Bispecific antibodies binding CD3 and BCMA for the treatment of MM, such as teclistamab, have been developed to induce T-cell mediated cytotoxicity against BCMA expressing MM cells and/or RRMM cells, alone or in combination with an immunotherapeutic drug such as thalidomide or an immunotherapeutic derivative such as an anti-PD-1 antibody and an anti-PD-Ll antibody (US11124577B2).

Exceptional overall response rate has been observed using bispecific antibodies or chimeric antigen receptor (CAR) T cells immunotherapy, in which T lymphocytes are engineered with synthetic chimeric antigen receptors. Nevertheless, durable responses beyond 2 years are still limited (Progression-free survival is below 40% for treatment with idecabtagene vicleucel (Munshi, N. C. et al. Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma. N. Engl. J. Med. 384, 705-716 (2021)) or teclistamab (Moreau, P. et al. Teclistamab in Relapsed or Refractory Multiple Myeloma. N. Engl. J. Med. NEJMoa2203478 (2022) doi:10.1056/NEJMoa2203478). It has been proposed that one of the potential reasons for patient relapse may be downregulation of the target or expansion of clones lacking sufficient expression of targets (Rodriguez-Lobato, L. G., Oliver-Caldes, A., Moreno, D. F., Fernandez de Larrea, C. & Blade, J. Why Immunotherapy Fails in Multiple Myeloma. Hemato 2, 1-42 (2020)). This low expression of targets in the MM population has been observed after treatment with CD38-targeted daratumumab (Nijhof, I. S. *et al.* CD38 expression and complement inhibitors affect response and resistance to daratumumab therapy in myeloma. 128, 12 (2016)), and BCMA specific CAR T cells (Cohen, A. D. et al. B cell maturation antigen-specific CAR T cells are clinically active in multiple myeloma. J. Clin. Invest. 129, 2210-2221 (2019)). Consequently, the development of approaches that prevent tumor escape, often associated with lower surface expression of targeted tumor associated antigens remain a challenge.

Although promising treatments of hematological cancers, such as multiple myeloma, are nowadays available, the improvement of therapies, for instance effector cell redirecting antibody-based therapies, still remains a need. In fact, despite the increasing number of available treatments, the prognosis for multiple myeloma and relapsed/refractory multiple myeloma patients is still poor given the increasing evidence of resistance to the currently available treatments, and the necessity to maximise the therapeutic window.

Summary

In one aspect, provided herein is a trispecific antibody or antibody fragment thereof comprising at least three binding portions, at least one of which binds to human CD3, at least one which binds to human BCMA and at least one of which binds to human CD38.

In another aspect, provided herein is use of the trispecific antibody or antibody fragment thereof as described herein, in the manufacture of a medicament to treat a BCMA and/or a CD38 expressing cancer.

In another aspect, provided herein is the trispecific antibody or antibody fragment thereof as described herein for use in therapy.