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REVIEW

Bispecific antibodies for non-Hodgkin's lymphomas and multiple myeloma

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Abstract

Immunotherapy has revolutionized the treatment of cancers. There are several approaches, including naked monoclonal antibodies, antibody–drug conjugates, immune-checkpoint inhibitors and chimeric antigen receptor T cell therapies with important success. Bispecific antibodies represent a novel immunotherapeutic approach for the treatment of several malignancies, in particular non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM). Early-phase studies have shown encouraging clinical activity in poor-risk B cell NHL and MM. Several constructs are currently available and in clinical development for the treatment of these malignancies. Here, we present a narrative review of the most current data on bispecific antibodies in B cell NHL and MM.

Keywords: bispecific, immunotherapy, multiple myeloma, non-Hodgkin's lymphoma.

Citation

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Introduction

B cell non-Hodgkin's lymphoma (NHL) represents a heterogenous group of mature B cell malignancies. In 2020, B-cell NHL was estimated to be the seventh most common diagnosed malignancy.[1] The most common B cell NHL subtypes are diffuse large B cell lymphoma (DLBCL) and follicular lymphoma (FL). DLBCL is a curable disease; however, about a third of patients will become refractory to standard anthracycline-based chemoimmunotherapy, and many will become refractory to subsequent lines of therapy, especially those with early relapse/primary refractoriness.[2] Whilst FL is considered an incurable cancer, many will have long-term survival and/or will exhibit long-term remissions with standard alkylating-based therapies along with anti-CD20 monoclonal antibodies (MAbs). However, approximately 10–20% of patients with primary refractoriness or early relapse will have a poor prognosis and early death.[3] Novel agents, such as new generation MAbs, antibody–drug conjugates (ADCs), immunomodulators (IMiDs), chimeric antigen receptor (CAR) T cell therapy and other targeted therapies, are changing the treatment landscape of B cell NHLs.[4,5]

Multiple myeloma (MM) is a malignancy of terminally differentiated plasma cells representing the second most common haematological malignancy with a globally marked increase in incident cases over the past 25 years.[1,6] MM remains an incurable disease despite the continued advances in treatment including IMiDs, proteasome inhibitors (PI) and targeted immunotherapy. Relapses in MM are inevitable, and survival is significantly affected by the level of refractoriness to anti-MM therapy; patients who are penta-refractory have a median overall survival (OS) of 5.6 months, which is 5 months less than the median OS in patients who are either refractory to IMiD and PI.[7] The evolution of MM treatment has rapidly expanded, focusing on targeted immunotherapy. Many known myeloma antigens serve as therapeutic targets, including CD38, B cell maturation antigen (BCMA), CD138, SLAMF7 and GPRC5d. Multiple anti-MM therapies are being developed for the treatment of MM, including bispecific antibodies (BiAbs), ADCs and CAR T cells.[8–12]

T cell-redirecting therapies represent a novel immunotherapeutic approach for several haematological malignancies. One type of T cell-based therapy is CAR T cell therapy, which showed impressive results in these malignancies, specifically in B cell lymphomas and myeloma.[5,10] Whilst the process of CAR T cell generation and administration is well established, it is expensive, time consuming and not readily available. In addition, post-CAR T cell relapses do occur in approximately 50% of cases, and treatment options are limited.[13] In contrast, BiAbs are

available as 'off the shelf' treatment and do not require a manufacturing process or lymphodepleting chemotherapy. The toxicities seem to be lower and hospitalization may not be required as oppose of CAR-T therapy. Large-bore central catheters are needed for CAR T cell infusion; however, BiAbs can be administered through ports or even through the subcutaneous route, making them more user friendly. Additionally, BiAbs have been studied in the post-CAR T cell therapy relapse setting. Thus, BiAbs may fill not only disease-related gaps in poor-prognosis B cell NHLs and MM but also in the logistics needed for CAR T cell therapy.[14]

Structure and mechanism of action of BiAbs

BiAbs consist of two single-chain variable fragments (scFvs) that target specific antigens. Each scFv has heavy (H) and light (L) chains that are derived from MAbs with affinity to the specific target.[12,15] In the vast majority of BiAbs, the preferred scFv T cell effector target is CD3. The other scFv-binding molecule targets specific antigens (i.e. CD19, BCMA, CD20, etc.). First-in-class BiAbs combined the binding molecules without an Fc portion. These BiAbs (i.e. blinatumomab) are very efficacious in generating a T cell effector response against the antigen and, hence, have good clinical activity. However, these non-Fc domain BiAbs have a short half-life (1.5–2 hours) and require continuous intravenous infusion, which may not be very practical.[12,14] New generations of BiAbs formats contain Fc domains (full-length BiAbs) that have longer half-lives and the possibility to generate a long-lasting immune antitumor response.

In general, the mechanism of action of BiAbs consists of engaging immune system cells to attack tumour cells by targeting the respective tumour-associated antigen. As the majority of BiAbs bind to the CD3 antigen on T cells, they induce T cell activation and proliferation in an MHC-independent manner. Due to the effector properties of the Fc domain, these BiAbs may have better antibody-dependent cellular cytotoxicity, antibody-dependent phagocytosis and even complement-dependent cytotoxicity.[12,16]

BiAbs for lymphomas: clinical studies

Blinatumomab

Blinatumomab is the first bispecific T cell engager (BiTE) developed for B cell malignancies. It is constructed with a single antibody Fab chain that binds CD19 linked to a Fab chain that targets CD3 T cells. Blinatumomab is currently approved for relapsed/refractory B cell acute lymphoblastic leukaemia and for patients with persistent minimal residual disease (MRD) after frontline therapy for B cell acute lymphoblastic leukaemia.[17,18] Due to its reduced half-life (2 hours), blinatumomab is administered as a continuous infusion. A phase II study of 76 patients with B cell NHL including DLBCL (*n*=14), FL (*n*=28), mantle cell lymphoma (MCL; *n*=24) and others (*n*=10) showed efficacy at doses of >60 μg/m^2 with an overall response rate (ORR) and complete response (CR)/CR unconfirmed of 69% and 37%, respectively. Pyrexia/fevers of all grades and grade ≥3 were 76% and 4%, respectively. All grades and grade ≥3 neurological events were noted in 71% and 22% of patients, respectively. The maximum tolerated dose (MTD) was 60 μg/m^2.[19] In a phase I escalation study in DLBCL (*n*=25), blinatumomab was administered to a target dose of 112 μg/m^2 (stepwise and flat dosing). Patients had relapsed disease within 6 months or were refractory to last therapy in 65.2% of cases, prior autologous haematopoietic cell transplantation (HCT) was performed in 26.1% of cases and bulky disease occurred in 26.1%. For the 21 patients evaluable for efficacy, the ORR and CR rates were 43% and 19%, respectively. The median progression-free survival (PFS) and OS were 3.7 and 5 months, respectively. All grades and grade ≥3 neurological events were reported in 70% and 22%, respectively.[20] Patients (*n*=2) who received a flat dose at 112 μg/m^2 developed grade 3 neurological events. Whilst these results were encouraging, the need for 2–3 weeks on lower doses of blinatumomab (potentially ineffective in aggressive NHL) makes this regimen challenging for patients with rapidly aggressive disease (about 65% dropped during cycle (C)1 due to disease progression).[21] The median duration of CR and progression-free survival (PFS) was not reached and 2.1 months, respectively. The median PFS and OS for the small proportion of patients who achieved CR were not reached.[22] Blinatumomab has been also combined with lenalidomide in a small study of B cell NHL. Preliminary results showed an ORR and CR of 83% and 50%, respectively; however, the PFS was 3.8 months.[23]

Mosunetuzumab (RO7030816)

Mosunetuzumab is an IgG1 full-length humanized anti-CD20/CD3 BiAb that targets malignant B cells. Mosunetuzumab induced potent T cell activation against CD20$^+$ normal and neoplastic B cells via the granzyme–perforin pathway even at low concentrations of CD20 and despite the presence of high levels of rituximab.[24] The initial clinical studies with mosunetuzumab were reported in the phase I dose-escalation clinical trial GO29871 (NCT02500407) in relapse/refractory heavily pretreated B cell NHL, including DLBCL/transformed follicular lymphoma (tFL), FL, MCL and other subtypes. The GO29871 trial is currently the largest study presented so far. Mosunetuzumab was administered as an IV infusion every 21-day cycle (group B was administered on an ascending dosing on C1 on days 1, 8 and 15 and then on fixed doses on subsequent cycles on an every-3-week cycle).[25] In the initial phase I interim analysis of efficacy and safety, the recommended dose was determined and the MTD was not reached. Additionally, the single-patient escalation was an effective strategy to mitigate cytokine release syndrome (CRS) and neurotoxicity. Mosunetuzumab half-life was determined to be between 6 and 11 days. It also showed CD4$^+$CD8$^+$ T cell activation and proliferation. Clinical activity was noticed at doses of ≥1.2 mg with an ORR of 41%. The response rates were somewhat different in DLBCL/tFL

and FL with an ORR (CR) of 61% (50%) and 33% (21%), respectively. CRS (all grades 1–2) was reported in 21% of patients with one case of neurotoxicity. One patient who had chronic Epstein–Bar infection developed haemophagocytic lymphohistiocytosis.

The expansion phase (*n*=270 patients) used step-up dosing in C1 and fixed dosing from C2 (to a maximum of 17 cycles). Pretreatment with steroids was required in C1 and C2. Patients who achieved CR after six cycles discontinued therapy. The study included heavily pre-treated aggressive B cell NHL with mostly DLBCL/tFL (*n*=180, 83%) and indolent B cell NHL, mostly FL (*n*=82, 96%).[26] Thirty patients (11%) had prior CAR T cell therapy with 22 patients being refractory. The ORR (CR) rates were 37.1% (19.1%) and 62.7% (43.3%) in aggressive NHL and indolent NHL, respectively. Clinical responses were seen in the post-CAR T setting in DLBCL and FL with an ORR of 21.4% and 100%, respectively. All grade CRS occurred in 28.9% of cases with grade ≥3 in 3 (1.1%) patients, tocilizumab was used in 3% of cases. Neurological adverse events (AEs) of all grades (headaches, insomnia, dizziness) occurred in 43.7% of patients; however, immune effector cell–associated neurotoxicity syndrome (ICANS)-like AEs were noted in 1.1% of patients (all grades 1–2). The median duration of CRS and ICANS were 2 and 3 days, respectively.

A longer follow-up of the FL cohort was presented (*n*=62) that included grade 1–3a FL refractory to at least two lines of therapy. Patients belonged to high-risk FL subgroups such as POD24 (46.8%), double refractory to anti-CD20 antibody and an alkylating agent (61.3%), and prior autologous HCT (19.4%). With a median follow-up of 18.4 months, the ORR and CR were 67.7% and 51.6%, respectively. The median duration of response (DoR) and PFS were 20.4 and 11.8 months, respectively.[27]

Odronextamab (REGN1979)

Odronextamab, a fully human IgG4 anti-CD20/CD3 BiAb developed using an Fc domain, showed deep B cell depletion and T cell cytotoxicity against malignant B cells. Mutation in the protein A of the Fc portion improves the purification and may reduce immunogenicity. The half-life was noted to be 14 days.[28] The initial human studies of odronextamab included a variety of B cell NHLs and involved the IV administration of the drug weekly for 12 weeks followed by every 2 weeks for 12 doses for a total of 36 weeks. Due to toxicity (infusion-related reaction or CRS), a step-up dosing schema was developed. The concentration of odronextamab was dependent on the dose level.[29] Across all dose levels, the ORR in the NHL cohort was 20%, with higher response rates at higher dose levels. The incidence of CRS was 24% (mostly grades 1–2).

The most recent update of REGN1979 was presented recently and included 136 patients with DLBCL (*n*=78), FL grades 1–3a (*n*=38), mantle cell lymphoma (*n*=12) and other B cell NHLs (*n*=8). The regimen varied with dose splitting on days 1 and 2 of the first 2 weeks of therapy. Thirty-five patients (25.7%) had post-CAR T cell failure. Patients were heavily treated, including three median lines of therapy, prior autologous HCT (7.5%) and double refractory cases (66.9%).[30] In FL, odronextamab was efficacious at doses from 5 to 320 mg (*n*=30) with an ORR of 90% and CR of 70%. The median DoR was not reached and the median PFS was 12.8 months. In DLBCL, the best responses were seen at ≥80 mg with an ORR of 60% and 33% in the non-prior CAR T cell cohort (*n*=11) and post-CAR T cell patients (*n*=25), respectively. The toxicity profile was consistent with other BiAbs. The rates of CRS (all grades) and grade ≥3 were 61% and 7.3%, respectively. Grade >3 ICANS-like AEs were noted in 3.7% of patients treated.[30]

Biomarker studies showed that $CD4^+CD8^+$ tumour-infiltrating T cells were significantly increased in responders *versus* non-responders and responses were seen even at low CD20 expression in malignant B cells. Post-progression biopsies showed CD20 loss in 6 out of 9 patients with available tissue. CD20 gene mutations were also observed, underscoring a possible mechanism of resistance.[31]

Epcoritamab (GEN3013)

Epcoritamab is a full-length IgG1 anti-CD20/CD3 BiAb. The format is a DuoBody, which introduces point mutations in the Fab portion of the Fc of the antibody that leads to more heterodimerization and, hence, stabilization of the antibody and less T cell depletion. As opposed to other studied BiAbs, epcoritamab is given as subcutaneous (SC) administration. The median peak was delayed, and the half-life was 8.67 days. Pharmacodynamics and pharmacokinetics data showed a gradual increase and lower peak levels of inflammatory cytokines that could potentially be associated with a better toxicity profile.[32] Clinical data of the dose escalation and initial dose expansion were presented recently. In a phase I–II dose-escalation study, epcoritamab was given as a flat SC injection on an every-28-days cycle weekly on C1–2, every 2 weeks on C3–6 and every 4 weeks continuously until progressive disease or intolerable adverse effects. At the last cut-off, the study enrolled 68 patients with heavily pretreated DLBCL, FL and MCL with prior autologous HCT (11%) and prior CAR T cell therapy (9%). With a median follow-up of 8.3 months, the drug showed promising activity. Data were provided for evaluable patients with DLBCL and FL with a median follow-up of 10 months. In DLBCL at doses ≥12 mg and ≥48 mg, the ORR (CR) were 68% (48%) and 91% (55%), respectively. In FL, at doses from 0.76 to 48 mg, the ORR and CR were 90% and 50%, respectively. There were 4 patients with prior CAR T cell therapy, and all had any type of response (2 CRs and 2 partial responses (PRs)).

Epcoritamab was well tolerated with CRS rates at 59%, all grades 1–2 and most occurring in C1. There was no grade >3 CRS despite dose escalation. Neurotoxicity was reported in 9% (grade 3 in 3%). There were no dose-limiting toxicities (DLTs), neutropenic fever events or treatment-related deaths.[33] Integrated pharmacokinetics/pharmacodynamics modelling, exposure–response and exposure–AE analysis with clinical efficacy and safety information, the recommended phase 2 dose (RP2D) was recommended at 48 mg without the need to step-up dosing as for other BiAbs.[34]

Plamotamab (XmAb13676)

Plamotamab is a IgG1 bispecific anti-CD20/CD3 antibody that has a heterodimeric Fc portion without effector activity that showed potent T cell activity against malignant B cells.[35] The first- in-human (FIH) study was reported in 44 patients (36 with B cell lymphomas and 8 with chronic lymphocytic leukaemia or CLL) heavily pretreated (median number of therapies of 3). In the NHL cohort, there were 7 (20%) responses with 2 (5%) CRs at doses >20 µg/kg. In DLBCL, the best responses were seen at doses ≥80 µg/kg with ORR and CR rates of 38.9% and 27.8%, respectively. CRS (all grades) occurred in 52.8% of cases, with CRS grades ≥3 in 5.7%. Neurological events occurred in 49.1% of patients and involved mainly headaches, paraesthesia, lethargy and dizziness. No grade 3 neurological events were reported. The study continues in dose escalation at this time.[36]

Glofitamab (RG6026)

Glofitamab is an IgG1 fully humanized anti-CD20/CD3 T cell-dependent BiAb. It is composed of two Fab binding sites for CD20 and one for CD3 ('2:1' format). One of the CD20 Fab is fused to the CD3 Fab binding site. The Fc portion is a heterodimeric IgG1-like unit that carries mutations that provide more stability and a longer half-life (10 days). The bivalent binding of CD20 provides stable and deeper anti-tumour activity even in the presence of anti-CD20 monoclonal Abs.[37,38] Glofitamab had a 40 times higher potency than 1:1 T cell BiAbs and at lower effector to target ratios (0.02–0.8). FIH studies were conducted in B cell NHL (aggressive and indolent lymphomas) in a phase I dose-finding study. Glofitamab was given at doses of 5–1800 µg in an every-2-weeks schedule with one single infusion of obinutuzumab as pretreatment 7 days prior to cycle1, D1 (C1D1).[39] Best responses were seen at >300 µg, with ORR and CR rates at 38% and 24%, respectively. CRS was noted in 21.8% of patients (all grades 1–2) with no neurological toxicity.

Most recently, updated data of glofitamab were presented and included 52 patients with $CD20^+$ B cell NHL, the majority with DLBCL/tFL/high-grade B cell lymphoma (*n*=18) and FL (*n*=24). Patients had a median age of 68 years and had three median lines of therapy. Patients also had poor prognosis features, including prior autologous HCT (21.2%), prior CAR T therapy (5.8%), or were refractory to the most recent therapy (76.9%). The ORR (CR) for aggressive NHL and indolent NHL (in the stepping up dosing) was 60.7% (53.6%) and 66.7% (54.2%), respectively. All grades CRS were noted in 63.5%, with grades ≥3 CRS in 3.8%. CRS events were confined to C1 and C2 of glofitamab administration.[40] The median duration of response for DLBCL and FL was 5.5 and 10.8 months.[41]

A summary of BiAbs in NHL is shown in Table 1.

BiAbs in multiple myeloma

AMG 420

AMG 420 (previously BI 836909) is a BiTE that targets BCMA and CD3ε, inducing highly selective T cell-driven lysis of

Table 1. Bispecific antibodies in B cell NHL: reported clinical studies.

Antibody (ref.)	Phase	Dose	NHL sub-types	Efficacy (%) ORR (CR)	CRS (%) All (G≥3)	NT (%) All (G≥3)
Blinatumomab (*n*=25)[19]	II	9–112 µg/m^2	DLBCL: 25	43 (19)	NR	70 (22)
Mosunetuzumab (*n*=270)[24]	I/II	aNHL: 2.8–40.3 mg iNHL: 2.8–13.5 mg	aNHL: 180 iNHL: 90	aNHL: 37 (19) iNHL: 63 (43)	28.9 (1.1)	1.1 (0)
Odronextamab (*n*=136)[28]	I/II	5–320 mg	DLBCL: 78 FL: 38 MCL: 12 Other: 12	DLBCL: 55 (55) FL: 90 (70)	61 (7.6)	NR (1.5)
Epcoritamab (*n*=68)[31]	I/II	12–60 mg	DLBCL: 46 FL: 12 MCL: 4	DLBCL: 76 (48) FL: 87 (53)	59 (0)	9 (3)
Glofitamab (*n*=52)[38]	I	2.5–30 mg	DLBCL: 18 FL: 24 RT: 5 MCL: 5	DLBCL: 61 (54) FL: 67 (54)	64 (3.8)	NR (0)
Plamotamab (*n*=44)[34]	I	20–125 µg/kg	DLBCL: 18 Other: 18 CLL: 8	DLBCL: 39 (28)	53 (5.7)	49.1 (0)

aNHL, aggressive NHL; CLL, chronic lymphocytic leukaemia; CR, complete response; CRS, cytokine release syndrome; DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma; iNHL, indolent NHL; MCL, mantle Richter's transformation; NHL, non-Hodgkin's lymphoma; NT, neurologic toxicity; ORR, overall response rate.

BCMA-positive MM cells, release of cytokines and T cell proliferation. AMG 420 was the first BiTE to have reported data on the treatment of MM. In an FIH study, 42 patients received up to 10 cycles of continuous IV infusions of AMG 420 at 0.2–800 µg/day (4-week infusions/6-week cycles).[42,43] Eligible patients had relapsed/refractory (R/R) MM that had progressed to at least two treatment lines with no extramedullary disease. Median age was 65 years. Patients had a median of five lines of therapy but only 48%, 38%, 36% and 21% were refractory to IMiDs, PIs, IMiD/PI and daratumumab, respectively. Of the total enrolled patients, 16 had CRS, the majority with grades 1–2 that were treated supportively. Treatment was discontinued with a grade 3 CRS case. Of those with serious AEs (SAEs; *n*=20; 48%), the most common SAEs were infection (*n*=14) and polyneuropathy (*n*=2). There were four deaths in this study, two as a result of AEs (influenza/aspergillosis and adenovirus-related fulminant hepatitis), which were not considered related to AMG 402. Due to grade 3 CRS in one patient and grade 3 peripheral neuropathy, the MTD was deemed at 400 µg/d. At the MTD, the ORR was 70% (95% CI 34.8–93.3), including 5 (50%) MRD-negative CRs (MRD measured at a sensitivity of 10^{-4} by flow cytometry), 1 very good PR (VGPR) and 1 PR. The median DoR was 8 months. Long-term outcomes have been reported.[44] The OS for the entire 23 patients was 34.9 months, the median OS for the responders was 32 months and for the 13 non-responders 39 months with a medium follow-up of 35 months. The PFS for the 10 responders was 23.5 months, who received, on average, 7 cycles of AMG 420; 2 patients are still in CR and 1 patient remains in continuous PR. Despite the encouraging results, the continued intravenous infusion presents a logistical challenge for which the sponsor decided to solely develop a half-life extended BCMA×CD3 BiAb (AMG 701) that allows for weekly dosing.

AMG 701

AMG 701 is a half-life extended anti-BCMA BiTE that also induces cellular-dependent cytotoxicity of BCMA-expressing cells as well as T cell proliferation/expansion.[45] In an FIH study, 75 patients received weekly IV infusions of AMG 701 in 4-week cycles in different dose-escalation cohorts. Eligible patients had MM R/R or intolerant to more than three lines (PI, IMiD, anti-CD38 antibody).[46] Patients with solitary extramedullary disease, central nervous system involvement, prior allogeneic stem cell transplant (past 6 months) or prior anti-BCMA therapy were excluded. Patients were heavily pretreated with a median of six prior therapy lines, including 68% that were triple refractory to a PI, an IMiD and an anti-CD38 antibody. Median age was 63 years. CRS cases were seen, with 61% having mostly grade 1 (*n*=19, 25%) or grade 2 (*n*=21, 28%). There were 5 (7%) cases of grade 3 CRS, all reversible with tocilizumab and steroids. Neurotoxicity was seen in 6 patients, all grade 1–2, reversible and mostly associated with CRS. DLTs included grade 3 CRS, grade 3 atrial fibrillation (*n*=1), transient grade 3 acidosis (*n*=1) and grade 4 thrombocytopenia (*n*=1). SAEs were present (*n*=29, 39%) with the most common being infection (*n*=13) and CRS (*n*=7). There were four deaths that were not deemed to be related to AMG 701 (sepsis, retroperitoneal bleeding and subdural haematoma). MRD was measured by next-generation sequencing ($\leq 10^{-5}$) or flow cytometry ($\geq 3 \times 10^{-5}$). Across the study, there were 4 stringent CRs (3 MRD negative, 1 not tested), 1 MRD-negative CR, 6 VGPRs and 6 PRs. Median time to best response and DoR were 2.8 and 23 months. During the last assessment, responses were ongoing in 14/17 patients. Serum BCMA levels were identified as a determinant of AMG 701 free drug exposures. The results support further evaluation of AMG 701.

PF-06863135

PF-06863135, also known as PF-3135, is a fully-human IgG CD3 bispecific molecule targeting BCMA.[47] Data from 17 heavily pretreated patients were presented recently. PF-3135 was received once weekly via non-continuous IV infusion in six escalation groups.[48] The median age was 61 years (47–82 years). Patients had 11 median lines of therapy, with 5 patients having received prior BCMA-targeted therapy. Treatment-related AEs included grade 1–2, including CRS (24%), thrombocytopenia (24%) and anaemia (18%). Three patients had grade 3 AEs (increased liver function tests, leukopenia, neutropenia and lymphopenia). There was only 1 minimal response, 6 stable disease (SD) and 9 disease progression, which may reflect the overall poor health of the T cells following several lines of therapy. SC dose escalation was investigated to reduce the maximum concentration, expecting less CRS and inflammatory responses.[49] Eighteen patients received weekly SC dosages of PF-3135 at 80–360 µg/kg. Eligible patients had R/R MM previously treated with IMiDs, PIs and anti-CD38 mAb. The number of prior therapies was 7 (median); all patients had received prior daratumumab and 4 patients had received prior BCMA-targeted therapy (ADC or CAR T cell). No DLT was observed nor was MTD reached. CRS, the most frequent treatment-related AE, was seen in 61% of patients (*n*=11), all grade 1 (50%) and grade 2 (11%). Across the study, there were two stringent CRs (sCR), two VGPRs, two PRs and seven had SD. Free BCMA levels decreased with increasing doses and demonstrated a sustained decrease throughout each dose interval.

REGN5458

REGN5458 is a human BiAb that binds to BCMA and CD3.[50] FIH study data of three patients treated on the initial dose level of REGN5458 were presented at the 61st American Society of Haematology (ASH) annual meeting.[51] All patients were older than 75 years. No DLTs or infusion-related reactions were reported. One patient had VGPR and another had SD. Updated data were presented at the 62nd ASH annual meeting.[52] Forty-five patients were treated with REGN5458 at weekly doses followed by every 2 weeks of maintenance therapy. REGN5458 doses ranged from 3 to 96 mg (escalation over six dose levels). Patients had R/R MM to at least three prior lines of therapy with the inclusion of extramedullary disease cases. Median age was 64 years (34% of patients were >70 years). Patients were heavily

pretreated, with a median of prior treatment lines of 5 (2–17). All patients were refractory to anti-CD38 antibody. Penta-refractory, quad-refractory and triple-refractory patients represented 53.3%, 33.3% and 6.7% of the cohort, respectively. The most common AEs were CRS (37.8%) and infections (46.7%, grade ≥3 were 20%). CRS was mostly grade 1 (88.2%), and no patient had grade >3 CRS. The most common grade >3 AEs were anaemia (8.9%) and lymphopenia (6.7%). DLTs included grade 4 acute kidney injury and grade 3 liver transaminases associated with CRS. SAEs were seen in 22.2% of patients, with the most common being CRS (11.1%). Grade 5 AEs occurred in three patients (two sepsis and one COVID-19), all unrelated to the study drug. Across the study, ORR was 35.6%, with 81.3% and 31.3% of responders achieving at least a VGPR and CR/sCR, respectively. A total of 43.8% of responders had a DoR >4 months. Patients with extramedullary MM had an ORR of 16.7%.

Teclistamab

Teclistamab, also known as JNJ-64007957, is a humanized IgG-4 BCMA×CD3 BiAb that induces BCMA-directed T cell-mediated cytotoxicity.[53,54] An updated phase I study was recently presented.[53] Teclistamab was given IV (0.3–720 µg/kg) and SC (20–3000 µg/kg) to 84 and 44 patients, respectively. Eligible patients had R/R MM. Median age was 64 years (24–82), and the median number of prior treatments was 6 (2–14). A total of 79% and 38% of patients were triple-refractory and penta-refractory, respectively. The frequency of CRS was 50% and 55% (with IV and SC dosing), all grade 1–2 and limited to the initial doses. Grade ≥3 treatment-related AEs were seen in 39%. Neutropenia (23%) and anaemia (9%) were the most frequent treatment-related AEs. Neurotoxicity occurred in 5%, with grade ≥3 in 2%. Four deaths were reported during treatment (all IV dosing) and were considered not related to the study drug (except for one case of lung infection). A total of 120 patients were evaluable for response, combining a total of four IV and SC dose levels (270 µg/kg and 720 µg/kg weekly for IV and 720 µg/kg and 1500 µg/kg weekly for SC), and the ORR was 63.8% (24 patients with responses better than VGPR and 9 better than CR). From patients with MRD data available, 4/5 had CR in the IV cohorts and 2/2 had CR in the SC cohorts (MRD negative at 10^{-6}). The recommended phase II dose was 1500 µg/kg SC. Across the IV and SC cohorts, the median time to response was 1 month and the median duration of response was not reached.

TNB 383B

TNB 383B is a BCMA×CD3 T cell-engaging BiAbs that preferentially activates effector over regulatory T cells. In an FIH study,[22] 38 patients received TNB 383B infusions every 3 weeks (0.025–40 mg).[55] Eligible patients had R/R MM to at least three prior regimens including a PI, an IMiD and an anti-CD38-directed therapy. The median number of prior lines of therapy was 7 (4–13). Prior BCMA-targeted therapy was not allowed. Median age was 68 years. The most common AEs were CRS (*n*=8; 21%), all cases were grade 1 (*n*=5) and grade 2 (*n*=3), all patients received supportive care, and three patients received one dose of tocilizumab. One DLT, grade 3 confusion was seen at 20 mg dose. Five patients died from underlying disease, and 15 patients discontinued treatment for disease progression. The ORR for the cohort was 37% and 52% for the patients receiving ≥5.4 mg (including 3 sCR/CR, 3 VGPR and 6 PR). Median DoR was 9 (3–27) weeks for the entire cohort.

Cevostamab

Cevostamab, also known as BFCR4350A, is a humanized IgG-based T cell-engaging BiAb targeting FcRH5 and CD3. In a phase I study, 51 patients received BFCR4350A via IV infusion in 3-week cycles (initial dose 0.05–3.6 mg and target dose 0.15–132 mg).[56] Median age was 62 years. The median number of lines of therapy was 6 (2–15). Refractoriness to PIs, IMiDs and anti-CD38 mAbs was 94.1%, 98% and 92.5%, respectively. Approximately 66.7% of patients were triple-class refractory. Prior exposure to BCMA-targeted therapy (ADC, CAR T cell or BiTE) was allowed. The most common AE was CRS (74.5%), mostly grade 1 (39.2%, *n*=20) and grade 2 (33.3%, *n*=17). Only one grade 3 CRS (transaminase elevation, grade 4) was observed; 43.3% of patients with CRS received tocilizumab and/or steroids. No treatment-related fatal AEs were observed. One DLT was observed (pneumonia, grade 3). At data cut-off, 46/51 patients were evaluable for efficacy. Responses were observed at the 3.6/20 mg dose level and above, with ORR of 51.7%, including 3 stringent CRs, 3 CRs, 4 VGPRs and 5 PRs. Responses were observed in 2/3 patients previously exposed to CAR T cell therapy and 2/2 ADC. Preliminary biomarker data suggest that patients who respond to BFCR4350A have more pronounced T cell expansion in peripheral blood as well as higher levels of $CD8^+$ tumour-infiltrating T cells.[57]

Talquetamab

Talquetamab, is also known as JNJ-64407564, is a first-in-class BiAb that binds to both GPRC5D and CD3 inducing T cell-mediated cytotoxicity of $GPRC5D^+$ MM cells.[25,58] A phase I study included 137 patients receiving talquetamab, 102 by IV (0.5–180 µg/kg) and 35 by SC (5–800 µg/kg) dosing. Eligible patients had R/R MM. Median age was 64 years (33–80; 31% ≥70), and the median number of prior therapies was 6 (2–20). A total of 79% and 31% of patients were triple-refractory and penta-refractory, respectively. Prior BCMA-directed therapy was received by 21 (15%) patients. The incidence of CRS was 47%, mostly grade 1–2, except for 5 patients with grade 3 CRS (<8% of patients with CRS with the IV dosing). Neurotoxicity occurred in 7 (5%) patients; 4 had grade 1–2 and 3 had grade 3. Two DLTs were observed: grade 4 lipase elevation and grade 3 maculopapular rash. MTD has not yet been determined. At the most active doses of 20–180 µg/kg IV and 135–400 µg/kg SC, the ORR was 78% and 67%, respectively,

with a cohort ORR of 66% as presented in the update. Across the IV and SC cohorts, the median DoR was not reached. The RP2D was 405 µg/kg SC.

Many other BiAbs targeting not only BCMA but also CD38, CD16 and NKp30, amongst other targets,[59–62] are under development, which may help revert mechanisms of resistance in heavily pre-treated MM patients. Moreover, the best drug partners as well as how to sequence these new therapies and strategies for the selection of therapy based upon cytogenetic risk or disease presentation still need development.

A summary of BiAbs in MM is shown in Table 2. Novel bispecific antibodies are shown in Table 3.

Table 2. Summary of BiTE clinical trials presented.

Study agent	Median number of previous lines	Dosing	CRS	Responses
AMG 420 (*n*=42)	5 Dara refractory: 21% BCMA-T: NA	IV	38% Grade 2: *n*=2 Grade 3: *n*=1	ORR (at MTD): 70% CR: *n*=5 VGPR: *n*=1 PR: *n*=1
AMG 701 (*n*=75)	6 Triple-refractory: 68% BCMA-T: NA	IV	61% Grade 1: 25% (*n*=19) Grade 2: 28% (*n*=21) Grade 3: 7% (*n*=5)	ORR (3–12mg): 36% sCR: *n*=4 CR: *n*=1 VGPR: *n*=6 PR: *n*=6
PF-06863135 (*n*=35)	11 (IV) 7 (SC) BCMA-T: Allowed (*n*=9)	IV/SC	24% (IV) All grade 1–2 61% (SC) All grade 1–2	IV cohort MR: *n*=1 SD: *n*=6 DP: *n*=9 SC cohort sCR: *n*=2 VGPR: *n*=2 PR: *n*=2 SD: *n*=7
REGN5458 (*n*=45)	5 Triple-refractory: 6.7% Quad-refractory: 33.3% Penta-refractory: 53.3% BCMA-T: NA	IV	37.8% Grade 1: 88.2% No Gr >3	ORR: 35.6% ORR (EMP): 16.7% ≥ sCR/CR: 31.3% ≥ VGPR: 81.3%
Teclistamab (*n*=128)	6 Triple-refractory: 79% Penta-refractory: 38% BCMA-T: NA	IV/SC	55% (IV) All grade 1–2 50% (SC) All grade 1–2	ORR: 63.8% ≥ CR: 9 ≥ VGPR: 24
TNB-383B (*n*=38)	7 BCMA-T: NA	IV	21% (*n*=8) Grade 1: 13% (*n*=5) Grade 2: 8% (*n*=3)	ORR: 37% sCR/CR: 7.9% VGPR: 11% PR: 18% mDOR: 9 weeks
Cevostamab (*n*=51)	6 Triple-refractory: 66.7% BCMA-T: Allowed (*n*=3)	IV	74.5% Grade 1: 39.2% (*n*=20) Grade 2: 33.3% (*n*=17) Grade 3: 2.0% (*n*=1)	At ≥ 3.6/20 mg dose level ORR: 51.7% sCR: 10.3% CR: 10.3% VGPR: 13.8%
Talquetamab (*n*=137)	6 Triple-refractory: 79% Penta-refractory: 31% BCMA-T: Allowed (*n*=21)	IV/SC	47% Mostly grade 1–2 Grade 3 (only IV): *n*=5	Most active IV/SC doses ORR: 66% ORR (IV): 78% ORR (SC): 67%

BCMA-T, BCMA-targeted therapy; BiTE, bispecific T cell engager; CR, complete response; CRS, cytokine release syndrome; DP, disease progression; EMP, extramedullary plasmacytoma; IV, intravenous; mDOR, median duration of response; MTD, maximum tolerated dose; NA, not-allowed; ORR, overall response rate; PR, partial response; SC, subcutaneous; sCR, stringent CRs; SD, stable disease; VGPR, very good partial response.

Table 3. Agents in clinical development.[5]

Agent	Targets	Phase	Clinical trial number
AMG 420	BCMA×CD3	I	NCT02514239
AMG 701	BCMA×CD3	I/II	NCT03287908
CC-93269	BCMA×CD3	I	NCT03486067
PF-06863135	BCMA×CD3	I	NCT03269136
REGN5458	BCMA×CD3	I/II	NCT03761108
Teclistamab (JNJ-64007957)	BCMA×CD3	Ib I	NCT04108195 NCT03145181
TNB-383B	BCMA×CD3	I	NCT03933735
ISB 1342 (GBR 1342)	CD38×CD3	I/II	NCT03309111
AMG 424	CD38×CD3	I	NCT03445663
Talquetamab (JNJ-64407564)	GPRC5d×CD3	Ib I	NCT04108195 NCT03399799
Cevostamab (BFCR4350A)	FCRH5×CD3	I	NCT03275103

Conclusions

Current data on BiAbs show promising efficacy and tolerable AE profile in NHL and MM. The follow-up time is still short (between 3 and 10 months), and studies have just completed dose-escalation phases. Thus, longer follow-up studies with the RP2D are recommended. Given the treatment options available for NHL and MM, the right sequence of therapies for this condition remains unknown. The availability of CAR T cell therapy for MM and NHL makes the choice more complicated, especially because both have similar mechanisms of action and (very often) share the same antigen targeting. As mentioned earlier, there are several advantages of BiAbs over CAR T cell therapy, such as availability ('off the shelf' product), the lack of a requirement of a manufacturing process and perhaps lower cost. BiAbs also appear to have a better toxicity profile than CAR T cell therapy.

Other therapies are available for either DLBCL and FL, such as lenalidomide-tafasitamab, selinexor and Pi3K inhibitors. A cross-comparison of the activity of these therapies with BiAbs is essentially impossible given the different study designs, current status of the clinical trials and variability of the study populations. However, it appears that the clinical responses are better with BiAbs. For instance, the CR rate with lenalidomide and tafasitamab was 43% with about half of the patients having relapsed after one line of therapy and primary refractory cases not being included. With BiAbs, the CR rate ranged from 33% to 55% albeit in more heavily pretreated patients with higher risk features.[63]

Another aspect is the access to treatment. Currently, cell therapies for MM and NHL are available, almost exclusively in academic centres. Therefore, referral to tertiary centres will be needed, and patients may incur long distances to receive these therapies. Meanwhile, BiAbs have the potential to be administered in the community. However, BiAbs still have the potential of CRS and neurotoxicity risks (although with lower incidence and severity), and thus risks mitigation strategies and appropriate training will be needed for clinicians who will prescribe these therapies.

Further development of BiAbs is warranted, and longer follow-up of current clinical data is needed. Additionally, BiAbs have the potential to be combined with other agents that could improve the efficacy and durability of responses.

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