that many patients may be weighing life-changing decisions related to *BRCA* variants, such as whether to pursue prophylactic surgery.

In addition, the database will be helpful for researchers studying *BRCA* variants. Zhang says that bringing all of these data together will be especially helpful for investigators seeking to better understand the effects of the relatively rare, nontruncating *BRCA* variants, which will ultimately improve patient care and management.

To expand the BRCA Exchange's reach, GA4GH is developing data-sharing relationships with labs worldwide. The group is also interested in incorporating additional types of data, such as the results of functional assays.

In addition, now that the BRCA Exchange has launched, GA4GH plans to use the methods and relationships it has developed in the past few years to create similar exchanges for other clinically important genes. *–Kristin Harper* ■

Experts Question Recent Pharma Acquisitions

The purchase of Celgene by Bristol-Myers Squibb (BMS) and Eli Lilly's acquisition of Loxo Oncology may not boost drug development but will likely lead to higher prices, experts say. That means patients and shareholders might not gain much from the acquisitions.

The two deals, announced in quick succession in early January, involve companies that make some widely used cancer treatments and some innovative new compounds. BMS, which manufactures the checkpoint inhibitors nivolumab (Opdivo) and ipilimumab (Yervoy), is paying $74 billion for Celgene, whose biggest seller for cancer is lenalidomide (Revlimid), a thalidomide derivative. Eli Lilly, producer of, among others, the EGFR antagonist cetuximab (Erbitux), will pay about $8 billion for Loxo Oncology. The FDA recently approved Loxo's larotrectinib (Vitrakvi) for patients with any cancer showing *NTRK* fusions, making it the second tumor-agnostic drug on the market. Loxo's pipeline also includes LOXO-292, another tumor-agnostic compound that targets *RET* mutations and fusions.

The acquisitions come on the heels of GlaxoSmithKline's purchase of Tesaro, announced in December.

Kevin Schulman, MD, of Stanford University School of Medicine in California, says these deals are part of a continued pattern of acquisitions, but the timing isn't necessarily significant because purchases are usually a matter of opportunity. "All large companies are constantly looking for acquisitions to fill gaps in their pipelines," he notes.

The two most recent acquisitions, however, are unlikely to pay off as business deals, asserts Bernard Munos, MBA, a biomedical consultant with the Milken Institute who is based in Indianapolis, IN. (Munos previously worked for Eli Lilly but retired from the company in 2010.) Shareholders have often suffered losses after similar mergers, he says. Moreover, Loxo may not be the prize it appears to be, he adds, because Bayer shares the rights to larotrectinib and another compound in the Loxo pipeline, LOXO-195. "I am frankly not very optimistic that the shareholders of BMS or Lilly will see much benefit from the acquisitions."

Whether the deals will speed drug development or spark innovation is another issue. In principle, combining companies can increase the efficiency of R&D, says Anupam Jena, MD, PhD, of Harvard Medical School in Boston, MA. Still, some researchers have argued that mergers and acquisitions impede drug development because the united companies face less competition and have less motivation to create new products.

To evaluate that idea, in 2017, Schulman and colleagues analyzed the effects of pharmaceutical mergers and acquisitions between 1985 and 2009 (see http://scholarship.law.duke.edu/faculty_scholarship/3749/). The researchers found that companies that took part in more mergers and acquisitions did tend to spend less on R&D. However, those companies were also more likely to get their drugs into clinical trials.

Schulman thinks that "the mergers will potentially decrease internal R&D at the acquiring firms but might spur more investment in early-stage biotechnology companies that will hope to be similarly acquired."

Another consideration for R&D, Munos says, is how the acquisitions will affect innovation. "The jury is still out" on whether Loxo can continue to innovate as a part of Lilly, he says. BMS and Celgene, on the other hand, have had mixed records with their return on R&D in recent years, Munos says, and he predicts that they won't do any better together.

He and Schulman agree that the acquisitions will probably lead to increases in drug prices. "That $8 billion [for Loxo] has to come from somewhere," Schulman says.

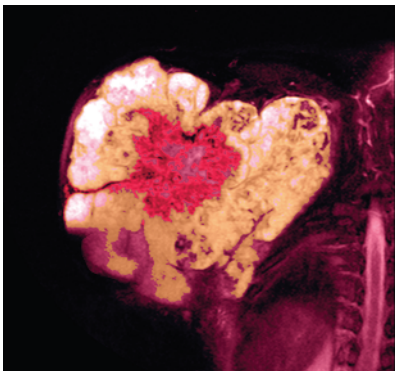
Jena says that the effect on prices is harder to predict and will depend on how much competition the combined companies encounter that might eventually curtail cost increases. "There may be an impact on prices in the short term—although the size of that impact is unknown," he says. *–Mitch Leslie* ■

Olaratumab for STS Disappoints in Phase III

Two years after receiving accelerated approval from the FDA as a first-line therapy with doxorubicin for patients with advanced or inoperable soft-tissue sarcoma (STS), olaratumab's (Lartruvo; Eli Lilly) potential has not held up in the phase III ANNOUNCE trial. At least for now, the company has no plans to continue promoting the anti-PDGFRα antibody.

"The sarcoma community is reeling from this outcome," says Gary Schwartz, MD, chief of hematology and oncology at NewYork-Presbyterian/Columbia University Irving Medical Center, who participated in the trial. "We'd had great confidence that this combination was here to stay and ANNOUNCE's findings would merely confirm what we'd already seen with the phase II trial."

In that study, for which Schwartz was an author, 133 patients were randomly assigned to receive olaratumab plus doxorubicin, or doxorubicin alone (Lancet 2016;388:488–97). The difference in median overall survival (OS) between the arms was sizeable: 26.5 months versus 14.7 months. Olaratumab showed particularly impressive activity in patients with leiomyosarcoma, a common form of STS originating in smooth muscle; responses were also seen across all other subtypes evaluated. This prompted the FDA to grant accelerated approval to olaratumab in December 2016—a much-cheered



Soft-tissue sarcoma of the shoulder.

decision, given that doxorubicin had been the mainstay for the last 40 years.

"The data were so positive, it's hard to fathom why olaratumab did not meet expectations in phase III," Schwartz says. Eli Lilly will present the full data from ANNOUNCE at an upcoming medical conference; for now, the key disclosure is that no significant differences in median OS were observed between study arms—for either the entire trial population or the leiomyosarcoma cohort.

One possible reason for this lack of survival benefit is that "the control arm really overperformed," Schwartz notes. The median OS for patients given only doxorubicin was "considerably longer than historical data have shown, which was surprising. I can't explain what might account for it." As well, there was no crossover from the control arm to the combination arm if the disease progressed, so "you have to wonder what, if any, subsequent therapies these patients received may have boosted their survival," he adds. Trabectedin (Yondelis; Janssen) and eribulin (Halaven; Eisai) are possibilities.

"Alternatively, it may be that our supportive-care measures are just that much better over the past 3 years, and this was sufficient to improve survival with doxorubicin alone," he suggests.

To Schwartz, a retrospective analysis attempting to tease out the reasons for olaratumab's disappointing performance is warranted. That said, although a phase II trial evaluating olaratumab combined with gemcitabine and docetaxel for advanced STS is ongoing, he thinks Eli Lilly may elect to abandon further development of the drug. "At least when combined with doxorubicin, it'll die by itself, whether or not the FDA withdraws approval—which should happen, given how the accelerated program is meant to work."

Global collaborations to explore expanding olaratumab's use beyond advanced or inoperable disease—for instance, as adjuvant therapy for patients with localized STS at high risk of developing metastases—will probably also be reconsidered, Schwartz adds. At Columbia, he and his colleagues were gearing up to evaluate an immunotherapy regimen for STS—a CD40 agonist, with olaratumab–doxorubicin as the backbone—but they'll now revise their study protocol.

ANNOUNCE's results are all the more frustrating because of the complexity of STS, which comprises more than 60 known subtypes, each histologically and biologically different. However, "it is what it is," Schwartz says, "and we'll just have to go back to the drawing board because there's a desperate need for new therapies." *–Alissa Poh* ■

Desmoid Tumors Respond to Sorafenib

Sorafenib (Nexavar; Bayer) shrinks desmoid tumors in one third of patients, according to a recent clinical trial that could lead to the first drug approval for the disease (N Engl J Med 2018;379:2417–28).

Desmoid tumors develop in connective tissue. Although they don't metastasize, they expand and force their way into other connective tissues, making them difficult to remove. More than 40% of tumors recur after surgery.

Although the tumors usually show mutations in the WNT pathway genes *APC* or *CTNNB1*, the molecular mechanisms driving their growth remain unclear. Because a standard treatment doesn't exist, physicians prescribe a variety of drugs, including doxorubicin and the receptor tyrosine kinase inhibitor (TKI) imatinib (Gleevec; Novartis). The rationale for using imatinib is that it blocks the receptor tyrosine kinases (RTK) KIT and PDGFR, which are often overexpressed in desmoid tumors, and has shown some effectiveness in clinical trials.

After one of his patients couldn't get into an imatinib clinical trial, Mrinal Gounder, MD, of Memorial Sloan Kettering Cancer Center in New York, NY, and his colleagues began to investigate sorafenib, which blocks some of the same RTKs. When they performed a retrospective study in 2011, they found that sorafenib induced tumor shrinkage in 25% of 24 patients (Clin Can Res 2011;17:4082–90).

That study inspired a phase III trial in which the researchers randomly assigned 87 patients with desmoid tumors to receive sorafenib or a placebo. The researchers measured tumor responses for a median of 27.2 months. At that time, median progression-free survival (PFS) had not yet been reached. However, the team estimated that the 1-year PFS for the sorafenib group was 89%, versus 46% for the placebo group. The estimated 2-year PFS was 81% and 36%, respectively. "Sorafenib is very active and could be considered as a front-line or second-line option," says Gounder.

As in other studies of desmoid tumors, patients who received a placebo experienced a high rate of spontaneous tumor regression: Tumors shrank in 20% of them versus 33% of the patients treated with sorafenib. Why these regressions occur remains unclear, says Gounder.

To limit side effects, the patients were given half the usual dose of sorafenib. The most common grade 1 or 2 adverse effects in the treatment group were rash, which affected 73% of patients, and fatigue, which affected 67% of them. In the placebo group, those side effects occurred in 42% and 61% of patients, respectively. The high rate of rash in the placebo patients is a mystery but may result from misattribution of symptoms by the investigators, says Gounder.

"It's a terrific study," says Chandrajit Raut, MD, of Brigham and Women's Hospital and Dana-Farber Cancer Institute in Boston, MA, who wasn't connected to the research. The results show that "this is an effective drug to consider in patients who need some kind of intervention for desmoid tumors that are refractory or symptomatic."

However, Keith Skubitz, MD, of the University of Minnesota in Minneapolis, notes that the trial didn't compare sorafenib to other potential treatments, such as imatinib. "It demonstrates that the drug is beneficial, but it doesn't clarify where among the possible treatments it fits in."