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The development of potential antibody-based therapies for myeloma

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Abstract

With optimal target antigen selection antibody-based therapeutics can be very effective agents for hematologic malignancies, but none have yet been approved for myeloma. Rituximab and brentuximab vedotin are examples of success for the naked antibody and antibody–drug conjugate classes, respectively. Plasma cell myeloma is an attractive disease for antibody-based targeting due to target cell accessibility and the complementary mechanism of action with approved therapies. Initial antibodies tested in myeloma were disappointing. However, recent results from targeting well-characterized antigens have been more encouraging. In particular, the CD38 and CD138 targeted therapies are showing single-agent activity in early phase clinical trials. Here we will review the development pipeline for naked antibodies and antibody–drug conjugates for myeloma. There is clear clinical need for new treatments, as myeloma inevitably becomes refractory to standard agents. The full impact is yet to be established, but we are optimistic that the first FDA-approved antibody therapeutic(s) for this disease will emerge in the near future.

Keywords

Multiple myeloma; Plasma cell myeloma; Antibody–drug conjugate; Monoclonal antibodies; Targeted cancer therapy; Immunotherapy

1. Introduction

The FDA approval of the monoclonal antibody (mAb) rituximab in 1997 was the harbinger of a significant change to the treatment of cancer. This single agent has become a component of first and subsequent line therapy in many subtypes of non-Hodgkin lymphoma [1, 2]. Central to efficacy of rituximab is the expression of its target antigen,

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CD20, on the cell surface. In solid tumors, the prototype for success is trastuzumab, a naked antibody that targets the human epidermal growth factor receptor 2 (HER2), which is approved for use in the treatment of breast cancer. Efforts to extend mAb therapy into other malignancies has been met with both resounding successes and costly failures, as only a small fraction of mAbs that have entered clinical trials in oncology have received FDA approval [3].

One potential way to improve upon the efficacy of mAbs is to use them as a targeted delivery system for chemotherapy. After years of research and development, antibody–drug conjugates (ADCs) have seen renewed excitement after the recent FDA approval for two new agents. The first is the anti-CD30 ADC brentuximab vedotin in Hodgkin lymphoma (HL) and anaplastic large cell lymphoma (ALCL). Early phase studies in patients with relapsed or refractory HL or ALCL have shown remarkable responses in the majority of patients, including significant numbers achieving complete response (CR), leading to accelerated FDA approval for these indications in 2011 [4,5]. Trastuzumab, targeting HER2, has also been utilized in this approach by linkage to another antitubulin cytotoxic (mertansine) to create ado-trastuzumab emtansine (T-DM1) [6]. T-DM1 is highly active in trastuzumab-resistant, HER2-positive breast cancer, leading to FDA approval in that setting [7]. Furthermore, T-DM1 was also found to be superior to trastuzumab in the first line setting, demonstrating the potential to improve upon the efficacy of naked antibodies [8]. Overall, the success of mAbs as novel cancer therapeutics has incited increasing efforts to broaden their application. Plasma cell myeloma (aka multiple myeloma) is one such disease where new therapy is needed, especially since this is an incurable disease and the development of resistance to current therapies is universal.

2. Rationale for developing antibody-based therapy for myeloma

Efforts to broaden the applicability of naked antibodies to myeloma by targeting antigens more specific to the disease are finally coming to fruition, after several years of mostly disappointing clinical trials. Extrapolating from established agents in other malignancies, there are several mechanisms by which an antibody therapeutic could potentially destroy myeloma cells [1]. Most mAbs function by binding to an appropriate cell surface antigen, where the “naked” antibody can direct the patients’ own immune system against the malignant cells, tagging them for elimination by antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) [9]. Many naked antibodies tested *in vitro* for myeloma have been shown to activate ADCC, but unfortunately this mechanism has demonstrated limited clinical activity by itself [2]. Inhibition of signal transduction is another mechanism that can contribute to the efficacy of clinically used antibodies. Thus, several antibodies were developed to target signaling pathways responsible for myeloma cell survival, proliferation and microenvironment interaction [3]. Efficacy can be accentuated by linkage of mAbs to cytotoxic small molecules (Fig. 1). These antibody–drug conjugates have the potential to be far more potent than their naked counterparts in tumor cell killing, when the target antigen is rapidly internalized. To date very few antibody–drug conjugates have been tested in myeloma. These “armed” antibodies may improve clinical efficacy and perhaps have the greatest promise for novel therapeutics in myeloma.

The treatment of myeloma has truly undergone a renaissance over the past 5–10 years. The use of proteasome inhibitors and IMiDs has drastically changed longevity for patients and the median overall survival now approaches a decade. Immunomodulatory drugs (IMiDs) have been thought to have pleiotropic immune effects. However, a critical mechanism of IMiD action was recently found to involve binding to Cereblon, a unique E3 ubiquitin ligase protein [10,11]. This interaction facilitates the degradation of Ikaros B-cell transcription factors [12]. The proteasome inhibitors also directly affect protein stability through inhibition of the chymotryptic site on the proteasome and producing a massive unfolded protein response [13]. The proteasome inhibitors and IMiDs have been used in combination with more traditional chemotherapy (alkylators and anthracyclines) and steroids to produce robust anti-myeloma effects in the frontline and relapse settings. However, despite these advances, resistance inevitably develops and the disease ultimately remains fatal. In addition, the disease can cause a debilitating course with a significant risk of skeletal disease (especially vertebral fractures), recurrent infections and/or kidney damage. Thus, there is still great need for novel therapeutics and new classes of drugs for this disease.

Antibody therapies provide exquisite targeting specificity and have the potential to greatly improve the outcome in this devastating disease. Malignant plasma cells (PCs) are primarily localized to the bone marrow (BM) and are readily accessible to intravenously infused antibody therapies through discontinuous capillaries (sinusoids) [14,15]. This contrasts to solid tumors, for which location and the capillary endothelium can present barriers to delivery [14,15]. The preclinical results for the many naked antibodies investigated for myeloma have been comprehensively reviewed previously [16]. Here, we will provide an update on a subset of the naked antibodies with emphasis on their clinical results, including CD38, signaling lymphocyte activation molecule family member 7 (SLAMF7/CS1), CD74, CD40 and insulin-like growth factor 1 receptor (IGF-IR/CD221). ADCs are now becoming the focus for this genre of drug development in myeloma. These will be emphasized here, with published targets consisting of CD138, CD56, Fc receptor-like 5 (FcRL5/CD307), CD74 and B-cell maturation antigen (BCMA).

3. Myeloma target antigens

One of the most important aspects of developing antibody-based therapeutic in myeloma is target antigen selection. Ideally the target should demonstrate selective overexpression on the malignant cells. HER2 is an analogous example, as the gene is amplified from 2 to greater than 20-fold and this is reflected in high cell surface expression in 30% breast cancer tumors [17]. Unfortunately, no marker has been identified to undergo consistent gene amplification in myeloma thus far. Toxicity is predicted by the target cell surface expression on non-malignant cells, and by taking into account the tissue distribution of the relatively large mAb molecules. It should be noted that the optimal level of target expression might differ for naked and “armed” antibodies. An example is brentuximab vedotin, where CD30 is expressed uniformly on malignant cells in HL, but not necessarily overexpressed [18,19]. Treatment with naked CD30 antibodies had little to no activity in Hodgkin lymphoma, whereas treatment with the ADC brentuximab vedotin has shown significant activity [20,21]. For ADCs, additional attributes of the target antigen’s biology are important for efficacy. These have been reviewed elsewhere [22]. In brief, internalization typically must

occur for the payload to have specific cytotoxic effect on the target cell. Rapid internalization of antigen and recycling to the surface are ideal for toxin delivery. Furthermore, an intracellular pathway that delivers ADC to early endosomes and lysosomes is important for delivery and activation of the attached warhead [23,24]. This allows specific release of the warhead to its site of action.

For myeloma, a standard panel of antigens has been used for immunohistochemical and flow cytometry identification and quantification of tumor cells. These antigens may also be appropriate targets for antibody-based therapy. Perhaps the best-known antigens are CD38, CD138 and CD56. The published frequency and specificity of expression for these markers in myeloma are summarized in Table 1. CD38 is expressed on nearly all PCs and myeloma cells, and is absent only rarely [25,26]. Staining of myeloma cells with fluorescently labeled anti-CD38 antibodies typically yields bright signals by flow cytometry [25]. CD38 is also expressed on immature B- and T-cells, NK cells, activated T-cells and monocytes [26]. CD138 is ubiquitously expressed on myeloma and normal PCs [27]. CD138 is also expressed on epithelial cells, immature B-cells and on cells involved in wound healing in mice [28,29]. CD138 expression has been found in breast and other carcinomas, possibly indicating other potential applications of CD138-targeted therapies [30]. CD56 is a unique marker for myeloma, in that it is expressed on malignant cells, but is absent or low on normal PCs [27,31]. Although 78% of myeloma patients express CD56 (n = 55), in one study it appears to be lost with progression to extramedullary disease and plasma cell leukemia [31–33]. CD56 is normally expressed on NK cells, some T-cells, and in neural and muscle tissue [34–36].

Two other well-characterized differentiation antigens are CD74 and CD40. CD74 is the invariant chain of the human leukocyte antigen (HLA)-DR major histocompatibility complex (MHC) class II molecule. CD74 has been reported to be expressed on myeloma cells in 86% (n = 22) patients [37]. It is normally expressed on B-cells and antigen presenting cells such as Langerhans cells in the skin [38,39]. CD74 is an attractive ADC target due to rapid internalization and recycling to the surface of B-cells [40]. CD74 is also expressed on melanoma and colon cancer cell lines, potentially expanding the role of anti-CD74 therapy to those diseases [41]. CD40 is a tumor necrosis factor (TNF) receptor superfamily member that is expressed on antigen presenting cells, B-lymphocytes, endothelial, smooth muscle and fibroblasts [42,43]. CD40 has been found to be expressed in ~70% myeloma patients (n = 37) [27,44]. Though expressed at a seemingly lower level as measured by flow cytometry than CD38, its expression can increase with disease progression [27].

Other B-cell specific targets and those important to the pathogenesis of myeloma include IGF-1R, IL6, SLAMF7 (aka CS1), FcRL5 and BCMA. IGF-1R and IL6 are principle components of growth factor signal transduction for myeloma. IGF-1R was expressed in 84% myeloma patients cumulatively from two studies (n = 91) [45,46]. IGF-1R overexpression is correlated with the t(4;14) translocation, disease progression and lack of CD45 [45]. Potentially problematic for selectivity, IGF-1R is widely expressed in normal tissue [47]. SLAMF7 is expressed on myeloma cells from 95% of patients (n = 20), albeit at relatively lower levels than CD38 and CD138 [48,49]. The normal expression pattern of

SLAMF7 is restricted to PCs, NK cells, activated lymphocytes, monocytes and dendritic cells [48–50]. FcrL5 protein is specifically expressed on B-cells and PCs [51]. FcrL5 was proposed as a target for myeloma based on this high degree of specificity and that expression levels were >3-fold higher on myeloma cells compared to normal PCs, by median fluorescence intensity (MFI) [52]. This antigen has been found to be expressed on 100% (n = 24) of cumulative myeloma cases examined, although the expression level appears low compared to that of CD38 or CD138 [52, 53]. FcrL5 was observed to internalize within 2 h of mAb binding, and delivered to lysosomes within 13 h by colocalization with Lysosomal-associated membrane protein 1 (LAMP1) by immunocytochemistry, making it an reasonable candidate for ADC development [52]. BCMA is expressed specifically in the plasma cells, with expression on 92% of myeloma patient samples tested across four studies (n = 27), though cell surface expression level was heterogeneous [54–57]. As seen in Table 1, the current myeloma antigens mostly have good specificity for myeloma and PCs. Thus, the on-target side effects are often expected be immune, especially B-cell mediated deficiency.

4. Myeloma antibody–drug conjugate construction

Antibody–drug conjugates utilize the cell specificity of a monoclonal antibody to preferentially deliver their cytotoxic payload to cells with higher surface expression levels of the target antigen. In addition to the previously mentioned choice of antigen, the selection of a proper linker and drug are also important. To prevent premature release of the drug in the circulation, the linker must have a half-life in blood comparable to that of the antibody. The first ADC approved by the FDA, gemtuzumab ozogamicin (GO), utilized an acid sensitive acyl hydrazone linker that was designed for hydrolysis in the low pH environment of the lysosome. Unfortunately this class of linker has been shown to have a significant rate of drug release in plasma, and GO was eventually withdrawn from the US market in 2010 [58]. Significant hepatotoxicity was seen perhaps due to nonspecific drug release. Despite this, recent meta-analysis of randomized trials has reported that GO improves outcomes for a subset of patients with acute myeloid leukemia and efforts are ongoing to potentially revive its clinical use [59].

Newer linkers have shown improved serum stability while maintaining proper release function after internalization into cells. Brentuximab vedotin utilizes a valine-citrulline dipeptide linker that can be cleaved by lysosomal proteases such as cathepsin B [60]. Numerous experiments have demonstrated that this linker has excellent serum stability, but is readily cleaved once internalized into cells. In contrast, T-DM1 contains a non-cleavable linker for the covalent attachment of the cytotoxic drug to the antibody [6]. This ADC relies on lysosomal digestion of the antibody component to liberate the drug metabolite consisting of the drug still attached to the amino acid to which it was conjugated (Fig. 2). Yet another linker is the sterically-hindered disulfide linker. The disulfide is readily cleaved once introduced into the reducing environment of the cell, but methyl groups adjacent to the disulfide bond are necessary to slow the rate of premature release in circulation. Though this linker has not yet been used in any approved ADCs, it has been used in several conjugates in clinical trials, including the anti-CD138 ADC [61].

The proper drug selection is also important for creating an effective antibody–drug conjugate. Many steps are necessary for the successful delivery of an ADC drug component to its intracellular target (ADC tumor localization *in vivo*, cell internalization, cleavage and lysosome escape), so only a low percentage of the injected payload eventually reaches the desired target [62]. For this reason, most successful ADCs utilize extremely potent drugs. Monomethyl auristatin E (MMAE), a synthetic derivative of the natural product dolastatin, is the drug used in brentuximab vedotin and in several other ADCs entering clinical trials. Average EC50 (half maximal effective concentration) of 1–5 nM on a wide range of cancer cells has been observed with this drug which was approximately 50- and 200-fold more potent than vinblastine and doxorubicin, respectively [58]. Derivatives of the natural product maytansine have similar potency as the auristatins and have found use in T-DM1, as well as a number of other ADCs entering clinical trials.

The antibody–drug conjugates being tested as myeloma therapeutics utilize a variety of these drugs and linkers (Fig. 2). Indatuximab ravtansine consists of an antibody targeting CD138, a maytansine analog (DM4), and a sterically-hindered disulfide bond linker. This ADC composition was the most potent after testing multiple cleavable and non-cleavable versions in preclinical myeloma models [61]. The drugs are attached to lysine side chains by titrating the concentration of drug during conjugation and with this strategy an average ratio of 3.5 drugs per antibody is achieved. Similarly, lorvotuzumab mertansine (IMG901) utilizes the same drug but with a less hindered disulfide bond linker (DM1) [63]. The drug is attached to the lysine side chains of an antibody targeting CD56, in the same manner as indatuximab ravtansine. The recently published GSK2857916 anti-BCMA ADC utilizes a non-cleavable linker conjugated to another auristatin derivative, monomethyl auristatin F (MMAF) [57].

A distinctly different antibody–drug conjugate is milatuzumab–doxorubicin, which consists of an anti-CD74 antibody conjugated to doxorubicin [64]. Possible disadvantages to this ADC are that doxorubicin is a much less potent drug than either the maytansines or auristatins and the acid labile hydrazone linker, which may result in premature release of the drug while still in circulation. While premature drug release is undesirable, this may pose less of a problem than with gemtuzumab ozogamicin because of the diminished potency of the doxorubicin. One topic of debate is whether drugs that have efficacy in myeloma treatment as chemotherapies (like doxorubicin) would be more effective payloads, given that antitubulin agents are not useful alone in myeloma therapy. However, this argument may not be applicable to ADCs utilizing maytansines or auristatins due to their much higher potency. It will be interesting to see which of these strategies results in the most effective myeloma treatment.

Since it is often difficult to predict which linker and drug combination will be most effective, some companies will develop multiple ADCs during for preclinical evaluation. Genentech, for example, tested several versions of its anti-FcRL5 ADC [52]. Two versions were prepared using auristatin derivatives, one with a dipeptide cleavable linker and the other with a non-cleavable linker. In addition, they also tested two maytansine derivative ADCs with either a cleavable disulfide linker or a non-cleavable linker. There were significant differences between the *in vivo* potency of these ADCs in xenograft mouse

models, thus demonstrating the importance of testing different combinations of drugs and linkers [52]. As more ADCs are tested in clinical trials it will hopefully become possible to better predict which combination of drug and linker is best suited for a particular type of disease.

5. Myeloma clinical response criteria

For the discussion herein, the updated response criteria by European Group for Blood and Marrow Transplant (EBMT) were used to assess response [65]. In general, these criteria attempt to assess myeloma disease burden by the amount of monoclonal proteins present, and the amount of PCs found in the marrow or in isolated tumors (plasmacytomas). In review, normal PCs have an important role in immune function by manufacturing and secreting diverse antibody proteins. When a monoclonal PC population persists and expands inappropriately, the monotypic antibody produced can be readily detected as a monoclonal "M-spike" on serum protein electrophoresis (SPEP), urine protein electrophoresis (UPEP) and/or through serum free light chain assays.

Disease progression, and response to therapy, can be followed quantitatively by the trend of M-spike and corresponding serum free light chain levels. The EBMT criteria categorizes responses as minimal response (MR) with 25–49% decrease in M-spike concentration, partial response (PR) with greater than 50%, very good partial response (VGPR) with greater than 90%, CR with negative SPEP immunofixation and BM PCs are less than 5%, and stringent CR (sCR) when light chain ratio is normal and multiparametric BM flow cytometry does not detect a clonal PC population [65,66]. The stable disease (SD) category consists of nonresponders who have less than 25% decrease or increase of the M-spike from baseline. A caveat is that SD can be misleading because it does not accurately reflect time to progression (TTP) [65]. However, SD is included in the trial descriptions here, since the phase I trials are not designed to assess TTP. Of note, MR was not included in the EBMT update, but is also included here since many trials report these responses.

6. Anti-myeloma naked antibodies: preclinical & clinical results

Numerous naked antibodies have been tested in preclinical myeloma models. Antibodies raised against six antigens have been tested clinically: CD38, SLAMF7, CD74, CD40, IL-6 and IGF1R. It should be emphasized that the phase I trials discussed herein cannot be compared to each other directly, as they are designed to assess safety alone. Furthermore, patients enrolled vary according to disease characteristics and prior therapies. The response rate in these trials is generally an underestimate, as significant (and variable) numbers of patients in a dose-escalation scheme are likely to be treated with small doses that do not achieve enough target occupancy for effect. Still, the ease of monitoring for response in myeloma allows for observation of activity, when present. A summary of the phase I dose-escalation trials of antibody therapeutics in myeloma is shown in Table 2.

6.1. Anti-CD38: daratumumab and SAR650984

Two anti-CD38 mAbs are currently in clinical trials. Daratumumab is a CD38 mAb that was shown to exhibit *in vitro* anti-myeloma cell proliferation, ADCC, CDC and *in vivo* activity

against myeloma cell line xenografts [67]. In phase I dose-escalation trials, Daratumumab was well-tolerated and has shown single-agent activity, with an ORR of 24% (n = 29) [68]. A phase II study of daratumumab in proteasome inhibitor and IMiD refractory myeloma and a phase I/II in combination with lenalidomide and dexamethasone are currently open (clinicaltrials.gov ID NCT01985126 and NCT1615029). The second CD38 mAb, SAR650984, is currently being tested in a phase I dose-escalation and phase Ib combination study with lenalidomide and dexamethasone (clinicaltrials.gov ID NCT01749969 and NCT01084252). The phase I single-agent trial of SAR650984 has been completed and presented at the American Society of Hematology (ASH) 2013 annual meeting, showing good tolerance and promising activity, with an ORR 28% (n = 18, clinicaltrials.gov ID NCT01084252) [69]. The Phase I combination study of SAR650984 with lenalidomide and dexamethasone was recently reported at the American Society of Clinical Oncology (ASCO) 2014 annual meeting, demonstrating an ORR of 58% in heavily pre-treated patients (clinicaltrials.gov ID NCT01749969) [70]. Preclinical study of SAR650984 found this antibody to antagonize ADP-ribosyl cyclase activity of CD38 and induce apoptosis in primary myeloma patient cells *ex vivo* in addition to ADCC and CDC induction [71]. Thus, both anti-CD38 antibodies appear active and the FDA has designated breakthrough drug status for daratumumab in relapsed/refractory myeloma.

6.2. Anti-SLAMF7: elotuzumab

Elotuzumab, an anti-SLAMF7 antibody, is the most extensively studied naked antibody tested clinically for myeloma thus far [72]. Preclinical study of elotuzumab showed induction of ADCC *in vitro* and activity in myeloma xenografts into immunocompromised mice [48,49]. However, in phase 1 clinical trial of elotuzumab, this antibody was shown to be safe, but no objective responses were observed and only a portion had SD [73]. Thus, the clinical testing shifted to focus on combination regimens [74,75]. In a phase II trial, the combination of elotuzumab with lenalidomide and dexamethasone resulted in an ORR of 84% (n = 73) in relapsed myeloma [75]. This high response rate led to recent breakthrough designation by the FDA. Two randomized trials in both newly diagnosed and relapsed/refractory myeloma have been done to examine whether addition of elotuzumab to steroids, IMiDs and/or proteasome inhibitors increases the efficacy of those regimens (clinicaltrials.gov ID NCT01239797, NCT01891643, NCT01478048). These phase III trials are now complete and report of their results is awaited.

6.3. Anti-CD40 and Anti-CD74 antibodies

Other differentiation antigens on myeloma cells that have been targeted by mAbs in clinical trials include CD40 and CD74. Dacetuzumab (SGN-40) is an anti-CD40 antibody that shows both ADCC and signal transduction-mediated apoptosis in myeloma cells [76]. Again, a single-agent phase I trial showed no objective responses [77]. Studies have since been completed with dacetuzumab in combination with lenalidomide and dexamethasone, showing some mild activity in heavily pre-treated patients [78]. No current trials with dacetuzumab are open in myeloma. A second CD40 monoclonal antibody lucatumumab (HCD122) has also been studied in dose-escalation phase I trial in myeloma, with similar activity [79]. CD74 has been evaluated as a potential therapeutic target in myeloma with the antibody milatuzumab. Phase I trial with milatuzumab showed stable disease in a portion of

patients, but no objective responses [80]. Thus, CD40 and CD74 do not appear to be fruitful naked mAb targets in myeloma.

6.4. Anti-IGF-1R and Anti-IL6 Antibodies

Antigens important for myeloma pathogenesis that have been evaluated as targets for naked antibodies are IGF-1R and IL6. There are two antibodies to IGF-1R that have reached early clinical trials for myeloma. Preclinical evidence showed sensitivity of myeloma cell lines and primary samples to IGF-1R inhibition [46,81]. Figitumumab (CP-751871) is an IGF-1R antibody tested in phase 1. Partial responses were observed in combination with steroids, but not as a single agent [82]. AVE1642 is the other clinically tested anti-IGF-1R antibody, for which no responses were observed as a single agent and unclear contribution evident when combined with bortezomib. These results led to cessation of testing for myeloma [83]. One lesson taken from AVE1642 may be the importance for biomarker use in patient selection. IGF-1R expression and low CD45 have been shown *in vitro* to be critical to sensitivity for IGF-1R inhibition [83]. Those markers could have helped to pick patients most likely to respond. The antibody siltuximab utilized a different approach than targeting a cell surface protein. Siltuximab targets the secreted cytokine IL6. Multiple reports have shown that IL6 contributes to myeloma cell survival and proliferation, and confers resistance to bortezomib and steroids [84–86]. In phase I studies a small portion of patients responded to single-agent siltuximab in myeloma, with 2 of 13 patients achieving CR in one trial [87,88]. Unfortunately, single-agent activity was not confirmed in phase II, although activity was seen when combined with steroids [89]. Siltuximab is not currently undergoing further clinical study in myeloma, but rather is being pursued in Castleman's disease. Thus, naked antibodies targeting IGF-1R and IL6 have been disappointing in clinical trials for myeloma. However, in light of the documented importance of IGF-1R and IL6 to myeloma pathogenesis, they remain possible targets to explore with other modalities.

Overall, serious adverse events have been infrequent for mAbs tested in myeloma, with infusion-related reactions being the most common. These have been manageable with steroid premedication and administration adjustments. Unfortunately, naked antibody therapies based on pathogenically altered pathways in myeloma have thus far been disappointing. CD38 has emerged as the most promising mAb target thus far, with 2 independent agents producing substantial single-agent responses. There appear to be multiple mechanisms for the anti-myeloma activity of these naked anti-CD38 antibodies [67,71]. Although single-agent activity for mAb targeting SLAMF7 was modest, phase III trials to elucidate possible synergism with other effective myeloma treatments have recently reached completion and results are awaited.

7. Myeloma antibody–drug conjugates: preclinical & clinical results

7.1. Antibody–drug conjugates in clinical trials

Antibody–drug conjugates for myeloma are earlier in the pipeline than naked antibodies, and are garnering attention from recent successful examples of brentuximab vedotin and T-DM1. The furthest along is the anti-CD138 ADC indatuximab ravtansine (BT062). In preclinical testing, the EC50 *in vitro* was ~1 nM from negatively selected CD138-positive

cells from one myeloma patient [61]. Cytotoxicity for PMNCs was reported not present at the relatively low concentration of 12 nM [61]. The first-in-man, single-agent phase I study of indatuximab ravtansine in myeloma showed an ORR of 11%, with 41% achieving SD (n = 27) [90]. A phase I/IIa trial of indatuximab ravtansine in combination with lenalidomide and dexamethasone in 9 evaluable patients was recently reported at the annual ASH 2013 meeting, with 78% ORR [91]. The anti-CD56 ADC, lorvotuzumab mertansine, showed an EC50 in the range of 10–50 nM in 3 CD56 expressing myeloma cell lines, with maximum effect observed at 96 h [63]. Interestingly, cell surface expression did not correlate with sensitivity in the lines tested, possibly bringing in question the concept that expression level will always predict efficacy. Besides intrinsic sensitivity differences to mertansine, internalization could be another explanation for such variability in ADC efficacy. A phase I study presented for Lorvotuzumab mertansine in myeloma patients selected for CD56 expression produced an ORR 17%, with 28% SD [92]. Unfortunately, ImmunoGen later announced that the phase II study in myeloma and small cell lung cancer was discontinued due to lack of efficacy and infection-related adverse events. In sum, while clinical study of these new agents for myeloma is in its infancy, preliminary presentations have indicated single-agent activity is present for anti-CD138 and -CD56-ADCs, although indatuximab ravtansine is the sole agent being taken forward in further trials.

7.2. Preclinical antibody–drug conjugates

The antibody–drug conjugates in preclinical development target CD74, FcRL5 and BCMA. The preclinical characteristics of ADCs developed for myeloma are summarized in Table 3. Milatuzumab, anti-CD74 antibody conjugated to doxorubicin showed *in vitro* EC50 of 900 nM at 4 h with MC/CAR cells and *in vivo* activity against MC/CAR xenografts in SCID mice [64]. A phase I clinical trial for milatuzumab–doxorubicin is registered, but currently on hold (clinicaltrials.gov ID NCT01101594). Recently, Genentech developed ADCs targeting the FcRL5 protein. While expressed on myeloma cells from primary samples, FcRL5 was surprisingly not expressed on myeloma cell lines tested [52]. When stably expressed in the OPM2 myeloma cell line, anti-FcRL5 DM4, MMAF and MMAE conjugates each had EC50 of 50 ng/ml (0.33 nM) [52]. *In vivo*, DM4 and MMAE conjugates with cleavable linkers effectively inhibited tumor growth (by volume) in SCID mouse subcutaneous xeno-grafts of OPM2-FcRL5 and EJM-FcRL5 cells, showing similar activity as biweekly bortezomib [52]. Testing in monkeys was also performed to demonstrate tolerability prior to human testing [52]. Human testing for anti-FcRL5 ADC has not yet been registered.

A third target evaluated for antibody–drug conjugate development is BCMA. Preclinical presentation at ASH 2013 for an anti-BCMA antibody conjugated to MMAF, reported rapid internalization, trafficking of antibody to lysosomes and antigen recycling by 6 h [93]. They reported ADC cytotoxicity from 500–1000 ng/ml (3.3–6.6 nM) with primary myeloma cells [93]. A recently published report of anti-BCMA-ADC GSK2857916 further showed *in vitro* myeloma cell line EC50 ranging from 11.5–1000 ng/ml (0.08–6 nM) and potent elimination of myeloma cell line xenografts [57]. BCMA-ADC phase I trial is planned, but not yet open (clinicaltrials.gov ID NCT02064387). Also of interest, brentuximab vedotin is also in clinical trials for CD30-positive myeloma, although this is likely to be a minority of patients

(clinicaltrials.gov ID NCT01461538). On a limited number of samples (n = 7), plasma cells from 43% myeloma patients express CD30 [94]. Of ADC targets under study in myeloma, CD74, FcRL5 and BCMA have been shown to rapidly internalize bound antibody, whereas this has not been specifically addressed for CD138 or CD56 [40,52,93]. However, all of the discussed ADCs for myeloma appear potent *in vitro* and active by *in vivo* preclinical models. The phase I trials with these agents will likely open soon and hopefully will show promise for patients with relapsed or refractory disease.

8. Other antibody-related approaches to myeloma

8.1. Chimeric antigen receptor t-cell therapy

A discussion of immunotherapy for any hematologic malignancy nowadays must also mention the potential for chimeric antigen receptor T-cell (CAR-T) therapy and checkpoint inhibitors. CAR-T therapy genetically engineers a patient's collected T-cells to express a chimeric protein composed of an antibody variable domain and the T-cell receptor (TCR) signaling domain (CD3z), along with a fused or coexpressed coactivator protein. These T-cells are then re-infused and home to target antigen, where binding leads to TCR engagement, coactivator signaling and a potent proliferative and cytotoxic immune response. This approach has been surprisingly effective in producing long-term disease control in small clinical trials in acute lymphoblastic leukemia (ALL) and chronic lymphocytic leukemia (CLL) [95,96]. Complete response rate as high as 88% (n = 16) has been seen in ALL [97]. The possibility of CAR-T as a salvage strategy in myeloma has also begun to receive attention [56,98]. In the case of CAR-T therapy, antigen selection it is critically important to avoid even low level expression on normal cells, which has been shown to cause serious on-target organ toxicity from the potent T-cell activity [98]. For the CAR-T approach in myeloma, the only published construct thus far targets the BCMA receptor that is strictly confined to the B-cell lineage [56]. There is also a clinical trial in China currently recruiting to evaluate CD138 as the target for CAR-T therapy for resistant myeloma patients (clinicaltrials.gov ID NCT01638936). The CAR-T approach is a high-risk, high-reward strategy with potential for long-term disease control or cure at the expense of significant cytokine storm that often necessitates ICU-level care [96]. Plans to scale up this approach to increasing numbers of patients and new target malignancies are underway at select centers.

8.2. Immune checkpoint blockade

A second strategy for immunotherapy of cancer gaining interest is immune checkpoint blockade. This can be achieved through antibodies targeting surface receptors or ligands responsible for silencing the immune response. In theory disruption of these checkpoints may help the immune system recognize malignant cells. This is being validated by remarkable responses seen in solid tumors such as metastatic melanoma with the programmed death 1 (PD1) antibody nivolumab [99]. PD1-ligand (PD-L1) has been shown to be expressed on myeloma cells isolated from patients (n = 82), but was only present on a fraction (median 23%) of CD138-positive cells [100]. When present it is likely to silence prospective T-cell attack. Interestingly, in phase I dose-escalation study of the anti-PD1 antibody pidilizumab (CT-011) in hematologic malignancies, one myeloma patient was

included and had SD for over one year [101]. Two clinical trials are now recruiting for myeloma using PD1 antibodies nivolumab and pidilizumab (clinicaltrials.gov ID NCT02077959 and NCT01592370). One group has shown antibody blockade of PD1 with pidilizumab augments T-cell cytotoxicity of a dendritic anti-myeloma vaccine *ex vivo* [102]. A clinical trial is now recruiting patients to test antibody alone or in combination with vaccine after autologous stem cell transplant (clinicaltrials.gov ID NCT01067287). It is currently unclear whether the level of expression of PD-L1 in myeloma will be sufficient to translate to responses to this approach. Thus, we are eager to see clinical results from this immune cell-activating strategy for myeloma.

9. Conclusion and future directions

Antibody therapies are poised to aid in the treatment of myeloma. CD38 and CD138 were among the earliest markers used to identify myeloma cells and appear so far to translate to suitable antigens for targeted antibody therapy for this disease. Just recently, clinical trial abstracts for CD38 naked mAbs and CD138 ADC have showed encouraging single-agent ORR of 24–28% and 11%, respectively. By comparison, the phase I study of bortezomib in myeloma showed responses in 33% patients (n = 9) [103]. In the IMiD class, the lenalidomide phase I trial found ORR of 71% (n = 24) [104]. Elotuzumab has just completed two large Phase III trials, and has the potential of being the first FDA-approved mAb in myeloma. In the cases of CD38 mAb and CD138 ADC, single activity is clearly being seen, as it was at similar phase of development for proteasome inhibitors and IMiDs. As evidenced by the FDA breakthrough designation for daratumamab and elotuzumab, the enthusiasm for the new agents is widespread.

Important considerations remain in developing the future of antibody-based therapy in myeloma. These potential translational challenges are outlined in Table 4. Current myeloma treatments can induce deep remission, but relapse inevitably develops due to incomplete elimination of tumor cells and regrowth of resistant clones. Operationally speaking, those residual tumor cells with self-renewal potential may be considered myeloma initiating cells (M-IC). These cells may have different surface antigen expression than terminally differentiated myeloma cells. One possible limitation of targeting markers of terminal plasma cell differentiation, such as CD138, is the possible lack of their expression on M-IC [105,106]. Whether many of the markers discussed here, such as CD38, are expressed on M-IC is unknown. The lack of progress is due in part to the lack of appropriate markers that precisely de-fine M-IC. Thus, the reproducible characterization of cell surface markers on M-IC has clear implications on the curative potential of antibody-based therapies in this disease.

Another important issue is how these new antibodies, either naked or armed, will be integrated with currently used myeloma treatments. Combination therapy with steroids, proteasome inhibitors and IMiDs reduce ability of malignant cells to develop resistance to each individual agent. Combinations may also provide synergism in some cases. Of note, it has been shown that bortezomib influences the expression level of cell surface markers [107]. In the case of CD138 and CD38, both have been shown to have decreased expression after bortezomib treatment [107]. Other surface antigens may be unaffected or upregulated

by bortezomib. Thus, the influence of proteasome inhibitors on-target antigen expression is an important consideration for antibody directed therapies that will warrant investigation for each antigen. As these agents have widely different mechanisms of action, it may be anticipated that they will work well together and be synergistic in eliminating myeloma cells.

All together, the future treatment landscape for myeloma is taking shape rapidly. Whereas CD38 has emerged as the most promising naked antibody target, several ADCs have potential to improve the efficacy of naked antibody treatments. In addition to indatuximab ravtansine and lorvotuzumab mertansine, more ADCs are sure to undergo clinical testing in myeloma soon. These can conceivably improve on naked mAb efficacy as they have done with the examples discussed of HER2-positive breast cancer and Hodgkin lymphoma. Also, new technologies such as site-specific drug conjugation could further improve therapeutic index of current ADCs [108,109]. CAR-T approaches may also be another potent way to take advantage of the known myeloma antigens for improved therapies. Already in clinic, the new proteasome inhibitor carfilzomib and IMiD pomalidomide have improved the established drug classes and have good activity in bortezomib and lenalidomide refractory patients [110,111]. Combination of these next-generation agents with mAbs or ADCs may further improve response rate and depth of response. The full extent of benefit antibody therapies will contribute to this therapeutic armamentarium awaits randomized studies in the near future. These have exciting potential to enhance efficacy in combination regimens and importantly, to provide additional options to patients with proteasome inhibitor and IMiD refractory myeloma, a population without approved therapies available.

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Abbreviations

ASCO	American Society of Clinical Oncology
ASH	American Society of Hematology
ALL	acute lymphoblastic leukemia
ALCL	anaplastic large cell lymphoma
ADCC	antibody-dependent cellular cytotoxicity
ADC	antibody–drug conjugate
BM	bone marrow
CAR-T	chimeric antigen receptor T-cell
CLL	chronic lymphocytic leukemia

CDC	complement-dependent cytotoxicity
CR	complete response
EC50	half maximal effective concentration
EBMT	European Group for Blood and Marrow Transplant
GO	gemtuzumab ozogamicin
FcrL5	Fc receptor-like 5
HLA	human leukocyte antigen
HER2	human epidermal growth factor receptor 2
HL	Hodgkin lymphoma
IMiDs	immunomodulatory drugs
IGF-IR	insulin-like growth factor 1 receptor
LAMP1	lysosomal-associated membrane protein 1
MHC	major histocompatibility complex
mAb	monoclonal antibody
MFI	median fluorescence intensity
MMAE	monomethyl auristatin E
MMAF	monomethyl auristatin F;
M-IC	myeloma initiating cells;
ORR	overall response rate;
MR	minor response
PR	partial response
PD-L1	PD1-ligand
PC	plasma cell
PD1	programmed death 1
SPEP	serum protein electrophoresis
SLAMF7	signaling lymphocyte activation molecule family member 7
SD	stable disease
T-DM1	ado-trastuzumab emtansine
TCR	T-cell receptor
TTP	time to progression
TNF	tumor necrosis factor
VGPR	very good partial response

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Practice points

- Although myeloma treatment has seen great advances with the emergence of proteasome inhibitors and IMiDs, myeloma remains an incurable disease and development of resistance to standard agents remains inevitable.
- Efforts to broaden the applicability of antibody-based therapies to myeloma are approaching realization. One or more agents in this class may become FDA-approved in the next 1–2 years.
- Antibody–drug conjugates have entered early phase clinical study and hold promise to improve anti-myeloma activity over their naked antibody predecessors.

Research agenda

- Improved description of cell surface antigens present on myeloma initiating cells for targeting with antibody-based therapeutics with potential to eliminate the regenerative potential of the disease.
- Preclinical and clinical combination studies of antibody-based therapies with standard agents to find how these therapies interact and describe how they can best work together.
- Relapsed, high risk (*e.g.* loss of chromosome 17p containing p53) and newly diagnosed settings may each derive unique benefits and warrant studies to specifically address each.
- The technology for linkers and payloads used in antibody–drug conjugates continues to evolve. An important ongoing effort will be to incorporate the cutting-edge approaches into novel conjugates for clinical application.

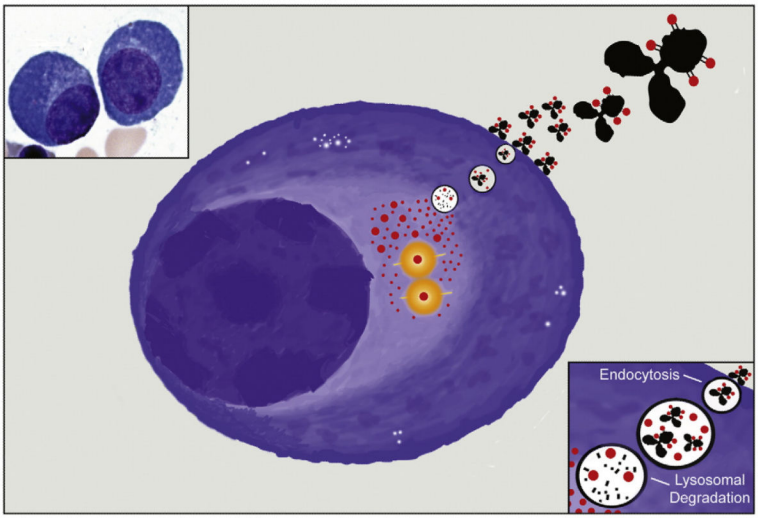

Fig. 1.

Illustration of a malignant plasma cell showing the mechanism of action for antibody–drug conjugates. ADC targets are ideally selected for endocytosis and trafficking into lysosome (upper right corner, magnified in lower right corner), where the antibodies are broken down (black), leaving the cytotoxic payloads (red) to diffuse out into the cytosol. In the case of commonly employed auristatin and maytansine derivatives, the payloads bind at their sites of action and induce microtubule catastrophe (yellow/orange) and lead to cell death. Upper left myeloma cell micrograph courtesy Kristie White, UCSF Hematopathology.

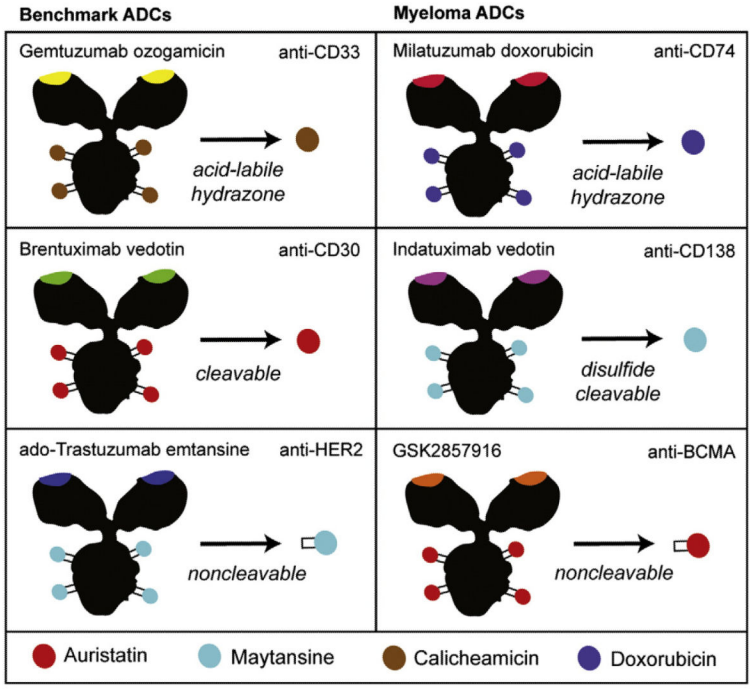

Fig. 2.

Mix-and-match antibody–drug conjugate construction. FDA-approved ADCs (left column) have consisted of gemtuzumab ozogamicin for AML (later withdrawn), brentuximab vedotin for Hodgkin lymphoma and ado-trastuzumab emtansine for breast cancer. The linkers and drugs used for this approach have evolved and diversified over this time. GO used a labile hydrazone linker connected to a DNA-damaging agent, whereas newer ADCs mostly utilize cleavable or non-cleavable linkers with potent antitubulins that optimize intracellular delivery. These technologies, which were pioneered by Seattle Genetics and Immunogen, have been adapted for other malignancies such as myeloma. Examples of ADCs developed for use in myeloma are shown in the right column, showing a mix of constructions similar to the previously FDA-approved agents.

Table 1

Summary of current antibody targets for myeloma.

Antigen	Protein description	Notable functions	Normal expression	% Patients	References
CD38	Cyclic ADP ribose hydrolase	Ectoenzyme, immune cell adhesion, cell signaling	Lymphocytes, monocytes, NK cells	100%	Leo et al. [25], Funaro et al. [112]
CD138	Heparin sulfate proteoglycan	Cell adhesion and signaling	Plasma cells, epithelial cells	100%	Bataille et al. [26], Sanderson et al. [28], and Hayashi et al. [29]
CD56	Neural cell adhesion molecule	Cell adhesion	NK cells, lymphocytes, neurons, muscle	78%	Van Camp et al. [31], Abo et al. [34], Lanier et al. [35], and Mechtersheimer et al. [36]
CD74	HLA-DR MHC-class II invariant chain	Antigen presentation	Lymphocytes, antigen presenting cells	86%	Burton et al. [37], Wraight et al. [38], and Claesson-Welsh et al. [39]
CD40	TNFR superfamily member	Antigen presentation, T-cell activation, B-cell growth and differentiation, cytokine production	Antigen presenting cells, B-cells, endothelium, smooth muscle, fibroblasts	70%	Uckun et al. [42], Mach et al. [43], Pellat-Decunynkck et al. [27], and Westendorf et al. [44]
IGF-1R	Insulin-like growth factor-1 receptor	Cell survival and proliferation	Ubiquitous	84%	Bataille et al. [45], Mitsiades et al. [46]
SLAMF7	Signaling lymphocyte activating-molecule related receptor family member	Cell adhesion	NK cells, T-cells, monocytes, dendritic cells	95%	Hsi et al. [48], Tai et al. [49], and Murphy et al. [50]
FcRL5	Immunoglobulin superfamily member	Proliferation and isotype expression of antigen-primed B-cells	B-lymphocytes	100%	Davis et al. [51], Elkins et al. [52], and Ise et al. [53]

Table 2

Summary of antibody therapeutics developed for the treatment of myeloma.

Agent	Company	Target	Description	Dose range	Phase I activity*	Notable AEs	Current status	References
Naked antibodies								
Daratumumab	Genmab, Janssen	CD38	Human IgG	0.005–16 mg/kg Q1W	ORR 24%, SD NR	Infusion-related events (G3, 6%)	Phase II (open)	Plesner et al. [68]
SAR650984	Sanofi	CD38	Humanized IgG1	1–10 mg/kg Q1–2 W	ORR 28%, SD 11%	Pneumonia (G3, 6.3%), hyperglycemia (G3, 3.1%), infusion reaction (G2, 3.1%)	Phase I, Ib (open)	Martin et al. [69,70]
Elotuzumab	Bristol-Myers Squibb	SLAMF7	Humanized IgG1	10–20 mg/kg Q2W	ORR 0%, SD 26%	Acute kidney injury (G4, 3%), hypersensitivity (G3, 3%), bradycardia (G2, 3%), chest pain (G2, 3%), pyrexia (G2, 3%), chills (G2, 3%)	Phase III (results awaited)	Zonder et al. [73]
Dacetuzumab	Seattle Genetics	CD40	Humanized IgG	0.5–12 mg/kg Q1W	ORR 0%, SD 20%	Aseptic meningitis (G3–4, 5%), ocular inflammation (G1–2 21%), cytokine release syndrome (G3, 5%), transaminitis (G2–3, 9%)	No current myeloma trials	Hussein et al. [77]
Lucatumumab	Novartis	CD40	Human IgG	1–6 mg/kg Q1W	ORR 4%, SD 43%	Thrombocytopenia (G4, 4%), transaminitis (G3, 4%), and increased lipase (G4, 1%)	No current myeloma trials	Bensinger et al. [79]
Figitumumab	Pfizer	IGF-1R	Human IgG2	0.025–20 mg/kg Q4W	ORR 0%, SD 59%	Anemia (G2–3, 9%), hyperglycemia (G3, 2%)	No current myeloma trials	Lacy et al. [82]
AVE1642	Sanofi	IGF-1R	Humanized IgG	3–18 mg/kg Q2W	ORR 7%, SD 47%	Hyperglycemia (G3, 7%)	DC in myeloma	Moreau et al. [83]
Siltuximab	Janssen	IL6	Chimeric IgG	5–40 mg daily × 14 days (Ref 87), 3–12 mg/kg Q1–3 W (Ref 88)	ORR 0%, SD NR (Ref 87), ORR 15%, SD 61% (Ref 88)	Neutropenia (Ref 60, G1–4, 46%), thrombocytopenia (Ref 60, G1–4, 46%), infection (Ref 60, G1–4, 66%)	No current myeloma trials	Van Zaanen et al. [87], Kurzrock et al. [88]
Milatuzumab	Immunomedics	CD74	Humanized IgG	1.5–16 mg/kg BIW	ORR 0%, SD 26%	Anemia (G3, 4%), infusion reaction (G3 4%)	No current myeloma trials	Kaufman et al. [80]
Antibody–drug conjugates								
Indatuximab Ravtansine	Biotest	CD138	Chimeric IgG-DM4	10–200 mg/m^2 Q3W	ORR 11%, SD 41%	Mucositis, stomatitis or hand–foot syndrome (G2–3), dry eyes or blurred vision (G1–2)	Phase I/Iia (open)	Jagannath et al. [90]

Agent	Company	Target	Description	Dose range	Phase I activity*	Notable AEs	Current status	References
Lorvotuzumab mertansine	ImmunoGen	CD56	Humanized IgG-DM1	40 to 140 mg/m^2 Q1W	ORR 18%, SD 28% (all doses)	Fatigue, renal failure, weakness, and absence of deep tendon reflexes (each G3, 4%)	DC in myeloma	Chanan-Khan et al. [92]

*Cross-comparison of Phase I activity is not possible due to multiple variables, including varying dose-escalation schemes, patient disease characteristics and prior treatment regimens. AE = adverse events, BIW = dose twice weekly, DC = discontinued. G = adverse event grade, NR = not reported, ORR = overall response rate, Q1W = dose weekly, Q2W = dose every 2 weeks, Q4W = dose every four weeks, Q1–2 W=dose every 1–2 weeks, Q1–3 W = dose every 1–3 weeks, SD = stable disease.

Table 3

Summary of preclinical results for antibody–drug conjugates developed for myeloma.

	Company	Target	Linker	Payload	MM cell EC50*	Pros	Cons	Trial status
Indatuximab Ravtansine	Biotest	CD138	Cleavable	DM4	1 nM	Good target cell specificity	Internalization efficiency unknown	Phase I/Iia (open)
Lorvotuzumab mertansine	ImmunoGen	CD56	Cleavable	DM1	10–50 nM	Upregulated expression on MM cells	Expression on other cell types	Development discontinued
Milatuzumab–DOX	Immunomedics	CD74	Acid labile hydrazone	Doxorubicin	900 nM	Rapid internalization and recycling	Lower potency, labile linker	Phase I (not open)
anti-FcrL5 ADC	Genetech	FcrL5	Cleavable & non-cleavable	DM4, MMAF and MMAE	0.33 nM	High target cell specificity	Low expression level?	Not yet registered
GSK2857916	GlaxoSmith Kline	BCMA	Non-cleavable	MMAF	0.08–6.6 nM	High target cell specificity	Variable expression level	Phase I (not open)

*Cross-comparison of agent EC50s is limited due to varying assay conditions and cell lines used in the study.

Table 4

Future challenges to the application of antibody-based therapies to myeloma.

Challenges	Clinical relevance	Research objectives to be addressed	
Target expression on M-IC	Finding curative potential	**1**	M-IC characterization & clarification of published discrepencies (M-IC markers may vary patient–patient).
		2	Characterize antigen of interest in (various) population(s) of M-IC.
Ideal drug combinations	Finding synergism and avoiding antagonism	**1**	Study antigen expression *in vitro* with proteasome inhibitors, IMiDs and steroids.
		2	*In vivo* animal model assessment of agent in combination with standard drugs.
Disease setting	Utility in relpased, refractory or newly diagnosed disease	**1**	Clinical need in relapsed disease where resistance to current agents has evolved.
		2	Patients with high risk and/or refractory myeloma, such as patients with deletion of 17p and plasma cell luekemia.
		3	Potential for cure (or deeper remission) in standard induction regimens with or without autologous stem cell transplant.
Optimization of ADCs	Maximizing efficacy	**1**	Selection of ideal antigens for this modality (*e.g.* internalization kinetics, expression level and pattern).
		2	Companion biomarker development (*e.g.* immunohistochemistry, flow cytometry).
		3	Incorporation of linker and payload technology improvments.

ADC = antibody–drug conjugate, M-IC = myeloma initiating cells.