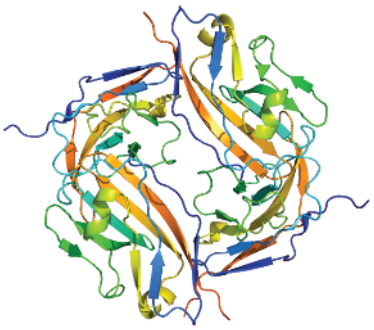


Hu5F9-G4 blocks CD47 and its ligand, SIRPα, thus provoking macrophages to recognize and attack cancer cells.

side effects were chills, headache, and anemia, and most were grade 1 or 2.

"It's really encouraging to have a novel target that shows efficacy and is extremely well tolerated," says senior author Ranjana Advani, MD, also of Stanford. She acknowledges that the results need to be validated in a larger patient cohort, and a phase II trial of the drug duo is under way. Other trials are testing 5F9 alone and in combination with other therapies for various types of hematologic malignancies and solid tumors.

"It looks like a promising combination that warrants more study," says Brad Kahl, MD, of Washington University School of Medicine in St. Louis, MO, who was not involved in the study. "It's very nice to see a clinical experience that validates what was seen in the laboratory." He notes that because the combination has mild, manageable side effects, it may prove particularly beneficial in older patients with aggressive, relapsed lymphomas who cannot tolerate other treatments.

Stephen Ansell, MD, PhD, of Mayo Clinic in Rochester, MN, who was also not connected to the research, is impressed that the combination elicited responses in patients who were refractory to rituximab alone. He says that this may be because CD47 inhibition amplifies rituximab's ability to attract macrophages to cancer cells.

The study not only demonstrates the potential of 5F9 as a treatment for NHL, Ansell adds, but also may signal a broader shift in the field. "We've predominantly focused on T cells as the way in which the immune system is getting after the tumor. This now allows us to take cells like macrophages and get them to be part of the antitumor response as well," he says. "I would hope that this will become something that's beneficial across many diseases and many malignancies." *–Catherine Caruso* ■

ZW25 Effective in HER2-Positive Cancers

A novel anti-HER2 therapy, ZW25 (Azymetric), is effective and well tolerated in patients with a variety of HER2-positive cancers, according to results presented at the 2018 EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics in Dublin, Ireland. In a phase I basket trial, patients treated with the drug—most of whom had gastroesophageal or colorectal cancer—had a high objective response rate with only mild side effects.

HER2 can be overexpressed in various cancers, including breast, gastroesophageal, colorectal, biliary, and salivary gland. However, although several HER2-targeted therapies have been FDA approved for HER2-positive breast cancer, trastuzumab (Herceptin; Genentech) is the only one approved for a HER2-positive cancer other than breast cancer: Its use is limited to first-line treatment of metastatic gastroesophageal cancer.

"There is an unmet need towards developing better treatment approaches for these other cancers that have a high expression of the HER2 receptor," says Murali Beeram, MD, of the START Center for Cancer Care in San Antonio, TX, who presented the findings.

ZW25 is a bispecific antibody that simultaneously binds to two HER2 epitopes: ECD4, the trastuzumab binding domain, and ECD2, the pertuzumab (Perjeta; Genentech) binding domain. Preclinical research suggested that ZW25 has strong antitumor activity at a range of HER2 expression levels and may more effectively silence HER2 signaling than trastuzumab or pertuzumab. It also stimulates the immune system. Now, researchers are testing the agent in a phase I basket trial of HER2-positive cancers.

Researchers enrolled 24 patients with HER2-positive cancers other than breast cancer, including 10 with gastroesophageal, five with colorectal, and nine with other malignancies. Patients had received a median of three prior therapies, and 71% had previously received trastuzumab.

Overall, patients had a median progression-free survival of 6.2 months. Of 17 evaluable patients, seven (41%) had an objective response to the drug, and seven (41%) had stable disease, for a disease control rate of 82%. Diarrhea, infusion reactions, and nausea were the most common side effects, and most were classified as grade 1 or 2; no grade 4 or 5 side effects were observed.

"These are very exciting results, especially for the kind of tumors that we're talking about—if we can reproduce these results consistently in additional testing, it may mean an effective treatment for patients who, at this point, don't have a treatment option," Beeram says. He notes that the trial is still ongoing, with expansion cohorts being added for gastroesophageal cancers. Planning is also under way for phase II trials that will test the drug alone and in combination with chemotherapy.

ZW25 is also under study in HER2-positive breast cancers. Results from the same phase I trial presented at the 2018 American Society of Clinical Oncology Annual Meeting in Chicago, IL, indicated that six out of 13 patients with breast cancer (46%) responded to the drug.

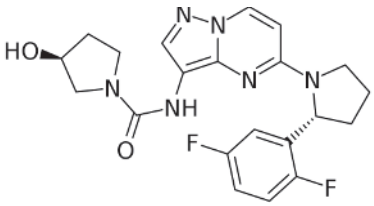
To symposium co-chair Antoni Ribas, MD, PhD, of the University of California, Los Angeles, who is not involved in the research, ZW25 stands out due to its novel binding mechanism and strong early clinical data. "The fact that this HER2-targeted bispecific antibody has responses in a phase I trial, even in patients who have progressed on trastuzumab, is really remarkable," he says.

Ribas adds that "these are promising results that warrant further clinical testing in HER2-positive cancers, and in particular, gastroesophageal cancers." *–Catherine Caruso* ■

Larotrectinib OK'd for Cancers with *TRK* Fusions

A first-in-class TRK inhibitor has received accelerated approval for patients of all ages who have solid tumors harboring fusions in *NTRK1*, *NTRK2*, or *NTRK3*.

The tissue-agnostic approval of larotrectinib (Vitrakvi; Loxo Oncology) marks only the second time the



Structural formula for larotrectinib.

FDA has granted marketing authorization based on a common molecular marker, irrespective of tissue of origin, but it's the first time the agency has done so for a targeted therapy. It's also the first time a drug's initial approval has been site-independent. "This is an affirmation of the precision-medicine approach," says David Hyman, MD, of Memorial Sloan Kettering Cancer Center in New York, NY, who led larotrectinib's clinical development.

In May 2017, the PD-1 inhibitor pembrolizumab (Keytruda; Merck) became the first agent approved for cancer independent of tumor site—specifically for tumors exhibiting two forms of genomic instability: mismatch repair deficiency and microsatellite instability–high. The immunotherapeutic was initially greenlighted 3 years earlier for patients with melanoma.

The efficacy and safety of larotrectinib were demonstrated in three trials that included two cohorts: a primary group of 55 patients, an analysis of which was published earlier this year (N Engl J Med 2018;378:731–9); and a supplementary group of 67 patients described at the European Society for Medical Oncology 2018 Congress in October. Thirty-two of the 122 patients were younger than 15; the youngest was just 1 month old. Collectively, they had 24 types of *NTRK* fusion–positive tumors, the most common being salivary gland cancer, thyroid cancer, infantile fibrosarcoma, and various soft-tissue carcinomas.

Overall, the response rate was 81%, with 63% experiencing partial responses and 17% exhibiting complete responses. Importantly, "the responses were pretty uniform across histologies," notes Trever Bivona, MD, PhD, of the University of California, San Francisco, who was not involved in the drug's testing. "You're seeing efficacy across the board," he says—regardless of age, tumor type, the *NTRK* gene involved, or the fusion partner.

In the primary group of 55 patients, 75% of responders remained disease-free a year after treatment, and the median duration of response had not yet been met after a median follow-up of nearly 18 months. One patient—the first ever treated—is still on therapy with a response that's lasted more than 3.5 years.

These kinds of responses are unprecedented, says trial investigator Noah Federman, MD, of the University of California, Los Angeles. "In over a decade of experience treating advanced solid tumors in children, adolescents, and young adults, I have never witnessed the responses seen with larotrectinib," he says.

Larotrectinib proved safe, with only one of the 122 patients discontinuing treatment due to side effects; 9% of recipients needed a dose reduction owing to spikes in liver enzymes, drops in neutrophil count, or other tolerability issues. "You'd be hard-pressed to find any agent in oncology that has such a low rate of dose reduction," says Hyman, who describes the toxicity profile as more akin to an antihypertensive agent than an anticancer one.

Other clinical-stage drug candidates directed at TRK fusions include entrectinib (Roche), repotrectinib (TP Therapeutics), DS-6051b (Daiichi Sankyo), and LOXO-195 (Loxo Oncology). Of these, repotrectinib and LOXO-195 are designed to treat tumors that develop resistance to larotrectinib. All except LOXO-195 are less-selective agents that target tyrosine kinase receptors such as ALK and ROS1 as well as TRK fusions. The drug that's closest to a regulatory filing, entrectinib, seems to be slightly less effective and somewhat more toxic than larotrectinib when tested in patients with *NTRK* fusion–positive tumors. *–Elie Dolgin* ■

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

NOTED

The FDA approved brentuximab vedotin (Adcetris; Seattle Genetics) plus chemotherapy as a first-line therapy for systemic anaplastic large-cell lymphoma and other CD30-expressing peripheral T-cell lymphomas. The approval was based on the ECHELON-2 trial, in which the combination extended overall survival by 27.4 months compared with chemotherapy alone. The drug was the first approved through the FDA's Real-Time Oncology Review Pilot Program.

The FDA announced a plan to combat underage use of nicotine products that would limit sales of certain flavored electronic cigarette cartridges to age-restricted stores or sections of stores, and would require more stringent age verification online. The FDA also proposed bans on menthol-flavored combustible cigarettes and all flavored cigars.

GlaxoSmithKline's experimental RIP1 inhibitor **GSK547 may boost the effectiveness of immune checkpoint inhibitors** against pancreatic cancer (Cancer Cell 2018;34:757–74). In mice, the combination extended survival compared with immune checkpoint inhibitors alone; in human pancreatic cancer cells, GSK547 increased cytotoxic T-cell activation and decreased activation of immune system–suppressing T cells.

Boston Scientific announced it will acquire British-based BTG for $4.2 billion. BTG specializes in medical devices that are used as interventional therapies: It has developed radiotherapy microspheres and a cryoablation system to treat patients with kidney, liver, and other cancers.

Women with early-stage cervical cancer who have open surgery may have better outcomes than those who have minimally invasive hysterectomies (N Engl J Med 2018;379:1895–1904). In a prospective study, 96.5% of those who had open surgery were disease-free at 4.5 years, compared with 86% of those who had a minimally invasive procedure.

A federal judge declared that **a patent on abiraterone (Zytiga) was invalid.** The company wanted to patent the combination of abiraterone, a CYP17 inhibitor approved for prostate cancer, with steroid prednisone. The decision clears the path for generic versions of the drug.