

# LUNG CANCER IN FOCUS

Current Developments in the Management of Lung Cancer

Section Editor: Mark A. Socinski, MD

## Angiogenesis Inhibition for the Treatment of Non–Small Cell Lung Cancer



Mark A. Socinski, MD  
Professor of Medicine and Cardiothoracic Surgery  
University of Pittsburgh Medical Center  
Pittsburgh, Pennsylvania

### **H&O** When were angiogenesis inhibitors first used to treat non–small cell lung cancer (NSCLC)?

**MS** The use of anti-angiogenic agents to treat NSCLC started approximately a decade ago, based on the results of Eastern Cooperative Oncology Group (ECOG) Trial 4599. This trial, which was published in the *New England Journal of Medicine* in 2006, showed improved overall survival (OS) and progression-free survival (PFS) after the addition of bevacizumab (Avastin, Genentech) to treatment with carboplatin and paclitaxel in 878 patients who had recurrent or advanced NSCLC. Bevacizumab is a humanized monoclonal antibody that works by binding to the vascular endothelial growth factor A (VEGF-A) protein, inhibiting the process of angiogenesis.

The results of ECOG 4599 ushered in the era of angiogenesis inhibition in lung cancer and led to approval by the US Food and Drug Administration (FDA) of bevacizumab in combination with carboplatin and paclitaxel for the first-line treatment of unresectable locally advanced, recurrent, or metastatic nonsquamous NSCLC. Despite the clear benefit shown in ECOG 4599, interest in using anti-angiogenic agents for lung cancer has waxed and waned since then.

One of the more controversial trials that came after ECOG 4599 was AVAiL (A Study of Avastin [Bevacizumab] in Patients with Non-Squamous Non-Small Cell Lung Cancer), which was published in 2010. This trial was not very well executed. It started with 3 arms and was supposed to be collapsed to 2 arms, but the collapse never happened. In addition, the primary

endpoint was changed from OS to PFS approximately 75% of the way through the trial. Even though the trial failed to show a survival advantage for bevacizumab, my counter-argument has always been that the trial never had a chance to show this because OS was not the final primary endpoint. In my opinion, any conclusions about survival from this study are suspect.

More recently, we saw the results of BEYOND (A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Phase III Study of First-Line Carboplatin/Paclitaxel Plus Bevacizumab or Placebo in Chinese Patients With Advanced or Recurrent Nonsquamous Non–Small-Cell Lung Cancer), which were reported by Zhou and colleagues in the *Journal of Clinical Oncology* in 2015. This trial showed an improvement in median OS with the addition of bevacizumab to treatment with carboplatin and paclitaxel, from 17.7 to 24.3 months. The hazard ratio (HR) was 0.68, which is similar to the HR of 0.79 that was seen in ECOG 4599. So, we have 2 big trials showing that inhibition of angiogenesis improves survival in NSCLC and is a first-line treatment option in eligible patients.

Bevacizumab is often added to other combinations as well. For example, PointBreak (A Study of Pemetrexed, Carboplatin and Bevacizumab in Patients With Nonsquamous Non-Small Cell Lung Cancer) showed that pemetrexed (Alimta, Lilly) can be used in place of paclitaxel without compromising OS in a carboplatin/bevacizumab regimen. Although survival is the same, the toxicity profiles are different for pemetrexed and paclitaxel; pemetrexed can be used if neuropathy or alopecia is a concern.

### H&O Could you talk about the results of the PASSPORT trial, which you led?

**MS** What made PASSPORT (Safety of Bevacizumab in Patients with Non–Small-Cell Lung Cancer and Brain Metastases) important is that it included patients with brain metastases, whereas ECOG 4599 had excluded these patients because of concern about central nervous system hemorrhage. Brain metastases are very common in NSCLC, so it was important to determine the safety of bevacizumab in patients who have them. We designed this trial so that any brain metastases had to be treated and controlled for at least 1 month—with magnetic resonance imaging used to make sure the lesions were stable—before bevacizumab could be administered. We showed that as long as the brain metastases were treated and controlled, there was no increase in central nervous system hemorrhage with bevacizumab.

### H&O Should bevacizumab be used through multiple lines of therapy?

**MS** An ongoing trial, A Study of Avastin (Bevacizumab) in Combination With Standard of Care Treatment in Patients With Lung Cancer (NCT01351415), is addressing that issue. Until we have results, I think that bevacizumab should be used until progression. We refer to that strategy as “continuation maintenance,” although it was considered “treatment until progression” in ECOG 4599.

### H&O What other anti-angiogenesis agents have been used to treat NSCLC?

**MS** After bevacizumab came the small-molecule tyrosine kinase inhibitors (TKIs), which include sunitinib (Sutent, Pfizer), sorafenib (Nexavar, Bayer/Onyx), vandetanib (Caprelsa, AstraZeneca), pazopanib (Votrient, Novartis), and many others. The mechanism of action of these drugs is totally different from that of bevacizumab; they work by inhibiting the internal tyrosine kinase domain of the VEGF receptor. The problem with these “ib” drugs is that they are not completely selective for the VEGF receptor and can hit other targets, such as platelet-derived growth factor (PDGF), fibroblast growth factor receptor (FGFR), RET, and KIT. In certain cases, hitting other targets may be useful, but many of us believe that it contributes to the toxicity profile of these drugs.

These small-molecule TKIs have been shown to have activity against NSCLC in phase 1 and phase 2 trials. Unfortunately, the results of most of the phase 3 trials in NSCLC have been negative. Several phase 3 trials showed improved PFS with vandetanib, but the magnitude of the benefit was not clinically impressive. As a result, none of

these agents are approved in the United States for use in patients with NSCLC. However, nintedanib is approved in Europe for use in combination with docetaxel based on the results of LUME-Lung 1 (BIBF 1120 Plus Docetaxel as Compared to Placebo Plus Docetaxel in 2nd Line Non Small Cell Lung Cancer).

### H&O What was the next anti-angiogenesis agent to be tested for use in NSCLC?

**MS** After the era of all the “ib” drugs, REVEL (A Pivotal Phase III Trial in Patients With Metastatic NSCLC [Nonsquamous or Squamous Histologies] With Disease Progression on or After Platinum-Based Therapy) tested ramucirumab (Cyramza, Lilly) as a second-line treatment for NSCLC. Ramucirumab is a fully human monoclonal antibody that works by binding to vascular endothelial growth factor receptor 2 (VEGFR-2).

REVEL showed advantages in OS, objective response rate, and PFS for ramucirumab plus docetaxel compared with docetaxel alone. This finding led to the approval of ramucirumab in December of 2014 as a second-line option for patients with metastatic NSCLC. What was interesting about REVEL is that it included patients with squamous cell NSCLC as well as patients with nonsquamous cell NSCLC, so that was reflected in the approval.

The addition of ramucirumab nearly doubled the objective response rate in REVEL, but the improvement in median OS was modest: 10.5 months with ramucirumab vs 9.1 months without ramucirumab (HR, 0.86). Many people have focused on the HR of 0.86 because it did not meet the definition of clinically meaningful benefit for expensive drugs, according to recommendations from the American Society of Clinical Oncology (ASCO). However, many of us consider the ASCO definition of clinical benefit to be aspirational rather than literal because none of the drugs we use in metastatic NSCLC have an HR of 0.76 to 0.77 or lower or an improvement in median OS of at least 2.5 to 3.25 months.

More recently, a study by Perol and colleagues found that the addition of ramucirumab to docetaxel in REVEL did not decrease the patients’ quality of life.

### H&O How significant is the finding that ramucirumab can be used to treat both squamous and nonsquamous cancer?

**MS** I think that was a significant finding. Before ramucirumab, we did not have an anti-angiogenic drug that we could use in patients with squamous NSCLC. In addition, REVEL did not find any additional safety issues in patients with squamous cell vs those with nonsquamous cell NSCLC.

Of course, it is important to highlight that not every patient with squamous cell NSCLC is eligible; REVEL excluded patients with major blood vessel involvement, intratumor cavitation, poorly controlled hypertension, gastrointestinal perforation or fistulae, an arterial thromboembolic event less than 6 months before randomization, hemoptysis within 2 months, or grade 3 or 4 gastrointestinal bleeding within 3 months. It also excluded those whose only previous therapy for advanced or metastatic disease was EGFR tyrosine kinase inhibitor monotherapy.

### H&O What are the most important considerations for physicians deciding whether to use bevacizumab or ramucirumab?

**MS** The most important consideration is the line of therapy because bevacizumab is approved as a first-line drug and ramucirumab as a second-line drug.

An interesting finding about ramucirumab is that a small subset of patients in REVEL had received bevacizumab as first-line therapy, and this prior exposure to bevacizumab did not appear to make any difference in benefit from ramucirumab. Although this subset was small, at present there is no reason to avoid using ramucirumab in a patient who has already received bevacizumab.

Regardless of the agent selected, the patient has to be a candidate for the therapy. As I mentioned earlier, histology is an important determinant—bevacizumab is only for patients with nonsquamous cell NSCLC. Patients should also have a performance status of 0 or 1. Patients who have factors that excluded them from ECOG 4599 should not take bevacizumab, and those with an uncontrolled comorbidity such as hypertension or unstable angina or with a recent arterial clot, stroke, or heart attack are ineligible. Age is also an issue with bevacizumab because older patients are more likely to experience toxicity. As for ramucirumab, all of the exclusion criteria for the REVEL study apply to patient eligibility.

I use bevacizumab in approximately one-quarter to one-third of my first-line patients with NSCLC, and I use ramucirumab in approximately 40% to 50% of my second-line patients with NSCLC.

### H&O What special considerations exist for patients who have an epidermal growth factor receptor (EGFR) mutation?

**MS** Patients whose tumors possess an *EGFR* activating mutation are at an advantage because they usually respond to treatment with one of the oral EGFR TKIs: gefitinib (Iressa, AstraZeneca), erlotinib (Tarceva, Genentech/Astellas), or afatinib (Gilotrif, Boehringer Ingelheim); these drugs are generally well tolerated. Once we know that a

patient is responding to one of these agents and after we have managed side effects, we need to see the patient only every couple of months. To date, no agent added to one of the EGFR TKIs has been shown to improve survival.

A phase 2 Japanese trial that was published in *Lancet Oncology* in 2014 looked at the addition of bevacizumab to treatment with erlotinib in patients with *EGFR*-mutant NSCLC and found an impressive difference in PFS. This was an intriguing finding, but the trial was small, and I do not think that bevacizumab should be considered the standard-of-care treatment for patients with *EGFR* mutations at this time. Integrating bevacizumab into a patient's regimen means that the patient has to visit your office every 3 weeks for an intravenous infusion. The treatment is also very expensive and is not without risk—although the *EGFR*-mutant population is probably at relatively low risk for side effects. Of course, if further trials of this combination show improvements in OS, the equation would change. But for now, I do not use bevacizumab in combination with an EGFR TKI in these patients.

### Suggested Readings

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