During the AACR Annual Meeting 2023, NCI Director Monica Bertagnolli, MD; Chair of the President's Cancer Panel Elizabeth Jaffee, MD; and Deputy Assistant to the President for the Cancer Moonshot Danielle Carnival, PhD (from left to right), spoke about research funded by—and what's ahead for—the Cancer Moonshot initiative.

importance of tailoring solutions to the specific needs of different underserved communities. To that end, she said the NCI will seek to partner with and fund people and organizations already integrated into these communities and familiar with the barriers patients face.

Bertagnolli noted that although the NCI received a much-needed 5.9% funding boost for fiscal year 2023, paylines increased by just 1% and many planned initiatives remain unfunded. Annual, consistent budget increases are needed to fund new grants while covering the ongoing costs of previous multiyear commitments.

The director said she is working closely with Renee Wegrzyn, PhD, head of the Advanced Research Projects Agency for Health (ARPA-H), a new independent agency within the NIH that funds high-risk, high-reward projects aimed at speeding development of treatments for cancer and other serious medical conditions. The two agencies have complementary approaches, she remarked, as ARPA-H focuses on rapidly attacking specific problems from multiple angles, while the NCI launches many parallel efforts that may continue for decades.

"We are working closely with their team to make sure good ideas from NCI researchers are integrated into ARPA-H plans," she said. Similarly, "we want to make sure that what gets developed at ARPA-H gets deployed at NCI."

Tackling issues around data processing, storage, and sharing is a major area of focus and collaboration for the two agencies, said Bertagnolli. Although it's premature to disclose details of specific projects, she said, improving access to real-time clinical information is critical.

"We don't yet know the real impact that the pandemic has had on cancer survival because we lack the ability to obtain, process, and properly analyze data quickly from the clinical care environment," she said. "We don't get real-time cancer data, and without that data and knowledge it's hard to respond to problems strategically and properly."

Bertagnolli, who discussed her own recent experience being diagnosed with and treated for breast cancer, noted that the overarching vision for the National Cancer Plan is identical to that set by the Cancer Moonshot—to cut the cancer death rate by 50% within 25 years and improve the lives of those diagnosed and living with cancer (see http://nationalcancerplan.cancer.gov and http://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative).

"For me, ending cancer as we know it means that one day every person who has cancer will live a full and active life free from any of the effects of their cancer," she said. "That includes freedom from every kind of toxicity, including financial toxicity, as well as other lingering effects of treatment."
–Janet Colwell ■

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Pragmatica-Lung Trial to Mimic "Real-World" Conditions

The NCI, in collaboration with the SWOG Cancer Research Network and the Alliance for Clinical Trials in Oncology, has launched the Pragmatica-Lung Study (S2302), a phase III randomized study of treatment for late-stage or recurrent non–small cell lung cancer (NSCLC). The trial, which was designed and will be led by SWOG, aims to mimic conditions in "real-world" clinical settings as closely as possible.

The trial is notable in that it is intended as a registration trial but will not collect the reams of data normally associated with massive and lengthy clinical studies. Investigators hope that it will begin to modernize clinical trials and become a template for future ones.

As the name implies, Pragmatica-Lung has a pragmatic design with relaxed eligibility and exclusion criteria with the intention of making it simpler and faster for clinicians to enroll patients, for investigators to accrue a study population that more closely reflects the general population of patients with stage IV or recurrent NSCLC, and for easier and less complex data gathering and reporting while "upholding rigorous scientific and safety standards."

The trial asks the straightforward question of whether a combination of two FDA-approved drugs—the antiangiogenic agent ramucirumab (Cyramza; Lilly) and the PD-1 checkpoint inhibitor pembrolizumab (Keytruda; Merck)—can help patients with previously treated late-stage or recurrent NSCLC live longer compared with standard-of-care chemotherapy. Overall survival is the sole primary endpoint, and the frequency of unexpected adverse events of grade 3 or greater is the only secondary endpoint.

The goals of the trial "are to empower investigators as they would [treat patients] in their real-world practice," said principal investigator Karen Reckamp, MD, of Cedars-Sinai Medical Center in Los Angeles, CA, at an NCI briefing announcing the trial's start.

"We want to decrease barriers to enrollment to allow more patients and diverse patients to enroll into the trial, and we also want to minimize the data collection burden. Trials are becoming more and more complex, and the actual staff time and collection time for getting this data has also increased over time," she said.

"It is a lot of work to manage a clinical trial, and the more data that you have to collect, the more work it is," commented briefing participant Judy Johnson, MBA, an advocate for patients with lung cancer through SWOG. She previously worked as a clinical trial research coordinator on lung-related studies.

"When I did this for a living, I noticed how little of that data was actually utilized, how it felt like we were

spinning our wheels sometimes doing our jobs as research coordinators when we could really be spending more time looking at potential eligibility and supporting the patients," Johnson said.

The investigators maintain that the eligibility criteria, while still extensive, "are notable for items that have been removed from historical eligibility lists to increase inclusion and generalizability."

The inclusion criteria primarily focus on prior treatment, previous exposure to anti–PD-1/PD-L1 therapy, and any targeted therapies that patients with known sensitizing mutations have received.

The trial's only exclusion criteria are having already received more than one anti–PD-1 or anti–PD-L1 agent for stage IV or recurrent disease, and current or planned receipt of another investigational therapy for NSCLC during the study period.

The criteria do not automatically disqualify patients with comorbidities, such as brain metastases, cardiovascular disease, diabetes, or hypertension.

The phase III S2302 trial will build on the phase II S1800A substudy of the Lung-MAP umbrella trial. In that study, the combination of ramucirumab and pembrolizumab was associated with significantly improved overall survival compared with standard of care in patients with NSCLC whose disease had progressed while on or after receiving an immune checkpoint inhibitor and platinum-based chemotherapy. Investigators plan to enroll 700 patients in the S2302 trial from across the United States by the end of 2025. *–Neil Osterweil* ■

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BCMAxCD3 Bispecific Yields Robust Responses in Myeloma

In a phase I/II study of REGN5459 (Regeneron), patients with relapsed/refractory multiple myeloma (RRMM) responded robustly to the investigational BCMA-targeting bispecific T-cell engager, which features a design tweak—low affinity for CD3 on T cells—aimed at mitigating toxicity.

Last fall, the FDA granted accelerated approval to teclistamab (Tecvayli; Janssen), the first BCMAxCD3 bispecific for RRMM, "so we now have 16 different classes of agents available," noted Kenneth Anderson, MD, of Dana-Farber Cancer Institute in Boston, MA. "For many patients, multiple myeloma has been transformed to a chronic illness."

Cytokine release syndrome (CRS) is a long-standing problem with bispecific T-cell engagers, however, so the field has started to explore "manipulating binding affinity to CD3 to lower CRS risk and improve the therapeutic index," Anderson explained. Data in mice and monkeys "showed that even with a very low affinity for CD3, [REGN5459] effectively cleared myeloma cells—notably, without high levels of cytokines such as IFNγ, IL2, and IL6," which prompted the drug's clinical evaluation.

During the American Association for Cancer Research Annual Meeting 2023 in Orlando, FL, April 14–19, Attaya Suvannasankha, MD, of Indiana University's Simon Cancer Center in Indianapolis, reported preliminary findings on 43 patients treated with REGN5459. All had disease progression after a median of five prior therapies and, for the vast majority, an autologous stem cell transplant. The objective response rate to REGN5459 was 65.1%; 32.6% were classified as stringent complete responses, and another 7% were very good partial remissions.

Responses occurred early and were durable, Suvannasankha added, "passing the 26-month mark in several patients" at the latest data cutoff. REGN5459's common side effects included neutropenia, anemia, and diarrhea. Low-grade CRS occurred in 53.5% of patients, and infections—of the urinary tract, as well as pneumonia—in 62.8%.

"Looking at CRS severity, which was the premise for this trial, I'd say there wasn't a major change" compared with another Regeneron candidate targeting BCMA, REGN5458, Anderson pointed out. At the American Society of Hematology's annual meeting in December 2022, phase I/II findings on this bispecific—which has regular CD3 affinity—indicated a CRS rate of 44% among 252 patients. Tinkering with CD3 binding in REGN5459, then, "really didn't reduce CRS overall."

Attaya Suvannasankha, MD.

The toxicity should be manageable with steroids such as tocilizumab, he added, being largely low-grade.

To Anderson, "there are other ways we can exploit this wonderful [bispecific] modality and boost efficacy," including figuring out strategies to limit $CD8^+$ T-cell exhaustion, which can otherwise provoke relapse and increase infection risk. Tumor-intrinsic adaptations, including loss of MHC class I expression and antigen (BCMA) escape, "are also going to become a major issue as we decide when, and for how long, to treat patients with these engagers" (Cancer Cell 2023;41:711–25).

Alternative targets and additional immune cell–engaging approaches may help address these complexities: Talquetamab (Janssen), a bispecific that goes after GPRC5D, has shown promise in patients who developed resistance to BCMA therapies. As well, next-generation trispecifics that engage not just T cells, but also natural killer cells, are in the pipeline.

The jury may yet be out, too, as to whether modulating CD3 affinity improves bispecific characteristics on the toxicity front, with other agents—for instance, Y150 (Wuhan YZY Biopharma)—still in early clinical development.

RRMM's therapeutic landscape has truly burgeoned over the last two decades, Anderson said, and it continues to thrive, with median survival now prolonged three- to four-fold. Back in 1986, "when my first patient, Francesca Thompson, was asked how she'd know she was cured, she said something very prescient: 'Cure is growing old and dying from something else,'" he remarked. "I think this is happening more and more frequently, and the best is yet to come." *–Alissa Poh* ■

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