seems comparable based on published data.

In addition, although the toxicities of PARP inhibitors are generally similar, "there will be some innate and unique side effects among the different PARP inhibitors," says Ursula Matulonis, MD, of Dana-Farber Cancer Institute in Boston, MA. For example, she notes that rucaparib is more likely to cause liver enzyme abnormalities as well as grade 3 anemia, potentially complicating prescribing decisions and making personalized treatment plans and follow-up essential for patients taking the drugs.

Because many patients don't benefit from PARP inhibitors, or may not benefit for very long, physicians want to test the drugs in combination with other therapies, such as antiangiogenic agents or PI3K inhibitors. "Can we make the cancer cell more homologous repair–deficient?" asks Matulonis. Also, "after there's evidence of cancer growth, could we add something to a PARP inhibitor to continue to make it work? These are good questions, but they're not answered yet," she says. *–Suzanne Rose* ■

Benefit Mixed with Caution for Buparlisib

New findings from the BELLE-3 trial suggest that adding the investigational PI3K inhibitor buparlisib (Novartis) to endocrine therapy may improve outcomes for patients with hormone receptor (HR)–positive advanced breast cancer whose tumors become resistant to mTOR inhibition. However, the drug was also associated with dose-limiting side effects in a significant number of patients, investigators said during the 2016 San Antonio Breast Cancer Symposium in Texas, December 6–10.

In the phase III trial, 432 postmenopausal women who had received a prior aromatase inhibitor and the mTOR inhibitors everolimus (Afinitor; Novartis) or ridaforolimus (Ariad) were assigned to receive buparlisib plus fulvestrant or fulvestrant alone. Almost 70% had received two or more lines of endocrine therapy and 90% experienced disease progression while, or after, taking an mTOR inhibitor. Patients in the buparlisib group had longer progression-free survival (PFS) compared with the control group (3.9 vs. 1.8 months) and a higher 6-month PFS rate (31% vs. 20%).

Among those who took buparlisib, median PFS was higher in patients whose tumors had mutant, not wild-type, *PIK3CA* (4.7% vs. 2.8%), and in patients with nonvisceral disease versus those with metastasis to the liver or lung (4.2 vs. 3.1 months).

"Some patients who did not benefit from prior endocrine therapy with mTOR inhibition did benefit from taking buparlisib," said study co-author Ruth O'Regan, MD, of the University of Wisconsin-Madison, who presented the findings during a press briefing. "It suggests that buparlisib may be useful in many cancers that become resistant to mTOR inhibitors."

However, concerns remain about toxicities associated with buparlisib, including increased liver enzymes. Also troubling, the drug was associated with severe anxiety and depression, and several patients attempted suicide during the trial, said O'Regan.

These serious adverse events led to medication interruptions or dose reductions in a higher percentage of patients taking buparlisib plus fulvestrant compared with fulvestrant alone, researchers reported.

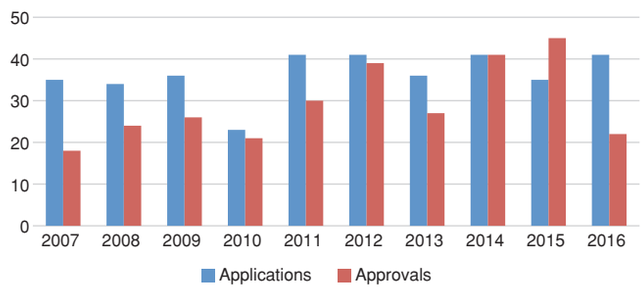
"We need to be cautious about [using drugs that cross] the blood–brain barrier due to the psychiatric effects of inhibiting PI3K in the brain," said Carlos Arteaga, MD, of Vanderbilt-Ingram Cancer Center in Nashville, TN, who commented on the study. He added that future research should focus on developing isoform-specific PI3K inhibitors that act on the mutated form of the protein while sparing the wild-type version that is essential for normal body function.

Several studies are currently testing next-generation PI3K inhibitors that specifically target the alpha isoform encoded by the *PIK3CA* gene in patients with advanced disease. They include the SOLAR-1 trial of fulvestrant combined with alpelisib (Novartis) and the SANDPIPER study of fulvestrant plus taselisib (Genentech). Researchers are also investigating the effectiveness of combining PI3K inhibitors and CDK4/6 inhibitors, said O'Regan.

"Our findings provide a nice view into the biology of PI3K inhibition," she said. "We now need to focus on developing new PI3K inhibitors with comparable activity and a better safety profile." *–Janet Colwell* ■

BY THE NUMBERS

New Biologic License Application Filings and Drug Approvals, 2007–2016



Source: FDA

In 2016, the FDA's Center for Drug Evaluation and Research approved 22 novel drugs, down from 45 in 2015 and below the average of about 29 drugs per year over the last decade. One reason for the decline, according to the FDA, is that five drugs were greenlighted in 2015, ahead of the 2016 dates that had been set for a decision.

The number of novel drugs for cancer treatment authorized by the FDA in 2016 also dropped, from 14 in 2015 to four. However, the agency did approve two diagnostic imaging agents and new indications for already approved therapies, such as the PD-1 inhibitors nivolumab (Opdivo; Bristol-Myers Squibb) and pembrolizumab (Keytruda; Merck).

BLU-285, DCC-2618 Show Activity against GIST

Mutations in *KIT* and *PDGFRA* are genetic drivers in more than 85% of gastrointestinal stromal tumors (GIST). Tyrosine kinase inhibitors (TKI), such as imatinib (Gleevec; Novartis), may