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

payments) for Peloton Therapeutics, developer of a HIF2α inhibitor in late-stage testing for kidney cancer.

All three transactions "appear to be guided by the idea that Keytruda plus some other therapy would improve efficacy [and] expand indications for the product," says Joshua Cohen, PhD, an independent healthcare analyst in Boston. –*Elie Dolgin* ■

Aiming TILs at Melanoma, Cervical Cancer

For patients with advanced melanoma or cervical cancer whose disease is refractory to standard treatment, tumor-infiltrating lymphocyte (TIL) therapy may merit a closer look, according to two ongoing multisite phase II trials. Findings were presented during the 2019 American Society of Clinical Oncology Annual Meeting in Chicago, IL, in June.

The studies, innovaTIL-01 and innovaTIL-04, are evaluating two autologous cell therapies—lifileucel/LN-144 and LN-145 (Iovance Biotherapeutics), respectively. Enrolled patients have a tumor lesion resected for TIL harvesting; the cells are then massively expanded in number at a central facility, aided by high amounts of IL2, as well as allostimulation with donor-derived irradiated feeder cells. After this 22-day process, the TILs are cryopreserved and can be infused at patients' convenience, explained principal investigator Amod Sarnaik, MD, of Moffitt Cancer Center in Tampa, FL.

Unlike chimeric antigen receptor (CAR) T cells, "these TILs aren't really manipulated in any way," Sarnaik added. "The idea is that because they've previously trafficked into the tumor, hopefully they can do so again after *in vitro* expansion."

Sarnaik reported results from 66 patients with advanced melanoma who had all relapsed on immune checkpoint blockade and, where appropriate, BRAF/MEK inhibitors (J Clin Oncol 37, 2019 [suppl; abstr 2518]). Nearly half (44%) also had brain or liver metastases. The objective response rate (ORR) to lifileucel was 38%, including two complete responses. Another 42% experienced stable disease, and the median duration of response (DOR) has not been reached.

"This is pretty much unmatched when compared with any other treatment we've seen for melanoma following progression on anti–PD-1 therapy," Sarnaik observed.

Among 27 patients with metastatic cervical carcinoma refractory to the standard of care—chemotherapy, VEGF-targeted agents, and radiation—the ORR with LN-145 was 44.4%, including three complete responses (J Clin Oncol 37, 2019 [suppl; abstr 2538]). Stable disease was seen in another 40.7%, and the median DOR has not been reached.

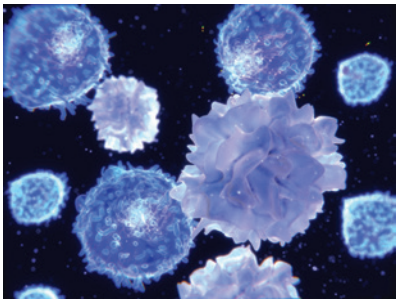
"These are striking results so far," said principal investigator Amir Jazaeri, MD, of The University of Texas MD Anderson Cancer Center in Houston. "We need longer follow-up to see how the DOR translates to progression-free survival, but I think this is pretty exciting for a difficult-to-treat population."

In both studies, most toxicity issues were due to patients receiving preparatory regimens of lymphodepleting chemotherapy as well as six doses of IL2 to spur TIL growth *in vivo*. "There were some cases of febrile neutropenia and chills right after TIL infusion," Sarnaik said; otherwise, lifileucel and LN-145 were well tolerated.

Ignacio Melero, MD, PhD, of Clínica Universidad de Navarra in Pamplona, Spain, suggested that in cases of melanoma progression after lifileucel, the investigators might want to consider re-treating these patients with checkpoint inhibitors. "It makes sense, because once TILs have been engrafted, the rules of the game could be different" in the tumor microenvironment, he said.

"A tumor's immune responsiveness is certainly dynamic, and any therapeutic intervention could change it in some way," agreed Tara Mitchell, MD, of the University of Pennsylvania in Philadelphia. Overall, lifileucel and LN-145 appear "really impressive," she said, showing significant promise in solid tumors, where CAR T cells have been more disappointing than not.

"I think many clinicians are convinced that the efficacy is there" with TIL therapy, Mitchell added, but because its potential has so far been reported anecdotally, studies such as Iovance's are "a big step forward in demonstrating that this technology is feasible and more broadly accessible."



Therapies involving tumor-infiltrating lymphocytes (shown above with other immune cells) have demonstrated effectiveness in patients with certain cancers who have relapsed despite receiving immune checkpoint blockers.

The innovaTIL-01 trial is enrolling 75 more patients to support lifileucel's FDA registration. Meanwhile, LN-145 has received the agency's fast track and breakthrough therapy designations, Jazaeri said, and "considering that pembrolizumab [Keytruda; Merck] was approved for PD-L1–positive cervical cancer based on an ORR of just 14%, I think our data, although early, could be registration-enabling." –*Alissa Poh* ■

Mechanism of Cediranib–Olaparib Combo Revealed

The combination of olaparib (Lynparza; AstraZeneca) and cediranib (Recentin; AstraZeneca) has shown promise in recurrent non–*BRCA*-mutant ovarian cancer, and a recent study offers a possible mechanistic explanation: Cediranib may confer sensitivity to olaparib by increasing tumor hypoxia and inhibiting platelet-derived growth factor receptor (PDGFR), which reduces *BRCA1/2* and *RAD51* expression, thus decreasing homology-directed DNA repair (Sci Transl Med 2019;11:eaav4508).

A PARP inhibitor, olaparib was developed for patients with cancers such as ovarian and breast that harbor *BRCA* mutations, which interfere with DNA repair, thus making cancer cells more dependent on PARP to fix DNA. However, in a 2014 phase II trial, combining olaparib with the antiangiogenic VEGFR inhibitor cediranib significantly increased progression-free