VIEWPOINTS

Recent Progress in Immunotherapy for RRMM: Updates from EHA 2023 Congress

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RedirecTT-1: Teclistamab plus talquetamab show favorable responses with tolerable safety in RRMM

RedirecTT-1 is a phase Ib study investigating the combination of teclistamab,[1] a first-in-class bispecific B-cell maturation antigen (BCMA)-directed antibody, and talquetamab,[2] a bispecific antibody targeting the novel myeloma antigen GPRC5D, in 93 patients with heavily pretreated multiple myeloma (MM). This is the first study on combinations of two bispecific antibodies that has ever been reported in hematologic malignancies.

Data presented at this year's European Hematology Association (EHA) showed that the safety profile of the combination therapy was consistent with prior reports for the teclistamab and talquetamab as single agents, with no new safety signals or additive toxicity.[3] Cytokine release syndrome (CRS) of any grade occurred in around three-quarters of patients in both the overall population and the recommended phase II regimen (RP2R) group, while only five patients experienced immune effector cell-associated neurotoxicity syndrome (ICAN). Notably, the infection rate was similar to that reported with single-agent teclistamab at approximately 80% for RP2R.

In terms of efficacy, the overall response rate (ORR) was 86.6% across dose levels and 96.3% in the RP2R group, including a complete response (CR) rate of 42.9% in patients receiving the optimal dose. The median duration of response (DoR) was not reached in either population but over 70% of patients continued the therapy at the last follow-up. Importantly, high response rates were also observed in patients with extramedullary disease (EMD) (n=35). In this challenging MM patient population, the ORR and CR rates were 85.7% and 28.6% in the RP2R group, with a median DoR not reached.

These exciting data from RedirecTT-1 represent a new hope for patients with relapsed/refractory multiple myeloma (RRMM) that may prove especially relevant for aggressive hard-to-treat EMD. Indeed, an EMD expansion cohort is planned to confirm these promising data.

Although it is too early to draw definite conclusions, the combination of teclistamab plus talquetamab appears very effective in MM patients. Potentially, this regimen may become a new standard of care (SoC) not only in heavily pretreated patients but also as an early-line treatment option for RRMM. It is, however, important to keep in mind that these two molecules are currently being also investigated in various combinations with other treatment options, such as anti-CD38 monoclonal antibodies, immunomodulatory drugs (IMiDs), γ-secretase inhibitors and programmed cell death protein (PD-1) inhibitors. A longer follow-up and more data are needed to identify optimal combinations for each disease stage and MM patient populations that would benefit the most.

Emerging novel agents and combinations in MM

The therapeutic landscape of RRMM is rapidly evolving with many novel molecules being developed over the past years, including highly active bispecific antibodies targeting BCMA, GPRC5D and FcRH5. After demonstrating clinical activity as single agents, these new immunotherapy drugs are currently being combined with various SoC regimens in the MM setting. The attractive combination partners for the new immunotherapy approaches are IMiDs and CD38 antibodies, while combinations with proteasome inhibitors are also being evaluated in earlier clinical trials. Data of all these upcoming combinations, not only in heavily pretreated MM patients but also in earlier lines or even as upfront therapy, are eagerly awaited.

Expanding treatment armamentarium for MM

The EHA 2023 Congress corroborated that new immunotherapy strategies remain the key players in the field of MM. Among them, ciltacabtagene autoleucel (cilta-cel), a BCMA-targeting chimeric antigen receptor (CAR) T-cell therapy, was the first to demonstrate unprecedented antitumor activity in earlier lines of RRMM versus SoC in a phase III trial.[4] In the randomized CARTITUDE-4 study, patients with lenalidomide-refractory RRMM after 1–3 prior lines of therapy who received cilta-cel versus SoC were associated with significantly prolonged progression-free survival (PFS) (median, not reached vs 11.8 months), resulting in a 74% reduction in the risk of disease progression or death (HR: 0.26 [95% CI: 0.18–0.38]; p<0.0001) at a median follow-up of 15.9 months. Data further showed the superiority of cilta-cel over SoC in terms of ORR (84.6% vs 67.3%) and CR rates (73.1% vs 21.8%). Alongside acceptable and consistent safety profile, these data support cilta-cel as a new early SoC therapy for lenalidomide-refractory RRMM.

This congress also offered diverse presentations reporting updated efficacy data on bispecific or monoclonal antibodies directed at targets like BCMA, GPRC5D and FcRH5RC. Several other studies showed management options for MM patients treated with these novel immunotherapy

approaches. These include prophylaxis with tocilizumab to mitigate or prevent CRS and the use of immunoglobulin therapy to prevent treatment-induced infectious diseases.

Conflict of interest

The author served on a board of directors or advisory committee and received honoraria from Janssen, Celgene, Takeda, Amgen, GSK, AbbVie, Pfizer, Regeneron, Roche, Sanofi, and Oncopeptides; and received honoraria from Seagen. These funding entities did not play a role in the development of the manuscript and did not influence its content in any way.

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Author Contributions

The author created and approved the final manuscript.

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