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Emerging Monoclonal Antibodies for the Treatment of Multiple Myeloma

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Abstract

Therapeutic measures designed to treat multiple myeloma (MM) have undergone a fundamental shift over the past two decades as a number of small molecules that attack this cancer by different mechanisms, including proteasome blockade, immunomodulation, and histone deacetylase (HDAC) inhibition, have been introduced. The insertion of monoclonal antibodies (mAbs) into the mix began in 2015 with the U.S. Food and Drug Administration (FDA) approval of daratumumab and elotuzumab, which target CD38 and SLAMF7, respectively. In 2020, they were joined by another anti-CD38 mAb, isatuximab, and the bispecific antibody-drug conjugate (ADC) belantamab mafodotin, which targets the B-cell maturation antigen (BCMA). This review focuses on additional mAbs currently under clinical study for MM. These include several BCMAxCD3-directed bispecifics (AMG 420, AMG 701, REGN5458, REGN5459, teclistamab, and TNB-383B), the ADCs indatuximab ravtansine and STRO-001, and checkpoint inhibitors, although the future status of the latter is in a state of flux due to toxicity issues that arose in trials in which these drugs, especially PD-1 or PD-L1 blockers, were combined with immunomodulators.

Keywords: CD38, B-cell maturation antigen, daratumumab, elotuzumab, isatuximab, belantamab mafodotin, indatuximab ravtansine, STRO-001

1. Introduction

Multiple myeloma (MM), a malignancy of plasma cells, ranks second among all blood cancers in the U.S., representing about 1% of all diagnosed malignancies. In 2020, an estimated 32,270 individuals (54.3% male), the majority over age 65, will be diagnosed with the disease and approximately 12,830 will succumb to it [1]. Classical symptoms of active MM include hypercalcemia, renal insufficiency, anemia, and bone lesions (CRAB) and often are preceded by an asymptomatic stage referred to as monoclonal gammopathy of undetermined significance (MGUS). The risk of progression from MGUS to MM is about 1% per year [2] and may include another asymptomatic state known as smoldering myeloma [3]. Current guidelines for the diagnosis and treatment of MM have been published by the National Comprehensive Cancer Network (NCCN) [4]. Treatment modalities for MM have seen enormous advances since the beginning of the current century with the introduction of drugs working by different mechanisms, e.g., proteasome inhibition (bortezomib, carfilzomib, and ixazomib) and immunomodulation (lenalidomide

and pomalidomide), which were added to the long-established treatments based on alkylating agents (melphalan and cyclophosphamide) and corticosteroids (dexamethasone). These measures, together with autologous stem cell transplantation (ASCT), first introduced for MM in the 1990's, have increased the five-year survival rate for the disease from 24% in the mid-1970s to 55% in the 2010–2016 period [5]. Furthermore, the relatively recent arrival on the scene of monoclonal antibodies (mAbs), beginning with the U.S. Food and Drug Administration (FDA) approval of daratumumab in 2015, has greatly expanded the therapeutic options available to treat MM. However, in spite of these advances, MM remains incurable as patient relapse and refractoriness to treatment continue as major issues. This review focuses on the contributions made by those mAbs currently approved for MM, as well as on those under investigation as potential future therapies for this disease.

2. mAbs targeting CD38

CD38 is a multifunctional 45 kDa type II transmembrane glycoprotein, lacking an internal signaling domain, that is expressed at high levels on both malignant and normal plasma cells and has attracted much interest as a target for drug development in MM [6]. It also is found normally, but at lower levels, on the surfaces of T and B lymphocytes, natural killer (NK) cells, and monocytes. Among its several roles, CD38 acts as a receptor for CD31 (platelet endothelial cell adhesion molecule; PECAM-1) [7] and as a cyclic ADP ribose hydrolase, an ectoenzyme whose reaction products play an essential role in regulation of intracellular calcium levels [8].

Antibodies directed against CD38 kill myeloma cells by a number of possible mechanisms, chief among them being antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and complement-dependent cytotoxicity (CDC). Intracellular signal cascade disruption, the result of crosslinks formed between myeloma cell CD38 and Fc γ receptors on effector cells, may also play an important role in initiating apoptotic events in myeloma cells [9]. In addition, anti-CD38 antibodies have been shown to exhibit immunomodulatory effects that cause blockage of regulatory T- and B-cells and myeloid-derived suppressor cells [10].

Daratumumab (Darzalex®), a fully human IgG1 κ mAb targeting CD38, initially was approved for the management of MM in patients who had relapsed following at least three prior therapies including an immunomodulator and a proteasome inhibitor [11]. Approval was supported by the results of two phase III trials - POLLUX (NCT02076009) and CASTOR (NCT02136134) - in which daratumumab/dexamethasone was combined respectively with either lenalidomide [12] or bortezomib [13]. Further encouraging data from phase III trials, demonstrating deeper and more sustained responses combined with good tolerability, soon enabled daratumumab/corticosteroid combinations with immunomodulators or proteasome inhibitors to assume an important role in even earlier courses of treatment [14, 15], as well as in newly diagnosed patients, whether ASCT-eligible [16] or -ineligible [17, 18]. Several network meta-analytic studies of random controlled trials covering a number of different settings, including in patients with newly diagnosed disease, have demonstrated the benefits of daratumumab-containing regimens in MM therapy with respect to efficacy and safety [19]. Furthermore, several reports have indicated the efficacy of daratumumab monotherapy in patients who have failed earlier lines of anti-myeloma therapy [20], as well as in patients with smoldering MM [21]. Also, the FDA recently has approved a subcutaneous formulation of daratumumab plus hyaluronidase, which enables shorter infusion times without compromising safety or efficacy [22].

Isatuximab (Sarclisa®, SAR650984) is a chimeric mouse-human IgG1κ CD38-targeting mAb that was approved by the FDA in March 2020 for the treatment of relapsing and/or refractory MM (RRMM) in combination with pomalidomide and dexamethasone in patients who have received at least two prior therapies, including lenalidomide and a proteasome inhibitor [23]. Approval was predicated primarily on the results of the phase III ICARIA-MM trial (NCT02990338) in which addition of isatuximab to a pomalidomide/dexamethasone regimen resulted in a five month increase in median progression free survival (PFS), from 6.5 to 11.5 months [24]. Upper respiratory infections and diarrhea were the most frequently encountered adverse events noted in both groups. Although infusion reactions (mostly, grades 1 and 2) were reported in 38% of patients in the isatuximab cohort, this reaction was not noted in any patients in the pomalidomide/dexamethasone group. An additional five phase III trials that include isatuximab/dexamethasone currently are in progress for: newly diagnosed MM (NDMM) (NCT03617731 and NCT03319667 IMROZ - lenalidomide/bortezomib; NCT04483739 - lenalidomide/carfilzomib); RRMM (NCT03275285 IKEMA - carfilzomib); and high-risk smoldering MM (NCT04270409 - lenalidomide).

The mechanism of action of isatuximab exhibits some significant differences from that of daratumumab. For example, the former appears to work principally through ADCC with only minor contributions from CDC [25]. Also, unlike daratumumab, crosslinking induced by isatuximab is not a prerequisite for initiation of target cell apoptosis [26]. Moreover, isatuximab is a much more potent inhibitor of ectoenzyme activity although the significance of this is unknown [27].

MOR202 (MOR03087, TJ202) is a fully humanized IgG1λ mAb that exhibited an objective response rate (ORR) of 29% in a phase II trial with dexamethasone in patients who had previously received four lines of therapy [28]. In addition, this drug has shown some promising efficacy when combined with immunomodulators [29, 30]. MOR202 also appears to offer the advantage of requiring reduced infusion times and is associated with reduced infusion-related reactions compared to daratumumab or isatuximab, possibly due to its lack of dependency on CDC as a function of its activity. However, the drug's sponsor, MorphoSys AG, recently decided to discontinue further development of MOR202 for MM. Two additional anti-CD38 mAbs from Takeda Oncology currently are in the early stages of clinical development for RRMM: TAK-573, an IgG4 antibody conjugated to an attenuated form of interferon α [31], and TAK-079, a fully humanized IgG1λ mAb [32].

3. mAbs targeting SLAMF7

A group of surface proteins belonging to the signaling lymphocytic activation molecule family (SLAMF) has elicited considerable interest in recent years due to the high expression of four family members (SLAMF2, 3, 6, and 7) on both normal plasma cells and those from MM patients at all stages of disease. No trials of SLAMF2-targeting mAbs have been initiated and clinical studies of the SLAMF3 and SLAMF6 mAbs SGN-CD48A and azintuxizumab vedotin (ABBV-838), respectively, both were halted early in phase I trials. On the other hand, SLAMF7 (CS1 or CD319) has emerged as the principal focus for new anti-myeloma mAb development in this group of targets with the introduction of elotuzumab (Empliciti®), a humanized IgG1κ mAb [33]. Preclinical studies revealed that the anti-myeloma activity of elotuzumab is the result of ADCC involving direct activation and engagement of NK cells [34]. FDA approval in 2015 of elotuzumab, which lacks activity as a single agent, was the result of the ELOQUENT-2 trial (NCT01239797) involving 646 randomly assigned RRMM patients who received the mAb plus dexamethasone

with or without lenalidomide. The cohort receiving elotuzumab exhibited a PFS of 19.4 months and an ORR of 68% at one year and 41% at two years, compared to 14.9 months and 57% and 27% for the control [35]. These results were confirmed further by a subsequent four-year follow-up study [36]. Similar benefits of elotuzumab in RRMM were observed in combination with pomalidomide-dexamethasone in the ELOQUENT-3 trial (NCT02654132) [37], which included patients refractory to both lenalidomide and a proteasome inhibitor and resulted in the 2018 FDA approval of this combination [38]. Favorable data also have been generated in a trial (NCT01478048) in which bortezomib-dexamethasone was included with elotuzumab [39].

4. BCMA-targeting antibody-drug complexes

The cytokines BAFF (B-cell activating factor) and APRIL (a proliferation-inducing ligand) have received much attention in recent years for their roles in the pathophysiology of autoimmune diseases [40]. In addition, there is evidence that these two homologous members of the tumor necrosis factor (TNF) superfamily play roles in myeloma cell viability and proliferation [41]. Two other TNF family members - transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI) and B-cell maturation antigen (BCMA), located on the surface of myeloma cells, serve as ligands for both BAFF and APRIL [42]. While the respective BAFF and APRIL inhibitors, ataccept and tabalumab (LY2127399), as well as the anti-APRIL mAb BION-1301, showed poor efficacy in MM trials [43–45], BCMA has surfaced as a compelling target in anti-myeloma drug research [46].

BCMA normally plays a key role in B-cell differentiation into plasma cells [47]. Myeloma cells, whether from cell lines or patient samples, exhibit not only consistent and virtually exclusive elevation of BCMA levels and its mRNA during malignant transformation but also at similar levels during the various stages of MM from previously untreated to relapse [48]. A soluble form of BCMA (sBCMA), which results from the shedding of BCMA from the plasma cell surface by the action of γ -secretase, is an important factor that, by lowering the density of the target antigen while also providing a soluble decoy, potentially limits the efficacy of BCMA blockers in clinical development, accounting for the inclusion of γ -secretase inhibitors in a number of BCMA-targeted trials [49].

Removal of several of the fucosyl groups normally found in the N-linked biantennary complex oligosaccharides in the Fc region of IgG antibodies is a well-established approach for enhancing ADCC through binding of Fc γ IIIa receptors on NK cells [50]. One such anti-BCMA mAb is the afucosylated antibody-drug conjugate (ADC) belantamab mafodotin (Blenrep®, GSK2857916), in which the antibody is coupled to the microtubule inhibitor monomethylauristatin F (MMAF) through a protease-resistant maleimidocaproyl linker. While the antibody component disrupts BAFF/APRIL myeloma cell signaling by binding to the BCMA receptor to induce ADCC, the MMAF component causes cell cycle arrest at the G2/M interface [51]. Belantamab mafodotin continues to be the subject of the DREAMM series of trials in RRMM patients. An early exploratory study (NCT02064387, DREAMM-1) found an ORR of 60% in 35 heavily pre-treated RRMM patients when the immunoconjugate was used as a single agent [52]. This encouraging response level dropped to 31% (30/97) in RRMM patients refractory to proteasome inhibitors, immunomodulators, and/or anti-CD38 therapy, who received the drug as monotherapy at 2.5 mg./Kg. in the ensuing phase II DREAMM-2 trial (NCT03525678) [53]. However, the efficacy level was considered comparable to that observed with other therapies for RRMM patients with similar

numbers of prior therapies. Analysis of adverse event data in the DREAMM-2 trial concluded that belantamab mafodotin exhibits an acceptable safety profile with ocular toxicity, primarily in the form of keratopathy as the most commonly reported adverse event and attributable to the microtubule-inhibitor payload [54], presenting the greatest concern. Based on these data, in August, 2020, belantamab mafodotin was approved by the FDA, under the provisions of accelerated review, as monotherapy for RRMM patients who have received at least four prior treatments that included an immunomodulator, a proteasome inhibitor, and an anti-CD38 monoclonal antibody [55]. In addition to these two milestone studies, a phase II trial (NCT04126200; DREAMM-5) has been initiated that includes belantamab mafodotin monotherapy with two T-cell costimulatory agonist mAbs – the OX40-targeting GSK3174998 and the inducible co-stimulator (ICOS) GSK3359609, along with nirogacestat (PF-03084014), a γ -secretase inhibitor [56]. The ADC plus low-dose dexamethasone also is incorporated into four phase III investigations that include standard therapies such as: pomalidomide (NCT04162210; DREAMM-3, RRMM); bortezomib and daratumumab (NCT04246047; DREAMM-7, RRMM); pomalidomide and bortezomib (NCT04484623; DREAMM-8, RRMM); and lenalidomide and bortezomib (NCT04091126; DREAMM-9, NDMM) [57].

Another BCMA-targeted ADC that has elicited much interest for its anti-myeloma action is MEDI2228, which is comprised of a fully human mAb attached to a minor-groove binding pyrrolobenzodiazepine (tesirine) payload via a protease-cleavable valine-alanine linker [58]. Release of the warhead following internalization of the immunoconjugate and trafficking to the lysosome results in DNA damage and subsequent apoptosis. Preclinical studies in mice revealed this agent's potent anti-myeloma activity even when clinically significant levels of sBCMA were present [59]. Currently, MEDI2228 is the subject of a phase I clinical trial (NCT03489525) to determine appropriate dosing as monotherapy in RRMM patients; however, no results have been reported as yet. Another anti-BCMA ADC that has entered clinical studies for MM is AMG 224 (NCT02561962), comprised of a maytansine analog connected to a non-cleavable 4-(*N*-maleimidomethyl) cyclohexane-1-carboxylate linker [60]. CC-99712 is yet another BCMA-targeted ADC (undisclosed composition) that recently entered a clinical trial (NCT04036461) for RRMM. Other anti-BCMA ADC mAbs that have demonstrated promise in preclinical work but for which human studies have not yet begun include two proprietary products, referred to as BCMA-077 and BCMA-024 [61], and HDP-101, in which the conjugate is the potent RNA polymerase II subunit A (POLR2A) inhibitor α -amanitin [62].

5. T-cell-engaging bispecific antibodies

The T-cell-engaging bispecific antibody (T-BsAb) concept, originally developed by Nisonoff in 1961 [63], is based on the design of a dual-targeting antibody whereby one arm initially binds to the T-cell CD3 co-receptor complex while the other arm is subsequently directed to a tumor-associated antigen. The immunological synapse created between the two cells causes release of two cytolytic-initiating proteins: perforin, which causes formation of transmembrane pores in the malignant cell and granzyme B, which traverses the pores thus produced to initiate tumor cell apoptosis. The T-BsAb strategy differs from normal T-cell mediated cytotoxicity by removing requirements for costimulatory signals, formation of an antigen-major histocompatibility complex (MHC), and for *ex vivo* T-cell manipulation, thus permitting the possibility of “off-the-shelf” product manufacture. Furthermore, persistent T-cell activation enables polyclonal expansion of T memory cells. In addition, the

therapeutically relevant properties of constructs may be fine-tuned to optimization by altering biodistribution characteristics and the relative binding affinities of each arm for their respective targets [64].

Amgen's proprietary BiTE® platform represents an innovative subclass of T-BsAb in which tandem single-chain variable fragments (scFvs) provide the cross-link [65]. The first successful application of BiTE® technology was the CD3-CD19 cross-linking construct blinatumomab (Blinicyto®), which was approved by the FDA in 2014 for Philadelphia chromosome-negative B-cell precursor acute lymphocytic leukemia (B-cell ALL). Although a single trial (NCT03173430) of blinatumomab in RRMM patients had to be terminated because of "slow patient accrual", the majority of myeloma-related work using BiTE® constructs have been based on recombinant antibodies designed to cross-link surface tumor-specific T-cell CD3 ζ chains and targeted myeloma cell BCMA.

Initial results with the BCMA \times CD3 BiTE® product AMG 420 (BI-836909), which was accorded fast-track status by the FDA in 2018, showed an ORR of 31% in 42 RRMM patients, including seven of ten patients refractory to at least two lines of therapy who received the maximum tolerated dose of 400 μ g/day. Infections and polyneuropathy were the most serious adverse events noted in this trial. Cytokine release syndrome (CRS; cytokine storm), predominantly grade 1, was observed in 38% of patients in the study [66, 67]. Monotherapy with AMG 701, a related BiTE® construct with a longer serum half-life than AMG 420, currently is the focus of a phase I trial (NCT03287908) for RRMM. Data generated in a preclinical investigation suggests that future consideration of a trial of AMG 701 in combination with an immunomodulator may be warranted [68]. In addition, two other BCMA \times CD3 bispecific antibodies from Regeneron, REGN5458 (NCT03761108) and REGN5459 (NCT04083534), are in phase I RRMM studies. Preliminary data on the first three patients treated with the former agent have been reported [69].

Following favorable safety results in a monkey model [70], two phase I RRMM clinical trials of the BCMA \times CD3 bispecific teclistamab (JNJ-64007957) have been initiated. In addition to a dose-escalation study (NCT03145181), this agent has been incorporated into a trial (NCT04108195) that includes subcutaneous daratumumab and talquetamab (JNJ-64407564), a CD3 \times GPRC5D bispecific construct. Another BCMA \times CD3 formatted product under scrutiny for RRMM is PF-06863135 (PF-3135) (NCT03269136), the result of hinge-mutation engineering of an IgG2a backbone [71]. CC-93269, a T-cell engager whose arms bind in a 2 + 1 arrangement, monovalently to CD3 ϵ and bivalently to BCMA, is another member of this class in a myeloma-based trial (NCT03486067) [72].

TNB-383B, a BCMA \times CD3 T-BsAb resulting from collaboration between Tenebio and Abbvie and designated as an orphan drug by the FDA, differs from other drugs in this class in that its structure consists of a single immunoglobulin light chain and two variable heavy chains. The product, which recently began a phase I trial for RRMM (NCT03933735), is noteworthy for its strong T-cell activation kinetics and low affinity anti-CD3 arm, which results in reduced release of cytokines while retaining high cytotoxicity toward myeloma cells [73]. A number of other bispecific antibodies have exhibited promise for RRMM in preclinical work. These include TNB-381 M [74], FPA-151 [74], EM801 [48], and AP163 [75]. HPN217, developed by Harpoon Therapeutics, is a tri-specific antibody possessing three binding domains in a single chain – a C-terminal single-chain CD3 ϵ T-cell receptor-(TCR)-binding component, a human serum albumin-binding central domain, and an N-terminal BCMA-binding portion. This product, which is in a phase I/II trial for RRMM (NCT04184050), has an extended half-life compared to bispecific formats, a property ascribed to its smaller size and flexibility [76]. Moreover, bispecifics based on myeloma surface antigens other than BCMA have been developed

as alternative CD3 epitope binding partners. In addition to the aforementioned talquetamab (NCT03399799) [77], these include the CD3xCD38 construct found in GBR 1342 (NCT03309111) [78] and the CD3xFcRH5 design incorporated into BFCR4350A (NCT03275103) [79].

In addition to the BCMAxCD3 bispecific formats noted above, creation of BCMA-targeted constructs directed to receptors on NK cells has been described. Like cytotoxic T-cells, NK cells are known to mediate cytotoxicity through a variety of mechanisms, including granzyme-perforin release and through expression of various apoptosis-inducing ligands [80]. A tri-specific product that binds both BCMA and CD200 on myeloma cells to CD16A on NK cells represents one such drug [81]. Similarly, CTX-4419, which binds BCMA to both NK cell CD16A and p30, has shown initial promise in preclinical models although CD16A binding does not appear to be a requirement for the anti-myeloma activity of this product [82]. Other BCMA-NK cell-engaging antibodies, such as CTX-8573 [83] and AFM26 [84], also have shown some potential as RRMM therapies.

6. Immune checkpoint inhibitors

Over the past decade, immune checkpoint blockade has emerged as a principal strategy for new antitumor drug development. This immunotherapeutic approach is based on identification of biomarkers and their cognate ligands that enable the body's immune system to overcome the capacity of tumor cells to evade immune surveillance and elimination, as well as on the design of mAbs to block these interactions. In its most successful application to date, discoveries made concerning the roles played in this process by cytotoxic T-lymphocyte-associated protein-4 (CTLA-4), the first member of this class to serve as a clinical target, and the programmed death (PD) receptor, have given momentum to this innovative line of attack on a variety of tumor types [85].

Costimulatory signals resulting from interaction of CD28 on the surface of T-cells with its CD80 (B7-1) ligand on antigen-presenting cells play an important role in activating T-cells. CTLA-4, expressed on the T-cell plasma membrane, competes with CD80-CD28 binding to downregulate T-cell activation and thus represents an important mechanism that suppresses immune responses and, as a consequence, enables tumor cells to evade detection. CTLA-4-directed mAbs, by competing with the CD80-CD28 interaction, enhance the ability of T-cells to generate an antitumor response. This strategic approach was successfully applied to the immunotherapy of advanced melanoma by the anti-CTLA-4 mAb ipilimumab, which was approved by the FDA in 2011 and has been extended since to include a number of other solid tumors [86]. However, the drug has shown less than impressive results in hematologic cancers, such as acute myeloid leukemia [87]. One trial (NCT02681302) of ipilimumab combined with nivolumab that included both lymphoma and MM patients is currently active but so far only preliminary efficacy and toxicity data have been reported [88].

Binding of PD-1, expressed on the surface of T-cells, to PD-L1 or PD-L2 on tumor cells inhibits cytotoxic T lymphocyte proliferation and cytokine secretion while also causing an increase in the T regulatory cell population. These combined effects produce immune tolerance, enabling unrestrained tumor cell growth and survival [89]. Since 2014, the FDA has approved three PD-1 inhibitors – pembrolizumab (Keytruda®), nivolumab (Opdivo®), and cemiplimab (Libtayo®) and three PD-L1 blockers – avelumab (Bavencio®), durvalumab (Imfinzi®), and atezolizumab (Tecentriq®). Pembrolizumab, the first to be approved and the most versatile member of the checkpoint blocker group, has been approved for

17 different indications, many as front-line therapy for solid tumors ranging from melanoma to small-cell lung cancer to metastatic Merkel cell carcinoma [90]. In 2017, the FDA in an unprecedented move approved pembrolizumab for the treatment of solid tumors having a microsatellite instability (mismatched repair

Trial ID [reference]	N	Trial title
PD-1 Inhibitors		
NCT03848845 [102]	40	A phase I/II single arm open-label study to explore safety and clinical activity of GSK2857916 administered in combination with pembrolizumab in subjects with relapsed/refractory multiple myeloma (DREAMM 4)
NCT03506360	41	Phase II trial of pembrolizumab, ixazomib, and dexamethasone for relapsed multiple myeloma
NCT04361851	33	Phase II study of daratumumab-pembrolizumab for multiple myeloma patients with \geq three prior lines of therapy
NCT03168438 [103]	20	NY-ESO-1 ^{c259} T alone and in combination with pembrolizumab for multiple myeloma
NCT03782064	25	A phase II trial of vaccination with dendritic cell (DC)/myeloma fusions in combination with nivolumab in patients with relapsed multiple myeloma
NCT03292263 [104]	30	Autologous stem cell transplantation with nivolumab in patients with multiple myeloma
NCT04119336	50	A phase II study of nivolumab in combination with ixazomib, cyclophosphamide, and dexamethasone in relapsed and refractory multiple myeloma
NCT03194867	109	A phase I/II study to evaluate safety, pharmacokinetics and efficacy of isatuximab in combination with cemiplimab in patients with relapsed/refractory multiple myeloma
NCT03111992	26	Phase I/Ib, multi-center, open-label, study of single agent CJM112 (anti-IL17A mAb), and spartalizumab (PDR001) in combination with LCL161 (SMAC mimetic) or CJM112 in patients with relapsed and/or refractory multiple myeloma
PD-L1 Inhibitors		
NCT02431208 [105, 106] Trial Start: 7/22/15	300	A phase Ib study of the safety and pharmacokinetics of atezolizumab alone or in combination with an immunomodulatory drug and/or daratumumab in patients with multiple myeloma (relapsed/ refractory and post-autologous stem cell transplantation)
NCT03910439	30	A phase II pilot study of avelumab in combination with hypofractionated radiotherapy in patients with relapsed refractory multiple myeloma
CD47 Inhibitors		
NCT03530683	156	A phase Ia/Ib dose escalation and expansion trial of TTI-622 in patients with advanced relapsed or refractory lymphoma or myeloma
LAG-3 and TIGIT Inhibitors		
NCT04150965	104	A phase I/II assessment of combination immuno-oncology drugs elotuzumab, anti-LAG-3 (BMS-986016) and anti-TIGIT (BMS-986207)
<i>Trial start date on or after July 1, 2017, unless otherwise noted.</i>		

Table 1.
Selected active trials of checkpoint inhibitors in MM.

deficiency). Known as a tissue agnostic approach to cancer diagnosis and treatment, this marked the first drug approval based on a specific biomarker instead of on the tissue or organ of origin [91].

In terms of hematologic malignancies, pembrolizumab has been approved for treatment of Hodgkin's lymphoma while both pembrolizumab and nivolumab have been approved for primary mediastinal large B-cell lymphoma (PMBCL). While studies of checkpoint inhibitors in both chronic and acute leukemias generally have been disappointing [87], work in the area of MM has shown some degree of efficacy but major issues concerning toxicity have arisen. Following favorable results in early phase trials [92, 93], pembrolizumab/dexamethasone was included in two phase III trials with and without the immunomodulators lenalidomide (NCT02579863—KEYNOTE-185; NDMM) and pomalidomide (NCT02576977—KEYNOTE-183; RRMM). However, in July 2017, the FDA placed clinical holds on both trials due to the higher risk of death in the cohorts receiving the PD-1 blocker [94]. This suspension soon was expanded to include partial or full holds on all myeloma trials using combinations of immunomodulators and checkpoint inhibitors, an action that later was reversed in the case of three myeloma trials that employed nivolumab (NCT03023527, NCT01592370, and NCT02612779); however, no data have been forthcoming for these resumed studies. At this point, any future role that checkpoint inhibitor-immunomodulator combinations may play in MM therapy is very much in a state of flux [95]. Other checkpoints that may serve as targets for MM but for which only limited preclinical or clinical studies are currently available include killer-cell immunoglobulin-like receptors (KIR) [96], CD47 [97], LAG3 [98], TIGIT [99, 100], and TIM-3 [101]. **Table 1** contains a partial list of checkpoint inhibitors currently in clinical trials for MM.

7. Additional mAbs and their targets

CD138 (syndecan-1), which is overexpressed in MM [107], is the target of indatuximab ravtansine (BT-062), an ADC whose anti-CD138 mAb is linked to a cytotoxic microtubule destabilizing maytansinoid. This agent has been studied in RRMM both in combination with immunomodulators (NCT01638936) and as a single agent (NCT01001442 and NCT00723359). The 34 patients (median 5 prior therapies) in the monotherapy study who received a multi-dose regimen showed a median PFS of three months and median overall survival (OS) of 26.7 months while diarrhea and fatigue were the most commonly reported adverse events [108]. In addition, an anti-CD138 mAb, known as mAb 1610, has shown some potential anti-myeloma promise in a preclinical study [109].

CD74 plays a key role as a chaperone, enabling the proper folding and trafficking of MHC Class II proteins in antigen-presenting cells. In addition, this type II transmembrane protein activates the NF κ B signaling pathway following the binding of its intracellular domain to macrophage migration inhibitory factor (MIF) and translocation to the nucleus where it induces proliferation and survival, especially in B-cells. Elevated expression of CD74 in B cell malignancies, such as non-Hodgkin's lymphomas and MM, has made this an attractive target for these types of cancer [110]. STRO-001, which has received Orphan Drug status from the FDA, is an anti-CD74 ADC in which an aglycosylated human IgG1 antibody is conjugated to a maytansinoid linker-warhead. A phase I trial (NCT03424603) of STRO-001 in B-cell malignancies, including MM, recently was initiated [111]. Two other CD74-targeting agents, milatuzumab and its doxorubicin-linked ADC, that had been under study in MM, both have been dropped from further consideration.

Another conjugate linked to a maytansine derivative, the anti-CD56 ADC lorvotuzumab mertansine (IMGN901; BB-10901), had been the focus of a phase I trial in CD56-positive RRMM patients (NCT00346255) but insufficient efficacy and dose-related toxicity reportedly led to discontinuation of further studies of this agent [112, 113]. Other mAbs that have been dropped from further consideration in MM following demonstration of only modest efficacy and/or unacceptable toxicity in trials include the following (target in parentheses): dacetuzumab and lucatumumab (CD40); F50067 (CXCR-4); AVE1642 and figitumumab (IGF-R1); IPH 2101 (KIR); PAT-SM6 (GRP-78); BI 505 (intercellular adhesion molecule-1, ICAM-1), and siltuximab (IL-6).

8. Conclusion

The number of therapeutic options available to treat MM has witnessed a remarkable upsurge since the turn of the current century. The advent of proteasome inhibitors and immunomodulators, in addition to other small molecules working by additional mechanisms, such as histone deacetylase (HDAC) blockade and nuclear export inhibition, has resulted in a major alteration in the clinical approach to the disease. Over the past half-decade, the introduction of mAbs into the fight against this malignancy has further shifted the landscape of how this disease is treated both in newly diagnosed patients and in the relapsed/refractory setting. Chief among these newer entries are daratumumab and elotuzumab, and more recently the anti-CD38 mAb isatuximab and the bispecific antibody belantamab mafodotin. Although employment of mAbs in combination with small molecule agents, such as bortezomib and lenalidomide, has been of immense value in extending patients' ability to achieve deep and durable remissions, relapse and refractoriness to therapy remain as major obstacles to attainment of a cure. Work on checkpoint inhibitors, which have been employed successfully in several tumor types and had shown early promise in MM, continues to move forward in clinical studies of MM, although tempered by recent setbacks stemming from toxicity concerns when used in combination with immunomodulators.

It is evident that future advances in treating MM will be dependent on gaining even deeper insight into the transformative molecular events leading to the disease. As new biomarkers that drive this unrelenting malignancy are identified, design and discovery of innovative target-based therapeutic approaches that will find their way into clinical practice will be established. The attainments already realized by the advent of mAbs, particularly daratumumab, in recent years offers some prospect for even greater success in the application of mAbs in MM over the coming decade.

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