view, the future seems bright. As blood-based assays are further refined, perhaps fragmentomics should also be incorporated"—whereby analyses of cell-free DNA fragment sizes could complement epigenetic (methylation patterns) knowledge, potentially improving predictive power.

An updated version of Galleri is already being used in PATHFINDER 2, which aims to screen 20,000 individuals, Schrag said. As well, several other large studies, including NHS-Galleri, STRIVE, and REFLECTION, should help optimize this test's real-world performance.

Meanwhile, the NCI is also going all out on investigating MCED's future promise. With a plethora of biotechs developing various assays, there is a pressing need to examine their actual utility. To that end, as part of the reignited Cancer Moonshot, the agency plans to launch a feasibility study in 2024 and evaluate such tests in 24,000 participants. This will lay the groundwork for an even larger trial down the road, involving up to 225,000 people.

For now, current screening procedures with established effectiveness should still be prioritized, Schrag stressed, even as MCED's possibilities are explored. Ultimately, too, "it will be important to assess whether MCED reduces mortality," she noted. "That's the primary goal of all cancer screening." *–Alissa Poh* ■

doi: 10.1158/2159-8290.CD-NB2022-0058

Leading Oral SERD Shows Prolonged Activity

The leading oral drug candidate designed to degrade the estrogen receptor (ER) can maintain prolonged antitumor activity, with data presented at the ESMO Congress 2022, held September 9–13 in Paris, France, showing that some recipients of elacestrant (Menarini) have lived without disease progression for 18 months and counting.

But not all oral selective estrogen receptor degraders (SERD) have demonstrated such impressive efficacy. In August, Sanofi announced that it was ending development of its oral SERD, amcenestrant, after an interim analysis of the pivotal AMEERA-5 trial found that the study would likely end in failure. Data presented at the ESMO meeting from an earlier phase II trial also showed that amcenestrant did not improve progression-free survival (PFS) compared with standard therapy.

Oral SERDs are vying to supplant the injectable SERD fulvestrant, a mainstay of treatment for ER-positive breast cancer, especially among patients who develop resistance to aromatase inhibitors (AI) or tamoxifen.

Fulvestrant both antagonizes ER-dependent transcriptional activity and harnesses the cell's natural protein disposal system to mediate receptor destruction. But owing to poor oral bioavailability, it must be given intramuscularly, a route of administration that can be painful and inconvenient for patients. Fulvestrant is also inferior to many newer oral SERDs—elacestrant included—in terms of absorption rates, pharmacokinetics, and inhibitory effects on the ER.

Analysts and clinicians now expect elacestrant to earn the FDA's blessing and become the first SERD in pill form approved for patients with previously treated ER-positive/HER2-negative advanced breast cancer. A regulatory decision is expected early next year.

Initial data from the phase III EMERALD trial showed that elacestrant was tolerable and reduced the risk of progression or death by 30% compared with standard-of-care options (J Clin Oncol 2022;40:3246–56). That benefit was especially pronounced among patients with *ESR1* mutations, who had a reduction in the relative risk of disease progression or death of 45%. (*ESR1* encodes the ER protein and, when mutated, can make breast tumors resistant to standard hormonal therapies.)

Updated trial results presented at the ESMO meeting then further demonstrated elacestrant's superior efficacy. Landmark PFS analyses at 15 and 18 months showed that a greater percentage of the oral SERD recipients were living without disease progression.

Elacestrant's effects on overall survival are not yet fully known. However, an analysis of the initial EMERALD data indicated that, as with PFS, the drug's life-extending benefits were greatest among patients with *ESR1* mutations—a result that leads trial investigator Virginia Kaklamani, MD, of The University of Texas Health Science Center in San Antonio, to conclude that elacestrant is "an improved version of fulvestrant, at least in the *ESR1* mutants."

Kaklamani continued: "Then the question is: Is it an improved version of fulvestrant regardless [of mutational status]? And we don't know that." But "it's at least equivalent—and it's an oral drug." As such, it could become the treatment of choice for many patients—especially as adjuvant therapy, for which at-home administration is the norm.

Several other companies, including the makers of camizestrant (AstraZeneca), imlunestrant (Eli Lilly), and giredestrant (Roche), are running phase III trials of their oral SERDs. However, as Aditya Bardia, MD, MPH, of Massachusetts General Hospital in Boston, points out: "It's tough to know without head-to-head comparisons" if one is better than any other and why some earlier studies have yielded disappointing results. As Bardia and his colleagues reported at the ESMO meeting, giredestrant showed signs of efficacy in phase II development but did not prove statistically superior to physician's choice of endocrine therapy as a second- or third-line treatment.

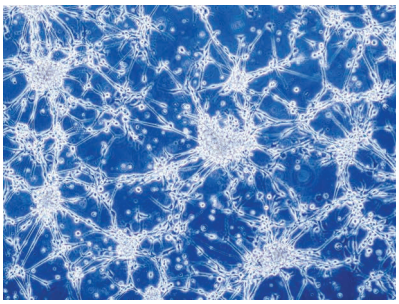
Drugmakers are also investigating earlier use of oral SERDs. According to Bardia, who has been involved in testing several of these products, that's where the drugs could truly shine.

"In the earlier setting, the tumors are generally more endocrine-responsive and -sensitive," he says. "So, if any of these agents are truly better than AIs or fulvestrant, it's in the early breast cancer setting that we should be able to see a signal." *–Elie Dolgin* ■

doi: 10.1158/2159-8290.CD-NB2022-0057

New Strategy May Thwart Glioblastoma Resistance

Temozolomide has been a first-line glioblastoma treatment for almost 20 years, but tumors can develop resistance to it. Researchers have developed a new approach that may overcome resistance by targeting cells lacking



Glioblastoma cells.

a key DNA repair enzyme (Science 2022;377:502–11).

Temozolomide attacks DNA by adding a methyl group to the oxygen atom in the base guanine. Healthy cells and about half of glioblastomas don't respond to the drug because they make ample amounts of the enzyme MGMT, which reverses this DNA alteration. But for unknown reasons, about half of glioblastomas have reduced MGMT production, leaving them vulnerable to temozolomide. In these tumors, cells try to use another DNA-mending mechanism, the mismatch repair (MMR) pathway, to restore their DNA. However, MMR cannot remove the altered guanine, leading to DNA breaks that cause the cells to die. Glioblastomas are continually accumulating mutations, and some tumors that lack MGMT become resistant to temozolomide when they pick up mutations that inactivate MMR.

A team led by Seth Herzon, PhD, and Ranjit Bindra, MD, PhD, of Yale University in New Haven, CT, devised an approach for killing MGMT-lacking tumor cells that doesn't depend on whether MMR is functional. Their idea was to create a drug that induces a DNA lesion that becomes more severe when it isn't fixed. Healthy cells with plenty of MGMT would repair the lesion quickly, the researchers predicted. But they also hypothesized that in cells without MGMT, as in about half of glioblastoma cells, the lesion would lead to cross-links between DNA strands, blocking replication and promoting apoptosis. Even if tumor cells accrue mutations that disable MMR, they could not survive.

To test the approach, the scientists synthesized a molecule dubbed KL-50 that produces a DNA lesion by affixing a fluoroethyl group to the oxygen in guanine. They studied a panel of isogenic cell lines that expressed or lacked MGMT and had functional or nonfunctional MMR. Comparing temozolomide with KL-50 in these cells, the researchers found that neither drug performed well when cells had MGMT and functional MMR. But when MGMT was absent and MMR was inactive, KL-50 was much better at killing cells than temozolomide.

The team also implanted tumors that lacked MGMT and working MMR into the brains of mice and gave the animals KL-50, temozolomide, or a control compound. Mice treated with KL-50 lived significantly longer than control animals and those that received temozolomide.

KL-50 "might offer hope for patients with MGMT-negative, mismatch repair–silenced tumors," says Herzon. He and his colleagues have formed a company to further develop the drug, and they hope to begin clinical trials in 2024, he says.

Outside experts give the researchers credit for investigating a novel strategy. "Thinking about ways to overcome DNA damage repair is worthwhile," says John de Groot, MD, of the University of California, San Francisco.

"Their approach is interesting," adds Fabio Iwamoto, MD, of the Columbia University Vagelos College of Physicians and Surgeons in New York, NY.

However, both scientists raise questions about the study's methods and are skeptical that the approach will provide much clinical benefit. One significant limitation, Iwamoto says, is the lack of an *in vivo* comparison with lomustine, a treatment widely used against glioblastomas that has clinical activity against MMR-deficient tumors. And de Groot notes that temozolomide resistance could arise from many factors, including the cancer microenvironment, that may not respond to the new strategy. *–Mitch Leslie* ■

doi: 10.1158/2159-8290.CD-NB2022-0055

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

NOTED

The European Commission blocked Illumina's $8 billion acquisition of GRAIL, which the companies announced in 2020. The deal "would have enabled and incentivized Illumina to foreclose GRAIL's rivals, who are dependent on Illumina's technology, from access to an essential input they need to develop and market their own tests." Illumina makes next-generation sequencing systems; GRAIL is developing blood tests to aid early cancer detection.

In an international phase II clinical trial, **63.3% of 79 patients with stage II–IV cutaneous squamous cell carcinoma had their tumors nearly or completely eradicated with neoadjuvant cemiplimab** (Libtayo; Regeneron/Sanofi), researchers reported at the ESMO 2022 Congress; results were simultaneously published (N Engl J Med 2022 Sep 12 [Epub ahead of print]). Study presenter Neil Gross, MD, of The University of Texas MD Anderson Cancer Center in Houston said that "if you can avoid radiation or have a smaller surgery, and you can keep your eye, ear, or nose, that's a huge win for people."

The FDA approved durvalumab (Imfinzi; AstraZeneca) plus gemcitabine and cisplatin for certain biliary tract cancers (BTC). The decision was based on the phase III TOPAZ-1 trial, in which 685 patients with locally advanced inoperable or metastatic BTC who had not received systemic therapy received all three drugs or a placebo plus gemcitabine and cisplatin. Median overall survival was 12.8 months and 11.5 months in the durvalumab and placebo arms, respectively.

U.S. President Joe Biden appointed Renee Wegrzyn, PhD, as the first director of the Advanced Research Projects Agency for Health (ARPA-H), which was created in 2020 to drive biomedical innovation and research on some of the most intractable diseases, including cancer. Currently working at Ginkgo Bioworks, Wegrzyn previously served as a program manager at the Defense Advanced Research Projects Agency, an institution that inspired ARPA-H's creation.

The American Association for Cancer Research released its 12th annual Cancer Progress Report, which provides cancer incidence, mortality, and survivorship statistics and discusses the latest research in cancer biology, detection, diagnosis, treatment, and prevention (https://cancerprogressreport.aacr.org).

doi: 10.1158/2159-8290.CD-12-11-NOTED