New bispecific antibody demonstrates clinical activity in patients with multiple myeloma

April 17 2023

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Patients with relapsed or refractory multiple myeloma who were treated with the two highest doses of REGN5459, a bispecific antibody targeting BCMA and CD3, experienced a 90.5% overall response rate,

according to results of a phase I/II clinical trial presented at the AACR Annual Meeting 2023, held April 14-19.

REGN5459 binds to BCMA on malignant plasma B cells that constitute multiple myeloma and CD3 on T cells, bringing the two cell types together so that the latter can attack the former.

In October 2022, teclistimab-cqyv (Tecvayli), another bispecific antibody therapy targeting BCMA and CD3, received accelerated approval from the U.S. Food and Drug Administration (FDA) to treat myeloma that persisted after four or more lines of prior therapy.

A common side effect of bispecific antibody immunotherapy is cytokine release syndrome (CRS), a potentially life-threatening complication in which activated immune cells release a large number of cytokines into the bloodstream, resulting in systemic inflammation, explained Attaya Suvannasankha, MD, an associate professor of clinical medicine in the Division of Hematology and Oncology at Indiana University School of Medicine and a physician-scientist at the Indiana University Melvin and Bren Simon Comprehensive Cancer Center, who presented the study.

CRS can cause symptoms including fever, low blood pressure and low oxygen levels, which often occur before the patient can receive the intended full dose. In order to mitigate these early events, patients receive progressive increments of the bispecific antibody therapy and are monitored to treat these adverse events. These challenges can create barriers to effective treatment.

The advantage of REGN5459 is that it binds relatively loosely to CD3 on T cells, which may mitigate CRS and decrease T-cell exhaustion, Suvannasankha said. "Dialing down the strength of binding to CD3 might sound contradictory; why would we not want the therapy to grab the T cells very hard? Preclinical data suggested that decreasing the

binding affinity to T cells might reduce CRS, which may enable us to more safely deliver treatment to patients, particularly those who are older or more frail," she explained.

In this study, Suvannasankha and colleagues recruited 43 patients with multiple myeloma that stopped responding to or relapsed following three or more prior lines of treatment. In the phase I portion of the trial, patients were treated with full doses of REGN5459 ranging from 3 to 900 mg; 480 mg was selected as the recommended phase II dose.

The overall response rate in the study population was 65.1%. Among the 21 patients treated at the higher doses (480 mg and 900 mg), the response rate was 90.5%, of which 61.9% were complete responses or better, including 38.1% that were stringent complete responses, a deeper response category characterized by the absence of clonal myeloma cells in the bone marrow and a normal blood test result for free light chains.

Responses occurred early and deepened with time, with a projected 78.1% of patients continuing to respond at a year. "In comparison to the average lifespan of heavily pretreated patients at this stage, which is six to nine months, that the one-year progression-free survival may be more than 70% is very promising," Suvannasankha said.

In terms of adverse events, across all dose levels, 53.5% of patients experienced CRS, of which none were grade 4 or 5 and 87% were grade 1. In all cases, Suvannasankha said, the condition did not lead to discontinuation and the patients were able to escalate treatment to the full planned dose.

Continuous T-cell activation can also cause T-cell exhaustion, in which T cells stop functioning properly. This not only decreases the efficacy of the immune system against the cancer but can also leave the body vulnerable to infection, Suvannasankha said. Infections occurred in

62.8% of patients, 30.2% of which were grade 3 or higher, requiring hospitalization. "While infections continue to occur with bispecific antibody treatments, we are excited about the data in this study. The severity of infection and the disruption to treatment were manageable," she added.

According to Suvannasankha, the response rate demonstrates that binding affinity can be reduced without sacrificing clinical activity.

"Low-affinity T-cell engagers potentially result in T cells that continue killing the cancer cells but with fewer side effects," she said.

Limitations of this study include a relatively small number of patients treated at the recommended phase II dose and a population of patients who reside exclusively in the U.S.

More information: Conference: www.aacr.org/meeting/aacr-annual-meeting-2023/

Provided by American Association for Cancer Research

Citation: New bispecific antibody demonstrates clinical activity in patients with multiple myeloma (2023, April 17) retrieved 19 April 2024 from https://medicalxpress.com/news/2023-04-bispecific-antibody-clinical-patients-multiple.html