

Bevacizumab (Avastin) in Combination with Interferon Alfa

On July 31, 2009 the U.S. Food and Drug Administration granted approval for the use of bevacizumab (Avastin, Genentech, Inc.) in combination with interferon alfa for the treatment of patients with metastatic renal cell carcinoma. The approval was based on results from the BO17705 trial which demonstrated a 5 month improvement in median progression-free survival (PFS) in bevacizumab-treated patients.

The BO17705 trial was a randomized, double-blind, placebo-controlled, multinational, clinical trial conducted in patients with metastatic renal cell carcinoma who had undergone nephrectomy. The study compared the combination of bevacizumab plus interferon alfa-2a to interferon alfa-2a plus placebo. This trial was conducted by Hoffmann-La-Roche in Europe, Asia, and Australia. The primary outcome measure of the trial, assessed by study investigators, was PFS. The determination of PFS by an independent review committee, blinded to treatment assignment, supported the investigators' PFS assessment.

A total of 649 patients (327 bevacizumab plus interferon, 322 interferon plus placebo) were enrolled. The median PFS was 10.2 months for the bevacizumab plus interferon arm compared to 5.4 months for the interferon and placebo arm [hazard ratio (HR) 0.60 (95% CI: 0.49, 0.72) $p < 0.0001$]. The independent review committee analysis of 569 patients with radiographs available for review yielded similar results [median PFS 10.4 versus 5.5 months, HR 0.57 (95% CI: 0.45, 0.72)].

The BO17705 trial did not demonstrate a statistically significant advantage in overall survival for bevacizumab plus interferon arm compared to interferon plus placebo treatment [HR 0.86 (95% CI: 0.72, 1.04), $p = 0.13$].

Additional support for the results of the BO17705 trial was provided by the published results of the 90206 trial, a randomized, open label, study of bevacizumab plus interferon alfa-2b compared to interferon alfa-2b alone in patients with metastatic renal cell carcinoma. The Cancer and Leukemia Group B conducted this trial in North America. A similar prolongation in PFS was reported in the 90206 trial with a median PFS of 8.4 versus 4.9 months for the bevacizumab-containing combination and the single agent interferon alfa-2b arms, respectively. An improvement in overall survival was not observed.

In the BO17705 trial, the combination of bevacizumab plus interferon alfa-2a resulted in a higher overall incidence and more severe toxicities than observed with interferon alfa-2a alone.

Serious adverse events were reported in 31% of patients on the bevacizumab plus interferon arm and in 19% of patients on the interferon plus placebo arm. NCI CTCAE grade 3 and greater adverse events were reported in 63% versus 47% of patients on the bevacizumab- plus interferon and interferon plus placebo arms, respectively.

Grade 3 and greater adverse events attributable to bevacizumab ($\geq 2\%$ greater incidence in the bevacizumab plus interferon arm compared to the interferon plus placebo arm) included bleeding, hypertension, proteinuria, and venous or arterial thrombosis. Two patients with grade 5 bleeding events (ruptured aneurysm and hemoptysis), two patients with hypertensive encephalopathy, and four patients with grade 4 pulmonary embolism were reported in the bevacizumab plus interferon arm.

The most common bevacizumab-related toxicities were bleeding/hemorrhage, hypertension, proteinuria and venous or arterial thromboembolic events. Among the 20% of patients with reports of proteinuria, the median onset of proteinuria was 5.6 months (range 15 days to 37

months) after initiation of bevacizumab. The median time-to-resolution was 6.1 months. Proteinuria did not resolve in 40% of patients after a median follow-up of 11.2 months. Bevacizumab was permanently discontinued in 30% of the patients who developed proteinuria.

Full prescribing information, including clinical trial information, safety, dosing, drug-drug interactions and contraindications is available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/125085s0168lbl.pdf