their clinical advancement. Earlier this year, Roche halted development of its β-sparing PI3K blocker taselisib following disappointing results from the SANDPIPER trial. In that phase III study of women with PIK3CA-mutant disease, taselisib plus fulvestrant offered only a 2-month PFS advantage over placebo plus fulvestrant, and 17% of taselisib recipients discontinued treatment due to side effects.

Part of the difference between the success of alpelisib and taselisib may be attributed to clinical management, says Filip Janku, MD, PhD, of The University of Texas MD Anderson Cancer Center’s Department of Investigational Cancer Therapeutics in Houston, who was not involved in either trial. In SOLAR-1, he says, researchers seem to have done “a far better job of proactively managing side effects,” such as hyperglycemia and rash, with quick and early interventions that helped avoid the high rate of withdrawal from SANDPIPER.

Juric, however, thinks the lower discontinuation rate with alpelisib—and thus higher efficacy with more patients staying on the drug—boils down to pharmacology. “The main reason is a much wider therapeutic index with alpelisib,” he says. Taselisib, owing to its action against the gamma and delta isoforms of PI3K, can trigger gastrointestinal side effects such as colitis that can be difficult to manage. Alpelisib, because it hits only the alpha isoform, avoids these problems. It does, however, cause a high rate of hyperglycemia, which can be reversed with metformin.

The only PI3K-targeted agents currently approved—the PI3Kα inhibitor idelalisib (Zydelig; Gilead) and the pan-PI3K inhibitor copanlisib (Alispor; Bayer)—are reserved for hematologic malignancies. Alpelisib could join that list based on SOLAR-1 data, but the “holy grail,” says Juric, would be “an inhibitor that preferentially hits just the mutant PI3Kα and not the wild-type enzyme.” He and others are now clinically evaluating a next-generation inhibitor called GDC-0077 (Genentech) that, based on preclinical data, may do exactly that. —Elie Dolgin

**Anti-CD47 Agent Boosts Macrophage Activity in NHL**

Patients with diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma, two forms of non-Hodgkin lymphoma (NHL), who become resistant to or relapse after standard chemotherapy and antibody-based regimens have a poor prognosis.

Seeking a more effective treatment for NHLs, researchers developed a macrophage-activating monoclonal antibody dubbed HuSF9-C4 (hereafter SF9; Forty Seven). In a recently reported phase Ib trial, the drug induced a high rate of durable responses in patients with DLBCL and follicular lymphoma (N Engl J Med 2018;379:1711–21).

Forty Seven cofounders Ravi Majeti, MD, PhD, and Irv Weissman, MD, of Stanford University in California, and their colleagues previously established that some cancer cells express high levels of CD47, an antiphagocytic signal that allows them to evade macrophages (Cell 2009;138:286–99). “It drew our attention because CD47 is essentially a checkpoint inhibitor for the innate immune system, for macrophages,” Majeti says.

The researchers developed SF9 to block CD47 and its ligand, SIRPα—and thus provoke macrophages to recognize and attack cancer cells. In preclinical studies, they showed that the drug is active in various forms of lymphoma (Cell 2010;142:699–713). Moreover, they demonstrated that the drug augmented the activity of rituximab (Rituxan; Genentech), an anti-CD20 therapy commonly used to treat B-cell lymphomas.

For the clinical trial—the first to test SF9 in combination with rituximab—researchers enrolled 22 patients: 15 with DLBCL and seven with follicular lymphoma. Patients had received a median of four prior therapies, and 95% had disease that was resistant to rituximab.

Overall, 11 patients responded to the drug, with eight complete responses—five in DLBCL and three in follicular lymphoma. Additionally, at a median follow-up of 6.2 months in the DLBCL group and 8.1 months in follicular lymphoma group, 91% of patients continued to respond. The most common
NEWS IN BRIEF

ZW25 Effective in HER2-Positive Cancers

A novel anti-HER2 therapy, ZW25 (Asymmetric), 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...