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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