With patent protection on Genentech's blockbuster drug trastuzumab (Herceptin) set to expire in the United States in 2019, several companies, including Mylan Pharmaceuticals, are developing their own versions of the biologic.

Amgen's Neupogen (filgrastim), used to treat neutropenia.

In contrast to generic drugs, biosimilars are not exactly identical to their corresponding brand-name counterparts. Whereas generic drugs are copies of small-molecule drugs with relatively simple chemical compositions, biosimilars correspond to complex large-molecule biologics and must be synthesized from living organisms.

Because biosimilars are impossible to precisely replicate, the FDA requires manufacturers to perform extensive analyses and conduct confirmatory clinical studies demonstrating that the products are highly similar to their branded counterparts, without any clinically meaningful differences.

"This is one of the first trials with biosimilars in oncology to demonstrate similar efficacy, safety, and immunogenicity against the reference product," said Rugo. *–Janet Colwell* ■

Piecing Together the Adrenal Cancer Puzzle

Researchers from 39 institutions in six countries have joined forces to extensively characterize adrenocortical carcinoma (ACC), a rare endocrine cancer that affects just two in every million people worldwide. ACC is often diagnosed at an advanced stage, so its 5-year survival rate ranges from 6% to 13%. Standard treatments for metastatic disease—chemotherapy, radiation, and the hormone-blocking agent mitotane—are palliative and have remained unchanged since the 1970s.

The analysis, part of The Cancer Genome Atlas, was led by Thomas Giordano, MD, PhD, and Gary Hammer, MD, PhD, at the University of Michigan in Ann Arbor; and Roel Verhaak, PhD, at The University of Texas MD Anderson Cancer Center in Houston.

The team used several molecular platforms to scrutinize 91 tumors, including whole-exome and RNA sequencing, and DNA methylation profiling (Cancer Cell 2016;29:723–36). They found that 8% of the samples harbored inactivating *PRKAR1A* mutations—"a new twist in the story," Giordano says, given that alterations in this gene were thought to occur only in benign adrenal disease. They also observed loss of *ZNRF3* in almost 20% of cases, resulting in constitutive activation of Wnt signaling.

"We knew Wnt signaling is important in adrenal cancer biology—some tumors have an initiating mutation in the β-catenin gene [*CTNNB1*], which correlates with poor survival," Hammer explains. "This discovery that *ZNRF3* is a critical mediator adds another level of complexity to Wnt pathway activation." Small-molecule inhibitors of Porcupine, an enzyme that processes Wnt ligands, are in phase I clinical trials for various cancers, he adds, and "we're looking forward to testing their efficacy in ACCs lacking *ZNRF3*."

Additionally, the researchers noted that a sizeable proportion of ACCs displayed evidence of profound genomic instability—often whole-genome doubling, which was associated with more aggressive disease and decreased survival. Why this happens so frequently "is an open mechanistic question," Giordano says.

By clustering their data, the researchers pinpointed three ACC subtypes with different DNA methylation levels: low, intermediate, and high. Statistical analyses showed distinct clinical outcomes—the corresponding tumor recurrence and/or metastasis rates were 7%, 56%, and 96%. The median progression-free survival was not reached in the first subtype; in the intermediate- and high-methylation subtypes, it was 38 months and 8 months, respectively.

"It looks like DNA methylation is a major driver [of the different subtypes]," Giordano observes, "so we're looking to develop this signature into a full, analytically valid prognostic assay." Currently, ACCs are classified as low- or high-grade based on mitotic activity under the microscope, "which isn't all that informative," he adds. "A three-group classification would enable more confident treatment decisions."

Ultimately, "we view our study as more of a hypothesis generator," Hammer says, "and although it's a long road ahead, I think we have the first steps to facilitating targeted therapy development for ACC."

"There's much to do, to better understand all our observations," Giordano agrees, "but the fact that clinical outcome is linked means we're at least barking up the right tree." *–Alissa Poh* ■

FDA Approves Drug Combo for Kidney Cancer

The FDA approved the combination of lenvatinib (Lenvima; Eisai) and everolimus (Afinitor; Novartis) to treat advanced or metastatic renal cell carcinoma (RCC) in mid-May. The approval marks the first time that a tyrosine kinase inhibitor (TKI) and an mTOR inhibitor have been combined successfully as a second-line treatment for patients with RCC whose tumors advance despite previous VEGF-targeted treatment.

"We have been hoping to treat kidney cancer with this type of vertical blockade for some time, but previous combinations have been unsuccessful due to high toxicity," says Ana Molina, MD, a medical oncologist at NewYork–Presbyterian Hospital and Weill Cornell Medicine in New York, NY.

Until recently, oncologists had two second-line treatment options: everolimus and the TKI axitinib (Inlyta; Pfizer). New approvals over the past few months have increased that number to five, including the new lenvatinib–everolimus combination; the PD-1 checkpoint inhibitor nivolumab (Opdivo; Bristol-Myers Squibb); and cabozantinib (Cabometyx; Exelixis), another TKI.

Together, lenvatinib and everolimus have a synergistic effect by blocking multiple points along the VEGF and mTOR signaling pathways that are critical to tumor growth, says Molina. In addition, lenvatinib is a strong inhibitor of FGF receptors, which have been implicated as a potential mechanism of resistance to VEGF-targeted treatments.

The approval was based on a phase II trial in which 153 patients with advanced or metastatic RCC whose disease progressed within 9 months