0.03$) in the high-dose group compared with placebo. ORRs were 20.1%, 34.1%, and 30.4% for placebo, low-dose bev, and high-dose bev plus cis and gem, respectively. No significant difference in OS was observed, possibly because of high use of efficacious second-line therapies.²⁹ The rates of \geq grade 3 hypertension, vomiting, neutropenia, bleeding, and proteinuria were modestly higher in the bev arms than in the placebo arm.

Analyzing the results of five randomized clinical trials (2,252 patients) comparing platinum-based chemotherapy

doublets with or without bev in the first-line setting, Lima et al² showed that the addition of bev to chemotherapy resulted in a significant improvement in both PFS (absolute benefit of 1.4 months in median) and response rate (RR) (absolute difference of 16%). Moreover, it has been also observed that there is a small homogeneous but significant OS improvement with an 11% reduction in risk of death, but with an estimated absolute benefit of less than 1 month in median survival.

The randomized, open-label, Phase III PRONOUNCE trial compared the efficacy and safety of pemetrexed + carbo followed by pemetrexed (Pem + Cb) with paclitaxel + carbo + bev followed by bev (Pac + Cb + Bev) in patients with advanced nonsquamous NSCLC. The primary endpoint was PFS without grade 4 adverse events (G4PFS). Secondary endpoints included OS, PFS, RR, safety, and tolerability. Pem + Cb did not produce significantly better G4PFS compared with Pac + Cb + Bev. Pem + Cb was not superior in PFS, OS, or ORR compared with Pac + Cb + Bev. Both regimens were well tolerated, although toxicity profiles differed.³⁰

The emerging role of pemetrexed in treatment of non-squamous NSCLC has aroused great interest in evaluating this agent in combination with bev. In the Phase III POINT-BREAK trial, 939 patients were randomized to receive pemetrexed–carbo–bev, followed by pemetrexed plus bev in maintenance therapy or paclitaxel–carbo–bev followed by maintenance therapy with bev alone.³¹ PFS was statistically significantly longer for pemetrexed–carbo–bev than for paclitaxel–carbo–bev group (6.0 vs 5.6 months; HR,

0.83; 95% confidence interval [CI], 0.71–0.96; $p=0.012$). Median PFS for the maintenance population was 8.6 months for pemetrexed–carbo–bev and 6.9 months for paclitaxel–carbo–bev groups. However, improvements in PFS did not translate into an OS advantage.

In the Phase III AVAPERL trial, 376 patients received four cycles of chemotherapy with cis, pemetrexed, and bev; those achieving response or stable disease were randomly assigned to maintenance therapy with bev or bev plus pemetrexed. A significant PFS benefit was associated with bev plus pemetrexed maintenance compared with bev alone, and the combination was well tolerated.³² However, this study had some limitations that should be considered. First, survival data were based on selected patients who were eligible for bev and maintenance therapy. Second, there was no arm with pemetrexed alone as maintenance therapy.

Recently, treatment with dose-dense pemetrexed, gem, and bev demonstrated promising efficacy and manageable safety profile in patients with untreated advanced NSCLC.³³

Several trials have been designed to define bev's role in maintenance beyond progression and in an adjuvant setting. Nadler et al³⁴ have retrospectively analyzed US Oncology network's electronic medical records, dividing patients with advanced nonsquamous NSCLC treated from July 2006 through June 2008, in two cohorts based on whether or not they received bev monotherapy to progression (BTP) after completion of first-line chemotherapy plus bev. From the total 498 patients, 403 received first-line chemotherapy plus bev: 154 received BTP, 249 did not. Longer PFS and OS times were observed in patients who received BTP than in those who received no BTP (median OS, 20.9 months vs 10.2 months; median PFS, 10.3 months vs 6.5 months). Therefore, continued VEGF suppression led to more favorable clinical outcomes. According to promising results of this retrospective analysis, the multicenter, open-label, randomized, Phase IIIb AvaALL trial has randomized patients with advanced nonsquamous NSCLC whose disease has progressed after four to six cycles of first-line treatment with bev plus a platinum-based doublet and a minimum of two cycles of bev (monotherapy) maintenance treatment to standard second-line therapy (pemetrexed, docetaxel, or erlotinib) with or without bev. The primary endpoint was OS. Secondary endpoints included the 6-month, 12-month, and 18-month OS rates, PFS, and time to progression at second and third progressive disease, response rate, disease control rates, and duration of response at second and third progressive disease. The study has been completed, but results are not yet available.³⁵

The ECOG E1505 study is currently assessing if adjuvant chemotherapy is more effective with or without bev in treating patients with completely resected stage IB–IIIA NSCLC.³⁶

About 20% of advanced NSCLC cases harbors somatic mutations in the tyrosine kinase domain of *EGFR* gene. In these patients, the standard first-line treatments are the EGFR-tyrosine kinase inhibitors, such as gefitinib, erlotinib, or afatinib. Most of these patients develop resistance and relapse within about 1 year of initiation of an EGFR-tyrosine kinase inhibitor. Consequently, it is important to develop new combination strategies to delay this resistance. Preclinical data have showed that EGFR and VEGF share a common downstream pathway, suggesting the important role of VEGF in the resistance to EGFR blockade. The combination of erlotinib and bev showed very interesting clinical results. The JO25567 study is an open-label, randomized, multicenter, Phase II study that was conducted in Japan in order to assess the efficacy and safety of the combination of erlotinib and bev compared with erlotinib alone as first-line regimen in patients with nonsquamous NSCLC with activating EGFR mutation-positive disease. Median PFS (primary endpoint) was 16 months with erlotinib plus bev and 9.7 months with erlotinib alone (HR 0.54, 95% CI, 0.36–0.79; log-rank test $p=0.0015$);³⁷ the BELIEF study (bev and Erlotinib In EGFR Mut + NSCLC) is the European ongoing equivalent clinical trial.³⁸

A randomized, double-blind, placebo-controlled Phase III study (ATLAS) enrolled 1,157 patients with NSCLC (stage IIIB with malignant pleural effusion, stage IV, or recurrent) to receive maintenance bev every 3 weeks with or without erlotinib after four cycles of platinum-based chemotherapy plus bev.³⁹ The addition of erlotinib to bev significantly improved PFS but not OS. Moreover, during the postchemotherapy phase, there were more adverse events (AEs) overall, more grade 3 and 4 AEs (mainly rash and diarrhea), more serious AEs, and more AEs leading to erlotinib/placebo discontinuation in the bev/erlotinib arm than the bev/placebo arm. A second randomized Phase III trial (the Bevacizumab/Tarceva (BeTa) lung trial) evaluated the addition of erlotinib to bev as second-line therapy in patients with recurrent or refractory NSCLC.⁴⁰ The combination therapy significantly improved PFS (3.4 vs 1.7 months; HR, 0.62, 95% CI, 0.52–0.75) and elevated the disease control rate (45% vs 34%) compared with erlotinib alone. However, there was no significant difference in OS between the two groups (9.3 vs 9.2 months; HR, 0.97, 95% CI, 0.80–1.18; $p=0.758$). In the BeTa trial, 355 (56%) patients were screened for EGFR mutations, and only 30 were positive (12 in the combination group and 18 in

the Erl group). Although the subgroup analysis data indicated a benefit in favor of patients with mutant EGFR compared with those with wild-type EGFR, the difference did not reach significance ($p=0.1826$). The ongoing randomized Phase III BEVERLY trial is evaluating if the first-line combination of erlotinib plus bev is better in terms of PFS than erlotinib alone in 200 Caucasian patients with NSCLC harboring activating EGFR mutations.⁴¹ The abovementioned randomized trials are summarized in Table 2.

Patient selection and future perspectives

The use of bevis indicated in selected patients only, because of its toxicity. Generally in subjects with NSCLC, it is safe and well tolerated.^{42–46} The most common AEs are hypertension, proteinuria, and epistaxis. Infrequent serious AEs include neutropenia complications, thromboembolic events, and pulmonary hemorrhage.

Hypertension appears to be dose dependent and related to increased peripheral vascular resistance induced by microcapillary rarefaction due to the inhibition of proangiogenic factors stimulating resident endothelial cells to proliferate and migrate to form new capillary tubes.⁴⁷ Another potential pathogenetic mechanism may be decreased production of nitric oxide induced by bev. Decreased serum levels of nitric oxide cause constriction of the vasculature and a reduction in sodium ion renal excretion, leading to increased blood pressure.⁴⁸

Bleeding in bev-treated patients may be related to inhibition of the endothelial repair processes mediated by VEGF and tumor erosion of vessels.

In order to reduce the incidence of severe hemorrhage, the first randomized clinical trials of bev in NSCLC excluded: 1) subjects with squamous histology; 2) subjects with significant hemoptysis; 3) subjects with tumors invading or abutting major blood vessels or with central tumor localization or with tumor cavitation, based on a radiological assessment; 4) subjects with hemorrhagic disorders or in treatment with anticoagulant therapy; 5) subjects with brain metastases; 6) subjects with ECOG>1; and 7) elderly patients (age ≥ 75 years). In these last couple of years, the scientific community is speculating if some of these exclusion criteria for bev could be too precautionary or scientifically not so much valid, leading clinicians to inappropriately avoiding the use of bev in patients who might benefit from it.^{49,50}

No statistically significant association was found between baseline or on-treatment cavitation tumor and severe pulmonary hemorrhage incidence in bev-treated patients.⁵⁰ Similarly, central tumor location has not been shown to be a consistent predictive factor for severe pulmonary hemorrhage in these patients.^{51,52}

Major blood vessel infiltration and bronchial vessel infiltration, encasement, and abutting may predict pulmonary hemorrhage. However, their valuation is an individual assessment, and divergence between trained observers may occur even when radiological criteria are standardized. In

Table 2 Randomized Phase III trials of bev in NSCLC

Study name	Treatment arms	Total pts (n) Pts (n) arm 1 Pts (n) arm 2	Outcomes	Safety
ECOG 4599 ¹³	Arm 1: bev + carbo + pac Arm 2: carbo + pac	878 444 434	Improvement in OS, PFS, ORR with bev HR (95% CI) for OS =0.79 (0.67 to 0.92); $p=0.003$ HR (95% CI) for PFS =0.66 (0.57 to 0.77); $p<0.001$ ORR: 15 % (arm 1) vs 35% (arm 2) ($p<0.001$)	Rates of significant bleeding: 4.4% (arm 1) vs 0.7% (arm 2) 15 treatment-related deaths with bev (5 from pulmonary hemorrhage)
AVAIL ²⁸	Arm 1: cis + gem + bev 7.5 mg/kg Arm 2: cis + gem + bev 15 mg/kg Arm 3: cis + gem + placebo	1,043 345 351 347	Improvement in PFS and ORR with both doses of bev. Limited follow-up for OS analysis HR (95% CI) for PFS arm 1=0.75 (0.62 to 0.91); $p=0.003$ HR (95% CI) for PFS arm 2=0.82 (0.68 to 0.98); $p=0.03$ ORR: 20.1% (arm 3) vs 34.1% (arm 1, $p<0.0001$) vs 30.4% (arm 2, $p=0.0023$)	Similar incidence of grade 3 or greater AEs

(Continued)

Table 2 (Continued)

Study name	Treatment arms	Total pts (n) Pts (n) arm 1 Pts (n) arm 2	Outcomes	Safety
PRONOUNCE ³⁰	Arm 1: pem + carbo followed by pem maintenance Arm 2: pac + carbo + bev followed by bev maintenance	361 182 179	Similar PFS, OS, and ORR HR (95% CI) for PFS = 1.06 (0.84 to 1.35); $p=0.610$ HR (95% CI) for OS = 1.07 (0.83 to 1.36); $p=0.615$ ORR: 23.6% arm 1 vs 27.4% arm 2 ($p=0.414$)	Tolerated but differed in their toxicity profiles
POINTBREAK ³¹	Arm 1: pem + carbo + bev followed by pem + bev maintenance Arm 2: pac + carbo + bev followed by bev maintenance	939 472 467	Improvement in PFS with arm 1 No significant difference in OS HR (95% CI) for PFS = 0.83 (0.71 to 0.96); $p=0.012$ HR (95% CI) for OS = 1.00 (0.86 to 1.16); $p=0.949$	Tolerated but differed in their toxicity profiles
AVAPERL ³²	bev + cis + pem (induction) if response or stable disease arm 1: bev maintenance arm 2: bev + pem maintenance	376 125 128	Improvement in PFS with arm 2 HR (95% CI) for PFS from random assignment = 0.48 (0.35 to 0.66); $p<0.001$ OS from random assignment: 12.8 months (arm 1), it was not yet reached in arm 2.	No new safety signals were observed
AvaALL ³⁵	Progressive disease on first-line treatment with 4–6 cycles of bev + platinum-doublet and at least 2 cycles of bev maintenance: Arm 1: bev + standard-of-care (erlo or doce or pem) as second-line treatment Arm 2: Standard of care (erlo or doce or pem) as second-line treatment	487	Results are not yet available	Results are not yet available
ECOG E1505 ³⁶	Arm 1: adjuvant chemotherapy + bev Arm 2: adjuvant chemotherapy	—	This study is ongoing, but not recruiting participants	—
ATLAS ³⁹	Bev + platinum-doublet (induction) Arm 1: bev maintenance Arm 2: bev + erlo maintenance	1145 373 370	Improvement in PFS but not in OS HR (95% CI) for PFS from random assignment = 0.708 (0.580 to 0.864); $p<0.001$ HR (95% CI) for OS from random assignment = 0.917 (0.698 to 1.205); $p=0.5341$	Higher degree of toxicity with arm 2
BeTa ⁴⁰	As second-line therapy: Arm 1: erlo + bev Arm 2: erlo + placebo	636 319 317	PFS and DCR seem to be better in arm 1 but they cannot be defined as significant No significant difference in OS HR (95% CI) for OS = 0.97 (0.80 to 1.18); $p=0.7583$ HR (95% CI) for PFS = 0.62 (0.52 to 0.75) DCR: 45% (arm 1) vs 34% (arm 2)	Mild toxicity with arm 1
BEVERLY ⁴¹	As first-line therapy: Arm 1: erlo + bev Arm 2: erlo + placebo	—	This study is currently recruiting participants.	—

Abbreviations: AE, adverse event; bev, bevacizumab; carbo, carboplatin; CI, confidence interval; cis, cisplatin; DCR, disease control rate; gem, gemcitabine; HR, hazard ratio; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; pac, paclitaxel; PFS, progression-free survival; pts, patients.

particular, in the retrospective multicenter study of Barlesi et al,⁵³ discordance in bev's eligibility decisions among radiologists and oncologists based on 150 chest computed tomography scans from patients with central NSCLC tumors has been demonstrated.

Several studies evaluated safety of bev in patients with NSCLC and brain metastases. In the Phase II PASSPORT trial, addition of bev to various chemotherapy agents or erlotinib in patients with NSCLC and treated brain metastases was found to be safe and related to a low incidence of central nervous system (CNS) hemorrhage.⁴⁵ The ATLAS and BeTa trials also included patients with treated brain metastases and recorded a low rate of CNS hemorrhage, similarly.^{39,40}

Besse et al⁵⁴ conducted a retrospective exploratory analysis using datasets from 17 clinical trials to assess the risk of cerebral hemorrhage in patients with brain metastases treated with bev for various solid tumors. The results of this study suggested that patients with brain metastases from advanced/metastatic breast cancer, NSCLC, renal, and colorectal cancer should not be generally excluded from bev therapy because they present similar risk of developing cerebral hemorrhage, independent of bev therapy.

Recruiting subpopulations either excluded or under-represented in clinical trials of bev in NSCLC (elderly aged ≥ 75 , patients with ECOG ≥ 2 , and/or patients receiving full-dose anticoagulation therapy), the Phase IV SAiL trial and observational ARIES registry have shown that severe hemorrhage incidence is low and similar to that in Phase III trials patients.^{42,55} The observational cohort study ARIES also showed that none of the 67 patients with brain metastasis at baseline developed CNS hemorrhage.⁵⁵

Recently, analyzing the efficacy and safety of bev, pemetrexed, and carbo as induction therapy, followed by maintenance therapy with bev plus pemetrexed in nonsquamous NSCLC patients with or without brain metastases, Stefanou et al⁵⁶ concluded that this regimen was effective and well tolerated in advanced NSCLC, whether brain metastases were present or not.

A cost analysis of pemetrexed–platinum with maintenance vs paclitaxel–carbo–bev with maintenance in patients with lung cancer has been performed. Mean total costs per patient per month were significantly lower for pemetrexed–platinum patients compared to paclitaxel–carbo–bev patients in the setting of first-line treatment to progression in lung cancer patients with commercial or Medicare supplemental health insurance.⁵⁷

Conflicting retrospective data have been generated about efficacy and safety of bev in elderly patients with NSCLC.

The elderly subset analysis of the ECOG 4599 study showed no statistically significant improvement in ORR, PFS, or OS in 224 patients aged ≥ 70 years (26% of cases). Grade III–IV AEs were significantly more frequent in the elderly subjects compared with the younger subjects (87% vs 61%).⁵⁸ In contrast, in the retrospective analysis performed on 304 elderly patients aged ≥ 65 years, out of a total of 1,430 patients enrolled in the AVAiL study, improved PFS, with no impact on survival and no significant toxicities, has been documented, as in the younger patients.⁵⁹

Similarly, no significant difference was shown in rates of OS, PFS, and overall AEs among older and younger patient subsets in the SAiL and ARIES studies, with the exception of lower survival rates in patients aged 80 years or above vs those below 80 years of age.^{31,60} Moreover, a recent Phase II study has documented the good safety and efficacy of carbo plus weekly paclitaxel with bev as first-line regimen for elderly NSCLC patients.⁶¹ It is possible that the following factors have led to this heterogeneity of results: a higher median age for the ECOG 4599 cases than the other abovementioned studies; difficulty in distinguishing between side effects caused by bev (such as hypertension and proteinuria) and complications associated with the disease and/or age; and increased attention by clinicians to the side effects of bev, with better management in the most recent studies.⁶²

Currently, there are no validated predictive biomarkers of response to treatment with bev according to which it could be possible to select patients with nonsquamous NSCLC without targetable molecular abnormality.⁶³ Potential biomarkers could be circulating levels of short VEGF-A isoforms, expression of neuropilin-1 and VEGFR-1 in tumors and plasma, genetic variants in VEGF-A and VEGFR, and TP53 mutations (which are associated with increased VEGF-A transcript levels).⁶⁴ Several recent studies suggest that these biomarkers could correlate with better clinical outcomes in NSCLC patients treated with antiangiogenesis agents.^{65–68} These preliminary interesting results merit an additional investigation. Therefore, currently the eligibility for bev in NSCLC is based solely on clinical and histopathological features.

Future clinical developments of bev in NSCLC treatment could include its combination with immunotherapy. This novel approach could have a synergistic effect and enhance the efficacy of both treatments, according to preclinical growing evidence that proangiogenic factors modulate the immune response (both by reducing T-cell infiltration into the tumor microenvironment and through systemic effects on immune-regulatory cell function).^{69,70}

Moreover, recent studies have documented that continued VEGF suppression with bev beyond progression on the first-line therapy in patients with nonsquamous NSCLC led to more favorable clinical outcomes when this agent is combined with second-line chemotherapy; positive results have been demonstrated also for bev plus pemetrexed maintenance after first-line chemotherapy with bev, carbo, and pemetrexed. Further well-conducted, large-scale trials are needed to validate these findings. Last, results of trials on efficacy of the addition of bev to adjuvant chemotherapy in patients with completely resected stage IB–IIIA NSCLC and results concerning benefit of first-line combination of erlotinib plus bev instead of erlotinib alone, in patients with NSCL, harboring activating EGFR mutations are still ongoing.

Cellular microRNAs (miRNAs) regulate gene expression through modulation of messenger RNA transcription and are involved in epigenetic regulation, metastasis, and cancer immunity. Recently, Huang et al⁷¹ have evaluated the changes in microRNA profile in lung cancer cell treated with cis and pemetrexed or pemetrexed–cisplatin with bev. There is a difference of the miRNA profile in these 2 treatment groups suggesting that they may influence the regulation of miRNA, which could be involved in the activity of chemotherapy and development of resistance.

Combretastatin A4-phosphate, fosbretabulin tromethamine, is a vascular disrupting agent that targets tumor vasculature. Combretastatin A4-phosphate plus carbo, paclitaxel, and bev appears to be a tolerable regimen with an acceptable toxicity profile in subjects with advanced NSCLC.⁷²

In nonsquamous NSCLC, the efficacy of combination of first-line chemotherapy with onartuzumab, a monovalent monoclonal antibody that binds with the extracellular domain of the MET receptor, has been investigated. Patients with untreated stage IIIB/IV nonsquamous NSCLC, stratified by MET diagnostic status, were randomized to receive onartuzumab (15 mg/kg intravenously every 3 weeks) or placebo in combination with either paclitaxel/platinum/bev (bev cohort), or in combination with platinum/pemetrexed (pemetrexed cohort) with maintenance bev or pemetrexed and onartuzumab/placebo as appropriate. The results of this Phase II study were negative: onartuzumab does not appear to provide any additional clinical benefit when given in combination with current first-line standard-of-care chemotherapy for nonsquamous NSCLC.⁷³

Patents for bev will soon expire in Europe and the US, and several bev biosimilars are in development.⁷⁴ A physician survey examined barriers to the access of bev in patients with advanced solid tumors and the potential impact of

biosimilars. Lack of reimbursement and high out-of-pocket costs were cited as predominant barriers to prescribing and as common reasons for reducing the number of planned cycles. Overall, ~50% of physicians reported they “definitely” or “probably” would prescribe a bev biosimilar, if available. Efficacy and safety data in specific tumor types and lower cost were factors cited that would increase likelihood to prescribe a bev biosimilar.⁷⁵

Conclusion

bev has led to improved clinical outcomes when added to standard first-line chemotherapy in patients with advanced or recurrent nonsquamous NSCLC without targetable molecular abnormality. Innovative combinations of bev and its maintenance beyond disease progression in NSCLC are currently under study.

Eligibility for bev is not affected by patient age, performance status, anticoagulation therapy, and brain metastases. The only absolute contraindications to its use are squamous histology and a history of clinically significant hemoptysis. There are as yet no validated predictive biomarkers of response to treatment with antiangiogenic therapy. Therefore, there is the need for additional translational research to identify those patients who can really benefit from the use of bev, through the identification of specific response markers.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA Cancer J Clin.* 2010;60(5):277–300.
2. Lima AB, Macedo LT, Sasse AD. Addition of bevacizumab to chemotherapy in advanced non small cell lung cancer: a systematic review and meta-analysis. *Plos One.* 2011;6(8):e22681.
3. Rizvi NA, Mazieres J, Planchard D, et al. Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): a phase 2, single-arm trial. *Lancet Oncol.* 2015;16:257–265.
4. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med.* 2015;373:123–135.
5. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med.* 2015;373:1627–1639.
6. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet.* 2016;387:1540–1550.
7. Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. *Lancet.* 2016;387:1837–1846.

8. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med*. 2016;375:1823–1833.
9. Folkman J. Tumor angiogenesis: therapeutic implications. *N Engl J Med*. 1971;285(21):1182–1186.
10. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011;144:646–674.
11. Ferrara N. Vascular endothelial growth factor as a target for anticancer therapy. *Oncologist*. 2004;9(Suppl 1):2–10.
12. Willett CG, Boucher Y, di Tomaso E, et al. Direct evidence that the VEGF-specific antibody bevacizumab has antivascular effects in human rectal cancer. *Nat Med*. 2004;10(2):145–147.
13. Sandler A, Gray R, Perry MC, et al. Paclitaxel carboplatin alone or with bevacizumab for non-small cell lung cancer. *N Engl J Med*. 2006;355(24):2542–2550.
14. Folkman J. What is the evidence that tumors are angiogenesis dependent? *J Natl Cancer Inst*. 1990;82:4–6.
15. Carmeliet P. VEGF as a key mediator of angiogenesis in cancer. *Oncology*. 2005;69(Suppl 3):4–10.
16. Potente M, Gerhardt H, Carmeliet P. Basic and therapeutic aspects of angiogenesis. *Cell*. 2011;146(6):873–887.
17. Iruela-Arispe ML, Dvorak HF. Angiogenesis: a dynamic balance of stimulators and inhibitors. *Thromb Haemost*. 1997;78(1):672–677.
18. Daniel TO, Abrahamson D. Endothelial signal integration in vascular assembly. *Annu Rev Physiol*. 2000;62:649–671.
19. Orimo A, Gupta PB, Sgroi DC, et al. Stromal fibroblasts present in invasive human breast carcinomas promote tumor growth and angiogenesis through elevated SDF-1/CXCL12 secretion. *Cell*. 2005;121(3):335–348.
20. Ferrara N, Gerber HP, LeCouter J. The biology of VEGF and its receptors. *Nat Med*. 2003;9(6):669–676.
21. Shikada Y, Yonemitsu Y, Koga T, et al. Platelet-derived growth factor-AA is an essential and autocrine regulator of vascular endothelial growth factor expression in non-small cell lung carcinomas. *Cancer Res*. 2005;65(16):7241–7248.
22. Koukourakis MI, Giatromanolaki A, Thorpe PE, et al. Vascular endothelial growth factor/KDR activated microvessel density versus CD31 standard microvessel density in non-small cell lung cancer. *Cancer Res*. 2000;60(11):3088–3095.
23. O'Byrne KJ, Koukourakis MI, Giatromanolaki A, et al. Vascular endothelial growth factor, platelet-derived endothelial cell growth factor and angiogenesis in non-small-cell lung cancer. *Br J Cancer*. 2000;82(8):1427–1432.
24. Kojima H, Shijubo N, Yamada G, et al. Clinical significance of vascular endothelial growth factor-C and vascular endothelial growth factor receptor 3 in patients with T1 lung adenocarcinoma. *Cancer*. 2005;104(8):1668–1677.
25. Takizawa H, Kondo K, Fujino H, et al. The balance of VEGF-C and VEGFR-3 mRNA is a predictor of lymph node metastasis in non-small cell lung cancer. *Br J Cancer*. 2006;95(1):75–79.
26. Chen ZJ, Le HB, Zhang YK, Qian LY, Li WD. Microvessel density and expression of thrombospondin-1 in non-small cell lung cancer and their correlation with clinicopathological features. *J Int Med Res*. 2009;37(2):551–556.
27. Devery AM, Wadekar R, Bokobza SM, Weber AM, Jiang Y, Ryan AJ. Vascular endothelial growth factor directly stimulates tumour cell proliferation in non-small cell lung cancer. *Int J Oncol*. 2015;47(3):849–856.
28. Reck M, Von Pavel J, Zatloukal P, et al. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small cell lung cancer: AVAiL. *J Clin Oncol*. 2009;27(8):1227–1234.
29. Reck M, von Pawel J, Zatloukal P, et al. Overall survival with cisplatin-gemcitabine and bevacizumab or placebo as first-line therapy for non-squamous non-small-cell lung cancer: results from a randomised phase III trial (AVAiL). *Ann Oncol*. 2010;21(9):1804–1809.
30. Zinner RG, Obasaju CK, Spigel DR, et al. PRONOUNCE: randomized, open-label, phase III study of first-line pemetrexed + carboplatin followed by maintenance pemetrexed versus paclitaxel + carboplatin + bevacizumab followed by maintenance bevacizumab in patients with advanced nonsquamous non-small-cell lung cancer. *J Thorac Oncol*. 2015;10(1):134–142.
31. Patel JD, Socinski MA, Garon EB, et al. 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(34):4349–4357.
32. Barlesi F, Scherpereel A, Rittmeyer A, et al. Randomized phase III trial of maintenance bevacizumab with or without pemetrexed after first-line induction with bevacizumab, cisplatin, and pemetrexed in advanced nonsquamous non-small-cell lung cancer: AVAPERL (MO22089). *J Clin Oncol*. 2013;31(24):3004–3011.
33. Schneider BJ, Kalemkerian GP, Gadgeel SM, et al. Phase II trial of dose-dense pemetrexed, gemcitabine, and bevacizumab in patients with advanced, non-small-cell lung cancer. *Clin Lung Cancer*. 2017;18(3):299–302.
34. Nadler E, Yu E, Ravelo A, Sing A, Forsyth M, Gruschko S. Bevacizumab treatment to progression after chemotherapy: outcomes from a U.S. community practice network. *Oncologist*. 2011;16(4):486–496.
35. Gridelli C, Bennouna J, de Castro J, et al. Randomized phase IIIB trial evaluating the continuation of bevacizumab beyond disease progression in patients with advanced non-squamous non-small-cell lung cancer after first-line treatment with bevacizumab plus platinum-based chemotherapy: treatment rationale and protocol dynamics of the AvaALL (MO22097) trial. *Clin Lung Cancer*. 2011;12(6):407–411.
36. A phase III randomized trial of adjuvant chemotherapy with or without bevacizumab for patients with completely resected stage IB (≥ 4 cm) - IIIA Non-small Cell Lung Cancer (NSCLC). Available from: <https://clinicaltrials.gov/ct2/show/NCT00324805>. Accessed February 7, 2017.
37. Seto T, Kato T, Nishio M, et al. Erlotinib alone or with bevacizumab as first-line therapy in patients with advanced non-squamous non-small-cell lung cancer harbouring EGFR mutations (JO25567): an open-label, randomised, multicentre, phase 2 study. *Lancet Oncol*. 2014;15:1236–1244.
38. An open-label phase II trial of erlotinib and bevacizumab in patients with advanced non-small cell lung cancer and activating EGFR mutations. Available from: <https://clinicaltrials.gov/ct2/show/NCT01562028>. Accessed July 29, 2017.
39. Johnson BE, Kabbinavar F, Fehrenbacher L, 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(31):3926–3934.
40. Herbst RS, Ansari R, Bustin F, 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(9780):1846–1854.
41. A randomized open-label phase 3 trial comparing bevacizumab + erlotinib vs erlotinib alone as first line treatment of patients with EGFR mutated advanced non squamous non small cell lung cancer. Available from: <https://clinicaltrials.gov/ct2/show/NCT02633189>. Accessed February 7, 2017.
42. Crinò L, Dansin E, Garrido P, 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(8):733–740.
43. Fishbach NA, Spigel D, Brahmer J, et al; ARIES investigators. Preliminary safety and effectiveness of bevacizumab (Bv)-based treatment in subpopulation of patients (pts) with non-small cell lung cancer (NSCLC) from the ARIES study: a bevacizumab Bv treatment observational cohort study (OCS). *J Clin Oncol*. 2009;27(15S):Abstract 8040.

44. Polikoff J, Hainsworth JD, Fehrenbacher L, et al. Safety of bevacizumab (Bv) therapy in combination with chemotherapy in subjects with non small cell lung cancer (NSCLC) treated on ATLAS. *J Clin Oncol*. 2008;26(15S):Abstract 8079.
45. Socinski MA, Langer CJ, Huang JE, et al. Safety of bevacizumab in patients with non-small cell lung cancer and brain metastases. *J Clin Oncol*. 2009;27(31):5255–5261.
46. Matikas A, Kentepozidis N, Ardavanis A, et al. Efficacy and tolerance of frontline bevacizumab-based chemotherapy for advanced non-small cell lung cancer patients: a multicenter, phase IV study of the Hellenic Oncology Research Group (HORG). *Cancer Chemother Pharmacol*. 2016;78(2):369–376.
47. Mourad JJ, des Guetz G, Debbabi H, Levy BI. Blood pressure rise following angiogenesis inhibition by bevacizumab. A crucial role for microcirculation. *Ann Oncol*. 2008;19(5):927–934.
48. Hood JD, Meininger CJ, Ziche M, Granger HJ. VEGF upregulates eNOS message, protein, and NO production in human endothelial cells. *Am J Physiol*. 1998;274(3 Pt 2):H1054–H1058.
49. Takagi Y, Toriihara A, Nakahara Y, et al. Eligibility for bevacizumab as an independent prognostic factor for patients with advanced nonsquamous non-small cell lung cancer: a retrospective cohort study. *PLoS One*. 2013;8(3):e59700.
50. Reck M, Barlesi F, Crinò L, 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(5):1111–1120.
51. Sandler AB, Schiller JH, Gray R, et al. Retrospective evaluation of the clinical and radiographic risk factors associated with severe pulmonary hemorrhage in first-line advanced, unresectable non-small-cell lung cancer treated with carboplatin and paclitaxel plus bevacizumab. *J Clin Oncol*. 2009;27:1405–1412.
52. Griesinger F, Bearz A, Eberhardt W, et al. Safety of first-line bevacizumab (BV)-based therapy in the sail (MO19390) trial: central tumour location (CTL) and hypertension (HTN) in patients (PTS) with advanced non-small cell lung cancer (NSCLC). *Ann Oncol*. 2010;21(Suppl 8):viii144.
53. Barlesi F, Balleyguier C, Besse B, et al. Inter- and intraobserver consistency in assessing eligibility for bevacizumab (BVZ) in non-small-cell lung cancer (NSCLC) patients with centrally located tumors. *Ann Oncol*. 2010;21:1682–1686.
54. Besse B, Lasserre SF, Compton P, Huang J, Augustus S, Rohr UP. Bevacizumab safety in patients with central nervous system metastases. *Clin Cancer Res*. 2010;16(1):269–278.
55. Lynch TJ Jr, Spigel DR, Brahmer J, 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(9):1332–1339.
56. Stefanou D, Stamatopoulou S, Sakellaropoulou A, et al. Bevacizumab, pemetrexed and carboplatin in first-line treatment of non-small cell lung cancer patients: focus on patients with brain metastases. *Oncol Lett*. 2016;12(6):4635–4642.
57. Sheffield KM, Winfree KB, Muehlenbein C, et al. MINI01.19: cost analysis of pemetrexed-platinum with maintenance vs. paclitaxel-carboplatin-bevacizumab with maintenance in patients with lung cancer: topic: medical oncology. *J Thorac Oncol*. 2016;11(11S):S268.
58. Ramalingam SS, Dahlberg SE, Langer CJ, et al. Outcomes for elderly, advanced-stage non-small-cell lung cancer patients treated with bevacizumab in combination with carboplatin and paclitaxel: analysis of eastern cooperative oncology group trial 4599. *J Clin Oncol*. 2008;26(1):60–65.
59. Leighl NB, Zatloukal P, Mezger J, et al. Efficacy and safety of bevacizumab-based therapy in elderly patients with advanced or recurrent nonsquamous non-small cell lung cancer in the phase III BO17704 study (AVAiL). *J Thorac Oncol*. 2010;5(12):1970–1976.
60. Laskin J, Crinò L, Felip E, et al. Safety and efficacy of first-line bevacizumab plus chemotherapy in elderly patients with advanced or recurrent nonsquamous non-small cell lung cancer: safety of Avastin in lung trial (MO19390). *J Thorac Oncol*. 2012;7(1):203–211.
61. Miura S, Maemondo M, Iwashima A, et al. A phase II study of carboplatin plus weekly paclitaxel with bevacizumab for elderly patients with non-squamous non-small-cell lung cancer (NEJ016). *Invest New Drugs*. 2017;35(2):227–234.
62. Antonelli G, Libra M, Panebianco V, et al. Molecular-targeted therapy for elderly patients with advanced non-small cell lung cancer. *Oncol Lett*. 2016;11(1):3–8.
63. Duda DG, Ancukiewicz M, Jain RK. Biomarkers of antiangiogenic therapy: how do we move from candidate biomarkers to valid biomarkers? *J Clin Oncol*. 2010;28(2):183–185.
64. Kurzrock R, Stewart DJ. Exploring the benefit/risk associated with antiangiogenic agents for the treatment of non-small cell lung cancer patients. *Clin Cancer Res*. 2017;23(5):1137–1148.
65. Dowlati A, Gray R, Sandler AB, et al. 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(5):1407–1412.
66. Lambrechts D, Lenz HJ, de HS, Carmeliet P, Scherer SJ. Markers of response for the antiangiogenic agent bevacizumab. *J Clin Oncol*. 2013;31(9):1219–1230.
67. Said R, Hong DS, Warneke CL, et al. P53 mutations in advanced cancers: clinical characteristics, outcomes, and correlation between progression-free survival and bevacizumab-containing therapy. *Oncotarget*. 2013;4(5):705–714.
68. Schwaederle M, Lazar V, Validire P, et al. VEGFA expression correlates with TP53 mutations in non-small cell lung cancer: implications for antiangiogenesis therapy. *Cancer Res*. 2015;75(7):1187–1190.
69. Manegold C, Dingemans AC, Gray JE, et al. The potential of combined immunotherapy and antiangiogenesis for the synergistic treatment of advanced NSCLC. *J Thorac Oncol*. 2017;12(2):194–207.
70. Martino EC, Misso G, Pastina P, et al. Immune-modulating effects of bevacizumab in metastatic non-small-cell lung cancer patients. *Cell Death Discov*. 2016;2:16025.
71. Huang CH, Motes H, Sharma M, Reyes EB, Kevern J. PS01.33: change in microRNA profile in lung cancer cell treated with chemotherapy cisplatin (C), pemetrexed (P) or PC with bevacizumab (B): topic: Medical oncology. *J Thorac Oncol*. 2016;11(11S):S289.
72. Garon EB, Neidhart JD, Gabrail NY, de Oliveira MR, Balkissoon J, Kabinavar F. A randomized Phase II trial of the tumor vascular disrupting agent CA4P (fosbretabulin tromethamine) with carboplatin, paclitaxel, and bevacizumab in advanced nonsquamous non-small-cell lung cancer. *Onco Targets Ther*. 2016;9:7275–7283.
73. Wakelee H, Zvirbule Z, De Braud F, et al. Efficacy and safety of onartuzumab in combination with first-line bevacizumab- or pemetrexed-based chemotherapy regimens in advanced non-squamous non-small-cell lung cancer. *Clin Lung Cancer*. 2017;18(1):50–59.
74. Biosimilars of bevacizumab. Available from: <http://www.gabionline.net/Biosimilars/General/Biosimilars-of-bevacizumab>. Accessed December 9, 2016.
75. Monk BJ, Lammers PE, Cartwright T, Jacobs I. Barriers to the access of bevacizumab in patients with solid tumors and the potential impact of biosimilars: a physician survey. *Pharmaceuticals (Basel)*. 2017;10(1). pii: E19.

Lung Cancer: Targets and Therapy

Dovepress

Publish your work in this journal

Lung Cancer: Targets and Therapy is an international, peer-reviewed, open access journal focusing on lung cancer research, identification of therapeutic targets and the optimal use of preventative and integrated treatment interventions to achieve improved outcomes, enhanced survival and quality of life for the cancer patient. Specific topics covered in the journal include: Epidemiology, detection and screening; Cellular research and biomarkers; Identification of biotargets and agents with novel

mechanisms of action; Optimal clinical use of existing anticancer agents, including combination therapies; Radiation and surgery; Palliative care; Patient adherence, quality of life, satisfaction; Health economic evaluations. The manuscript management system is completely online and includes a very quick and fair peer-review system. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/lung-cancer-targets--therapy-journal>