World Journal of Medical Oncology

Dual-targeting CAR-T cells and bispecific antibodies for multiple myeloma

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Received Date : *Dec 14 2023*
Accepted Date : *Dec 15 2023*
Published Date : *Jan 15 2024*

ABSTRACT

During the past few years, patients with relapsed or refractory multiple myeloma (RRMM) have been treated using bispecific antibodies (BsAbs) and dual-targeted chimeric antigen receptor T (CAR T) cells, as more and more patients were not adequately helped by at least three prior rounds of therapy. The most common combos are GPRC5D/CD3 and BCMA/CD3. According to clinical results, patients are more likely to experience stronger and longer-lasting responses. Here, we present the most recent information on BsAbs that target BCMA/CD3, GPRC5D/CD3, and BCMA/CD19 CAR T cells, as presented at the ASCO annual meeting in 2023.

Keywords : Multiple myeloma, Bispecific antibody, CAR T, Clinical trial

INTRODUCTION

Regarding the editor

Despite recent dramatic improvements in the prognosis for relapsed/refractory multiple myeloma (RRMM), a significant number of patients treated with immunotherapy experience relapse [1]. On the other hand, dual-targeting chimeric antigen receptor T (CAR T) cells and bispecific antibodies (BsAbs) have demonstrated good efficacy and safety in clinical scenarios [2–3] and can produce potent and long-lasting responses. The most recent information from the ASCO meeting in 2023 is summed up in this overview.

Antibodies that are bispecific

A paper mentioned the effectiveness of teclistamab, a commercial medicine approved by the FDA for treating RRMM, which is the first BCMA/CD3 BsAb. Ten had received anti-BCMA medication previously, eighty percent were penta-drug refractory, and all patients were triple class refractory (TCR). Grade 1-2 cytokine release and an overall response rate (ORR) of 60% (9/15) were observed syndrome (CRS) was noted in 41 percent of cases [4].

An other BCMA/CD3 BsAb is elranatamab. Out of all the phase 2 trials including this kind of BsAb, it had the longest median follow-up (15 months). Elranatamab treatment was administered to 123 individuals overall. Of these, 42.3% and 96.7% of the patients were penta-drug resistant and triple class, respectively. The duration of response (DOR) at 12 months (mo) was 74.1%, while the objective response rate (ORR) was 61% [5].

An oral abstract presented linvoseltamab's (a BCMA/CD3 BsAb) effectiveness. The ORR was 64% and 50% in two cohorts (200 mg vs. 50 mg), while the incidence of Grade 1-2 CRS was 36% and 51%, respectively [6].

At this meeting, a phase I trial evaluating the safety and initial efficacy of F182112, a BCMA/CD3 BsAb, was reported. This clinical trial involved the enrollment of sixteen participants. With an ORR of 43.8%, CRS accounted for the majority of treatment-related adverse events (AEs) (81%), all of which were Grade 1-2 [7].

The goal of the MonumenTAL-1 trial was to examine the safety and effectiveness of talquetamab, a GPRC5D/CD3 BsAb. For the 0.4 mg/kg QW, 0.8 mg/kg Q2W, and other dose groups (some patients with prior T-cell redirection therapy received either dose), the ORR was 74%, 73%, and 63%, respectively. There were three different median progression-free survival (mPFS) values: 7.5, 11.9 (61% censored), and 5.1 months. Every adverse event was clinically controllable [8].

At the ASCO meeting in 2023, the RedirecTT-1 study's initial findings were presented. The purpose of this study was to examine the effects of concurrently using two BsAbs, teclistamab

(tec) targeting BCMA/CD3 and talquetamab (tal) targeting GPRC5D/CD3. The rates of CR or better (≥ CR) were 34% (21/62) and 31% (8/26) among evaluable patients, and 84% (52/62) and 73% (19/26) among evaluable patients with extramedullary disease (EMD). At the suggested phase 2 regimen (RP2R), the ORR was 83% (5/6) in evaluable patients with EMD and 92% (12/13) in evaluable patients. AEs were tolerable, and the rates of CR or better (≥ CR) were 31% (4/13) and 33% (2/6), respectively [9].

In the TRIMM-2 study, tal + daratu-mumab was another combo medication. The ORR was 78% and in strongly pretreated RRMM patients, it demonstrated robust and long-lasting responses with a mPFS of 19.4 mo. The overall survival (OS) rate was 93% and the 12-month PFS rate was 76%. Furthermore, the safety profile was deemed appropriate [10]. Apart from the aforementioned trials, Shaji Kumar is presently carrying out investigations to examine the effectiveness and safety of cevostamab, a treatment that targets FcRH5 and CD3, in patients with TCR RRMM as part of the CAMMA 2 study [11].

While there is currently no empirical evidence available, relevant patient recruitment is underway.

Dual-purpose CAR-T lymphocytes Prior findings showed that RRMM patients treated with GC012F experienced a robust and long-lasting response. At the ASCO meeting in 2023, the same team presented updated trial findings (Abstract No. 8005). The rates of severe complete response (sCR) and very good partial response (VGPR) were 82.8% (24/29) and 89.7% (26/29), respectively, at the time of the data cutoff, with an ORR of 93.1%. 29 out of 29 individuals had limited residual disease (MRD) negative (flow cytometry at 10− 4–10− 6), and 24 out of 29 dose levels had an MRD-sCR rate of 82.8%. 37.0 mo (95% CI, 11.0-NR) for the mDOR and 38.0 mo (95% CI, 11.8-NR) for the mPFS. This encouraging result showed that RRMM patients can receive even more therapeutic benefit from GC012F [12].

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