PEOPLE


Grail, Inc.

Hans Bishop began his role as CEO of Grail on June 7, replacing Jennifer Cook, MBA, who stepped down. Previously, he founded Juno Therapeutics, serving as president and CEO until the company was acquired by Celgene in 2018 and he joined its board of directors. Bishop was also a cofounder and the executive chairman of Sana Biotechnology, the chairman of Lyell ImmunoPharma, and a director of Agilent Technologies. He has held various other executive roles at Dendreon, Bayer, Chiron Corp., and European Biopharmaceuticals.

Colon Cancer Data Key as Pfizer Buys Array

Last month, Array BioPharma announced that a pair of their drugs could dramatically improve outcomes for some patients with advanced colorectal cancer. Now, Pfizer has announced plans to acquire the Boulder, CO–based drugmaker in a deal valued at approximately $11.4 billion—and to maintain the company as a stand-alone research unit.

The agreement, unveiled on June 17, will give Pfizer two drugs, encorafenib (Braftovi) and binimetinib (Mektovi), approved by the FDA last year for patients with *BRAF*-mutant metastatic melanoma. Compared with other BRAF–MEK inhibitor combinations, the Array regimen is "better [than] or tied for best-in-class" in terms of efficacy and safety, according to Keith Flaherty, MD, of the Massachusetts General Hospital Cancer Center in Boston, MA, who led the drugs' clinical testing.

However, as this is the third BRAF–MEK inhibitor combination to reach the market for melanoma, that indication is unlikely to generate substantial revenues for Pfizer. What could push up sales of encorafenib–binimetinib is a supplemental approval for the treatment of *BRAF*-mutant metastatic colorectal cancer.

Currently, no drug regimens are specifically indicated for this type of disease. Patients often receive irinotecan-containing chemotherapy regimens plus the EGFR inhibitor cetuximab (Erbitux; Eli Lilly)—but encorafenib and binimetinib plus cetuximab looks to be a significantly better option.

In May, Array reported interim results from the phase III BEACON trial, which enrolled patients with colorectal cancer whose disease progressed despite treatment. (No other companies have advanced BRAF–MEK inhibitor combinations past phase II for this indication.) The data showed that Array's chemotherapy-free triplet regimen produced higher overall response rates (26% versus 2%) and longer overall survival times (9 months versus 5.4 months) compared with cetuximab and chemotherapy.

Array has said it intends to submit the data to U.S. regulators later this year, around the same time as the deal with Pfizer is expected to close. Meanwhile, Array is also evaluating its BRAF–MEK combo in patients with *BRAF*-mutant non–small cell lung cancer and as a first-line treatment with cetuximab for *BRAF*-mutant colorectal cancer.

In a statement, Pfizer CEO Albert Bourla, DVM, PhD, said the acquisition of Array's BRAF and MEK inhibitors "sets the stage to create a potentially industry-leading franchise for colorectal cancer." However, the financial benefits could take years to accrue, with encorafenib and binimetinib not projected to cross the $1 billion annual threshold until the middle of the next decade, with about half the revenue stemming from a colorectal cancer–label expansion.

Ironically, the regimen could soon face competition from a Pfizer spin-off company called SpringWorks Therapeutics. On June 18, BeiGene and SpringWorks announced the creation of a joint venture called MapKure that will advance BeiGene's BRAF inhibitor, BGB-3245, likely in combination with a former Pfizer asset, the MEK inhibitor PD-0325901.

Pfizer gains more in the deal than encorafenib and binimetinib, however. For example, the sale includes ARRY-382, an inhibitor of colony-stimulating factor-1 receptor in a phase II combination trial with pembrolizumab (Keytruda; Merck) for patients with advanced solid tumors, as well as a portfolio of royalty-generating medicines that originated with Array before the company licensed them to others.

The royalty-generating assets include two marketed drugs, the TRK inhibitor larotrectinib (Vitrakvi; Bayer) approved in the United States last year, and danoprevir (Ganovo; Roche), a hepatitis C drug available in China, plus a handful of late-stage clinical candidates—the AKT inhibitor ipatasertib (Genentech), the MEK inhibitor selumetinib (AstraZeneca), the HER2 inhibitor tucatinib (Seattle Genetics), and the RET inhibitor LOXO-292 (Loxo/Eli Lilly). *–Elie Dolgin* ■

AMG 510 First to Inhibit "Undruggable" KRAS

Amgen's novel small-molecule inhibitor AMG 510 has become the first drug to show activity in patients with $KRAS^{G12C}$-mutant solid tumors. In a phase I trial, AMG 510 elicited partial responses in half of patients with non–small cell lung cancer (NSCLC) and led to stable disease in patients with colorectal or appendix cancer. The striking results were presented at the 2019 American Society of Clinical Oncology Annual Meeting in Chicago, IL, in June (J Clin Oncol 37, 2019 [suppl; abstr 3003]).

"This is a population of patients that has not had targeted therapies, and the fact that they're now potentially being included in that approach is really a remarkable thing," said Pasi A. Jänne, MD, PhD, of Dana-Farber Cancer Institute/Harvard Cancer Center in Boston, MA, who was not involved in the trial.

KRAS alterations are the most prevalent oncogenic driver mutations in cancer. However, researchers have long considered KRAS undruggable due to its small size and relatively smooth surface—with few deep pockets where molecules can bind—as well as how rapidly and tightly it binds to GTP in its active state. AMG 510 binds to $KRAS^{G12C}$ via the cysteine

AMG 510 is the first drug to successfully target KRAS (pictured above), which has long been considered undruggable.

amino acid that replaces glycine when the mutation occurs, locking it in an inactive state. "This mutation occurs in approximately 13% of patients with NSCLC, and approximately 3% of colorectal and appendix, and 1% to 3% of other solid tumors," said Marwan Fakih, MD, of City of Hope Comprehensive Cancer Center in Duarte, CA, who presented the results.

Researchers enrolled 35 patients with *KRAS*^{G12C}-mutant solid tumors who had received at least two prior therapies in the trial: 14 patients with NSCLC, 19 with colorectal cancer, and two with appendix cancer. Five of 10 evaluable patients with NSCLC who received AMG 510 had a partial response and are still being treated; four more experienced stable disease. Additionally, 14 of 18 evaluable patients with colorectal or appendix cancer had stable disease. Adverse events were mild, mostly classified as grade 1 and 2.

"This is the clinical proof-of-concept that you can target KRAS^{G12C}, and you can get a clinical response, but even bigger than that is the potential impact here," Jänne said, noting that 40% of patients with *KRAS*-mutant NSCLC have a *KRAS*^{G12C} mutation. "I think that the fact that you're seeing five responses here is pretty stunning, actually."

Kwok-Kin Wong, MD, PhD, of the Laura and Isaac Perlmutter Cancer Center at NYU Langone Medical Center in New York, NY, who was also not involved in the trial, agreed. "I think this is an amazing day for targeted therapy," he said. However, Wong wants to know the duration of response, pointing out that, as with other targeted therapies, patients will likely develop resistance. "The future is trying to figure out what combinations would give you a durable response," he said.

Wong also wants to know why patients with NSCLC responded better than those with colorectal cancer, as well as how patients with other *KRAS*-mutant malignancies, such as pancreatic cancer, might respond.

Amgen is not the only company pursuing targeted therapies for *KRAS* mutations: Mirati Therapeutics is conducting a phase I trial on its *KRAS*^{G12C} inhibitor, MRTX849, and Dicerna is developing a therapy that targets *KRAS*^{G12D}, the most common *KRAS* mutation. *–Catherine Caruso* ■

Merck LAPs Up Tilos for Its TGFβ-Targeting Tech

Merck is joining the list of drug companies aiming to block TGFβ signaling to augment the tumor-killing potential of checkpoint inhibitors. The company announced in June that, in a deal potentially worth up to $773 million, it will acquire Tilos Therapeutics, a 3-year-old startup developing drugs to prevent the activation and release of TGFβ, a cytokine involved in thwarting anticancer immunotherapies.

Tilos's antibodies target latency-associated peptide (LAP), a protein that forms a cage around TGFβ and keeps the cytokine in check until it's deployed. The company's TLS-01 class of antibodies bind to LAP on immunosuppressive cells in the tumor microenvironment. This action prevents the localized release of TGFβ. However, the molecules avoid other LAP–TGFβ complexes involved in general tissue homeostasis.

"It gives you a really selective way to hit that cell-mediated immune suppression," says Tilos's founding CEO Barbara Fox, PhD, now a consultant for Merck.

Two years ago, company founder Howard Weiner, MD, and his colleagues at Brigham and Women's Hospital in Boston, MA, published a study demonstrating that an anti-LAP antibody decreased the infiltration of tolerogenic T cells in a mouse model of melanoma; it also increased the number of cytotoxic T cells and natural killer cells in tumors and draining lymph nodes (Sci Immunol 2017;2:aaj1738). Tilos scientists have also shown that TLS-01 antibodies work synergistically with radiation therapy to inhibit tumor growth in a mouse model of colorectal cancer (Proceedings of the 110th Annual Meeting of the AACR, 2019, abstract 93/12).

TGFβ has long been viewed as an attractive cancer target, but its dual role in the disease—acting as a tumor suppressor in premalignant cells and later promoting cancer progression, invasion, and tumor metastasis—prompted worries about inadvertently inducing tumor growth by suppressing TGFβ activity. "People were very concerned," says John McPherson, PhD, a former Genzyme executive who helped develop the anti-TGFβ antibody fresolimumab, "but that was in the context of not understanding the biology of that growth factor family."

With additional molecular insights, a growing appreciation that TGFβ in the tumor microenvironment helps cancer cells evade immune surveillance, and a surge of interest in immuno-oncology, the industry has begun to pursue the therapeutic strategy.

Several large firms, including Sanofi, Eli Lilly, and Novartis, are now coupling PD-1 inhibitors with experimental antibodies or small-molecule drugs that target TGFβ directly. GlaxoSmithKline and Merck KGaA are jointly developing a fusion protein designed to simultaneously block PD-L1 and TGFβ receptors, whereas AbbVie and Scholar Rock are aiming to sensitize tumors to PD-1 inhibition with antibodies directed at LAP or other targets linked to latent TGFβ complexes, à la Tilos.

The Tilos buyout is the third oncology-focused deal of the year for Merck, maker of the PD-1 inhibitor pembrolizumab (Keytruda). In February, the company spent about $300 million to procure Immune Design, which developed an experimental TLR4 agonist in phase II trials for lymphoma. In May, Merck doled out $1.05 billion (with up to $1.15 billion more in milestone