demonstrated a dramatic benefit (Cancer Discov 2020;10:1086–7). "That surprised me," says Forozan, who previously oversaw anti-TIGIT antibody programs at Bristol Myers Squibb.

Still, the NSCLC study was not a complete failure, notes Forozan. Genentech did report "numerical" improvements in final PFS and interim OS analyses among participants of SKYSCRAPER-01, although the magnitude of benefit was undisclosed. That trial will continue until more mature OS results are available, and "we'll get a better understanding once these data come in," Forozan says. "It did obviously miss its first endpoint, but let's see what happens" with OS, a coprimary endpoint.

If those trial results trend in the right direction, Graybosch anticipates that developers of other anti-TIGIT therapies may adapt their study designs accordingly—increasing sample sizes, for example, or altering endpoints—to maximize their likelihood of demonstrating a statistically meaningful benefit.

Graybosch also sees room for better patient selection criteria. For example, trial investigators could enroll only patients with high levels of CD226 on their NSCLC-infiltrating $CD8^+$ T cells. Genentech scientists reported that the expression of this costimulatory molecule, which competes with TIGIT for CD155 binding, was associated with responsiveness to atezolizumab—and they hypothesize that TIGIT blockade could help unleash the full benefit of CD226 signaling in these individuals (Immunity 2022;55:512–26).

The choice of combination checkpoint inhibitor could affect outcomes too, notes Terry Rosen, PhD, cofounder and CEO of Arcus Biosciences in Hayward, CA. For NSCLC trials of its drug, domvanalimab, Arcus and Gilead Sciences are pairing the anti-TIGIT therapy with the companies' experimental anti–PD-1 agent zimberelimab as well as with the approved PD-L1 inhibitor durvalumab (Imfinzi; AstraZeneca) in phase III trials launching this year.

"The science is strong," Rosen says. "We've got a randomized phase II dataset that looks great," with interim analyses showing an improved overall response rate and duration of response with domvanalimab. "So, we're full steam ahead," he says. *–Elie Dolgin* ■

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Bempeg Failure Unlikely to Affect Other IL2 Drugs

After the engineered IL2 cytokine bempegaldesleukin (bempeg; Nektar Therapeutics/Bristol Myers Squibb) fell flat in late-stage trials, its makers halted clinical development of the drug, which had been the focus of a multibillion-dollar deal a few years ago.

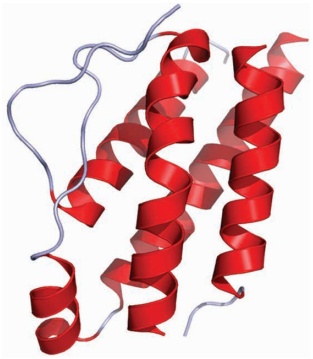
But with a pipeline of other IL2-based therapies—including fusion proteins, cytokine mimetics, engineered variants, and bispecific antibodies in various stages of development—researchers still believe that they can harness the cytokine's immune-modulatory potential to shrink tumors with minimal toxicity.

"Bempeg is a poor example of IL2 engineering, and there's a lot more to be expected from other IL2 programs," says Fahar Merchant, PhD, president and CEO of Medicenna Therapeutics in Toronto, Canada, a company with its own IL2 therapeutic in early clinical testing.

The first IL2 drug therapy, a recombinant cytokine called aldesleukin (Proleukin; Clinigen), was approved in 1992, but oncologists have long sought a better alternative. Even though aldesleukin yielded some dramatic responses, it proved difficult to use. At high doses, the drug killed cancer cells but caused severe toxicities, including potentially fatal capillary leak syndrome. At low doses, it dampened the body's immune responses with limited antitumor activity.

Bempeg was designed to offer a more tolerable and effective option. With a half dozen polyethylene glycol (PEG) groups attached, this pegylated form of IL2 gave the engineered cytokine a longer half-life, as it became active only after the chemical tags were released. The positioning of PEG molecules was also meant to bias the cytokine's activity toward engaging the β-chain of the IL2 receptor—necessary for activating cancer-fighting $CD8^+$ T cells—and away from the α-chain, the binding of which can stimulate immunosuppressive regulatory T cells (Clin Cancer Res 2016;22:680–90).

Initial clinical data looked promising, which is why Bristol Myers Squibb paid Nektar $1.85 billion in 2018 to



secure rights to the drug. But pivotal trials in melanoma and renal cell carcinoma found no clinical benefit in patients who received bempeg with the PD-1 blocker nivolumab (Opdivo; Bristol Myers Squibb) compared with standard therapy for each disease, the companies announced in March and April. A single-arm study of the combination in patients with bladder cancer did not show signs of efficacy either.

"It just goes to show how unpredictable things can be when you get to phase III," says former Nektar scientist Deborah Charych, PhD, who helped design bempeg—especially when evaluating a novel agent in tandem with another immunotherapy. "We may have to be more creative in how we combine this particular mechanism of action."

Nektar's oncology efforts now center on NKTR-255, an IL15 receptor agonist in early clinical development.

Other companies are forging ahead with IL2-based anticancer therapeutics—and they generally see bempeg as a flawed molecule rather than IL2 as a flawed target. Bempeg, says Merchant, "was really a slow-release version of Proleukin," not a drug with selective affinity for the β-chain of the IL2 receptor.

Merchant thus doesn't expect the failure of bempeg to have broad implications on the viability of other "not alpha" IL2 contenders in clinical development. These include Medicenna's MDNA11, which entered phase I testing last year, and more advanced candidates such as nemvaleukin alfa (Alkermes), now being evaluated in a phase III trial for ovarian cancer, and SAR444245 (Sanofi), in phase II trials for multiple tumor types.

As K. Christopher Garcia, PhD, of Stanford University School of Medicine in California, an originator of Medicenna's technology and a cofounder of Synthekine, another company with a

selective IL2 therapeutic in development, points out: "There will be many different flavors of IL2 that could likely be clinically differentiated." *–Elie Dolgin* ■

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Precancer Atlases Might Intercept Malignancies

Improvements in technology have been facilitating efforts to prevent cancer. The creation of a precancer atlas will be a critical step, researchers say.

A precancer atlas creates "a map of all the cellular and molecular changes in a precancerous lesion," explains Avrum Spira, MD, MSc, of Johnson & Johnson and Boston Medical Center in Massachusetts, who discussed the concept at the American Association for Cancer Research Annual Meeting 2022 in New Orleans, LA, held April 8–13. The atlas can show "molecular changes [in] all the cells in that lesion" and "how those changes evolve over time as the lesion either progresses to or regresses away from cancer."

Compiling spatial and genomic information into a map helps assign identities to single cells within these lesions, provides insight into how the microenvironment is organized, and shows how this organization could impact cancer development. Although "atlases are not hypothesis testing, they generate hypotheses," Spira said.

Spira and his team investigated the immune microenvironment in the early development of squamous lung cancer. Through a pilot precancer atlas, they found that in premalignant lesions with a lower chance of developing into invasive cancer, "there's a much higher number of immune cells, specifically $CD8^+$ T cells," Spira said. This "suggests the immune microenvironment may be a determinant of premalignant lung [cancer] progression."

The team subsequently performed miRNA sequencing "to see which miRNAs specifically acted on immune genes," says Jennifer Beane, PhD, of Boston University. An analysis by bioinformatics graduate student Boting Ning suggests that miRNA-149-5p is overexpressed in progressive premalignant lesions and downregulates *NLRC5*. "By suppressing *NLRC5*, MHC1 genes are suppressed and $CD8^+$ T cells are not recruited to the epithelium," explains Beane. The anticorrelation between miRNA-149-5p and *NLRC5* is thought to eliminate antigen presentation to immune cells, allowing oncogenic mutations to go unnoticed. Researchers are investigating this hypothesis in preclinical models.

Spira and his colleagues are not the only group using a precancer atlas to evaluate disease development. Researchers at Dana-Farber Cancer Institute, Harvard Medical School (HMS), and Brigham and Women's Hospital, all in Boston, explored the use of an early-stage precancer atlas to examine immune system shifts in premalignant melanoma lesions.

Although further investigation is needed to corroborate the findings, the team hypothesizes that some melanoma immunosuppressive mechanisms consist of immune cell types acting on one another rather than cancer cells. "We think it's macrophages and dendritic cells suppressing T cells, not tumor cells suppressing T cells," says Peter Sorger, PhD, of HMS. In other words, it's estimated that the "tumor can attract macrophages and put them into a state where they're immunosuppressive."

A precancer atlas "can visually discriminate where the immune system is having success and where it's failing," adds Sandro Santagata, MD, PhD, of Brigham and Women's. The team is using the maps of early-stage melanoma to find mechanisms that support successful immune responses, which they "hope to translate into better treatments for patients."

Both research initiatives show the potential of a precancer atlas in developing hypotheses about precancerous lesions and their microenvironments, but the tool's routine use isn't around the corner. "The Cancer Genome Atlas took more than a decade from inception before we saw it benefiting patients," Spira said. "We're at the beginning of the precancer atlas journey." *–Natalie DiDomenico* ■

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

NOTED

Pfizer launched a not-for-profit initiative to provide its current and future patent-protected drugs to 45 lower-income countries. The current assortment of 23 medicines and vaccines, which are patented in the United States or the European Union, treat some infectious, rare, and inflammatory diseases, as well as certain leukemias, breast cancers, and kidney cancers.

Atara Biotherapeutics and Bayer will end their $670 million exclusive worldwide licensing agreement for next-generation mesothelin-directed chimeric antigen receptor (CAR) T-cell therapies. The collaboration included the development and funding of ATA3271, an armored allogeneic T-cell immunotherapy, and an autologous version, ATA2271, for high mesothelin–expressing tumors.

Federal agencies, Congress, and others need to improve representation of minority groups and underrepresented populations in clinical trials, according to the National Academies of Sciences, Engineering, and Medicine (NASEM 2022 May 17 [Epub ahead of print]). Lack of representation may limit access to medical interventions and new therapies for some patients and increase health disparities, which could cost the United States hundreds of billions of dollars over the next 30 years.

In a phase I trial, Caribou Biosciences' CAR T-cell therapy, **CB-010, demonstrated an overall response rate of 100% in all five evaluable patients** with relapsed/refractory B-cell non-Hodgkin lymphoma (NHL); 80% experienced a complete response (CR) lasting up to 6 months. Caribou says that "CB-010 is the first allogeneic anti-CD19 CAR T-cell therapy in the clinic with a PD-1 knockout, a genome-editing strategy designed to limit premature CAR T-cell exhaustion."

Nkarta reported that two of its CAR natural killer (NK) cell therapies, **NKX101 and NKX019, showed promising efficacy in acute myeloid leukemia (AML) and NHL**. NKX101, which targets NKG2D, induced a CR rate of 60% with full hematologic recovery among five patients with relapsed/refractory AML. With NKX019, which targets CD19, the CR rate was 50% and the objective response rate was 83% among six patients with NHL.

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