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## Emerging immune targets for the treatment of multiple myeloma

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We reviewed emerging immune strategies for multiple myeloma (MM) therapy excluding US FDA approved drugs. In relapsed refractory MM, isatuximab (anti-CD38) monotherapy achieved overall response (OR) of 24%. Other monoclonal antibodies that have shown efficacy in combination therapy include siltuximab (OR: 66%), indatuximab (OR: 78%), isatuximab (OR: 64.5%), pembrolizumab (OR: 60%), bevacizumab (OR: 70%), dacetuzumab (OR: 39%) and lorvotuzumab (OR: 56.4%). No OR was observed with monotherapy using BI-505, siltuximab, bevacizumab, AVE-1642, figitumumab, atacicept, milatuzumab, dacetuzumab, lucatumumab, IPH2101, lorvotuzumab, BT062 and nivolumab. We included seven clinical trials on chimeric antigen receptor (CAR) T cells. CAR T-cell targets include BCMA, CD19, KLC and CD138. A recent experience of CAR T-cell (B-cell maturation antigen) therapy in advanced MM has shown global response of 100%. The future of monoclonal antibodies and adoptive T cells for MM treatment seems promising.

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Multiple myeloma (MM) is characterized by malignant proliferation of plasma cells. It is the second most common hematologic malignancy and fourteenth leading cause of cancer deaths in the USA [1]. According to NIH cancer statistics, in 2017, there will be an estimated 30,280 new cases and 12,590 deaths due to MM [1]. Over the past one and a half decade, development of novel agents including proteasome inhibitors (PI) and immunomodulatory drugs (IMiDs) have improved disease outcome and overall survival (OS). According to survival data over 25 years, median survival of MM patients with International Staging System stages I and III has been reported 62 and 29 months, respectively [2]. Despite significant advancements in antimyeloma therapy, MM remains an incurable disease. Development of relapse and resistance is inevitable that signifies the need to develop newer treatment strategies [3]. Immunotherapy as a treatment modality for MM has the potential to be highly effective and targeted and is postulated to carry a favorable side effect profile. Various immunotherapeutic approaches are in use to treat malignant hematologic disorders including monoclonal antibodies (MoAbs), antibody–drug conjugate (ADC), bispecific antibodies and adoptive cell therapy (ACT).

Pathogenesis of MM is complex and involves heterogeneous cytogenetic abnormalities. The bone marrow microenvironment promotes cell growth and resistance to conventional therapies. Adhesion of MM cells to bone marrow stromal cells promotes proliferation of malignant cells, production of anti-apoptotic signals, angiogenesis, bone resorption and tissue invasion. Pathogenesis involves various growth factors, cytokines, surface receptors and intracellular signaling molecules [4]. Potential immunotherapy targets for MM are cell surface molecules including adhesion molecules and transmembrane receptors for intracellular signaling such as CS1, CD38, CD138, CD40, CD47, CD74, CD54, CD56, CD19, IGF-1R, kappa light chain and BCMA). Targets also include growth factors and their receptors like VEGF and BAFF. Other targets include IL-6 and immune checkpoint signaling pathways using programmed death (PD-1 axis) [5,6]. MoAbs exert their antitumor effects through several mechanisms. Antibody-dependent cellular cytotoxicity (ADCC) occurs when MoAb binds to tumor cells through



their hypervariable region and immune cells through the Fc region triggering cell death. Complement-dependent cytotoxicity is a mechanism in which therapeutic antibodies activate proteolytic enzymes ultimately resulting in the formation of terminal lytic complex that attacks tumor cell membrane [7]. Alternatively, MoAb can act as an agonist to trigger apoptosis. Therapeutic antibodies can act as antagonists on cell surface receptors to block downstream signaling involved in cell proliferation. In ADCs antibodies serve as carriers to deliver cytotoxic drugs specifically inside tumor cells to exert their maximum antitumor effects while preventing their systemic adverse effects [8]. Elotuzumab and daratumumab are already approved for the treatment of MM and are currently under evaluation in phase III trials.

Adoptive cell therapy involves modification of autologous T cells or NK cells to express chimeric antigen receptors (CARs) that bind specifically to antigens expressed on tumor cells. CAR-modified T cells (CAR T cells) targeting CD19 have been used in treatment of chronic lymphocytic leukemia and acute lymphoblastic leukemia, which stimulated interest in the extension of ACT for treatment of MM. An ideal target for CAR T-cell therapy would be one that is exclusively expressed on MM cells to avoid systemic toxicity while playing a central role in tumorigenicity to restrict antigen escape. Several strategies are under evaluation to minimize systemic toxicity from CAR T-cell therapy. The suicide gene strategy stimulates the death of CAR T cells in the event of any toxicity [9]. An alternative strategy utilizes co-inhibitory receptors that are only expressed on healthy tissues and not on tumor cells. In the event of toxicity these receptors would inhibit CAR T cell effect on healthy tissues [10]. Another strategy is to minimize trafficking of CAR T cells to non-tumor sites by genetically engineering CAR T cells to express specific chemokine receptors [10]. Our aim is to summarize the current state of knowledge on the efficacy of non-US FDA approved MoAbs, CAR T cells and their targets.

## Methods

The systematic review was designed in accordance with the principles set by the preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist.

### Search strategy

Databases searched for English language studies included PubMed, Cochrane, EMBASE, Web of Science and Clinicaltrials.gov. For clinicaltrials.gov, only completed studies or those actively recruiting were included. In addition to English language filter, only studies from last 10 years were included.

A sample search strategy is given below: “Multiple myeloma”[MeSH Terms] AND “recombinant fusion proteins”[MeSH Terms] AND (“2007/07/05”[PDat] : “2017/07/01”[PDat] AND English[lang]).

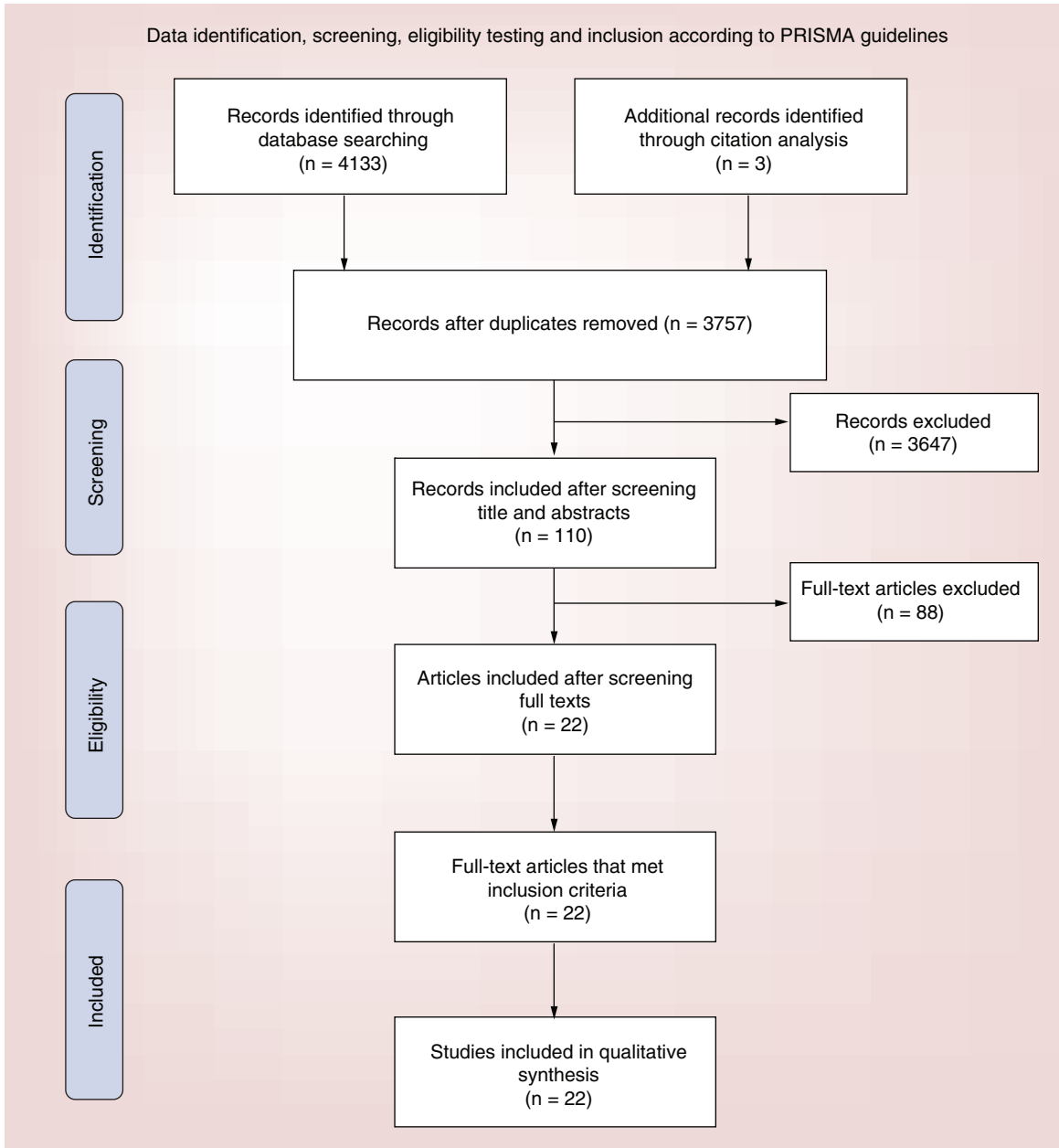
To avoid missing any potentially relevant studies, bibliographies of pertinent review articles were analyzed manually.

### Eligibility criteria

We included clinical trials on MoAb for treatment of MM that were complete or actively recruiting Phase I/II trials performed in the last 10 years with at least one efficacy outcome clearly described in both treatment and control arm (if any). We excluded studies on daratumumab and elotuzumab. We included clinical trials on CAR T cells that were Phase I/II clinical trials focusing on CAR T cells in relapsed and refractory MM (RRMM) with at least one efficacy outcome clearly described. We excluded studies in which no objective efficacy outcome was reported.

### Study selection & data extraction

Articles retrieved using aforementioned search strategy were imported to endnote. Articles were screened first based on title and abstract and then through full text by two independent reviewers. A standardized data extraction form was used to extract the fields: study, year, study design, number of patients, MoAb and its target, median number of prior lines of therapy, dose, number of cycles, regimen used, lymphodepletion therapy used before CAR T-cell infusion, targeted antigen and its location, outcome and adverse effects. Primary outcome was overall response (OR). Other outcomes were complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), progression-free survival (PFS) and OS. The toxicity data were analyzed for cytokine-release syndrome, common adverse effects and Grade  $\geq$ III adverse effects. Any conflicts during the process of study selection and data extraction were resolved with discussion and consensus.



**Figure 1. Records identified through PubMed, Embase, Cochrane, Web of Science, Scopus and ClinicalTrials.gov database searches.**

## Results

### Monoclonal antibodies

In total, we identified 4133 articles from the following resources: PubMed ( $n = 81$ ), Embase ( $n = 929$ ), Cochrane ( $n = 21$ ), SCOPUS ( $n = 2000$ ), Web of Science ( $n = 1481$ ) and clinicaltrials.gov ( $n = 47$ ). After excluding 379 duplicates, we first screened articles by reading titles and abstracts. Later, potentially relevant articles were screened through full texts (Figure 1). We excluded articles related to drugs that are already FDA approved as daratumumab or elotuzumab in RRMM. 22 clinical trials that met the inclusion criteria included a total of 1130 patients. Totally, 5 studies had control arms and 17 were single arm studies.

We evaluated following antibodies ( $n =$  number of studies): bevacizumab (anti-VEGF;  $n = 2$ ), dacetuzumab (anti-CD40;  $n = 2$ ), lucatumumab (anti-CD40;  $n = 1$ ), isatuximab (ISA) (anti-CD38;  $n = 3$ ), siltuximab (anti-IL-6;  $n = 3$ ), tabalumab (anti-BAFF;  $n = 2$ ), lorvotuzumab (anti-CD56;  $n = 2$ ), indatuximab (anti-CD138;  $n = 3$ ),

rituximab (anti-CD20; n = 1), nivolumab (anti-PD-1; n = 1), pembrolizumab (anti-PD-1; n = 1) and BI-505 (anti-ICAM-1; n = 1).

MoAb targets included ICAM-I (BI-505) = 1 study, IL-6 (siltuximab) = 5, VEGF (bevacizumab) = 4, GRP78 (PAT-SMX), CD40 (dacetuzumab, lucatumumab) = 4, CD138 (indatuximab) = 3, PD-1 (pembrolizumab, nivolumab, pidilizumab) = 3, CD20 (rituximab), CD38 (ISA), CD56 (lorvotuzumab) = 3, IGF-1R = 3, (AVE1642, figitumumab), BAFF (atacicept, tabalumab) = 3 and CD74 (milatuzumab) = 1 study.

### *Surface receptor-targeting antibodies*

#### *Anti-CD38 MoAb*

CD38 is a single chain transmembrane molecule that is expressed on cell surface and intracellular organelles of terminally differentiated B lymphocytes. It acts as a receptor to activate the proliferation of T cells via cytokine release and cell-to-cell adhesion and has a catalytic activity during synthesis of cyclic adenosine diphosphate ribose [5]. ISA is an anti-CD38 MoAb that produces its antitumor effects by ADCC, complement-dependent cytotoxicity or direct toxicity. Two trials with ISA as monotherapy by Martin *et al.* [11] and Richter *et al.* [12] have reported objective response rate (ORR) of 32 and 24% in patients with six and five prior lines of therapy, respectively. When ISA was used in combination with lenalidomide and dexamethasone (Dex), this combination produced an ORR of 65% in heavily pretreated RRMM patients with six prior lines of therapy [13]. With 10 mg/kg of ISA, no dose-limiting toxicity was reported. However, in Martin *et al.* study, grade III pneumonia, fever, hyperglycemia and hypophosphatemia were reported with higher dose of 20 mg/kg of ISA. After promising Phase I data, a randomized prospective multicenter Phase III trial (open-label study: NCT02990338; ICARIA-MM) to evaluate the clinical benefit of ISA in combination with pomalidomide (Pom) and low-dose Dex (ISA/Pom/Dex) versus Pom/Dex is ongoing [14,15]. Currently ISA is being tested in doses of 5, 10 or 20 mg/kg weekly for the first cycle and then every 2 weeks for subsequent cycles (Table 1).

#### *Anti-CD74 MoAb*

CD74 is a membrane-associated glycoprotein and is present in B cells, monocytes and myeloma cells. CD74 is important for MHC II trafficking and antigen loading. CD74 also has a particular importance because of its rapid internalization [25]. This property would help deliver cytotoxic agents inside the cells and a trial with anti-CD74 humanized MoAb milatuzumab combined with doxorubicin is evaluating the potential for its therapeutic target. In a Phase I multicenter clinical trial, 25 patients with advanced MM were treated with milatuzumab infusion that was given twice weekly for 4 weeks. Totally, 19 patients completed treatment. No OR was achieved but 5/19 patients had SD 3 months post-treatment, one patient had SD for 17 months, 20% patients experienced cytokine release syndrome (CRS) [16]. Current evidence supports the need for further testing of milatuzumab in combination chemotherapy trials (Table 1).

#### *Anti-IGF-1 receptor antibody*

IGF-1 receptor and binding proteins are involved in tumor survival, proliferation, angiogenesis and osteolysis and play a crucial part in the pathogenesis of MM. The increased expression of IGF-1 in MM cells correlates with poor outcome and resistance to standard treatment [26]. Anti-IGF-1 receptor MoAbs (AVE1642 and figitumumab) have been tested in Phase I trials as monotherapies versus in combination with Dex or bortezomib. When AVE1642 was used as monotherapy, no ORR was achieved. However, when AVE1642 was used in combination with bortezomib, this combination produced PR in 2 out of 11 patients [17]. Figitumumab in combination with Dex produced PR in 6 out of 27 patients [18]. Despite good safety profile, these responses are not considered clinically sufficient (Table 1).

#### *Antikiller-cell immunoglobulin-like receptor antibody*

Killer-cell immunoglobulin-like receptor (KIR) are transmembrane glycoproteins expressed on surface of NK cells. Most KIRs are inhibitory, in other words, they suppress cytotoxic activity of NK cells. IPH-2101 is an anti-KIR MoAb that augments antitumor activity of NK cells. However, this effect was limited when IPH-2101 was used as monotherapy in *in vivo* studies due to antibody-mediated hyporesponsiveness and contraction of NK cell subset [27]. As monotherapy, IPH2101 did not produce any objective response [20]. In a Phase I trial, IPH-2101 was used in combination with lenalidomide in 15 patients with RRMM. Dose ranging from 0.2–2 mg/kg was used on day 1 of 21–28 day cycle. An OR of 33.3% (n = 5) was achieved: two very good partial response (VGPR) and three PR. Six patients had stable disease (SD). This drug combination was well tolerated [19] but use of IPH-2101 in smoldering MM as monotherapy in a Phase I–II trial failed to produce any clinical response (Table 1) [28].

Table 1. Surface receptor-targeting antibodies in relapsed refractory multiple myeloma.

| Study (year) study design              | Number of patients | Antibody                   | Regimen   | Target | Median prior therapies | Dose                                       | Number of cycles | Outcome  | Ref. |
|--|--------------------|----------------------------|---|--------|------------------------|--|------------------|--|------|
| Vij <i>et al.</i> (2016) Phase II      | 97                 | Isatuximab SAR650984       | Isatuximab monotherapy                                | CD38   | 5 (2–14)               | 3–10 mg/kg                                 | NR               | OR = 24% at dose >10 mg/kg   | [12] |
| Martin <i>et al.</i> (2014) Phase Ib   | 31                 | Isatuximab SAR650984       | Isatuximab + Len + Dex                                | CD38   | 6 (2–12)               | 3, 5, 10 mg/kg                             | NR               | OR = 64.5%; CR = 76.8%; VGPR = 26%; PR = 32%; PFS = 6.2 m          | [13] |
| Martin <i>et al.</i> (2014) Phase I    | 35                 | Isatuximab (SAR650984)     | MoAb monotherapy                                      | CD38   | 6 (2–14)               | 0.1–20 mg/kg                               | 5–7              | OR = 32% (>10 mg); PR: n = 6; CR: n = 2                            | [11] |
| Kaufman <i>et al.</i> (2013) Phase I   | 25                 | Milatuzumab                | Monotherapy   | CD74   | 5                      | 1.5–16 mg/kg ×2 or 4 weeks                 | 8                | No OR; SD = 26% (5/19) >3 m; (1/19) >17 m                          | [16] |
| Moreau <i>et al.</i> (2011) Phase I    | 11                 | AVE1642                    | AVE1642 + bortezomib                                  | IGF-1  | 4                      | 0.5–12 mg/kg + 1.3 mg/m <sup>2</sup>       | 4                | CR: n = 1; PR: n = 1; SD: n = 3                                    | [17] |
|  | 15                 | AVE1642                    | AVE1642 monotherapy                                   | IGF-1  | 4                      | 3–18 mg/kg                                 | 2                | MR: n = 1; SD: n = 7; PD: n = 4                                    |      |
| Lacy <i>et al.</i> (2008) Phase I      | 47                 | Figitumumab (CP: 751, 871) | Figitumumab + Dex if no PR on figitumumab monotherapy | IGF-1  | 4 (0–8)                | 0.025–20 mg/kg for 4 weeks                 | 4                | No OR  | [18] |
|  | 27                 | Figitumumab (CP: 751, 871) | Figitumumab + Dex                                     | IGF-1  | 4 (0–8)                | 0.025–20 mg/kg for 4 weeks + 40 mg/day Dex |                  | PR: n = 6  |      |
| Benson <i>et al.</i> (2015) Phase I    | 15                 | IPH 2101                   | IPH 2101 + Len (10–25 mg)                             | KIR    | 1–2                    | 0.2–2 mg/kg                                | 4                | VGPR = 13%; PR = 20%; MR = 7%; SD = 40%; PD = 20%                  | [19] |
| Benson <i>et al.</i> (2012) Phase I    | 32                 | IPH 2101                   | Monotherapy   | KIR    | 2 (1–7)                | 0.0003–3 mg/kg every 28 days               | 4                | No OR; SD: n = 11 (34%)  | [20] |
| Agura <i>et al.</i> (2009) Phase Ib    | 36 (33 REP)        | Dacetuzumab                | Dacetuzumab + Len + Dex                               | CD40   | 4                      | 4–12 mg/kg                                 | 4                | OR = 39%; CR = 3%; PR = 33%; MR = 12%; SD = 30%; PD = 6%; NE = 12% | [21] |
| Hussein <i>et al.</i> (2010) Phase I   | 44                 | Dacetuzumab                | MoAb monotherapy                                      | CD40   | 5 (2–14)               | 4–12 mg/kg                                 | 4–5              | SD = 20%   | [22] |
| Bensinger <i>et al.</i> (2012) Phase I | 28                 | Lucatumumab                | MoAb monotherapy                                      | CD40   | NR                     | 1–6 mg/kg                                  | 4                | SD = 43%; PR = 4% >8 m   | [23] |
| Hansson <i>et al.</i> (2015) Phase I   | 35 (29 REP)        | BI-505                     | MoAb monotherapy                                      | ICAM-1 | 6                      | 0.0004–20 mg/kg                            | 1–2              | SD = 24% (2 m); PD = 65%   | [24] |

CR: Complete response; Dex: Dexamethasone; ICAM-1: Intercellular adhesion molecule-1; KIR: Killer-cell immunoglobulin like receptor; Len: Lenalidomide; m: Month; MoAb: Monoclonal antibody; MR: Minimal response; NE: Not evaluable; NR: Not reported; OR: Objective response; PD: Progressive disease; PFS: Progression-free survival; PR: Partial response; REP: Response evaluable patient; SD: Stable disease; VGPR: Very good partial response.

### Anti-CD40 MoAb

CD40 is a surface receptor of the TNF family and is expressed in B-cell malignancies including MM [29]. Dacetuzumab is the first anti-CD40 MoAb that was tested as monotherapy and in combination with lenalidomide and Dex. As monotherapy, it was tested in 44 RRMM patients with 5 prior lines of therapy with maximum tolerated dose of 12 mg/kg. No OR was achieved. Totally, 20% patients had SD [22]. When used in combination with lenalidomide and Dex in a population of 36 RRMM patients with four prior lines of therapy, dacetuzumab produced an OR of 39% [21].

Lucatumumab is also an anti-CD40 MoAb that has a dual mechanism of action. It blocks CD40-CD40L dependent tumor growth and induces cell lysis via ADCC [23]. Lucatumumab was tested as monotherapy in 28 RRMM patients with 3 prior lines of therapy. Only one patient achieved PR while 43% had SD (Table 1) [23].

### Anti-ICAM-1 (CD54) MoAb

ICAM-1 plays an important role in adhesion of myeloma cells to marrow stromal cells and helps in tumor proliferation. Overexpression of ICAM-1 has been associated with chemotherapy-resistant advanced disease [30]. BI-505 is fully humanized IgG1 MoAb that targets ICAM-1. In preclinical studies, BI-505 has shown potent

antimyeloma activity [31]. However, when tested as monotherapy in patients with RRMM (6 prior lines of therapy) and in smoldering MM patients, no OR was achieved (Table 1) [24,32].

### *Nonsurface target antibodies*

#### *Anti-IL-6 antibody*

IL-6 is a pleiotropic cytokine that plays a vital role in T- and B-cell immune responses. It is a potent mediator of inflammation, regulates hematopoiesis, and is involved in proliferation and differentiation of malignant plasma cells. Siltuximab is IL-6 blocking antibody that has already shown safety and efficacy in Castleman disease [33]. Preclinical studies of siltuximab showed significant anti-MM activity when used in combination of bortezomib and Dex [34,35].

For RRMM, there have been three trials with siltuximab by Orlowski *et al.*, Voorhees *et al.* and Suzuki *et al.* Orlowski *et al.* in a head-to-head comparison of siltuximab and bortezomib versus bortezomib alone found no statistically significant difference in ORR (55 vs 47%), median PFS (8 vs 7.6 months) and OS (30.8 vs 36.8 months), respectively. Their patient population had 1–3 prior lines of therapy [36]. Voorhees *et al.* compared activity of siltuximab alone versus siltuximab and Dex in patients with four prior lines of therapy and found no OR with siltuximab monotherapy. In combination with Dex, they reported an ORR of 23% [37]. Suzuki *et al.* studied siltuximab in combination with lenalidomide and Dex in nine RRMM patients with 1–2 prior lines of therapy. They reported CR of 22% and PR of 44% in their study [38].

For newly diagnosed MM, we summarized data from two trials by San-Miguel *et al.* and Shah *et al.* San-Miguel *et al.* performed head-to-head comparison of bortezomib, melphalan and prednisone (VMP) (n = 54) versus VMP + siltuximab (n = 52). The study did not reach the primary outcome that the addition of siltuximab to VMP regimen will increase CR by at least 10%. The CR for siltuximab + VMP and for VMP alone was 27 and 22%, respectively, without reported improvement in long-term outcomes [39]. Shah *et al.* studied siltuximab + RVd (lenalidomide, bortezomib and dexamethasone) in 11 newly diagnosed MM patients and reported an impressive ORR of 91% (Table 2) [40].

#### *BAFF*

BAFF and a proliferation inducing ligand (APRIL) are members of the TNF- $\alpha$  family. In MM patients, BAFF, APRIL, TNF- $\alpha$  and their receptors are present in higher concentrations [54] and their levels provide statistically significant correlation with disease activity [55]. These factors activate NF- $\kappa$  phosphatidylinositol-3 kinase and protect MM cells from Dex-induced apoptosis [54]. Two anti-BAFF MoAb, atacicept and tabalumab have been tested. Atacicept blocks both BAFF (soluble form) and APRIL [43]. Tabalumab blocks BAFF (both membrane bound and soluble forms). Rossi *et al.* studied atacicept monotherapy in 12 RRMM with no OR reported [43]. For tabalumab, we summarized data from two trials each testing tabalumab in combination with bortezomib and Dex. Shinsuke *et al.* reported an OR of 57% with tabalumab plus bortezomib and dexamethasone (Vd) in RRMM patients with 1–5 prior lines of therapy. Raje *et al.* found no significant difference in PFS and OR between tabalumab 100 mg, tabalumab 300 mg and placebo, each tested in combination with Vd. ORRs were 58.1, 59.5 and 61.1% with tabalumab 100 mg plus Vd, tabalumab 300 mg plus Vd and placebo plus Vd, respectively [41]. Patients with low BAFF levels had comparatively longer PFS so BAFF may play a role as a prognostic marker in RRMM patients (Table 2) [41].

#### *Vascular endothelial growth factor*

Bevacizumab, a MoAb, blocks angiogenic and proliferative effects of VEGF by binding with soluble VEGF [56]. We summarized data from three trials with bevacizumab in RRMM patients. Callander *et al.* studied bevacizumab in combination with lenalidomide and Dex in 31 RRMM patients with median 3 prior lines of therapy and reported an OR of 70% [57]. However, the outcome was not superior to lenalidomide and Dex without bevacizumab (OR of 60%) [58]. In a head-to-head comparison of bevacizumab (n = 6) versus bevacizumab  $\pm$  thalidomide (n = 6) in patients who had median three prior lines of therapy, Somlo *et al.* reported no OR with bevacizumab monotherapy. A PR of 33% was reported with bevacizumab  $\pm$  thalidomide [45]. White *et al.* in a head-to-head comparison of bevacizumab plus bortezomib (n = 49) versus bortezomib plus placebo (n = 53) in RRMM patients who had 1–3 prior lines of therapy, found no statistically significant difference in ORR (51 vs 43.3%) (Table 2) [44].



Table 2. Nonsurface receptor antibodies in relapsed refractory multiple myeloma.

| Study (year) study design                | Number of patients | Antibody                     | Target | Median prior therapies | Dose                           | Number of cycles | Regimen   | Outcome   | Ref. |
|--|--------------------|------------------------------|--------|------------------------|--------------------------------|------------------|---|---|------|
| Suzuki <i>et al.</i> (2015) Phase I      | 9                  | Siltuximab                   | IL-6   | 1–2                    | 5.5/11 mg/kg                   | ≥9               | Siltuximab + Bor (1.3 mg/m <sup>2</sup> ) + Dex (20 mg) | CR = 22%; PR = 44%  | [38] |
| Orlowski <i>et al.</i> (2015) Phase II   | 142                | Siltuximab + Bor             | IL-6   | 1–3                    | Siltuximab 6 mg/kg             | 4                | MoAb + Bor  | mPFS = 8 m; ORR = 55%; CR = 11%; OS = 30.8 m                  | [36] |
|  | 139                | Bor + placebo                |        |                        |                                |                  | Placebo + Bor   | mPFS = 7.6; ORR = 47%; CR = 7%; OS = 36.8 m                   |      |
| Voorhees <i>et al.</i> (2009) Phase II   | 14                 | Siltuximab                   | IL-6   | 4                      | 6 mg/kg                        | 4                | MoAb monotherapy  | No response (CR/PR); SD = 62%; PD = 39%                       | [37] |
|  | 39                 | Siltuximab + Dex             |        |                        | 6 mg/kg + 40 g                 |                  | Siltuximab + Dex  | ORR = 23%; PR = 17%; MR = 6%; SD = 57%; PD = 17%; PFS = 3.7 m |      |
| Raje <i>et al.</i> (2017) Phase II       | 74                 | Tabalumab                    | BAFF   | 1–3                    | 100 mg                         | 8 or 10          | Tab + Bor + Dex   | ORR = 58.1%   | [41] |
|  | 74                 | Tabalumab                    |        |                        | 300 mg                         |                  | Tab + Bor + Dex   | ORR = 59.5%   |      |
|  | 72                 | Placebo                      |        |                        | No MoAb                        |                  | Placebo + Bor + Dex                                     | ORR = 61.6%   |      |
| Iida <i>et al.</i> (2016) Phase I        | 16                 | Tabalumab                    | BAFF   | 1–5                    | 100–300 mg                     | ≥9               | Tab + Bor (1.3 mg/m <sup>2</sup> ) + Dex (20 mg/day)    | ORR = 56.3%; CR = 0%; VGPR = 18.8%; SD = 1.3%; PD = 18.8%     | [42] |
| Rossi <i>et al.</i> (2009) Phase I       | 12 (11 REP)        | Atacicept                    | BAFF   | NR                     | 2–10 mg/kg                     | 5                | MoAb monotherapy  | No ORR; PD = 54%; SD = 45%                                    | [43] |
| White <i>et al.</i> (2013) Phase II      | 49                 | Bevacizumab + Bor            | VEGF   | 1–3                    | Bevacizumab 15 mg/kg iv.       | 8                | MoAb + Bor  | ORR = 51%; PR = 16.3%; mPFS = 6.2 m                           | [44] |
|  | 53                 | Bor + placebo                |        |                        | Bor 1.3 mg/m <sup>2</sup>      |                  | Placebo + Bor   | ORR = 43.4%; PR = 7.5%; mPFS = 5.1 m                          |      |
| Somlo <i>et al.</i> (2011) Phase II      | 6                  | Bevacizumab                  | VEGF-A | 3 (0–5)                | Bevacizumab 10 mg/kg           | 4                | Monotherapy   | PD = 29–69 days; SD = 238 days; SD = 16.6%; PD = 83%          | [45] |
|  | 6                  | Bevacizumab ± thalidomide    | VEGF-A |                        |                                | 4                | Bevacizumab ± thalidomide                               | SD = 37–350 days; PR = 33%; PD = 67%                          |      |
| Badros <i>et al.</i> (2017) Phase II     | 48                 | Pembrolizumab                | PD-1   | 3 (2–5)                | 200 mg iv. ×2 wk               | 28               | Pem + Pom + Dex   | mPFS = 17.4 m; OR = 60%; VGPR = 19%; PR = 33%                 | [46] |
| Lesokhin <i>et al.</i> (2016) Phase Ib   | 27                 | Nivolumab                    | PD-1   | 3 (1–12)               | 1–3 mg/kg ×2 wk                | NR               | MoAb monotherapy  | mPFS = 10 wk; OR = 4%; SD = 63%; CR = 4%                      | [47] |
| Efebera <i>et al.</i> (2015) Phase I/II  | 12                 | Pidilizumab                  | PD-1   | 2 (2–11)               | 1.5–6 mg/kg every 28 days      | NR               | Pidilizumab + Len (15–25 mg)                            | VGPR: n = 3; PR: n = 1  | [48] |
| Berdeja <i>et al.</i> (2012), Phase I    | 44 (39 REP)        | Lorvotuzumab mertansine      | CD56   | 2 (1–11)               | 75–112 mg/m <sup>2</sup>       | NR               | LM + Len (20 mg) + Dex (40 mg)                          | ORR = 59%; sCR: n = 1; CR: n = 1; VGPR: n = 8; PR: n = 9      | [49] |
| Chanan <i>et al.</i> (2010) Phase I      | 37                 | Lorvotuzumab mertansine      | CD56   | 6                      | 40–140 mg/m <sup>2</sup> ×1 wk | NR               | Monotherapy   | SD = 41%  | [50] |
| Kelly <i>et al.</i> (2016) Phase I/IIa   | 47 (43 REP)        | Indatuximab ravtansine (ADC) | CD138  | 1–6                    | 80–100 mg/m <sup>2</sup>       | NR               | Indatuximab + Dex + Len                                 | ORR = 78%; PR = 33/47; mPFS 16.4 m                            | [51] |
|  | 17                 |                              |        | >2                     |                                | NR               | Indatuximab + Dex + pomalidomide                        | ORR = 79%; VGPR = 4; PR = 7                                   |      |
| Kelly <i>et al.</i> (2014) Phase I/IIa   | 45 (36 REP)        | Indatuximab ravtansine (ADC) | CD138  | 3                      | 80, 100, 120 mg/m <sup>2</sup> | NR               | Indatuximab + Len + Dex                                 | ORR = 78%; sCR = 1; CR = 2; VGPR = 10; PR = 15; SD = 2        | [52] |
| Heffner <i>et al.</i> (2012) Phase I/IIa | 29 (23 REP)        | Indatuximab ravtansine (ADC) | CD138  | 2 (1–11)               | 40–160 mg/m <sup>2</sup>       | NR               | Monotherapy   | PR = 1; SD = 11; mPFS = 112 days (90–245)                     | [53] |

ADC: Antibody drug conjugate; BAFF: B-cell activating factor; Bor: Bortezomib; CR: Complete response; Dex: dexamethasone; Len: Lenalidomide; LM: Lorvotuzumab mertansine; m: month; MoAb: Monoclonal antibody; mPFS: Median progression free survival; MR: Minimal response; NE: Not evaluable; NR: Not reported; OR: overall response; ORR: Objective response rate; OS: Overall survival; PD: Progressive disease; Pem: Pembrolizumab; Pom: Pomalidomide; PR: Partial response; REP: Response evaluable patient; sCR: Stringent complete response; SD: Stable disease; Tab: Tabalumab; VEGF: Vascular endothelial growth factor; VGPR: Very good partial response; wk: Week.

### *Immune checkpoint inhibitors*

PD-1/PD-L1 PD-1 axis is involved in regulating T-cell activation and their apoptotic pathways. PD-1 is expressed on T-cell surface and its ligand PD-L1 on tumor cells. Their interaction inhibits T-cell proliferation. MoAb against PD-1/PD-L1 disinhibit T-cell proliferation and blocks immune escape by tumor cells [59]. We summarized results from three studies with anti-PD-1 MoAb (nivolumab, pembrolizumab and pidilizumab) in RRMM patients. Lesokhin *et al.* studied nivolumab in 27 RRMM patients with median three prior lines of therapy. Only one patient achieved OR [47]. Badros *et al.* studied pembrolizumab in combination with Pom and Dex in 48 RRMM patients with median three prior lines of therapy. Objective response was seen in 29/48 (60%) patients: 4 stringent CR (sCR), 9 VGPR and 16 PR. Median PFS of 17.4 months was seen [46]. Efebera *et al.* studied pidilizumab and lenalidomide in 12 RRMM patients with median two prior lines of therapy. One patient achieved PR and three achieved VGPR [48]. Kelly *et al.* showed pretreatment with oncolytic virus reolysin, through IFN $\gamma$ /JAK/STAT axis, primarily regulated induction of PD-L1, induction of PD-L2 expression and improved anti-PD-L1 therapy in murine model (Table 2) [60].

### **Antibody–drug conjugate**

#### *CD56*

CD56 is a cell surface glycoprotein, first in line ADC. It is also called neuronal cell adhesion molecule as it is highly expressed on neuronal cells, NK cells and cytotoxic T cells [61,62]. CD56 expression is absent on benign B cells and can be present on more than 70% myeloma cells [50]. Lorvotuzumab is an anti-CD56 antibody that is conjugated with a maytansinoid cytotoxic agent called DM-1. We summarized results from two studies on lorvotuzumab in RRMM patients. Chanan-Khan *et al.* studied lorvotuzumab mertinase as monotherapy in 37 heavily pretreated RRMM patients with 6 prior lines of therapy and no OR was reported in their study. Berdeja *et al.* studied lorvotuzumab mertinase in combination with lenalidomide and Dex in 44 RRMM patients with median 2 prior lines of therapy. An ORR of 58%, 1 sCR, 1 CR and 8 VGPR were noted among 32/44 response evaluable patients (Table 2). The most common adverse effect noted was peripheral neuropathy. The spectrum of its toxicity can be explained by the distribution of CD56 on normal neuronal and NK cells [49].

#### *CD138*

CD138 is expressed on malignant cells in hematologic malignancies and solid tumors and is important for cell-to-cell adhesion as it acts as a co-receptor for MM growth factors [63]. In heavily pretreated patients, it is an important and reliable marker. Indatuximab ravtansine (IR, BT-062) is an immune conjugate of anti-CD138 chimerized MoAb and cytotoxic maytansinoid DM4. When BT062 binds to CD138, it is internalized and releases cytotoxic DM4, an antimicrotubule agent leading to death of MM cells. We summarized results from three studies on this ADC in RRMM patients. Heffner *et al.* studied IR as monotherapy in 29 RRMM patients, one patient achieved OR [53]. Kelly *et al.* studied this ADC in combination with lenalidomide and Dex in 64 RRMM patients with 3 median prior lines of therapy and reported an OR of 78% [52]. Kelly *et al.* in a head-to-head comparison of IR + lenalidomide and dexamethasone (Rd) versus IR + Pom and Dex found no significant difference in OR (78 vs 79%) (Table 2) [51].

### **CAR T-cell targets**

Our literature search identified a total of 287 articles on CAR T cells: PubMed: 46, Cochrane: 5, EMBASE: 105, Scopus: 42 and Web of Science: 89. After detailed scrutiny, we included six studies while manual citation analysis retrieved one additional study. A total of 7 studies with 86 RRMM patients were included in our review of CAR T-cells target therapy. Targeted antigens included BCMA (n = 4 studies), CD138 (n = 1), CD19 (n = 1) and kappa light chain (n = 1) (Table 3).

#### *B-cell maturation antigen*

BCMA receptor, a member of TNF family, helps B cells to differentiate into plasma cells and is highly expressed on malignant plasma cells and some B cells. It is not expressed on hematopoietic stem cells and nonhematopoietic tissues [71]. To date, 62 patients in 4 different trials received BCMA CAR T dose ranging from  $3 \times 10^6$  to  $5 \times 10^8$ . A maximum ORR of 100% was reported in one study [65]. Among other adverse effects, CRS was a major concern with use of BCMA CAR T cells, and preliminary results are very encouraging about its efficacy.



Table 3. Chimeric antigen receptor T cells in multiple myeloma.

| Author (year) study design               | Number of patients | Median number of prior therapy lines | Lympho-depletion therapy | CAR T-cell type                 | Intracellular domain | CARTs dose  | Targeted antigen, location                                       | Outcome  | Cytokine-release syndrome   | Other adverse effects   | Ref. |
|--|--------------------|--------------------------------------|--------------------------|---------------------------------|----------------------|---|--|--|---|---|------|
| Ali <i>et al.</i> (2016) Phase I         | 12                 | 7                                    | CF                       | CAR-BCMA                        | CD28<br>ICD-CD3zeta  | $0.3-9 \times 10^6/\text{kg}$                                   | BCMA, normal plasma cells, malignant plasma cells, some B cells  | $0.3 \times 10^6 = 1$ PR (2 wk), 2 SD (6 wk)<br>$1 \times 10^6 = 3$ SD (2-12 wk)<br>$3 \times 10^6 = 1$ VGPR (8 wk), 3 SD (2-8 wk)<br>$9 \times 10^6 = 1$ sCR (17 wk), 1 VGPR (26+ wk)             | $1 \times 10^6 =$ mild (2 pt)<br>$3 \times 10^6 =$ mild (3 pt)<br>Severe (1 pt)<br>$9 \times 10^6 =$ severe (2 pt) (required tocilizumab) | Anemia, neutropenia, nausea, hypocalcemia, hypophosphatemia   | [64] |
| Fan <i>et al.</i> (2017) Phase I         | 35 (19 REP)        | Not specified                        | Not reported             | LCAR-B38M                       | NS                   | $0.6-7 \times 10^6/\text{kg}$                                   | As above   | ORR: 100%<br>14 sCR (8 wk)<br>1 PR (8 wk)<br>4 VGPR (8 wk)   | Overall 74%<br>9 Grade I<br>2 Grade II<br>1 Grade III<br>1 Grade IV   | Anemia<br>fever<br>dyspnea  | [65] |
| Cohen <i>et al.</i> (2016) Phase I       | 6                  | 9                                    | Not reported             | CAR-BCMA                        | 4-1BB<br>ICD-CD3zeta | $1-5 \times 10^8/\text{pt}$                                     | As above   | $1.8 \times 10^8 = 1$ PD<br>$2 \times 10^8 = 1$ VGPR (5 m)<br>1 sCR (7+ m)<br>$5 \times 10^8 = 1$ MR (1+ m)<br>1 MR (2 m)<br>1 SD (2 m)  | 83%<br>2 Grade I<br>1 Grade II<br>2 Grade III (required tocilizumab)  | Anemia, neutropenia, pleural effusion (16%), hypocalcemia (33%), hypophosphatemia (50%)<br>PRES: 1 Grade IV | [66] |
| Berdeja <i>et al.</i> (2016) Phase I     | 9                  | 6                                    | CF                       | bb2121 anti-BCMA<br>CAR T cells | 4-1BB<br>ICD-CD3zeta | $5-45 \times 10^7$ cells  | As above   | $5 \times 10^7 = 1$ PR (2.9 m)<br>1 SD (2.1 m)<br>1 PD (2 m)<br>$15 \times 10^7 = 1$ sCR (6.4 m)<br>1 sCR (4.8 m)<br>1 VGPR (4.4 m)<br>$45 \times 10^7 = 1$ PR (3 m)<br>1 SD (2.5 m)<br>1 PR (1 m) | 67% Grade I/II  | Neutropenia (89%), leukopenia (67%), anemia (44%)   | [67] |
| Guo <i>et al.</i> (2015) Phase I         | 5                  | 5-8                                  | PCD, CP, VAD             | CART-138                        | CD28<br>ICD-CD3zeta  | 0.44-<br>$1.51 \times 10^7/\text{kg}$                           | CD 138 (syndecan 1), neoplastic and Non-neoplastic plasma cells  | 4 SD (3-7 m)<br>1 PD   | Not reported  | 4 Grade III<br>fever  | [68] |
| Ramos <i>et al.</i> (2016) Phase I       | 7                  | $\geq 1$ (2-8)                       | C                        | Kappa-CAR T cells               | CD28<br>ICD-CD3zeta  | $0.2-2 \times 10^8/\text{m}^2$                                  | Kappa light chain, mature B cells                                | 4 SD<br>3 Not reported   | None  | Grade III<br>lymphopenia  | [69] |
| Garfall <i>et al.</i> (2016) Pilot study | 12                 | 6                                    | Not reported             | CTL019 cells                    | 4-1BB<br>ICD-CD3zeta | $1-5 \times 10^7$ cells<br>Additional therapy: ASCT + Melphalan | CD-19. Rarely on MM Plasma cells and cancer stem cell population | Median PFS = 6 m<br>1 CR<br>6 VGPR (3.2 m)<br>2 PD (3.2 m)<br>2 PR (3.2 m)   | 1 Grade I   | Grade 3<br>GVHD: n = 1;<br>Grade 3 oral mucositis: n = 1  | [70] |

ASCT: Autologous stem cell transplantation; BCMA: B-cell maturation antigen; C: Cyclophosphamide; CART: Chimeric antigen receptor modified T cell; CF: Cyclophosphamide, fludarabine; CP: Carboplatin, paclitaxel; CR: Complete response; GVHD: Graft versus host disease; m: Month; MM: Multiple myeloma; MR: Minimal response; ORR: Overall response rate; PCD: Bortezomib, cyclophosphamide, dexamethasone; PD: Progressive disease; PFS: Progression-free survival; PR: Partial response; PRES: Posterior reversible encephalopathy syndrome; pt: Patient; REP: Response evaluable patient; sCR: Stringent complete response; SD: Stable disease; VAD: Vincristine, doxorubicin, dexamethasone; VGPR: Very good partial response; wk: Week.

**Table 4. Monoclonal antibodies in newly diagnosed multiple myeloma.**

| Author (year) study design               | Number of patients | Antibody       | Target | Dose                  | Number of cycles | Regimen          | Outcome  | Ref. |
|--|--------------------|----------------|--------|-----------------------|------------------|------------------|--|------|
| San-Miguel <i>et al.</i> (2014) Phase II | 54                 | Placebo        | IL-6   | 11 mg/kg siltuximab   | 9                | VMP              | ORR = 80%,<br>CR = 22%,<br>PR = 57%,<br>VGPR = 51%,<br>MR = 8%,<br>PD = 0% | [39] |
|  | 52                 | Siltuximab     |        |                       |                  | Siltuximab + VMP | ORR = 88%,<br>CR = 27%,<br>PR = 61%,<br>VGPR = 71%,<br>MR = 2%,<br>PD = 0% |      |
| Shah <i>et al.</i> (2016) Phase I/II     | 11 (9 REP)         | Siltuximab     | IL-6   | 8.3–11 mg/kg          | 4                | Siltuximab + RVD | ORR = 90.9%,<br>CR = 9.1%,<br>VGPR = 45.5%,<br>PR = 36.45                  | [40] |
| Baz <i>et al.</i> (2007) Phase II        | 45                 | Rituximab + MP | CD20   | 375 mg/m <sup>2</sup> | 3                | Rituximab + MP   | CR = 0,<br>PR = 58%,<br>MR = 13%,<br>SD = 18%,<br>PD = 11%                 | [75] |

CR: Complete response; MR: Minimal response; MP: Melphalan, prednisone; ORR: Objective response rate; PD: Progressive disease; PR: Partial response; REP: Response evaluable patient; RVD: Lenalidomide, bortezomib, dexamethasone; VGPR: Very good partial response; VMP: Bortezomib, melphalan and prednisone.

In a Phase I dose escalation trial, 12 patients with RRMM received second-generation BCMA-CAR T cells with CD28 ICD-CD3 zeta intracellular domain. Among two patients who received maximum dose of  $9 \times 10^6$  CAR T cells, one had stringent CR (sCR) for 17 weeks and other had an ongoing VGPR. The clinical response was lower in patients treated with lower doses of BCMA-CAR T cells. The main toxicity concern was CRS, and prolonged cytopenia in patients treated with higher doses [64]. In another Phase I trial, six patients received split doses of BCMA-CAR T cells. Patients were divided in three cohorts and two cohorts among them also received cyclophosphamide (CTX) as preconditioning or lymphodepletion therapy. One patient had Posterior Reversible Encephalopathy Syndrome treated with anti-epileptics, methylprednisolone and CTX. Totally, 5 patients (83%) had CRS and 2 of them required treatment with IL-6 blockage (tocilizumab). One patient who received  $2 \times 10^8$  CAR T cells had ongoing sCR for 7 months and one patient achieved VGPR at 5 months. In terms of disease-related challenges, evidence of antigen escape was noted by loss of BCMA expression [66]. Garfall *et al.* have also reported a case of steroid refractory PRES when the patient received  $2 \times 10^8$  41BB-CD3 zeta CART BCMA cells. She developed fever and altered mental status and steroids showed no benefit. She received CTX and showed symptomatic improvement [72].

In another Phase I trial, LCAR-B38M CAR T cells were infused in 19 patients with RRMM. Totally, 100% ORR was achieved. A total of 18 out of 19 patients had CR for a 6-month follow up period. A total of 14 out of 19 patients experienced CRS including one case each of Grades III and IV CRS [65]. Bb2121 is a CAR T cell construct with 41BB co-stimulatory motif. In a Phase I trial, nine patients with RRMM were given these CAR T cells after lymphodepletion with CTX and fludarabine. Three patients who were treated with  $5 \times 10^7$  CAR T cells achieved PR (1) and SD (2). Two out of three patients on  $15 \times 10^7$  CAR T-cells dose had sCR for 21+ and 18+ months. In addition to CRS in 67% patients, 89% had neutropenia, 67% had leukopenia and 44% had anemia (Table 3) [67].

### CD19

CD19 is expressed in a minor subset of drug-resistant MM as well as on precursor myeloma cells. Elimination of CD19 expressing cells can prevent MM recurrence [73]. The use of CD19-targeting CAR T cells in conjunction with standard of care therapy for MM has shown clinical benefit. Garfall *et al.* reported a patient who previously had MM refractory to melphalan and autologous stem cell transplantation (ASCT). Patient was again treated with melphalan and second ASCT followed by  $5 \times 10^7$  CTL019 CAR T cells, which were infused 12 days after transplant. Patient maintained CR and no progression was detected for 12 months after treatment [74]. In another Phase I trial, 10 out of 12 patients received up to  $5 \times 10^7$  CD19-directed CAR T cells after melphalan and ASCT.

Table 5. Adverse effects of antibody drugs.

| Author (year) study design              | Antibody                   | Adverse effects ≥ Grade III   | Common adverse effects  | Ref. |
|---|----------------------------|---|---|------|
| Hansson <i>et al.</i> (2015) Phase I    | BI-505                     | Headache (n = 4), pyrexia (n = 3), infusion-related reactions (n = 1), fluid overload (n = 1), T-wave inversion (n = 1) | Fatigue (47%), pyrexia (32%), headache (32%), nausea (29%), chills (24%)  | [24] |
| Callander <i>et al.</i> (2009) Abstract | Bevacizumab                | DVT (n = 3), SOB (n = 2), atrial fibrillation (n = 3)   | Fatigue   | [57] |
| Somlo <i>et al.</i> (2011) Phase II     | Bevacizumab                | Fatigue (16.6%), HTN (16.6%), neutropenia (16.6%), hyponatremia (16.6%)   | Not reported  | [45] |
|   | Bevacizumab ± thalidomide  | Lymphopenia (16.6%), fatigue (16.6%), pulmonary HTN (16.6%)   |   |      |
| White <i>et al.</i> (2013) Phase II     | Bevacizumab + bortezomib   | Thrombocytopenia (28%), neutropenia (18%)   | Anemia, diarrhea, fatigue, URTI, neuralgia  | [44] |
|   | Bortezomib + placebo       | Thrombocytopenia (30%), diarrhea (10%)  | Anemia, diarrhea, fatigue, URTI, neuralgia  |      |
| Rasche (2015) Phase I                   | PAT-SM6                    | Neutropenia (8.3%), back pain (8.3%), bile duct stone (8.3%)  | Neutropenia (50), leukopenia (67)   | [76] |
| Orlowski <i>et al.</i> (2015) Phase II  | Siltuximab + bortezomib    | Neutropenia (49%), thrombocytopenia (48%)   | Infections (62%), sensory neuropathy (49%)  | [36] |
|   | Bortezomib + placebo       | Neutropenia (24%), thrombocytopenia (34%)   | Infections (49%), sensory neuropathy (51%)  |      |
| Agura <i>et al.</i> (2009) Phase Ib     | Dacetuzumab                | Herpes zoster, renal failure  | Infusion reactions, Grade I/II, fatigue (47%), neutropenia (28%), thrombocytopenia (25%), diarrhea (22%), constipation (19%), headache (19%)        | [21] |
| Hussein <i>et al.</i> (2010) Phase I    | Dacetuzumab                | Total Grade III AE = 30%, thrombocytopenia (7%), aseptic meningitis (5%), renal failure (5%)                            | Fatigue (57%), headache (43%), nausea (23%), anemia (21%). Elevated LFTs (41%), anorexia, back pain, constipation, diarrhea, ocular hyperemia (21%) | [22] |
| Bensinger <i>et al.</i> (2012) Phase I  | Lucatumumab                | Thrombocytopenia (4%), increased LFTs (4%), increased lipase (4%)   | Infusion reactions, anemia (7%), hypercalcemia (7%), pyrexia (7%)   | [23] |
| Martin <i>et al.</i> (2014) Phase I     | Isatuximab (SAR650984)     | Pneumonia, fever, hyperglycemia, hypophosphatemia   | Pneumonia (9%), fever (3%), apnea (3%), fatigue (3%), hyperglycemia (3%)  | [11] |
| Martin <i>et al.</i> (2014) Phase Ib    | Isatuximab SAR650984       | No DLT reported, IAR (6%)   | Fatigue (41.9%), nausea (38.7%), URTI (38.7%), diarrhea (35.5%)   | [13] |
| Richter <i>et al.</i> (2016) Phase II   | Isatuximab SAR650984       | Not reported  | Nausea (33%), fatigue (30%), dyspnea (26%), infusion related (49%)  | [12] |
| Voorhees <i>et al.</i> (2009) Phase II  | Siltuximab                 | Thrombocytopenia, anemia, neutropenia, abnormal LFTs, fatigue   | Diarrhea (29%), nausea (22%), constipation (20%), fatigue (43%), peripheral edema (29%)   | [37] |
|   | Siltuximab + dexamethasone |   |   |      |
| Suzuki <i>et al.</i> (2015) Phase I     | Siltuximab                 | No DLT, lymphopenia (89%), neutropenia (44%)  | Abnormal LFTs (44%), rash (44%), hyperlipidemia (44%)   | [38] |
| Rossi <i>et al.</i> (2009) Phase I      | Atacept                    | Neuropathy, epiploic appendicitis.  | Infections, bone pains  | [43] |
| Iida <i>et al.</i> (2016) Phase I       | Tabalumab                  | Febrile neutropenia, tumor lysis syndrome, Ileus  | Thrombocytopenia (81.3%), lymphopenia (43.8%), increased alanine aminotransferase (43.8%)   | [77] |
| Raje <i>et al.</i> (2017) Phase II      | Tabalumab                  | Thrombocytopenia (12.8%), pneumonia (9.1%)  | Thrombocytopenia (37%), fatigue (37%), diarrhea (35%), constipation (32%)   | [41] |
|   | Placebo                    |   |   |      |
| Lesokhin <i>et al.</i> (2016) Phase Ib  | Nivolumab                  | Pneumonitis (4%), myositis (4%), raised CPK (4%)  | Seen in 52% patients  | [47] |
| Badros <i>et al.</i> (2017) Phase II    | Pembrolizumab              | Hematologic (40%), hyperglycemia (25%), pneumonia (15%)   | Pancytopenia (13%), hypothyroidism (10%)  | [46] |
| Efebera <i>et al.</i> (2015) Phase I/II | Pidilizumab                | Anemia 25%, neutropenia 23%, thrombocytopenia 34%   | Fatigue (50%), anorexia (17%), hypophosphatemia (17%)   | [48] |

ADC: Antibody drug conjugate; AE: Adverse event; CRS: Cytokine release syndrome; DLT: Dose-limiting toxicity; DVT: Deep venous thrombosis; GI: Gastrointestinal; HTN: Hypertension; IAR: Infusion-associated reaction; IRR: Infusion-related reaction; LFT: Liver function test; m: Month; MP: Melphalan, prednisone; PFS: Progression-free survival; SOB: Shortness of breath; URTI: Upper respiratory tract infection; VMP: Bortezomib, melphalan and prednisone.

Table 5. Adverse effects of antibody drugs (cont.).

| Author (year) study design               | Antibody                     | Adverse effects $\geq$ Grade III  | Common adverse effects   | Ref. |
|--|------------------------------|---|--|------|
| Chanan-Khan <i>et al.</i> (2010) Phase I | Lorvotuzumab mertansine      | Peripheral neuropathy, fatigue, acute renal failure   | Fatigue, peripheral neuropathy, headache, raised AST   | [50] |
| Berdeja (2012) Phase I                   | Lorvotuzumab mertansine      | Peripheral neuropathy, neutropenia (n = 1), hyperuricemia tumor lysis syndrome (n = 2)        | Peripheral neuropathy (42%)  | [49] |
| Heffner <i>et al.</i> (2012) Phase I/IIa | Indatuximab ravtansine (ADC) | Palmar-plantar erythrodysesthesia syndrome (n = 1), elevated LFTs                             | Fatigue, anemia, diarrhea  | [53] |
| Kelly <i>et al.</i> (2014) Phase I/IIa   | Indatuximab ravtansine (ADC) | Mucosal inflammation (n = 1), anemia (n = 1)  | Fatigue, hypokalemia, diarrhea   | [52] |
| Kelly <i>et al.</i> (2016) Phase I/IIa   | Indatuximab ravtansine (ADC) | Not reported  | Diarrhea, fatigue, nausea  | [51] |
| Benson <i>et al.</i> (2015) Phase I      | IPH 2101                     | Leucopenia (n = 1), neutropenia (n = 1)   | Myelodysplasia (n = 1), neutropenia, IRR   | [20] |
| Benson <i>et al.</i> (2012) Phase I      | IPH 2101                     | Not reported  | Fatigue (n = 10), chills (n = 5), pyrexia (n = 5)  | [19] |
| Kaufman <i>et al.</i> (2013) Phase I     | Milatuzumab                  | Anemia 20%, CRS 4%, hypokalemia 4%, epistaxis 4%  | Nausea (48%), fever (36%), CRS (20%), headache (20%), HTN (20%)  | [16] |
| Lacy <i>et al.</i> (2008) Phase I        | Figitumumab (CP 751, 871)    | Anemia (2.1%), hyperglycemia (2.1%)   | Anemia (6.4%), increased AST (6.4%)  | [18] |
| Moreau <i>et al.</i> (2011) Phase I      | AVE1642                      | Hypercalcemia (n = 1), renal vein thrombosis (n = 1)  | Not reported   | [17] |
| San-Miguel <i>et al.</i> (2014) Phase II | VMP + placebo                | All = 81%, neutropenia (43%), thrombocytopenia (25%), pneumonia (17%), median PFS = 17 months | Infections (17%), GI disorders (11%)   | [39] |
|  | Siltuximab + VMP             | All = 92%, neutropenia (62%), thrombocytopenia (44%), pneumonia (17%), median PFS = 17 months | Infections (29%), GI disorders (11.5%)   |      |
| Shah <i>et al.</i> (2016) Phase I/II     | Siltuximab                   | Pneumonia, thrombocytopenia   | Fatigue (63.6%), constipation (54.5%), paresthesia (45.5%), myalgia (56.4%)  | [40] |
| Baz <i>et al.</i> (2007) Phase II        | Rituximab + MP               | Diarrhea (31%), neutropenia (51%), anemia (47%), thrombocytopenia (40%)                       | Fever, fatigue, cough, dyspnea, diarrhea, nausea, diarrhea and constipation. Possible AE related to rituximab were IRR (11%) | [75] |

ADC: Antibody drug conjugate; AE: Adverse event; CRS: Cytokine release syndrome; DLT: Dose-limiting toxicity; DVT: Deep venous thrombosis; GI: Gastrointestinal; HTN: Hypertension; IAR: Infusion-associated reaction; IRR: Infusion-related reaction; LFT: Liver function test; m: Month; MP: Melphalan, prednisone; PFS: Progression-free survival; SOB: Shortness of breath; URTI: Upper respiratory tract infection; VMP: Bortezomib, melphalan and prednisone.

The therapy was well tolerated with incidence of only one Grade I CRS reported. A mean PFS of 185 days was achieved but all patients eventually progressed. The mean PFS of ASCT with CTL019 therapy exceeded PFS of primary ASCT alone (Table 3) [70]. A Phase II trial testing CTL019 post-ASCT is still ongoing (Clinicaltrials.gov ID: NCT02794246).

### *Kappa light chain*

B cells and plasma cells can express either kappa or lambda chains on their surface. In a Phase I study with selective targeting for kappa light chain, CAR T cells (k.CAR-T) with CD28 ICD-CD3 zeta intracellular domain were used in doses ranging from  $0.2\text{--}2 \times 10^8/\text{m}^2$ . Patients showed 50% reduction of B cells 2 weeks after treatment initiation. Out of seven patients who received k.CAR-T cells, four patients showed SD. After infusion, k.CAR-T cells were well tolerated and no CRS was reported [69]. This light chain selective therapy can be useful in the future to maximize antitumor effect without causing B-cell aplasia and further clinical trials are required to study this therapy (Table 3).

### *CD138*

CD138 is highly expressed on plasma cells and CAR T-cell therapy against CD138 was tested by Guo *et al.* in a Phase I clinical trial. Five patients were treated with CAR T cells with CD28 ICD-CD3 zeta intracellular domain in dose ranging from  $0.44\text{--}1.5 \times 10^7/\text{kg}$ , preconditioning regimen included multi-agent chemotherapy. Four patients showed SD for 3–7 months. In one patient, CD138 myeloma cells decreased from 10.5% to 1–3% in peripheral blood. A consistent increase of CD138 CAR T cells was noted in bone marrow after 7 weeks of initial treatment (Table 3) [68].

Role of antibodies in newly diagnosed MM and side effect profiling is summarized in Tables 4 & 5, respectively.

### Future perspective

The use of IMiDs and PIs has improved OS in MM but most patients will face relapse and refractory disease. Immune therapy is a relatively new but promising treatment modality for MM. Elotuzumab and daratumumab are two antibodies which are FDA approved for the treatment of MM. In our review, ISA (anti-CD38 antibody) was the only MoAb with encouraging (ORR: 24%) results as monotherapy. Most other MoAb therapies did not show promising results as monotherapy. CD38 represents a promising immunotherapy target for future trials and ISA data in combination trials is very promising for MM. As elotuzumab had limited efficacy as monotherapy, but showed efficacy in combination with other agents (ELOQUENT – 2 trial) [78], other MoAbs that failed to produce any OR as monotherapy should be tested further in combination therapy.

The MMY3004 (CASTOR) trial (bortezomib and Dex  $\pm$  daratumumab) [79] and MMY3003 (POLLUX) trial (lenalidomide and Dex  $\pm$  daratumumab) [80] revealed that addition of daratumumab led to superior outcomes for MM. Considering the immunomodulatory properties of IMiDs and superior efficacy with PI combination therapy, it seems reasonable to combine these agents with novel MoAb and evaluate their efficacy. Combination therapy using siltuximab, indatuximab, ISA, pembrolizumab, dacetuzumab and lorvotuzumab with IMiDs and PIs have produced positive results.

ADC seems an appealing treatment modality because of targeted nature of therapy. Indatuximab did not show activity as a single agent but produced encouraging results as ADC (IR), which highlights the need to test other MoAb as ADC.

CAR T-cell therapy has shown very encouraging results with BCMA CAR T cells being the one with most clinical efficacy. However, the CAR T toxicity profile remains a major concern. CD19 CAR T cells recently received FDA approval for ALL. Research data and lessons from drug development for ALL can pave the way for CAR T cells in the field of lymphomas, chronic leukemias, MM and other malignancies with a potential immune targets.

We conclude that with the improvement in the understanding of biological drivers, pathogenesis, role of tumor microenvironment, immunological targets, role of checkpoint inhibitors and immunotherapy for MM using MoAbs, CAR T cells will continue to evolve either as single agent, combination therapy or as sequential therapy. In the near future, with the aim to achieve cure or functional cure for MM, immunotherapy will play a bigger role for induction, consolidation and maintenance therapy.

### Conflict of interest

Authors declare that there is no conflict of interest with this manuscript.

### Financial & competing interests disclosure

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### Authorship statement

A Sohail, A Mushtaq, A Iftikhar and F Anwer designed the study. All authors performed the study, contributed to data extraction, analyzed the data, wrote the paper and approved the final manuscript.

## Executive summary

- Monoclonal antibodies (MoAbs) exert their antitumor effects through several mechanisms including antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, antibody drug conjugate and recruitment of immune cells like NK cells.
- Daratumumab and elotuzumab have been US FDA approved for treatment of relapsed refractory multiple myeloma (RRMM). Randomized Phase III trials (CASTOR/POLLUX/ELOQUENT-2) show higher efficacy in combination setting with immunomodulatory drugs and proteasome inhibitors (PIs). A large number of additional MoAbs are under evaluation either as single agent or as combination modality in early Phase clinical trials.
- Isatuximab is the only MoAb with encouraging (objective response rate: 24%) results as monotherapy. Most of MoAbs included in our review, such as milatuzumab (anti-CD74), AVE1642 and figitumumab (anti-IGF-1R), IPH 2101 (antikiller-cell immunoglobulin like receptor), dacetuzumab and lucatumumab (anti-CD40), PAT-5M6 (anti-GRP-78), BI 505 (anti-intercellular adhesion molecule-1), siltuximab (anti-IL-6), atacicept (anti-B-cell activating factor [anti-BAFF]), bevacizumab (antivascular endothelial growth factor) and lorvotuzumab mertansine (anti-CD56), failed to produce promising results when used as monotherapy. Further trials need to test these MoAbs in combination therapy.
- MoAbs producing positive outcomes in combination therapy include siltuximab (Siltuximab + bortezomib and dexamethasone; overall response [OR]: 66%), indatuximab (Indatuximab + lenalidomide and dexamethasone [Rd]; OR: 78%), isatuximab (Isatuximab + Rd; OR: 64.5%), pembrolizumab (Pembrolizumab + Pd; OR: 60%), bevacizumab (Bevacizumab + Rd; OR: 70%), dacetuzumab (Dacetuzumab + Rd; OR: 39%) and lorvotuzumab (Lorvotuzumab + Rd; OR: 56.4%).
- MoAb-based combination regimens whose outcomes were not statistically significant include bevacizumab + Rd, bevacizumab + bortezomib, siltuximab + bortezomib and siltuximab + bortezomib, melphalan and prednisone. Role of anti-PD1 MoAb and indatuximab (anti-CD138) as monotherapy is questionable and needs further evaluation.
- Preclinical studies of TTI-621(SIRP $\alpha$ Fc), an anti-CD47 antibody, in combination with PIs showed greater antimyeloma activity in combination as compared with monotherapy. These data provide a rationale to test this antibody in human patients.
- Atacicept and siltuximab were associated with increased incidence of infections. Higher incidence of neuropathy was reported with antibody drug conjugate (lorvotuzumab mertansine), which is concerning as most of RRMM patients have pre-existing PNP (peripheral neuropathy) partially due to disease itself and partially contributed to anti-MM agents (notably bortezomib and thalidomide). Thus, lorvotuzumab mertansine might not be an appealing immune therapy approach for treatment of MM.
- Although no MoAb has effectively targeted BAFF, but BAFF can be used as a prognostic tool in RRMM patients.
- Oncolytic reovirus is an emerging idea in immunotherapy and has shown to increase the levels of PD-L1 in malignant myeloma cells. It can also sensitize cancer cells with low PD-L1 expression to PD-1/PD-L1 antibody (nivolumab, pembrolizumab, pidilizumab) therapy.
- Chimeric antigen receptor (CAR) T-cells targeting B-cell maturation antigen (BCMA), CD19, KLC and CD138 have showed promising results in treatment of heavily pretreated and RRMM patients. CAR T cells acting on BCMA have been proved clinically more efficacious by Fan *et al.* with objective response rate of 100% (n = 19) but this efficacy is also associated with more severe cytokine release syndrome events. Most patients who received CAR T cells were heavily pretreated with  $\geq 6$  median prior lines of therapy. CAR BCMA T cells have also been associated with PRES and neurological deficits which are reversed with cyclophosphamide, steroids and anti-epileptics.
- The future of immune therapies in MM is promising, more clinical trials are needed to test MoAb in combination with immunomodulatory drugs, PIs and other MM therapies.

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