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NEWSLETTER

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Multiple Myeloma: Novel Therapies and New Targets

The arrival of bispecific antibody therapy and identification of new targets offer fresh options for patients with refractory or relapsed multiple myeloma.

Survival rates for patients with multiple myeloma have improved significantly over the last generation, thanks to improved therapies. One of the most recent additions to the armamentarium against the second-most common form of blood cancer, CAR T-cell therapy, has proved capable of inducing substantially longer periods of remission compared to other therapies. Still, durable responses to all available treatments remain elusive in most older patients and those with high-risk disease. Moreover, many low-risk patients develop resistance to treatment over time. Clearly, there remains an urgent need for new approaches to treating multiple myeloma.

A new option for patients with hard-to-treat multiple myeloma arrived last fall. In late October of 2022, the U.S. Food and Drug Administration (FDA) granted accelerated approval to the first bispecific antibody (BsAb) for treatment of multiple myeloma, teclistamab (Tecvayli). The drug is approved for treatment of adult patients with multiple myeloma who have failed at least four prior therapy regimens. Teclistamab is also approved in the European Union to treat adults with refractory/relapsed multiple myeloma who have had at least three previous treatments for this blood cancer.

Teclistamab targets B-cell maturation antigen (BCMA), a protein found on plasma cells, but that is highly expressed in multiple myeloma cells. BCMA is also the target of the two approved forms of CAR T-cell therapy for multiple

myeloma, vicleucel (Abecma) and ciltacabtagene autoleucel (Carvykti). As a BsAb, teclistamab engages BCMA on multiple myeloma cells, as well as the CD3 receptor on T cells. This dual action creates an immunological bridge between the cancer cell and T cell, which ultimately results in lysis (or disintegration) of the tumor cell.

The FDA granted accelerated approval for teclistamab based on the results of the phase 1-2 MajesTEC-1 trial, which included 165 adults with relapsed or refractory multiple myeloma who had previously been treated with at least three lines of therapy. Half of the participants had received five previous treatments; 82 percent had undergone stem cell transplants. In the trial, patients received a weekly subcutaneous injection of teclistamab (1.5 mg per kilogram of body weight) after receiving step-up doses of 0.06 mg and 0.3 mg per kilogram. The primary end point was the overall response (defined as partial response or better).

At median follow-up of 14.1 months, the overall response rate to teclistamab was 63 percent, with 65 patients (39.4 percent) having a complete response or better. Investigators determined that 44 patients (26.7 percent) had no minimal residual disease (MRD). Among patients with a complete response or better, the MRD-negativity rate was 46 percent. The median duration of response was 18.4 months, while the median duration of progression-free survival was 11.3 months. Investigators continue to follow patients enrolled in MajesTEC-1.

Side effects were common in the trial, with 95 percent of participants experiencing at least one serious adverse event, the most common being infections. Notably, 12 patients died of COVID-19, which had just emerged in the United States at the outset of the trial, in March 2020.

Other BsAbs are being evaluated in clinical trials. At the American Society of Hematology Annual Meeting last December, investigators reported that the BsAb talquetamab produced responses in more than 70 percent of patients with relapsed/refractory (R/R) multiple myeloma in the phase

1-2 MonumenTAL-1 trial. Unlike teclistamab, however, talquetamab targets G protein-coupled receptor, class C group 5 member D (GPRC5D), a surface protein that's highly expressed in multiple myeloma cells. (In September, investigators reported the results of a phase 1 trial of MCARH109, a novel form of CAR T-cell therapy that targets GPRC5D, in 17 patients with heavily treated multiple myeloma, including several who had previously received CAR T-cell therapy targeting BCMA; response to therapy was reported in 71 percent of patients. See story on page 5.) BsAbs that target other cell-surface proteins are also in development.

Clinicians and patients will be faced with decisions when choosing between CAR T-cell therapy and BsAbs for cases of R/R multiple myeloma. Data suggest that the former is somewhat more effective, though CAR T-cell therapy carries a higher risk for adverse effects compared to BsAbs. The process of obtaining and modifying a patient's T cells for use in CAR T-cells can take six to eight weeks, while teclistamab (and, presumably, other BsAbs) is available "off the shelf." On the other hand, CAR T-cell therapy requires a one-time infusion, while BsAbs must be administered weekly.

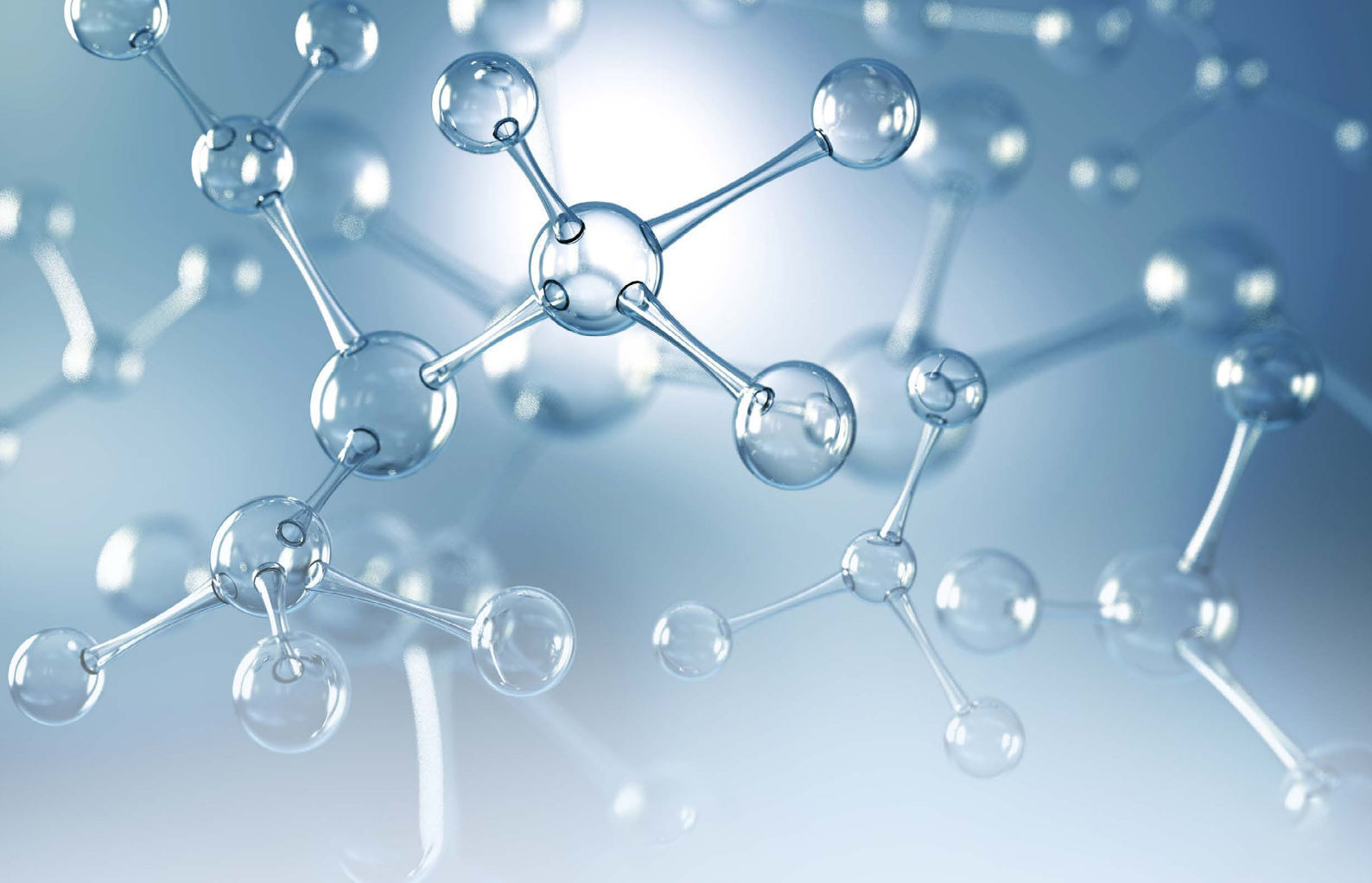
Research News

Second-Generation CAR T-Cell Therapy Shows Promise for Relapsed/Refractory Multiple Myeloma

The two approved forms of CAR T-cell therapy for treatment of relapsed/refractory (R/R) multiple myeloma—vicleucel (Abecma) and ciltacabtagene autoleucel (Carvykti)—target B-cell maturation antigen (BCMA), a protein that is highly expressed in multiple myeloma cells. While these treatments are effective, some patients do not respond to them, while those who do initially often develop resistance. Thus, new targets for CAR T-cell therapy are being investigated. They include G protein-coupled receptor, class C group 5 member D (GPRC5D), a surface protein that's highly expressed in multiple myeloma cells. Last October, a team led by researchers at the Roswell Park Comprehensive Cancer Center in Buffalo, NY, reported the results of a phase 1 trial of 17 patients with R/R multiple myeloma treated with a novel form of CAR T-cell therapy that targets GPRC5D. Overall, 71 percent of patients had a response to the treatment. However, at the highest doses, (450×106 CAR T-cell dose), one patient had grade 4 cytokine release syndrome and neurotoxicity, while two patients had a grade 3 cerebellar disorder of unclear cause. These adverse events were absent in patients treated with 25×106 to 150×106 cells, of whom 58 percent responded to treatment. Further evaluation of GPRC5D for R/R multiple myeloma in clinical trials is underway.

Newly Approved Bispecific Antibody Appears Effective in Combination with Other Multiple Myeloma Medications

The first-in-class bispecific antibody teclistamab (Tecvayli) was approved for treatment of R/R multiple myeloma in patients who have failed multiple lines of therapy last October (see main story). In the phase 1b MajesTEC-2 trial, a combined regimen of teclistamab plus the monoclonal antibody daratumumab (Darzalex) and the



thalidomide analog lenalidomide (Revlimid) was administered to 32 patients with R/R multiple myeloma who had failed one to three prior lines of therapy. As reported at the 2022 American Society of Hematology (ASH) Annual Meeting in December, at median follow-up of 8.4 months, the overall response rate was 93.5 percent, with 90.3 percent of patients attaining a very good partial response or better, while 54.8 percent achieved a complete response or better, according to *Cancer Therapy Advisor*. The most frequent nonhematologic adverse event was cytokine release syndrome, though all were grade 1-2. No neurotoxicity was reported.

First-in-Class Modakafusp Alfa Could Offer New Option in R/R Multiple Myeloma

In another study presented at the most recent ASH annual meeting, a team led by researchers at the University of Pennsylvania's Abramson Cancer Center discussed data from a phase 1-2 trial of modakafusp alfa in 100 patients previously treated for multiple myeloma. Modakafusp alfa is a first-in-class immune-targeting, attenuated cytokine that consists of two attenuated interferon molecules genetically fused to a monoclonal antibody. The goal of treatment with modakafusp alfa is to deliver attenuated interferon to innate and adaptive immune cells, and myeloma cells. Among 30 patients who received a dose of 1.5 mg/kg, the overall response rate was 43 percent and median time to response was 1.2 months. Median duration of response was not reached (range 1.0–18.9 months) and median progression-free survival was 5.7 months. Common adverse events included neutropenia, thrombocytopenia, and lymphopenia. A phase 2 trial is planned.

Newly Diagnosed High-Risk Multiple Myeloma May Benefit from Quad Therapy

In the phase 2 CONCEPT trial, a significant portion of newly diagnosed multiple myeloma patients had deep responses to a combination of satuximab (Sarclisa), carfilzomib (Kyprolis), lenalidomide (Revlimid), and dexamethasone, or Isa-KRd. The trial included transplant-eligible patients (99) and ineligible patients (26). The former underwent an induction of six cycles of Isa-KRd prior to chemotherapy and transplantation, followed by multiple consolidation and maintenance cycles of Isa-KRd. Transplant-ineligible patients received a slightly different regimen of induction, consolidation, and maintenance cycles of Isa-KRd induction. After consolidation, a majority of patients in both groups achieved minimal residual disease (transplant eligible, 67.7 percent; transplant-ineligible, 54.2 percent). Overall response rates were 94.9 percent and 88.5 percent, respectively. Grade 3 adverse events occurred in 78.4 percent and 72 percent of patients.

For Your Patients: Where To Turn for Support

LEUKEMIA & LYMPHOMA SOCIETY®

Patients with multiple myeloma and other blood cancers can find support, information, and other resources at the Leukemia & Lymphoma Society (LLS). The LLS traces its roots to 1949, when New Yorkers Rudolph and Antoinette de Villiers, the parents of a teen who succumbed to leukemia five years earlier, established a fundraising and education organization in his name, known as the Robert Roesler de Villiers Foundation. The organization has changed names several times over the years, but has always been guided by the conviction that blood cancers are curable diseases. Today, LLS not only funds research on cures, but also provides a variety of services for patients, such as support groups and financial assistance. Learn more at lls.org.