

July 2008

IMPORTANT DRUG WARNING
SUBJECT: Microangiopathic Hemolytic Anemia (MAHA) in Patients
treated with Avastin® (bevacizumab) and sunitinib malate

Dear Healthcare Provider:

Genentech, Inc. would like to inform you of several cases of microangiopathic hemolytic anemia (MAHA) that were reported in patients with solid tumors receiving Avastin in combination with sunitinib malate. Avastin is not approved for use in combination with sunitinib malate.

The use of Avastin in combination with sunitinib malate is not recommended.

In an investigator-sponsored Phase 1 dose-escalation study¹ combining Avastin and sunitinib malate, 25 patients were enrolled. The study explored 3 cohorts using a fixed dose of Avastin at 10 mg/kg/IV every 2 wks and escalating doses of sunitinib that included 25, 37.5, and 50 mg orally daily given in a 4 wk on / 2 wk off schedule. Five of 12 patients at the highest sunitinib dose level exhibited laboratory findings consistent with microangiopathic hemolytic anemia (MAHA). Two of these cases were considered severe with evidence of thrombocytopenia, anemia, reticulocytosis, reductions in serum haptoglobin, schistocytes on peripheral smear, modest increases in serum creatinine levels, and severe hypertension, reversible posterior leukoencephalopathy syndrome (RPLS), and proteinuria. The findings in these two cases were reversible within three weeks upon discontinuation of both drugs without additional intervention.

The information above led to the closure of a Genentech-sponsored Phase 2 trial of sunitinib at 50 mg +/- Avastin with a similar dosing schedule. Of the seven patients enrolled, two were found to have MAHA.

Two additional Genentech-sponsored randomized, Phase 2 studies of Avastin in combination with sunitinib and chemotherapy in patients with solid tumors were also closed due to poor tolerability primarily due to myelosuppression, fatigue and gastrointestinal complications (e.g., diarrhea, anorexia, dehydration, stomatitis). No events of MAHA have been reported in these studies.

Healthcare professionals should report cases of MAHA or any serious adverse events suspected to be associated with the use of Avastin to Genentech at 1-888-835-2555. Alternatively, report this information to FDA's MedWatch reporting system by phone (1-800-FDA-1088), by facsimile (1-800-FDA-0178), online (<https://www.accessdata.fda.gov/scripts/medwatch/>) or mailed, using the MedWatch for FDA 3500, to the FDA Medical Products Reporting Program, 5600 Fishers Lane, Rockville, MD 20852-9787.

Additional Information on the Safety of Avastin:

Gastrointestinal (GI) perforation: Avastin administration can result in the development of GI perforation, in some cases resulting in fatality. GI perforation, sometimes associated with intra-abdominal abscess, occurred throughout treatment with Avastin. Permanently discontinue Avastin therapy in patients with GI perforation.

Wound healing complication: Avastin administration can result in the development of wound dehiscence, in some instances resulting in fatality. Permanently discontinue Avastin therapy in patients with wound dehiscence requiring medical intervention. The appropriate interval between termination of Avastin and subsequent elective surgery has not been determined.

Hemorrhage: Severe, and in some cases fatal, pulmonary hemorrhage can occur in patients with NSCLC treated with chemotherapy and Avastin. Do not administer Avastin to patients with recent hemoptysis ($\geq 1/2$ tsp of red blood). Permanently discontinue Avastin in patients with serious hemorrhage and initiate aggressive medical management.

Additional serious adverse events included non-GI fistula formation, arterial thromboembolic events, hypertensive crisis, reversible posterior leukoencephalopathy syndrome, neutropenia and infection, nephrotic syndrome, and congestive heart failure.

The most common grade 3–5 (nonhematologic) and 4–5 (hematologic) events that may have occurred in Avastin indications (first-line NSCLC, first- and second-line MCRC) included neutropenia, fatigue, hypertension, infection, hemorrhage, asthenia, abdominal pain, pain, deep vein thrombosis, intra-abdominal thrombosis, syncope, diarrhea, constipation, leukopenia, nausea, vomiting, dehydration, ileus, neuropathy–sensory, neurologic–other, and headache.

The current Avastin package insert is enclosed. For questions regarding the use of Avastin please call our Medical Information/Communications Department at 1-800-821-8590. For information about Sutent® (sunitinib malate), please contact Pfizer Inc.

Sincerely,



Hal Barron, M.D.
Senior Vice President, Development
Chief Medical Officer
Genentech, Inc.

Reference: 1. Feldman DR, Ginsberg MB, Flombaum C, Hassoun H, Velasco S, Fisher P, Ishill NM, Ronnen EA, Motzer RJ. Phase I trial of bevacizumab plus sunitinib in patients with metastatic renal cell carcinoma. J Clin Oncol.26:2008 (May 20 suppl; abstr 5100).