

Gastric Cancer in Boston, MA. “So we determined reasonable markers for clustering these tumors.”

About 10% of the tumors were EBV-positive, with extensive DNA hypermethylation. Of this group, 80% harbored *PIK3CA* mutations, versus 3% to 42% for the remaining subtypes. Elevated PD-L1 and PD-L2 levels were also observed.

“The data from this group were intriguing,” says Bass. “Immune evasion could be a salient feature of EBV-positive gastric cancers.”

Ronan Kelly, MD, MBA, director of the Johns Hopkins Gastroesophageal Cancer Therapeutics program in Baltimore, MD, agrees, adding that immunotherapies are worth investigating. “We’ve reached a plateau with chemotherapy,” he says. “My colleagues at Johns Hopkins and I have data indicating that a significant number of these patients may benefit from PD-1/PD-L1 inhibitors.” He hopes to test this hypothesis in a clinical trial.

A second subtype, comprising 20% of tumors, displayed high MSI associated with mutations in *KRAS*, *ERBB3*, and *PTEN*. “In colon cancer, tumors with MSI respond differently to adjuvant chemotherapy, which is factored into the [treatment] decision process,” notes Bass. “We haven’t done the same for gastric cancer, but this could change.”

Fully half of the tumors made up a third subtype, featuring chromosomal instability (CIN) and amplification of key genes, including *EGFR*. These were more prevalent in the gastroesophageal junction (GEJ), and notably—given the activity of ramucirumab (Cyramza; Lilly Oncology) in GEJ adenocarcinoma—*VEGFA* was also recurrently amplified. It would be interesting, Kelly says, to retrospectively analyze data from the REGARD and RAINBOW trials, to see if patients who benefited from ramucirumab had CIN tumors, because “we still don’t have a biomarker for VEGF therapies.”

Finally, the researchers characterized a fourth group lacking extensive copy-number alterations, mainly diffuse-type gastric tumors, as “genomically stable.” They found *RHOA* mutations almost exclusively in this subtype, and hypothesized that dysfunctional *RHOA* signaling contributes to a hallmark of diffuse tumors: diminished cellular cohesion. It potentially

opens new therapeutic avenues for this deadly type of gastric cancer, says Bass.

“It’s too early to know if what we’ve found will have similar impact as the discovery of different breast cancer subtypes,” he adds, “but I think this is a more rational way of categorizing gastric cancer patients.” ■

## Avastin Approved for Some Cervical Cancers

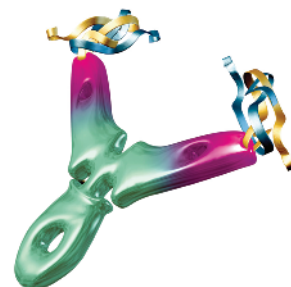
On August 14, the FDA approved the angiogenesis inhibitor bevacizumab (Avastin; Genentech) to treat recurrent or metastatic cervical cancer. The approval represents the first meaningful clinical advance for treating the disease since 2004, when platinum-based chemotherapy combinations, such as cisplatin and paclitaxel, were found to be more active than single-agent cisplatin.

Bevacizumab is also approved for the treatment of colorectal cancer, glioblastoma, non-small cell lung cancer, and renal cell carcinoma.

The FDA based its approval on results from a randomized phase III trial showing that the addition of bevacizumab to chemotherapy extended median overall survival from 13 to 17 months (N Engl J Med 2014;370:734–43). Chemotherapy alone typically results in median survival of 7 to 12 months. Bevacizumab is the first targeted therapy to extend survival.

“With bevacizumab, not only did patients live longer but they lived longer without any significant deterioration in quality of life,” says Krishnansu Tewari, MD, professor and director of research in the Division of Gynecologic Oncology at the University of California, Irvine, and principal investigator of the phase III study. Hinting at new research possibilities, he adds, “That may present a window of opportunity to offer additional treatment to patients who are responding to bevacizumab and possibly extend their lives further.”

Researchers could use that window to test the effectiveness of new molecular therapies and immunotherapy, says Tewari. For example, pazopanib, an intracellular small-molecule tyrosine kinase inhibitor that targets VEGF receptor, and sorafenib, a multi-kinase inhibitor, have shown promise in treating advanced cervical cancer.



Bevacizumab, the antibody in the antitumor drug Avastin (pink and green), binds to VEGFR.

Future studies will focus on how to identify the patients most likely to respond to bevacizumab, says Tewari. He is working with researchers in the UK who identified a proangiogenic signature in ovarian cancer associated with improved progression-free survival to see if that signature is also present in cervical cancer.

“If we can find a group of patients who are expressing those angiogenic proteins and show that those patients are the ones most likely to respond to bevacizumab,” says Tewari, “it will be a very big step forward in terms of personalized delivery of medicine.” ■

## Minor Clone May Drive Cancer Growth

The most dominant cell type within a tumor is not necessarily the most dangerous, new research suggests. Rather, a small population of cancer cells may be responsible for driving a cancer’s growth and spread.

The findings offer new information about the many genetically distinct cells within a tumor, a phenomenon called intratumor heterogeneity (Nature 2014 July 30 [Epub ahead of print]).

“Heterogeneity is important,” says the study’s senior author Kornelia Polyak, MD, PhD, a researcher at Dana-Farber Cancer Institute and professor of medicine at Harvard Medical School, both in Boston, MA. “We need to figure out what is really making tumors grow and target those cells, not just the cells that seem to be the most common within tumors.”

Researchers have generally assumed that a tumor’s growth was fueled by its largest subgroup of cells, the so-called dominant clone. This notion was based on what has been seen in lab-grown homogeneous cancer cell lines, not actual tumors, Polyak says.