Within the trial population, 66 of the 261 patients in the lenvatinib group and 27 of the 131 in the placebo group had received prior vascular endothelial growth factor–targeted therapy. However, this did not affect study outcomes. In addition, findings from subgroup analyses did not differ on the basis of baseline tumor burden, histology, or the status of bone or lung metastasis.

A large number of adverse events were seen in almost every patient. Treatment-related adverse events were reported in 260 (>99%) of the patients in the lenvatinib group and 118 (90%) of those in the placebo group. Most often these were hypertension, diarrhea, fatigue, and decreased appetite.

These adverse events were managed with dose modification and medication. However, 68% of the patients on lenvatinib required dose reduction, 82% required dose interruption, and 14% of patients were taken off the drug.

In the active-treatment arm, there were 20 fatalities, compared with 6 in the placebo arm. Investigators attributed 6 fatalities (2%) directly to the use of lenvatinib. One person died of a pulmonary embolism, 1 died because of hemorrhagic stroke, and 4 others died because of general health deterioration. Still, the study is considered a breakthrough for a fatal cancer with few treatment options [Stjepanovic N et al. *Biologics* 2014].

Ramucirumab Improves Survival in Stage IV NSCLC

Written by Rita Buckley

Ramucirumab (IMC-1121B) is a human immunoglobulin G1 monoclonal antibody that targets the extracellular domain of vascular endothelial growth factor receptor 2. A Study of Chemotherapy and Ramucirumab versus Chemotherapy Alone in Second Line Non–Small Cell Lung Cancer Participants Who Received Prior First Line Platinum Based Chemotherapy [REVEL; NCT01168973; Garon EB et al. *Lancet* 2014] showed that ramucirumab combined with docetaxel extended survival in patients with advanced non–small cell lung cancer (NSCLC) compared with placebo plus docetaxel, according to Maurice Perol, MD, Leon-Berard Cancer Research Center, Lyon, France, who presented the findings of this study.

This multicenter, double-blind, randomized Phase 3 trial was designed to compare survival of participants who received chemotherapy and ramucirumab versus chemotherapy alone as second-line treatment for NSCLC after first-line platinum-based chemotherapy. The primary end point was overall survival in all patients allocated to treatment.

The REVEL investigators enrolled patients with squamous or nonsquamous NSCLC who had progressed during or after a first-line platinum-based chemotherapy regimen. Patients were randomized 1:1 to receive docetaxel 75 mg/m^2 and either ramucirumab 10 mg/kg or placebo on Day 1 of a 21-day cycle until disease progression, unacceptable toxicity, withdrawal, or death. Patients were stratified by sex, region, performance status, and previous maintenance therapy (yes vs. no).

Between December 3, 2010, and January 24, 2013, the investigators screened 1825 patients; 1253 of them were randomly assigned to treatment. Median overall survival was 10.5 months (interquartile range [IQR], 5.1–21.2) for the 628 patients who received docetaxel plus ramucirumab and 9.1 months (IQR, 4.2–18.0) for the 625 patients who received docetaxel plus placebo (HR, 0.86; 95% CI, 0.75–0.98; p=0.023). Median progression-free survival was also longer in the docetaxel plus ramucirumab group (4.5 months; IQR, 0.76–0.86) compared with the docetaxel plus placebo group (3.0 months; IQR, 1.4–6.9; HR, 0.762; 95% CI, 0.68–0.86; p<0.0001). Although statistically significant, the degree of overall and progression-free survival extension conferred by the addition of ramucirumab was fairly modest.

Treatment-emergent adverse events were observed in 613 (98%) of 627 patients in the safety treatment population who received ≥1 dose of ramucirumab-docetaxol and 594 (95%) of 618 patients in the safety placebo population who received ≥1 dose of placebo-docetaxol. The most common Grade 3 or 4 adverse events were neutropenia in 306 patients (49%) in the ramucirumab group versus 246 (40%) in the control group; febrile neutropenia in 100 patients (16%) in the ramucirumab group versus 62 (10%) in the control group; fatigue in 88 patients (14%) in the ramucirumab group versus 65 (11%) in the control group; leucopenia in 86 patients (14%) in the ramucirumab group versus 77 (12%) in the control group; and hypertension in 35 patients (6%) in the ramucirumab group versus 13 (2%) in the control group.

Lung cancer is the leading cause of death from cancer in the world [Siegel R et al. *CA Cancer J Clin* 2012], and advanced NSCLC is responsible for most of those cases [Garon EB et al. *Lancet* 2014]. The REVEL trial showed that ramucirumab plus docetaxel improves survival as a second-line treatment of patients with stage IV NSCLC. This is the first time in a decade that a new drug has shown a survival benefit in advanced NSCLC, albeit with modest results. Further investigation is needed to determine whether particular subgroups of patients may benefit and achieve a more appreciable extension of survival.