Bispecific Antibodies in Multiple Myeloma

Subjects: Oncology

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Multiple myeloma, a cancer of the bone marrow, is the commonest cancer of adults in the Western World. Therapies have advanced dramatically in recent years, equating to improved survival and quality of life for patients, but those with resistant disease still have less favourable outcomes. Bispecific antibodies represent a new treatment option for patients with myeloma. These antibodies activate the patient's own T-cells to kill their tumour cells and have shown impressive results in relapsed refractory myeloma.

myeloma tumour T-cell

1. Introduction

Multiple myeloma (MM) is the second most common haematological malignancy of adults in the Western world, with increasing rates reported over recent years [1][2]. MM is characterized by the clonal expansion of neoplastic plasma cells, leading to the production of a paraprotein, anaemia, renal impairment, bone damage, and humoral and cellular immunosuppression [3][4]. Outcomes have improved significantly since the advent of proteosome inhibitors (PIs), immunomodulatory agents (IMiDs), and monoclonal antibodies. The median overall survival (OS) has doubled to approximately 5 years [5]. However, patients with adverse cytogenetics or high-risk disease as determined by the Revised International Staging System (R-ISS) continue to have less durable responses to treatment, and the majority of low-risk patients will eventually develop treatment-resistant disease [6][7][8].

Patients with ultra-high risk disease, so-called 'double-hit' myeloma, defined by the presence of biallelic inactivation of TP53 or 1q21 amplification and International Staging System (ISS) stage III disease, typically succumb to their disease within 2 years [9]. Those who are refractory to the 3 classes of novel agents (triple-refractory) have an OS of less than one year, whereas the median OS for penta-refractory patients (refractory to 2 PIs, 2 IMiDs and a monoclonal antibody) is a dismal 5.6 months [10]. Given this unmet need, novel therapies remain a priority in MM.

2. Overview of Bispecific Antibodies in Myeloma

Bispecific T-cell antibodies (BsAbs) are designed to simultaneously bind to a target moiety on tumour cells and to CD3 on T-cells. This causes direct T-cell activation and subsequent tumour cell killing [11][12]. The earliest BsAbs consisted of fragment antigen-binding (Fab) variable regions connected by a short flexible linker (non IgG-like BsAbs). Such small BsAbs have a short half-life and require continuous intravenous infusion. Newer agents include a fragment crystallizable (Fc) region (IgG-like BsAbs). These larger BsAbs can be administered via intermittent infusion or subcutaneous (S/C) injection [13].

Blinatumumab, the first licensed BsAb, is a CD19-directed non IgG-like construct that was approved for use in acute lymphoblastic leukaemia (ALL) in 2014 [14]. Since then, numerous BsAbs have been developed in a variety of conditions, including MM. Various targets on malignant plasma cells are being investigated, with the majority of work to-date focused on B-cell maturation antigen (BCMA) [15]. BCMA is a member of the tumour necrosis family receptor superfamily, expressed by mature B-cells, plasma cells and MM cells [16][17][18][19]. It has roles in MM cell survival through the upregulation of anti-apoptotic proteins [20][21][22]. Levels of soluble BCMA (sBCMA) increase with disease progression and correlate with adverse outcomes [23][24]. In 2022, two anti-BCMA BsAbs received regulatory approval. Teclistamab was approved by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) for use in relapsed refractory myeloma (RRMM), and elranatamab also received orphan drug designation by both the EMA and FDA [25][26].

Teclistamab is a humanized IgG Fc anti-BCMA BsAb. Regulatory approval was granted following the publication of results of the phase 1/2 MajesTEC-1 study (NCT03145181) in 165 RRMM patients with triple class-exposed disease. After a median follow-up of 14 months, the overall response rate (ORR) was 63%, and 39% achieved a complete response (CR) or better. The median duration of response (DOR) was 18 months, with a median progression-free survival (PFS) of 11 months. CRS occurred in 72%, immune effector cell-associated neurotoxicity syndrome (ICANS) in 3%, and infections in 76%, of which 45% were grade 3–4 events [27].

Elranatamab is a humanized IgG2A anti-BCMA BsAb. The phase 2 MagnetisMM-3 study (NCT04649359) enrolled and treated 123 RRMM patients. A total of 97% of the trial population were triple-refractory, and 42% were penta-refractory. After a median follow-up of nearly 7 months, the ORR was 61%. Some 51% of patients were still receiving elranatamab at data cut-off, with progressive disease accounting for 33% of those discontinuing therapy. Of 119 patients, CRS occurred in 56% and ICANS in 3%. Infections were reported in 62%, 32% being of grade 3–4 [28]. A summary of the published data for the reported BCMA BsAbs in MM in shown in **Table 1**.

Table 1. Published clinical trials of BCMA BsAbs in RRMM.

Bispecific Antibody	Clinical Trials Identifier	Antibody Structure	Administration	Safety	CRS/ICANS	Responses	Ongoing Studies
Teclistamab	MajesTEC-1 NCT03145181	humanized, IgG Fc	Teclistamab 1.5 mg/kg weekly S/C with a 2-step-up priming dose regimen (0.06 mg/kg and 0.3 mg/kg)	Anaemia 52%, neutropenia 71%, thrombocytopenia 40%, infections 76% (grade 3–4 45%), neurotoxicity 15%	CRS 72% (all but one case grade 1–2), ICANS 3% (all grade 1–2)	ORR 63%, 39% CR or better, median DOR 18.4 months	Several MagesTEC studies ongoing using teclistamab in RRMM and NDMM in combination therapies
Elranatamab	MagnetisMM-3 NCT04649359 Cohort A	full length, humanized, IgG2a	Elranatamab 76 mg weekly S/C on a 28 day cycles with a 2-step-	Anaemia 56%, neutropenia 53%, thrombocytopenia 27%, infection 62% (grade 3–4	CRS 56% (all grade 1–2), ICANS 3%	ORR 61%, median DOR not reached	Several MagnetisMM studies ongoing using elranatamab

Bispecific Antibody	Clinical Trials Identifier	Antibody Structure	Administration	Safety	CRS/ICANS	Responses	Ongoing Studies
			up priming dose regimen (12 mg and 32 mg)	32%), %, peripheral neuropathy 17%, nausea 30%, diarrhoea 45%	(all grade 1–2)		in RRMM and NDMM in combination therapies
AMG 420	NCT02514239	BiTE	Continuous 28 day IV infusion followed by 2 week break. Dose-escalation from 0.2–800 µg/day	Infection 33%, polyneuropathy 5%, 12% deranged liver enzymes	CRS 38% (94% Grade 1–2)	ORR 31% across all doses, 70% for the 400 ug/day cohort	Development discontinued by Amgen
AMG 701	NCT03287908	extended half-life, scFvs plus Fc region	Weekly IV. Dose-escalation from 5 µg–12 mg	Anaemia 43%, neutropenia 23%, thrombocytopenia 20%, diarrhoea 31%, fatigue 25%, infection 17%, elevated pancreatic enzymes 3%.	CRS 61% (90% Grade 1–2)	ORR 36% for 3–12 mg doses	Development discontinued by Amgen
Linvoseltamab (REGN5458)	NCT03761108	Fc Fab arms	IV weekly, then every 2 weeks. Dose escalation over 9 dose levels.	Anaemia 37%, neutropenia 29%, thrombocytopenia 21%, fatigue 34%	CRS 48% (all but one case Grade 1–2)	ORR 41% for doses <200 mg and 75% ≥200 mg, median DOR not reached	Phase 2 study of 200 mg REGN5458 is recruiting
Alnuctamab (CC-93269)	NCT03486067	2 arm humanized IgG1 Fc	Dose escalation of IV alnuctamab from 0.15–10 mg. S/C alnuctamab given on D1, 4, 8, 15 and 22 of C1, weekly in C2–3, every other week in C4–6 and every 28 days thereafter.	Anaemia 34%, neutropenia 34%	CRS 53% (all grade 1–2), 1 grade 1 ICANS	IV alnuctamab ORR 39%, median PFS 13 weeks, median DOR in responding patients 146 weeks. S/C alnuctamab ORR 51% across all doses,	Ongoing recruitment to the phase 1 study

3. Improving Efficacy

Bispecific Antibody	Clinical Trials Identifier	Antibody Structure	Administration	Safety	CRS/ICANS [15]	Responses	Ongoing Studies
			Dose escalation from 10–60 mg			77% for doses ≥30 mg	
Abbv-383	NCT03933735	IgG4 Fc. 2 heavy chain only anti-BCMA moieties	Dose escalation and expansion cohorts (n = 6 in 40 mg cohort, n = 60 in 60 mg cohort)	Infections in 50% of 40 mg cohort and 43% of 60 mg cohort, neutropenia in 67%/40%, anaemia in 33%/32%, thrombocytopenia 33%/25%	CRS 83% [29] (all grade 1–2) in 40 mg cohort [30] and 72% (2% grade 3–4) in 60 mg cohort [31]	ORR 57% across all groups, 83% at 40 mg and 60% at 60 mg. ≥CR 67% at 40 mg and 29% at 60 mg	Phase 1b study planned NCT05650632

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MM cells compared with both MGUS cells and healthy donor plasma cells [32][33].

Immunosuppressive Regulatory T-cells (Tregs) are enriched in MM peripheral blood samples. MM cells themselves can induce the formation of Tregs in vitro, [34], promoting immune escape, and perhaps explaining the increasing levels of Tregs present with increasing disease burden. In a murine model, the depletion of Tregs in mice with established MM promoted vigorous T-cell and NK cell-mediated responses, halting disease progression [35]. T-cell function is also impaired by myeloid-derived suppressor cells, present at 5 times the normal level in MM patients [36].

BsAbs rely upon a robust CD8+ cytotoxic T-cell response. Continuous antigen stimulation can lead to T-cell exhaustion, with resultant resistance to therapy anticipated [37]. In patients who respond to BsAb therapy, a selective expansion of clonotypic tumour-reactive CD8+ T-cells is produced, which replaces exhausted BM T-cells. This is not seen in non-responding patients [38]. An analysis of the MajesTEC-1 study of teclistamab in RRMM also showed that patients who failed to respond to treatment had lower peripheral CD8+ T-cell levels, increased levels of Tregs, and enhanced expression of markers associated with T-cell exhaustion in blood and BM samples. Higher levels of exhausted CD8+ T-cells and Tregs pre-treatment were associated with inferior PFS in this research [39].

Given the impairment of T-effector activity seen in MM, combining BsAbs with therapies which augment T-cell function may provide a means to improve efficacy.

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