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

of undergoing VEGF-targeted therapy received daily doses of either lenvatinib plus everolimus; lenvatinib alone; or everolimus alone (Lancet Oncol 2015;16:1473–82). The combination significantly prolonged median progression-free survival (PFS) compared with everolimus alone (14.6 vs. 5.5 months)—the current standard of care. Lenvatinib alone also prolonged PFS compared with standard of care (7.4 months).

Despite the combination's promising results, Molina says that the anti–PD-1 drug nivolumab may be even more appealing to many oncologists and patients given its favorable side-effect profile. In addition, FDA approval of nivolumab for advanced RCC was based on more robust phase III data.

"With the approval of lenvatinib plus everolimus, nivolumab, and cabozantinib, we have a number of promising second-line treatment options," says Molina. "However, we don't yet know what the best sequence should be." *–Janet Colwell* ■

Treating Tumors by Molecular Profile, Not Type

Preliminary findings from MyPathway, an ongoing Genentech-sponsored phase II basket trial, indicate that matching molecular abnormalities of patients' tumors to relevant targeted therapies—albeit outside a given drug's FDA-approved indication—is both feasible and promising. The results were presented by John Hainsworth, MD, a senior investigator at Sarah Cannon Research Institute in Nashville, TN, during the annual meeting of the American Society of Clinical Oncology (ASCO) in Chicago, IL, June 3–7.

"The same mutations for which targeted agents have been approved for specific cancers can be found in other tumor types—but usually at a lower incidence," Hainsworth said. "With an increase in comprehensive genomic profiling over the last few years, identifying sufficient patients to test these drugs' potential efficacy in nonindicated tumors has become easier."

Hainsworth reported data on MyPathway's first 129 patients, who had molecular abnormalities in HER2, *BRAF*, Hedgehog, or *EGFR*. They were matched to corresponding Genentech drugs: dual HER2 blockade with trastuzumab (Herceptin) plus pertuzumab (Perjeta); the BRAF inhibitor vemurafenib (Zelboraf); the Hedgehog inhibitor vismodegib (Erivedge); and the EGFR inhibitor erlotinib (Tarceva). All patients had tumor types outside of current indications for these therapies and were refractory to standard treatment options.

Twenty-nine patients with 12 types of advanced cancer achieved an objective response—tumor shrinkage of 30% or more—to their matched therapy, and another 40 saw their disease stabilize. There were responders in each of the four treatment arms, Hainsworth noted, and overall, no new side effects were observed with these therapies.

The most promising results were observed in patients with HER2-amplified tumors—seven of 20 with colorectal cancer, three of eight with bladder cancer, and three of six with biliary cancer had objective responses to trastuzumab plus pertuzumab.

Encouraging data was also seen in patients with *BRAF*-mutant non–small cell lung cancer (NSCLC): Three of 15 patients responded to vemurafenib, and two more had stable disease.

Based on these findings, the study investigators are enrolling additional patients with HER2-amplified colorectal, bladder, and biliary cancers, as well as patients with *BRAF*-mutant NSCLC. They'll also add the MEK inhibitor cobimetinib (Cotellic) to vemurafenib—a combination currently approved for advanced or unresectable melanoma—for the study's *BRAF*-mutant arm. Using ado-trastuzumab emtansine (T-DM1; Kadcyla) in the HER2-amplified arm is another possibility.

Sumanta Kumar Pal, MD, a medical oncologist at City of Hope Comprehensive Cancer Center in Duarte, CA, noted that trials like MyPathway include NCI-MATCH and ASCO's TAPUR study. "It's too early to draw any firm conclusions, but if the results hold, we may see a shift in the long-standing paradigm of treating patients based on their cancer type," he said. *–Alissa Poh* ■

NOTED

Technology entrepreneur **Larry Ellison announced that he will give $200 million to the University of Southern California** in Los Angeles to create the Lawrence J. Ellison Institute of Transformative Medicine, which will focus on cancer research. The gift will help fund the construction of a state-of-the-art building with interdisciplinary laboratories in which cancer researchers will draw upon the knowledge of experts from fields such as mathematics, physics, and engineering.

A recent study questioned the FDA's Accelerated Approval program for new cancer drugs. The analysis found that of 25 drugs approved between 2009 and 2014, 56% lacked supporting evidence aligning the surrogate measures used—including objective response rate and progression-free survival—with a survival benefit (Mayo Clin Proc 2016;91:713–25).

The NIH awarded $142 million over 5 years to the Rochester, MN–based Mayo Clinic to create a biobank for the Precision Medicine Initiative cohort program. The funds will be used to collect, store, and distribute more than 35 million biospecimens for comprehensive genomic analyses.

The FDA issued a new form for physicians to request expanded access to an investigational drug or biologic for patients who suffer from serious or life-threatening diseases and for whom no comparable or satisfactory alternative therapy or clinical trial is available. "We know that navigating this process can be challenging and time-consuming, and we are committed to reducing the procedural burdens on physicians and patients whenever possible," said FDA Commissioner Robert Califf, MD.

Former FDA Commissioner Margaret Hamburg, MD, and Sanofi research head Elias Zerhouni, MD, called for international harmonization of drug regulations. In an editorial, they wrote that "the mosaic of regulations that govern drug development and oversight nation by nation are creating unnecessary barriers to the efficient delivery of safe, innovative, and effective treatments to patients in need" (Sci Transl Med 2016;8:338ed6).

For more news on cancer research, visit *Cancer Discovery* online at http://cancerdiscovery.aacrjournals.org/content/early/by/section.