Monoclonal antibodies in the treatment of multiple myeloma

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Summary

Despite recent advances in treatment that have significantly improved overall survival, multiple myeloma (MM) remains incurable. Although rituximab, the first monoclonal antibody (MAb) evaluated in MM treatment, provided only very limited benefit, research is ongoing into a number of other MAbs directed against a variety of MM-related target antigens. Given the inherent immune dysfunction associated with MM, newer strategies that may enhance immune function in conjunction with antibodies may also provide a more fruitful clinical approach. Potential MAb targets in MM include growth factors and their receptors, other signalling molecules, and antigens expressed exclusively or predominantly on MM cells. MAb therapy involves a range of mechanisms, including antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, interference with receptor-ligand interactions, and MAb conjugation to radioisotopes or toxins. The antigens currently targeted in MM therapy are discussed, along with the development status of the corresponding MAb therapeutics. Elotuzumab, an anti-CS1 MAb, has recently achieved clinically meaningful responses when combined with lenalidomide or bortezomib in patients with relapsed and relapsed/refractory MM. Other MAbs are also showing early promise. More ongoing clinical research is required to identify optimal combination regimens and biomarkers that may help predict response to specific MAb-based combinations.

Keywords: multiple myeloma, monoclonal antibodies, novel therapies, novel targets, targeted therapies.

Multiple myeloma (MM) is a malignancy of plasma cells and represents about 15% of newly-diagnosed haematological cancers in the USA; specifically, about 20 000 new MM cases are diagnosed each year, with MM accounting for more than 10 000 fatalities annually (Jemal et al, 2010). Prior to the introduction of chemotherapy using the alkylating agent melphalan (in combination with prednisone) in the early 1960s, median survival in MM was <1 year after diagnosis; melphalan-prednisone combination therapy improved the median survival to 2–3 years at best (Kumar et al, 2008; San Miguel et al, 2008). Since then, clinical advances in MM therapy have included the use of high-dose chemotherapy supported by autologous stem cell transplantation (ASCT) in the mid-1990s; the development of bisphosphonates for the treatment of MM-related bone disease; the introduction of thalidomide as MM therapy in the late 1990s; the approval of the first-in-class proteasome inhibitor bortezomib in 2003; and the later introduction of the second generation immunomodulatory drug (IMiD®) lenalidomide in 2005 (Kumar et al, 2008; Mhaskar et al, 2010).

These therapeutic advances, particularly the introduction of bortezomib, thalidomide, and lenalidomide, have led to clinically significant increases in overall survival (OS). For example, a retrospective study of 2981 Mayo Clinic patients showed that median OS from date of diagnosis was 29·9 months [95% confidence interval (CI) 28·3–31·6 months] for patients diagnosed prior to December 1996, compared with 44·8 months (95% CI 39·6–50·0 months) for those diagnosed between January 1997 and December 2006 (Fig 1) (Kumar et al, 2008).

The observed gains in OS were achieved primarily by younger patients: for patients ≤65 years at diagnosis, median OS was 60 months for diagnoses between 1997 and 2006 and 33 months for diagnoses prior to 1997; in contrast, for patients >65 years at diagnosis, median OS was 32 months and 26 months for diagnoses between 1997 and 2006 and prior to 1997, respectively. OS gains were particularly important among patients who relapsed following ASCT, and these increases are clearly attributable to the introduction of novel agents, and in the case of this study predominantly thalidomide and lenalidomide (Fig 2). During the past decade, median OS among patients who received 1 or more of the newer drugs after post-ASCT relapse was 30·9 months (95% CI 23·6–38·2 months), compared to 14·8 months (95% CI 11·3–18·4 months) for those who did not ($P < 0·001$) (Kumar et al, 2008).

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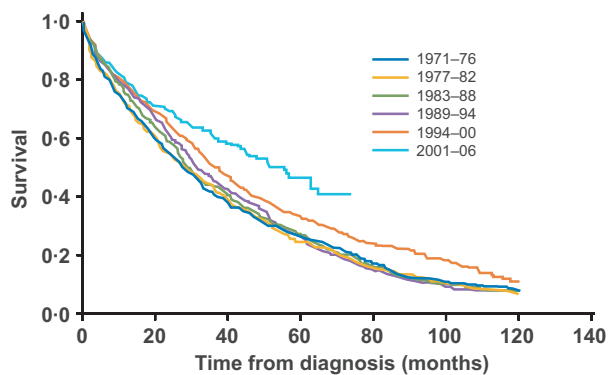E-mail: paul_richardson@dfci.harvard.edu

Fig 1. Improvements in multiple myeloma overall survival following diagnosis, 1971–2006.Source: *Blood* by American Society of Hematology. Copyright 2008 Reproduced with permission of American Society of Hematology (ASH) in the format Journal via Copyright Clearance Center.

Fig 2. Improvements in multiple myeloma overall survival following relapse after autologous stem cell transplantation.Source: *Blood* by American Society of Hematology. Copyright 2008 Reproduced with permission of American Society of Hematology (ASH) in the format Journal via Copyright Clearance Center.
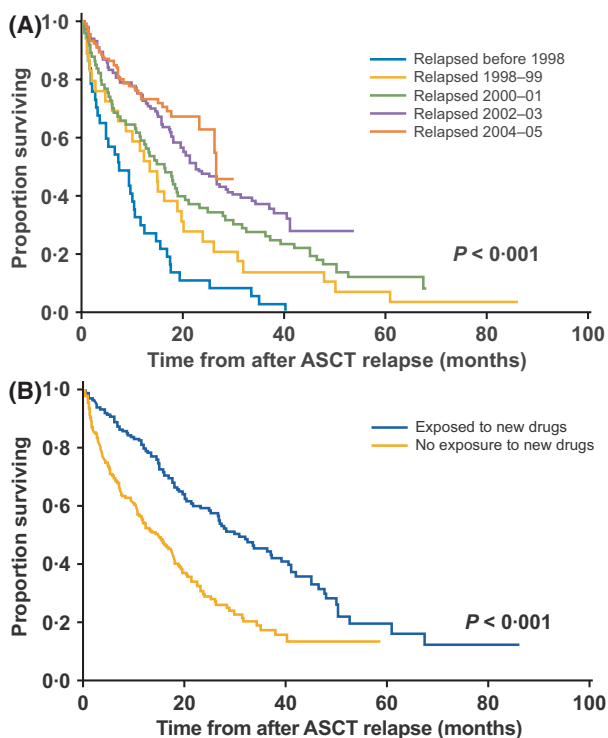
A similar pattern of improvements in OS was observed in a Swedish study of MM therapy, in which patients were stratified by date of diagnosis and age at diagnosis (Kristinsson *et al*, 2007). Across all age groups, 1-year survival improved significantly among patients diagnosed during 1994–2003 compared with those diagnosed during 1973–1979 and 1980–1986. However, as with the Mayo Clinic study, significant

improvements in 5-year and 10-year survival were confined to patients younger than 60 years and 70 years at diagnosis, respectively.

Despite these documented improvements in OS, MM remains incurable in the vast majority of patients. Although MM has become a more treatable disease, the development of resistant/refractory disease is inevitable, and leads to death. Thus, an urgent need remains for therapies that can further extend disease control, potentially achieving longer term remission in patients with MM, and ideally without the addition of significant treatment-related toxicities.

In addition to the established use of thalidomide, lenalidomide, and bortezomib-based combination therapies (Richardson *et al*, 2007), a number of new targeted agents, developed on the basis of disease biology, are being pursued both as monotherapy and in combination with established treatment options (Table I). These include second generation proteasome inhibitors (such as carfilzomib) and third generation immunomodulatory drugs (specifically pomalidomide) (Jagannath *et al*, 2010); inhibitors of histone deacetylase (vorinostat, panobinostat, romidepsin), heat shock protein 90 (tanespimycin), Akt (perifosine), and kinesin spindle protein (KSP; ARRY-520) (Jagannath *et al*, 2010; Shah *et al*, 2010; Niesvizky *et al*, 2011); enhancers of natural immune surveillance using vaccination or dendritic cell infusion (Rosenblatt *et al*, 2011); and a range of monoclonal antibodies (MAb) directed at mediators of MM cell survival, tumour progression, and interactions with the bone marrow (BM) microenvironment.

This review focuses on the role of MAb therapy in MM, describing potential targets and agents currently in development. We examine targets and MAbs that have demonstrated a high level of cytotoxicity/efficacy against MM in preclinical and clinical studies.

Monoclonal antibody therapy in multiple myeloma

General considerations

A wide range of antigens may ultimately be targeted in MM therapy, including those involved in cell survival, anti-apoptotic pathways, cell-to-cell communication, angiogenesis, and interactions between MM cells and bone marrow stromal cells (BMSCs) and/or other cells in the BM microenvironment (Kastritis *et al*, 2009; Di Bernardo *et al*, 2010). These potential targets include signalling molecules, cell surface receptors and other cell surface proteins, plasma cell growth factors, and mediators of adhesion. Ideally, a useful target for MAb-based MM therapy should be expressed exclusively on a majority of MM cells (or other target cells such as those involved in angiogenesis), or to a much higher level than on non-target cells (Di Bernardo *et al*, 2010).

Effective MAb-based MM therapy may involve a number of potential mechanisms, including direct cytotoxic effects and

Table I. Selected novel therapies in development for treatment of multiple myeloma (excluding monoclonal antibodies).

Name (Brand name)	Developer	Type	Status*	Regimen
Carfilzomib	Onyx Pharmaceuticals, San Francisco, CA, USA	Proteasome Inhibitor	Phase 3 enrolling	+ lenalidomide + dexamethasone
Pomalidomide	Celgene Corporation, Summit, NJ, USA	IMiD®	Phase 3 enrolling	Monotherapy + dexamethasone
Vorinostat (Zolinza®)	Merck & Co., Inc., Whitehouse Station, NJ, USA	HDAC inhibitor	Phase 3 ongoing	+ bortezomib
Panobinostat	Novartis Oncology, East Hanover, NJ, USA	HDAC inhibitor	Phase 3 enrolling	+ bortezomib + dexamethasone
Romidepsin	Celgene Corporation	HDAC inhibitor	Phase 2 ongoing	Monotherapy + bortezomib
Perifosine	Keryx Biopharmaceuticals, New York, NY, USA	Akt inhibitor	Phase 3 ongoing	+ bortezomib + dexamethasone
Arry-520	Array Biopharma, Boulder, CO, USA	KSP inhibitor	Phase 1/2 enrolling Phase 1 enrolling	Monotherapy + bortezomib + dexamethasone

HDAC, histone deacetylase; Hsp, heat shock protein; IMiD®, immunomodulatory drug; KSP, kinesin spindle protein.
*In most advanced clinical trial(s).

interference with cell-cell interactions. The most commonly observed cytotoxic mechanisms in preclinical and early clinical studies are antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). Other possible mechanisms include interference with ligand binding (e.g. growth factor or G-protein coupled receptors) and the use of MAbs as targeted 'carriers' of cytotoxic agents. The latter mechanism may be especially useful as a way of conveying intracellular toxins (in the case of MAbs that are internalized) or radioactive isotopes, which may have cytotoxic effects that extend beyond cells bearing specific MAb targets (Weiner *et al*, 2010).

Rituximab in MM

The earliest evaluations of MAb therapy targeting MM were based on the success of rituximab, an antibody to the B-cell specific antigen CD20, in the treatment of lymphoma. Rituximab was the first MAb approved for any cancer therapy, and is currently indicated for treatment of chronic lymphocytic leukaemia and non-Hodgkin lymphoma (http://www.gene.com/gene/products/information/pdf/rituxan-prescribing.pdf). Rituximab exhibits impressive activity in these disease states, especially in combination with cytotoxic chemotherapy and as maintenance therapy (Kapoor *et al*, 2008; Salles *et al*, 2011).

However, clinical studies of rituximab therapy in MM have generally been disappointing, with few patients achieving only minimal responses (MR) (Kapoor *et al*, 2008). The failure of rituximab in this setting is potentially attributable to the small number of MM patients (estimated at 13–22%) who express CD20 in primarily a low proportion of plasma cells. Another mechanism that may render MM refractory to rituximab is the possibility that MM cells express increased levels of comple-

ment-inhibiting proteins, reducing the effectiveness of CDC. In addition, Fc-γ receptor polymorphism may limit the effectiveness of ADCC as a killing mechanism. Finally, the use of rituximab in MM may induce a selective loss of CD20 expression.(Kapoor *et al*, 2008) Although it is conceivable that rituximab may be useful in certain carefully-selected MM patients, such as t(11;14) translocation patients, who exhibit relatively high CD20 expression (Robillard *et al*, 2003), it is unlikely to be of value in the majority of MM cases.

Novel targets and MAbs in development

A number of other potential antigen targets are being investigated in the context of MM therapy, and several have reached clinical trials. Some of the most promising MM-related antigen targets are described here, along with the corresponding MAb therapeutics in development (Table II).

Interleukin-6 (IL-6). IL-6 has been recognized as a key cytokine in the development and progression of MM, exerting anti-apoptotic activity and multiple additional effects within the BM. IL-6 is produced predominantly by BMSCs, and is upregulated by multiple cytokines (Kastritis *et al*, 2009). Both IL-6 and its receptor, IL-6R, are potential targets for MAb-based intervention.

A chimeric anti-IL-6 MAb, siltuximab (CNTO 328), enhances dexamethasone-induced cytotoxicity in MM cell lines and in MM cells from patients refractory to dexamethasone therapy; it also enhances the cytotoxicity of the bortezomib plus dexamethasone combination (Trikha *et al*, 2003; Voorhees *et al*, 2009). Siltuximab has demonstrated activity in the lymphoproliferative disorder Castleman's disease (van Rhee *et al*, 2010), and is currently being evaluated in MM in multiple single-arm and randomized

Table II. Monoclonal antibodies in development for treatment of multiple myeloma.

Antigen	Antibody name/Designation (Brand name)	Developer	Type	Status	Regimen*
CD138 (Syndecan-1)	B-B4	NA	Murine (conjugated to DM1)	Preclinical	NA
	nBT062	NA	Chimeric (conjugated to maytansinoids)	Preclinical	NA
CD20	Rituximab (Rituxan®)	Genentech (South San Francisco, CA, USA), a member of the Roche Group/Biogen Idec	Chimeric	Approved (for NHL and CLL); Phase 1 and Phase 2 studies in MM ongoing	+ cyclophosphamide; + melphalan + fludarabine (with ASCT)
	Yttrium-90 ibritumomab (Zevalin®)	Spectrum Pharmaceuticals, Henderson, NV, USA	Murine (radioconjugate)	1 Phase 1 study and 1 Phase 2 study recruiting	+ rituximab + melphalan (prior to ASCT); monotherapy (prior to ASCT)
	Iodine-131 tositumomab (Bexxar®)	GlaxoSmithKline, Brentford, Middlesex, UK	Murine (radioconjugate)	Phase 2 study recruiting	Monotherapy (consolidation therapy)
CD200	ALXN6000	Alexion Pharmaceuticals, Inc., Cheshire, CT, USA	Humanized	Phase 1/2 study ongoing	Monotherapy
CD38	HuMax-CD38	Genmab, Copenhagen, Denmark	Fully human	Phase 1/2 study recruiting	Monotherapy
CD40	Dacetuzumab (SGN-40)	Seattle Genetics, Bothell, WA, USA	Humanized	Phase 2 study completed	+ lenalidomide + dexamethasone
	Lucatumumab (CHIR-12-12, HCD122)	Novartis Oncology, East Hanover, NJ, USA	Fully human	Phase 1 study terminated (lack of activity)	Monotherapy
CD56	Lorvatuzumab mertansine (IMGN901)	ImmunoGen, Inc., Waltham, MA, USA	Humanized (conjugated to DM1)	2 Phase 1 studies recruiting	Monotherapy; + lenalidomide + dexamethasone
CD74	Milatuzumab (hLL1)	Immunomedics, Inc, Morris Plains, NJ,USA	Humanized (also conjugated with doxorubicin)	Phase 1 study completed (MAb alone); Phase 2 study recruiting (MAb + doxorubicin conjugate)	Monotherapy
CS-1 (CD2 subset 1, CD319, CRACC, SLAMF7, 19A24)	Elotuzumab (HuLuc63)	Abbott Biotherapeutics†/Bristol-Myers Squibb Company (Brentford, Middlesex, UK)	Fully human	Phase 1 study completed; 2 Phase 1/2 studies ongoing; Phase 3 study announced, not yet recruiting	Monotherapy; + bortezomib; + lenalidomide + dexamethasone; +/- elotuzumab as adjunct to lenalidomide + dexamethasone
Epidermal Growth Factor Receptor (EGFR)	Cetuximab (Erbitux®)	Bristol-Myers Squibb Company	Chimeric	Phase 2 study (EMMA-1) recruiting	+/- dexamethasone
GM-2 ganglioside	BIW-8962	Kyowa Hakko Kirin Pharma, Inc., Princeton, NJ, USA	Humanized	Phase 1/2 study ongoing	Monotherapy

Table II. (Continued)

Antigen	Antibody name/Designation (Brand name)	Developer	Type	Status	Regimen*
Interleukin-6 (IL-6)	Siltuximab (CNTO 328)	Centocor Ortho Biotech Inc, Horsham, PA, USA	Chimeric	Phase 2 study recruiting	+ melphalan + prednisone + bortezomib
	1339	NA	Fully human	Preclinical	NA
Killer Cell Immunoglobulin-like Receptors (KIR)	IPH 2101	Innate Pharma, Marseille, France	Fully human	Phase 2	Monotherapy; + lenalidomide
Vascular Endothelial Growth Factor (VEGF)	Bevacizumab (Avastin®)	Genentech (South San Francisco, CA, USA), a member of the Roche Group	Humanized	3 Phase 2 studies (1 recruiting, 1 ongoing, 1 complete)	+ bortezomib (2 studies); + lenalidomide + dexamethasone

ASCT, autologous stem cell transplant; CLL, chronic lymphocytic leukaemia; NA, not available; NHL, non-Hodgkin lymphoma.
*In most advanced clinical trial(s).
†Facet Biotech is now Abbott Biotherapeutics.

Phase 2 studies, either alone or in combination with bortezomib (NCT01219010, NCT00402181, NCT00911859, NCT00412321, NCT00401843). Preliminary results in combination with bortezomib have shown promise, with a 57% objective response rate (ORR), although grade 3+ haematological toxicities were somewhat common (Rossi et al, 2008). A Phase 3 study of siltuximab or placebo in combination with bortezomib and dexamethasone is underway (NCT01266811).

A murine anti-IL-6 MAb, BE-8, has been evaluated in combination with dexamethasone and high-dose melphalan as a conditioning regimen for ASCT; the combination induced a response in 13 of 16 patients (81%) and a complete response (CR) in 6 patients (37·5%). The overall response (OR) was similar to historical controls by the same group of high-dose melphalan; however, the CR rate appeared to be higher, and was correlated with IL-6 neutralization (Moreau et al, 2000). In a subsequent prospective, multicentre randomized trial by the same group, the addition of BE-8 to the melphalan plus dexamethasone conditioning regimen showed no improvement in response or survival rates for patients with high-risk MM (Moreau, et al 2006).

Tocilizumab is a humanized anti-IL-6 MAb currently approved for rheumatoid arthritis in several countries and for Castleman disease in Japan. Tocilizumab has demonstrated efficacy in a murine MM model (Yoshio-Hoshino et al, 2007) and is currently being evaluated clinically in MM. Another anti-IL-6 MAb, 1339, has demonstrated activity on MM cell lines (co-cultured with BMSCs) in vitro, and in murine xenograft MM models; it is not yet being evaluated clinically (Fulciniti et al, 2009a).

Vascular endothelial growth factor (VEGF). VEGF is a key cytokine that promotes angiogenesis in a variety of tumour types, facilitating improved blood flow that is critical to tumour cell survival (Veikkola et al, 2000). Bevacizumab, a humanized anti-VEGF MAb, is currently indicated for treatment of colorectal cancer (http://www.gene.com/gene/products/information/pdf/avastin-prescribing.pdf). In a Phase 2 study in patients with relapsed/refractory MM, seven of 10 patients responded [partial response (PR)] to bevacizumab in combination with low-dose dexamethasone and lenalidomide (Raschko et al, 2007). An additional Phase 2 study of the same combination reported similar results in a larger patient population (OR 19/27, 70%) (Callander et al, 2009), noting that this response rate was not significantly different from that seen in the pivotal Phase 3 trial of lenalidomide plus dexamethasone (61%) (Weber et al, 2007). An additional Phase 2 study of this combination is currently recruiting patients (NCT00410605) and the drug is also being evaluated in combination with bortezomib (NCT00464178, NCT00473590).

CD40. CD40 is a member of the tumour necrosis factor (TNF) receptor superfamily that is highly expressed on MM cells and on BMSCs (Tai et al, 2002, 2003). The activation of

CD40 by its ligand (CD40L) induces a range of biological effects, including MM cell proliferation and migration, mediated primarily via the PI3K/AKT pathway, and induction of VEGF overexpression. VEGF overexpression is especially pronounced in MM cells with mutated *TP53*, and VEGF also stimulates production of IL-6 by BMSCs (Tai *et al*, 2002, 2003).

Two anti-CD40 antibodies, dacetuzumab (SGN-40) and lucatumumab (CHIR-12·12, HCD122), have been evaluated in preclinical studies. SGN-40 is a humanized anti-CD40 MAb that induces cell death and/or growth arrest in MM cell lines; among other effects, dacetuzumab down-regulates IL-6R, rendering cell lines unresponsive to IL-6 stimulation (Tai *et al*, 2004). Cell line studies and a Phase 1 monotherapy study have shown that the primary cytotoxic mechanisms appear to be induction of apoptosis (potentially related to IL-6R suppression) and ADCC (Hayashi *et al*, 2003; Tai *et al*, 2004). The observation that SGN-40-induced MM cell death is enhanced by lenalidomide (Tai *et al*, 2005a) led to its evaluation in a Phase 1 study in combination with lenalidomide and dexamethasone in patients with relapsed or refractory MM; an OR of 39% (13/36) was seen, with some activity noted in patients receiving prior lenalidomide (Agura *et al*, 2009).

Lucatumumab is a fully human anti-CD40 MAb that inhibits MM cell growth *in vitro*, even when MM cells are cocultured with BMSCs. Animal studies have shown that the primary cytotoxic mechanism is ADCC (Tai *et al*, 2005b). Lucatumumab has been found to inhibit multiple pathways that are induced by CD40L binding to CD40, including AKT phosphorylation and signalling and MM cell adhesion to BMSCs and to fibronectin, in addition to suppression of IL-6 and VEGF (Tai *et al*, 2005b). However, a Phase 1 study of lucatumumab in patients with relapsed/refractory MM was terminated because of minimal biological and clinical activity (NCT00231166).

CD74. CD74 is a transmembrane protein that forms the invariant portion of HLA-DR; it is expressed on MM cells in a majority of patients. Because CD74 exists in a dynamic pool and is rapidly internalized, an anti-CD74 antibody might be useful as a carrier for cytotoxins (Burton *et al*, 2004). This approach is being employed with milatuzumab (hLL1), a humanized anti-CD74 MAb coupled with the anthracycline doxorubicin to form a conjugated antibody designated IMMU-110 (Sapra *et al*, 2005). In cell line and mouse xenograft experiments, IMMU-110 demonstrated high activity against MM, and it also appeared to be safe in a monkey model of MM (Sapra *et al*, 2005). IMMU-110 is being evaluated in a Phase 1/2 study (NCT00421525), and a Phase 2 study is currently ongoing (NCT01101594).

CD56. CD56 (neural cell adhesion molecule, NCAM) is expressed on neurons, muscle cells, and a variety of tumours, including MM; it appears to mediate cell adhesion, migration,

and invasion (Mechtersheimer *et al*, 1992; Lutz & Whiteman, 2009). Lorvotuzumab mertansine (IMGN901), an immunoconjugate composed of a humanized MAb to CD56 (huN901) conjugated to the maytansinoid DM1, has shown activity against MM cell lines (Tassone *et al*, 2004a; Lutz & Whiteman, 2009). Two Phase 1 studies (one as monotherapy, one in combination with lenalidomide and dexamethasone) are currently recruiting patients (NCT00346255, NCT00991562).

CD38. CD38 is a glycoprotein found on the surface of many immune system cells, including MM cells (Stevenson, 2006). A human anti-CD38 MAb, HuMax-CD38, has demonstrated preclinical activity against MM cell lines and patient-derived MM cells, with cytotoxic effects that involve both ADCC and CDC (Stevenson, 2006). HuMax-CD38 is being evaluated in a Phase 1/2 safety study in patients with relapsed or refractory MM that is currently recruiting participants (NCT00574288). Results of this preliminary study are awaited with interest, with early reports suggesting favourable tolerability and disease stabilization in some patients.

CD138 (Syndecan-1). CD138 is a cell surface heparin sulphate proteoglycan, highly expressed on plasma cells and MM cells, that is involved in cell adhesion and maturation (Tassone *et al*, 2004a; Ikeda *et al*, 2009). Two different MAbs conjugated to cytotoxic maytansinoid derivatives (which disrupt microtubule assembly) have been evaluated in preclinical studies. B-B4 is a murine MAb against CD138 that has been conjugated to the maytansinoid DM1; it is cytotoxic *in vitro* to MM lines, and to MM lines and patient-derived MM cells in mouse xenograft models (Tassone *et al*, 2004b). BT062 is a chimeric MAb conjugated to maytansinoid derivatives that demonstrates *in vitro* cytotoxicity and inhibition of MM cells in mouse xenograft models, apparently via apoptotic mechanisms; BT062 also inhibits the adherence of MM cells to BMSCs and abrogates the protective effects exerted by growth factors and BMSCs on MM cells (Ikeda *et al*, 2009). A Phase 1 dose-finding study of BT062 for patients with relapsed/refractory MM is underway (NCT00723359), and an additional Phase 1/2a study is recruiting patients with advanced MM (NCT01001442).

GM-2 ganglioside. GM-2 is a ganglioside expressed on MM cells. A humanized anti-GM-2 MAb, BIW-8962, has demonstrated *in vitro* killing of MM cell lines and *in vivo* effectiveness in mouse xenograft models, with ADCC and CDC the most prominent cytotoxic mechanisms (Ishii *et al*, 2008). BIW-8962 is being evaluated as monotherapy in a Phase 1/2 study for patients with relapsed/refractory MM (NCT00775502).

CD200. CD200 is a highly conserved transmembrane glycoprotein expressed on a wide range of cell types; however, expression of the receptor for CD200 (CD200R1) is

apparently limited to antigen-presenting cells of myeloid lineage and certain T-cell populations, and is thought to deliver inhibitory signals. The expression of the *CD200* gene by MM cells has been found to be a predictor of poor prognosis in patients with MM (Moreaux *et al*, 2006). ALXN6000 is a humanized anti-CD200 MAb that is currently being evaluated in a Phase 1/2 study in patients with MM or B-cell CLL (NCT00648739), with results expected in the near future.

Killer cell immunoglobulin-like receptors (KIR). KIRs are receptors expressed on natural killer (NK) cells and a subset of T cells and function as key regulators of NK cell activity (Campbell & Purdy, 2011). Several studies are currently underway in smouldering and first relapse MM (NCT01222286, NCT01217203, NCT00999830, NCT01248455), and safety and tolerability results are expected later in 2011 for a Phase 1 study in relapsed or refractory MM (NCT00552396).

CS1 (CD2 subset 1, CD319, CRACC, SLAMF7, 19A24). CS1 is a cell surface glycoprotein universally expressed at high levels on MM cells but with limited expression on normal cells (Hsi *et al*, 2008; Tai *et al*, 2008). The function of CS1 is not well characterized, but it appears to play a critical role in interactions between MM cells and BMSCs (Tai *et al*, 2008). Its expression pattern suggests that it may be an attractive target for MAb therapy in MM. Elotuzumab (HuLuc63) is a fully humanized MAb against CS1 that has shown significant *in vitro* activity as monotherapy against patient-derived MM cell lines, and *in vivo* activity in a mouse MM xenograft model (Tai *et al*, 2008). These studies showed that elotuzumab-induced cell death was mediated primarily via ADCC, and that elotuzumab was active even in MM cells refractory to conventional and targeted therapies (Tai *et al*, 2008).

Elotuzumab has also been evaluated in Phase 1 and Phase 2 clinical studies in patients with relapsed/refractory MM. In a Phase 1 monotherapy study, elotuzumab demonstrated acceptable toxicity but its antitumour activity was only modest: no responses were seen, although elotuzumab did induce stable disease (SD) in six of 19 patients (Zonder *et al*, 2008).

Despite the limited activity of elotuzumab monotherapy, preclinical data suggested that combinations of elotuzumab with novel agents (specifically bortezomib and lenalidomide) acted synergistically, enhancing ADCC in both cell line and xenograft models (Tai *et al*, 2008; van Rhee *et al*, 2009). Clinical studies of elotuzumab combined with either lenalidomide plus dexamethasone or with bortezomib were therefore initiated and are showing considerable promise. In a preliminary analysis of an ongoing Phase 1 study of elotuzumab plus bortezomib, the ORR (PR or better) was 48% of 27 evaluable patients, and responses were achieved in several bortezomib-refractory patients; a clinical response (≥MR) was seen in 17/27 (63%) patients. The response rate was lower among heavily-pretreated patients (≥3 prior therapies) and the

median time to progression was 9·46 months (Jakubowiak *et al*, 2010).

In a preliminary analysis of an ongoing Phase 1b combination study with lenalidomide and dexamethasone, the ORR was 82% for all treated patients ($N = 28$), 96% for lenalidomide-naïve patients ($n = 22$), and 82% among patients who had been refractory to their most recent treatment ($n = 11$) (Lonial *et al*, 2010). In a Phase 2 study of the same combination, the ORR was 85% for evaluable patients (22/26), and the remaining four patients had SD; 31% achieved either a CR or very good partial response (Richardson *et al*, 2010). For both studies, adverse events (AEs) were primarily infusion-related, and appeared to be readily manageable using adequate premedication.

Elotuzumab is therefore the first MAb in combination with either bortezomib or lenalidomide and dexamethasone to demonstrate clinically meaningful efficacy in relapsed/refractory MM. It is also an excellent example of rational design of combination therapies. In particular, given the modest results observed with monotherapy, further drug development may have been stopped if it were not for preclinical research demonstrating synergy in combination with bortezomib or the lenalidomide/dexamethasone combination. Across all clinical studies to date, most AEs attributable to elotuzumab included mild to moderate infusion reactions, and the implementation of more aggressive premedication regimens appeared to reduce the rate of infusion-related AEs (Zonder *et al*, 2008; Lonial *et al*, 2010; Richardson *et al*, 2010).

Monoclonal antibody therapy for myeloma-related end-organ complications

In addition to therapy directed at MM cells and tumour-promoting interactions, some efforts have been devoted to MAb therapy directed against the development of end-organ complications; to date, these efforts have been restricted to the suppression of myeloma-related bone disease.

RANK ligand (RANKL)

RANKL promotes bone loss in osteoporosis and contributes to the development of bone lesions in MM. The inhibition of RANKL may directly impact myeloma cells that express RANK and have a therapeutic role in the treatment of MM. The fully human anti-RANKL MAb, denosumab, has demonstrated some efficacy in a Phase 2 study of patients with plateau-phase or relapsed MM, including suppression of the bone turnover marker serum C-terminal telopeptide of type 1 collagen (sCTx) (Vij *et al*, 2009). Denosumab is currently being compared with zoledronic acid (the standard of care for prevention of bone disease in several cancers) in patients with advanced cancers or MM in a randomized Phase 3 trial (NCT00330759); results in the MM cohort have thus far been mixed although positive in other cancers; future trials are planned in MM to better define its role.

Dickkopf-related protein 1 (DKK1)

DKK1 facilitates the development of bone lesions in MM, primarily by inhibiting the activity of osteoblasts. A fully human anti-DKK1 MAb, BHQ880, has demonstrated improvement in bone parameters in murine models, and also appears to have direct effects on MM cell growth, possibly via interactions with BMSCs and IL-6 related pathways (Fulciniti et al, 2009b; Heath et al, 2009). BHQ880 is being evaluated in combination with zoledronic acid in a Phase 2 study in patients with relapsed/refractory MM (NCT00741377), and studies in early MM (i.e, smouldering MM) are also underway.

The role of monoclonal antibodies in multiple myeloma management

MM exhibits a number of potentially valuable targets for MAb therapy that await further investigation in clinical studies. As has been the case with other cancers, MAbs, when employed as monotherapy in MM, have generally not produced impressive levels of response with respect to either response rates or extent of response in individual patients. However, preclinical results in MM cell lines and murine explant models, and preliminary clinical results in patients with relapsed/refractory MM suggest that MAbs are likely to act synergistically with traditional therapies (dexamethasone), immune modulators (thalidomide, lenalidomide), and other novel therapies (such as the first-in-class proteasome inhibitor bortezomib); in addition, MAbs have shown the ability to overcome resistance to these therapies. These observations suggest that future work may be most productively directed at the rational development of multi-agent therapies incorporating specific MAbs on the basis of clinical trial results and, possibly, on the identification of patient-specific MM disease factors. To that end, response assessments in future clinical studies may incorporate biomarker evaluations to identify patient subsets that are most likely or unlikely to respond to specific MAbs.

The current model for the development and approval of novel cancer therapies involves a potential paradox, in that they are initially evaluated in patients with late-stage, metastatic, relapsed, and/or refractory disease; and only if activity is shown in these patients relative to existing standards of care are they likely to be evaluated in the treatment of early-stage disease. However, advanced malignancies are extremely challenging therapeutic targets (Rothenberg et al, 2003), involving extensive genetic heterogeneity and multiple resistance mechanisms; while targeted therapies, by definition, are directed against individual components or pathways (albeit with potentially pleiotropic effects). Therefore, the activity of novel targeted therapies (including MAbs) is likely to be greatest against early-stage disease that possesses far fewer mechanisms for resistance or escape. Evaluating novel therapies in earlier stage disease may therefore be beneficial with respect to identifying potentially useful agents that fail to show measurable activity against more advanced disease.

The natural history of MM, now well understood as a progression from monoclonal gammopathy of undetermined significance (MGUS) to asymptomatic (smouldering) MM, and then to symptomatic MM, often with extramedullary progression in the advanced and late stage setting, may afford additional targets for MAb therapy. As yet, treatment is not recommended for MGUS, and options are limited (e.g. bisphosphonate alone) in smouldering MM, as potential toxicities may outweigh the potential benefits. Future research should be directed at further elucidation of the molecular events involved in progression from MGUS to symptomatic MM, and the identification of targets that may prevent or reduce the risk of disease progression, for which MAbs, as an example and given their favourable side effect profile, may have a potential role.

Conclusions

MAb therapy for MM remains early in its development. As yet, it remains to be defined how MAb therapy can most productively be incorporated into the current therapeutic paradigms that have achieved significant survival gains in patients with MM. However, based on preclinical and preliminary clinical evaluation, as well as MAb therapy experience in other cancers, it is apparent that MAb therapy will probably be most effective when combined with existing MM therapies and, in particular, novel agents. The results of ongoing and future clinical studies of MAb therapy in MM should help identify rational combination strategies that produce improved patient outcome. This should be reflected both in terms of increased OS and of quality of life, given the favourable tolerability profile and the remarkable response rates and durations seen to date.

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