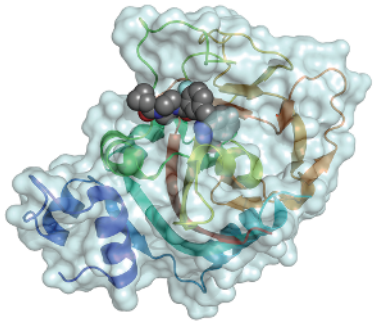

Ewing sarcoma cells with the *EWS–FLI1* translocation are sensitive to the PARP inhibitor olaparib, shown above binding to PARP.

as mutations, gene amplifications and deletions, gene fusions, and changes in gene expression. The project mainly tests approved drugs and those in clinical trials.

"I think the key selling point of our project is that we've got a huge range of diversity of cancer models that we're using," says Elizabeth Coker, PhD, of the Sanger. "You need a relatively small number of models to find the really big, really obvious hits, but you need statistical power to find the rarer biomarkers and the rarer variants, and that comes with an increased scale." For example, Sanger researchers used the data to establish that Ewing sarcoma cells with the *EWS–FLI1* translocation are sensitive to the PARP inhibitor olaparib (Lynparza; AstraZeneca; Nature 2012;483:570–5). Clinical trials are now testing olaparib and other PARP inhibitors against the disease.

Other institutions are querying the database, too: It is accessed by more than 350 people per day. "Because we do have the ability to hold these large numbers of cell models and to conduct these high-throughput drug screens, we are able to be a starting point for other labs to investigate drug response," Francies says. One research group is developing a method for predicting patient responses to chemotherapy based on gene-expression levels and *in vitro* drug sensitivity, whereas another is investigating why MEK inhibitors show activity in *BRAF*-mutant but not *KRAS*-mutant melanoma, and a third is exploring RANBP2 as a therapeutic target in colon cancers that resemble *BRAF*-mutant disease but lack a *BRAF* alteration (Genome Biology 2014;15:R47; Cancer Cell 2014;25:697–710; Cell 2016;165:317–30).

The researchers are now adding more models and drugs to the project. They are generating organoids to represent more cancer subtypes, and they also plan to begin testing drug combinations. "Right now, the majority of patients don't receive precision cancer medicine, and that is simply because we don't understand what targeted drugs we should be giving to what patients," Coker says.

Patricia Jaaks, PhD, also of the Sanger, adds, "We hope that finding new biomarkers will eventually help to position drugs in the right disease or cancer context." –*Catherine Caruso* ■

Collaborative Review, Concurrent Approval

In a regulatory first, the FDA has reviewed a cancer treatment with drug agencies from around the world, leading to simultaneous approvals in three countries.

The FDA joined Australia's Therapeutic Goods Administration and Health Canada in granting conditional approval in September to lenvatinib (Lenvima; Eisai) plus pembrolizumab (Keytruda; Merck) for recurrent endometrial carcinomas that are not microsatellite instability–high (MSI-H) or mismatch repair–deficient (dMMR).

The approvals came 3 months prior to the FDA's target decision date—and likely much earlier than would happen otherwise in Australia or Canada, where drug launches often lag a year or more behind those in the United States.

The regulatory bodies came to the shared decision as part of Project Orbis, an initiative of the FDA's Oncology Center of Excellence.

"This is a really important direction," says Frances Richmond, PhD, chair of the Department of Regulatory and Quality Sciences at the University of Southern California in Los Angeles. Having each agency independently review submissions is redundant "when they're essentially working from the same songbook," she notes. "The more they can do to reduce the timeline and the cost of [developing] these drugs is a good thing."

Since 2004, members of the FDA's oncology and hematology division have routinely held conference calls with their counterparts in Europe, Japan, and elsewhere. These virtual meetings have allowed the agencies to share confidential information about ongoing reviews and to identify any regulatory divergences across regions.

As highlighted in an August report from members of the FDA and European Medicines Agency (EMA), such exchanges provide "a form of peer review among fellow regulators," allowing "for more informed regulatory decision-making, and oversight of regulated industry in areas like inspections and data integrity." (Clin Pharmacol Ther 2019 Aug 26 [E pub ahead of print]).

Yet, the various agencies involved in these strategic partnerships had never synced the submission, appraisal, or approval of any marketing applications.

Through Project Orbis, review teams from Australia, Canada, and the United States collectively considered data from a phase II trial of 94 women with MSI-H/dMMR–negative endometrial tumors that had progressed following at least one systemic therapy.

In the single-arm study, participants received daily oral doses of lenvatinib, a multikinase inhibitor of VEGFRs and FGFRs, and infusions of pembrolizumab, a PD-1–targeted checkpoint inhibitor, every 3 weeks until unacceptable toxicity or disease progression. The objective response rate was 38%, with 10 patients experiencing complete responses and another 26 exhibiting partial tumor shrinkage. The benefit was generally durable, lasting 6 months or longer in 69% of responders, with a safety profile comparable to that reported previously for both drugs as monotherapies.

A randomized phase III trial evaluating the lenvatinib–pembrolizumab regimen against chemotherapy is currently enrolling patients. Continued approval of the drug combination in all three countries could rest on survival data from this 780-person study.

For now, Project Orbis will primarily consider expanding marketing authorization of new indications for previously approved agents. According to the FDA, future collaborative reviews may involve novel therapies—although because more proprietary information would be involved, sharing data becomes trickier. Future efforts could also involve the EMA, Japan's

Pharmaceuticals and Medical Devices Agency, and Switzerland's Swissmedic.

Jon Roffman, MBA, head of oncology strategy at the consulting firm ZS in Boston, MA, welcomes the launch of Project Orbis. "The regulatory process, in aggregate across participating countries, will be strengthened by collaboration and knowledge-sharing among multiple regulatory agencies," he says.

However, "a significant open question is whether or not reimbursement processes can keep pace with regulatory approval." *–Elie Dolgin* ■

Brain Tumors Feed off Healthy Neurons

Cancer cells in the brain—be they from primary gliomas or secondary metastases—can form synaptic connections with neighboring neuronal cells in the microenvironment, a trio of studies shows. These synapses, when activated, promote tumor proliferation, survival, and invasiveness. Disrupting the communication channels between neurons and cancer cells could therefore help blunt the growth of deadly brain tumors.

"These papers are amazing," says Paola Vermeer, PhD, a cancer biologist at Sanford Research in Sioux Falls, SD, who was not involved in the studies. Scientists had previously documented the presence of tumor-infiltrating nerves and shown that patients with densely innervated cancers tend to have worse prognoses, "but this is going a step further," Vermeer says. "These are bona fide synapses and important for disease progression. We need to take this knowledge and use it to find therapeutics."

Two of the recently published studies focused on the synaptic cross-talk between gliomas and neurons—and both came to similar, complementary conclusions.

In one, a team led by Frank Winkler, MD, PhD, and Thomas Kuner, MD, of Heidelberg University in Germany, demonstrated that patient-derived glioblastoma samples include excitatory contacts between presynaptic neurons that release glutamate and postsynaptic cancer cells containing long, finger-like protrusions called tumoral microtubes that receive the neurotransmitter signal through AMPA receptors (Nature 2019;573:532–8).

Activating AMPA receptors via optogenetic means stimulated the growth of gliomas transplanted into mice, whereas perturbing glutamate signaling—either genetically or pharmacologically with the antiepileptic drug perampanel (Fycompa; Eisai)—had the opposite effect, reducing the proliferative capacity of the tumors.

Michelle Monje, MD, PhD, of Stanford University in California, and her colleagues independently documented the same types of circuit dynamics in aggressive pediatric brain tumors known as diffuse midline gliomas (Nature 2019;573:539–45).

However, primary brain tumors are not the only cancers capable of co-opting neuronal synapses for their own selfish gain. A group led by Douglas Hanahan, PhD, of the Swiss Institute for Experimental Cancer Research in Lausanne, showed in a third paper that breast cancer cells that had spread to the brain express their own glutamate receptors of the NMDA subtype (Nature 2019;573:526–31).

Through these receptors, Hanahan's team reported, the cancer cells tap into existing neuronal junctions and feed off glutamate to boost their growth. "It's like they are parasitizing the neurons and synapses," says Hubert Hondermarck, PhD, a cancer neurobiologist from the University of Newcastle in Callaghan, Australia, who was not involved in the research.

The new studies highlight the possibility of developing drugs that disconnect neuronal linkups. To that end, Winkler cofounded Divide & Conquer in September. The company is focused on developing therapies that disrupt cellular communication networks to combat glioblastoma and other cancers.

Meanwhile, Monje is planning an academic trial that builds on her team's 2017 paper, which showed in xenograft mouse models of high-grade gliomas that pharmacologically blocking the release of neuron-secreted neuroligin-3 into the tumor microenvironment led to cancer growth inhibition (Nature 2017;549:533–7).

Avoiding toxicities may prove challenging because the ties that bind neurons and cancer cells rely on many of the same molecular players as those that unite healthy neurons. "If we start to drug those receptors or those neurotransmitters, we will probably impact the normal functioning of the brain," Hondermarck says. "At this stage, it's unclear how these findings are going to translate into therapeutic applications, but this is very promising." *–Elie Dolgin* ■

First RET Inhibitor on Path to FDA Approval

In the phase I/II LIBRETTO-001 trial, the experimental RET inhibitor selpercatinib (LOXO-292; Eli Lilly) elicited high response rates lasting more than a year and a half in patients with *RET*-altered non–small cell lung cancer (NSCLC) who had already received multiple treatments. The data were presented at the International Association for the Study of Lung Cancer's 2019 World Conference on Lung Cancer in Barcelona, Spain.

Selpercatinib produced an objective response rate (ORR) of 68% in 105 patients who had received a median of three prior treatment regimens, according to findings presented by the trial's lead investigator, Alexander Drilon, MD, of Memorial Sloan Kettering Cancer Center in New York, NY. Median duration of response and progression-free survival were 20.3 months and 18.4 months, respectively, and side effects were mostly low grade. The ORR was 85% in a group of 34 previously untreated patients.

"It really checks all the boxes of favorable features that we like to see in a targeted therapeutic," said Drilon.

RET alterations are relatively rare in NSCLC but are common in certain types of thyroid cancer. They have also been identified in colorectal, pancreatic, and breast cancers. In the absence of approved drugs that specifically target RET, patients have been treated with multikinase inhibitors, including cabozantinib (Cabometyx; Exelixis), vandetanib (Caprelsa; Sanofi), lenvatinib (Lenvima; Eisai), and sorafenib (Nexavar; Bayer), which have shown limited efficacy and often high toxicity.

In contrast, selpercatinib selectively blocks RET, avoiding other targets and the associated treatment-limiting side effects. It is one of two RET inhibitors currently in late-stage clinical trials—the other, pralsetinib (BLU-667; Blueprint Medicines), has shown promising activity in patients with