pandemics, Boffa argues. "Judging the importance of TERAVOLT on the impact of a single study is short sighted. It would be akin to asking the Wright brothers after their first flight, 'Who would ever need to fly 120 feet?'" *–Mitch Leslie* ■

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Cilta-cel OK'd for Multiple Myeloma

A second chimeric antigen receptor (CAR) T-cell therapy has been added to multiple myeloma's treatment arsenal, with ciltacabtagene autoleucel, or cilta-cel (Carvykti; Janssen/Legend Biotech), receiving the FDA's nod on February 28. Like idecabtagene vicleucel, or ide-cel (Abecma; Bristol Myers Squibb)—which was greenlighted less than a year ago—cilta-cel targets BCMA and is a fifth-line option for this disease.

Having two CAR T-cell therapies available "will be great," says Adam Cohen, MD, of the University of Pennsylvania in Philadelphia, given that "bottlenecks in manufacturing ide-cel have led to long waitlists at many centers."

Cilta-cel's launch "will take a few months—just because it's approved doesn't mean we can offer it to patients immediately," adds Eric Smith, MD, PhD, of Dana-Farber Cancer Institute in Boston, MA. "Even when it gets going, I don't know that both CAR-Ts will be able to fulfill the demand out there right away."

Updated, longer-term results from the pivotal CARTITUDE-1 trial, presented during the American Society of Hematology's annual meeting in December 2021, secured cilta-cel's approval. Among 97 patients who had received multiple prior treatments—including all three mainstays, proteasome inhibitors, anti-CD38 drugs, and immunomodulatory agents—the objective response rate to cilta-cel was 98%. After 22 months, the stringent complete response rate was 83%, and median progression-free and overall survival were not reached.

"These are really exciting, encouraging data," Smith says. Before CAR T-cell therapy, one of the most recent approvals for relapsed/refractory multiple myeloma was selinexor (Xpovio; Karyopharm), a selective inhibitor of nuclear export, "which benefited a minority of these difficult-to-treat patients, and on average, only for a few months," he points out. "By contrast, cilta-cel and ide-cel are dramatic advances."

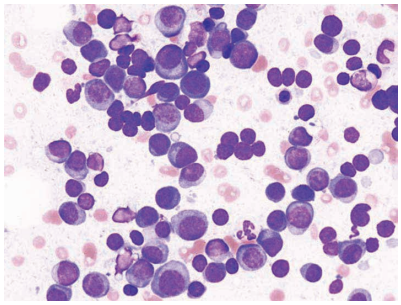
With all caveats of cross-trial comparisons duly noted, "the depth and duration of responses do seem better with cilta-cel" than ide-cel, Cohen says. However, "there could be an increased risk of late-developing neurotoxicity involving parkinsonian symptoms that we'd want to discuss with patients." One way to reduce this risk, clinicians have learned, "is to control the disease burden as much as possible—through aggressive bridging therapy, if necessary—before starting cilta-cel."

Both Cohen and Smith observed that cilta-cel doesn't stick around long—unlike ide-cel, where CAR-bearing T cells are detectable in many patients after 12 months. Interestingly, this lack of persistence doesn't appear to influence response durability, at least based on preliminary data. More analyses are underway to suss out whether persistence matters, and whether enriching for particular T-cell subsets—perhaps those with central memory or stem-like phenotypes—is important.

As well, trials of both immunotherapies are ongoing "in earlier disease settings," Cohen says, "and the hope is, ultimately, first-line CAR-T, which could benefit a subset of high-risk patients whose outcomes are consistently poor despite all the treatments we have."

Additional multiple myeloma targets, such as FcRH5 and GPRC5D, have recently emerged, Smith notes. He is interested in sending CAR T cells after the latter protein, with CC-95266 (Bristol Myers Squibb) among several products now in phase I trials stemming from his lab research. Others are pursuing T-cell–engaging bispecifics, including talquetamab (Janssen) for GPRC5D and cevostamab (Genentech) for FcRH5.

"My sense is these therapies will first be used for patients who have relapsed following BCMA CAR-T," Cohen



Multiple myeloma.

remarks. "However, once they're all on the market, we can begin testing the best sequences or, possibly, combinations. It could take years, but it's a good problem to have."

"A cure remains elusive," Smith adds, "but it's great to get patients into durable remissions and, meanwhile, find options for their next relapse. We can keep kicking the can down the road, so to speak, with new therapies becoming available each year." *–Alissa Poh* ■

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Assessing Toripalimab in NSCLC

Findings from CHOICE-01 indicate that toripalimab (Junshi Biosciences) prolongs the time to disease progression in patients with untreated non–small cell lung cancer (NSCLC) when added to chemotherapy. Data from the phase III trial were presented by Jie Wang, MD, of the Chinese Academy of Medical Sciences and Peking Union Medical College in Beijing, during the March session of the American Society of Clinical Oncology's monthly Plenary Series.

Toripalimab is one of China's domestically developed PD-1 inhibitors. Known there as Tuoyi, it is an approved second-line therapy for melanoma, urothelial cancer, and nasopharyngeal carcinoma. In the United States, it is under priority review for the latter cancer, with a decision expected in April.

CHOICE-01 enrolled 465 patients with advanced or metastatic NSCLC that lacked sensitizing *EGFR* or *ALK* mutations. They were randomly assigned 2:1 to receive toripalimab

or placebo combined with standard first-line chemotherapy. The median progression-free survival (PFS) with toripalimab was 8.4 months, Wang reported, compared with 5.6 months in the control arm. In subgroup analyses, a high tumor mutation burden further improved PFS among patients given toripalimab, as did the presence of focal adhesions along the PI3K–AKT signaling pathway. Although median overall survival (OS) was not a primary endpoint, in an interim assessment, it was not reached with toripalimab and was 17.1 months with chemotherapy alone.

Discussant Charu Aggarwal, MD, of the University of Pennsylvania in Philadelphia, noted that across multiple NSCLC studies, "long-term outcomes confirm that we're making a meaningful difference in overall survival through our current practice of integrating immunotherapy with chemotherapy." CHOICE-01's results are "very comparable" to KEYNOTE-189 and KEYNOTE-407, which evaluated pembrolizumab (Keytruda; Merck) alongside chemotherapy in similar patient populations, she said.

More broadly, though, "perhaps we should move away from PFS as a primary endpoint" in trials, Aggarwal observed, citing findings that it only modestly correlates with OS (J Immunother Cancer 2021;9:e002114). If nothing else, "we may want to critically think about whether PFS, as a term, affects patient choice," she added, "and whether something like 'progression-free interval' might better dissociate it from OS," which is more clinically meaningful (Lancet Oncol 2022;23:328–30).

CHOICE-01 is not unlike ORIENT-11, another Chinese study evaluating a different homegrown PD-1 inhibitor, sintilimab, in NSCLC. A recent commentary questioned the generalizability of such trial data—from a single country with less diverse demographics—to a more heterogenous U.S. population (Lancet Oncol 2022;23:323–5). This opinion was echoed by the FDA's Oncologic Drugs Advisory Committee, which has requested additional studies of sintilimab prior to deciding whether to recommend it for approval.

Asked about this issue, Wang responded that "we believe our findings could be applied to Western populations." She pointed out the "similar PFS observed in our study, compared with other PD-1 inhibitor trials" and "similar treatment guidelines for advanced NSCLC" between the National Comprehensive Cancer Network and the Chinese Society of Clinical Oncology. As well, she observed that the FDA's own meta-analysis of NSCLC trials did not uncover an appreciable difference between Asian and non-Asian patients in their magnitude of benefit from immune checkpoint inhibitors (J Clin Oncol 37, 2019 [suppl; abstr e20690]).

Even so, looking ahead, "multiregional trials with diverse populations and coordinated worldwide regulatory submissions should definitely be pursued," Aggarwal said. Meanwhile, CHOICE-01 joins the list of studies establishing that for NSCLC without actionable mutations, "frontline chemo–immunotherapy is the clear standard and should be used as the control—not chemotherapy alone—in new trials, if we are to keep moving the efficacy needle." *–Alissa Poh* ■

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NOTED

During his State of the Union address, **President Joe Biden emphasized his goal to cut cancer death rates by at least 50% over the next 25 years** by reigniting the Cancer Moonshot program launched in 2016 under President Barack Obama. The Moonshot will largely focus on screening, prevention, and early detection initiatives.

The U.S. **Congress gave the FDA's Center for Tobacco Products the authority to regulate synthetic nicotine.** The FDA has had the authority to regulate nicotine derived from tobacco plants but whether the agency could regulate nicotine from other sources has been unclear. Thus, some companies have continued to sell flavored electronic cigarettes, which appeal to children and teenagers, that contain synthetic nicotine. The agency can now regulate nicotine no matter its source.

Seagen and Genmab announced that the antibody–drug conjugate **tisotumab vedotin (Tivdak) demonstrated a manageable safety profile and promising preliminary antitumor activity** in patients with squamous cell carcinoma of the head and neck, with an objective response rate of 16% (five of 31 patients). In the phase II innovaTV 207 trial, the median follow-up was 10 months, disease control rate was 58.1%, median progression-free survival was 4.2 months, and median overall survival (OS) was 9.4 months.

The FDA approved olaparib (Lynparza; Merck) for the adjuvant treatment of patients with germline *BRCA*-mutant, HER2-negative high-risk early breast cancer who have already received chemotherapy. The approval was based on findings from the OlympiA trial, in which the drug reduced the risk of invasive breast cancer recurrences, second cancers, or death by 42% versus placebo.

However, Merck said **the combination of olaparib and the PD-1 inhibitor pembrolizumab (Keytruda) did not demonstrate an improvement** in OS in patients with metastatic castration-resistant prostate cancer compared with the control arm, in which patients received either abiraterone or enzalutamide. As a result, the phase III KEYLYNK-010 trial assessing the combination will be discontinued.

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