Despite recent advances in the treatment of multiple myeloma, new agents are still needed to improve the outcome for patients. The established success of monoclonal antibodies in the treatment of some cancers has promoted interest in developing antibody-based therapies for multiple myeloma. Efforts have included the development of antibodies conjugated to potent cytotoxic moieties that combine the specificity of anti-myeloma-targeting antibodies with highly active anti-tumor compounds. Two such immunoconjugates currently in clinical development are composed of antibodies that target cell surface proteins found on multiple myeloma cells, and are coupled to cytotoxic maytansinoids. IMGN901 targets the neural cell adhesion molecule, CD56, which is expressed on the majority of myeloma cells, as well as on other cancers, while BT062 targets CD138, a primary diagnostic marker for multiple myeloma. In this review, we discuss the preclinical and early clinical data for these two promising new antibody-based anti-myeloma agents.

**Introduction**

Multiple myeloma (MM) is a neoplasm of plasma cells and is the second most common hematologic malignancy in the US, with an estimated 20,000 new cases diagnosed and over 10,000 deaths due to the disease each year. The introduction of autologous stem cell transplant and new therapeutics such as thalidomide, bortezomib and lenalidomide over the last two decades has contributed to marked gains in overall survival for MM patients.2-4

Despite these advances, MM remains an incurable disease, and emphasis has been focused on the development of additional novel agents. These agents include not only second generation immunomodulatory agents and proteosome inhibitors, but also compounds with alternate mechanisms of action such as histone deacetylase inhibitors, heat shock protein inhibitors and inhibitors of the Akt pathway.5

Considerable interest has also focused on the development of antibody-based therapeutics for MM. The success of antibody-based treatments in other hematologic diseases, such as rituximab in B-cell lymphoma, has provided hope that antibody-based treatments may contribute to improved outcomes in MM as well. Monoclonal antibodies targeting cell surface antigens found on MM cells such as CD74,6 CD38,7 CD40,8 IGFR9 and FGFR3,10 are moving toward or are in clinical development based on encouraging results from preclinical studies. Along with efforts to develop functional antibodies that could provide benefit to MM patients, substantial efforts are underway to develop therapies using antibodies conjugated to potent cytotoxic agents. A variety of highly cytotoxic compounds are being evaluated for antibody-based delivery, including calicheamicin, doxorubicin, taxanes, maytansinoids, dolastatins and CC-1065 analogs.11,12

The first of these immunoconjugates to be approved by the FDA, gemtuzumab ozogamicin, is a calicheamicin conjugate targeting CD33 in acute myeloid leukemia.13,14 We have developed a family of antibody-maytansinoid conjugates, designed to improve the therapeutic window of potent cytotoxic maytansinoids by targeting these microtubule-disrupting agents to tumor cells, while limiting the exposure of normal tissues and thereby reducing side effects.15 The conjugates comprised anti-tumor targeting antibodies coupled to cytotoxic maytansinoids through optimized linker molecules (Fig. 1). Upon binding to a target tumor cell, the antibody-maytansinoid conjugate is internalized by natural processes, where the conjugate is metabolized and active maytansinoid metabolites are released.16 Several antibody-maytansinoid conjugates are in clinical evaluation, and the most advanced of these, trastuzumab-DM1 (T-DM1), is currently in phase III testing for the treatment of Her2-positive metastatic breast cancer.17

**IMGN901**

Immunoconjugate IMGN901 (BB-10901; huN901-DM1) is composed of a humanized monoclonal antibody that binds with high affinity to CD56 conjugated with the cytotoxic maytansinoid DM1 through a disulfide linkage. The expression of the CD56 antigen, which was identified as a neural cell adhesion molecule,18 has been noted on a variety of cancer cells including small cell lung carcinoma, neuroblastoma and other neuroendocrine malignancies,19,20 as well as ovarian cancers.21 Within the hematopoietic compartment, while CD56 expression is normally restricted to NK cells and a subset of T lymphocytes22 and is absent from normal plasma cells,23 it is strongly expressed on MM cells in a majority of MM patients.24-27 Tassone et al.24 demonstrated the activity of IMGN901 against CD56+ MM cells both in vitro and in vivo. Target-dependent cytotoxicity was shown in co-cultures of CD56+ and CD56- cells. Importantly,
component of the immunoconjugate and the intact immunoconjugate are similar, suggesting that clearance of IMGN901 is driven by antigen-dependent processes such as uptake by CD56+ NK cells or CD56+ tumor cells. Targeting of the immunoconjugate to myeloma cells in the bone marrow was confirmed by immunohistochemical analysis of a bone marrow biopsy one day post-treatment. Confirmed minor responses (MRs) were reported in three heavily pretreated patients according to the European Bone Marrow Transplant (EBMT) criteria with reductions in serum M component and urine M component noted. Eight of 19 patients remained on treatment with IMGN901 for at least 15 weeks, with five of these 8 on treatment for at least 24 weeks. Two patients remained on treatment for at least 45 weeks. Patients continued on treatment until evidence of progressive disease.

In addition to the clinical assessment of IMGN901 as mono-therapy, interest in the evaluation of IMGN901 activity in combination with drugs commonly used for the treatment of MM has been spurred by the favorable toxicity profile of IMGN901 observed in patients thus far, as well as encouraging preclinical data evaluating combination therapies in MM xenograft models. Additive-to-synergistic activity has been observed in combinations of IMGN901 with lenalidomide, bortezomib or melphalan.

The antibody-maytansinoid conjugate BT062 in development by Biotest AG targets CD138, a primary diagnostic marker for multiple myeloma. Immunohistochemical (IHC) and flow cytometric analysis of patient MM cells has shown that CD138 is expressed in a vast majority of cases. Within the hematopoietic compartment, CD138 expression is restricted to normal plasma cells, with no expression on hematopoietic stem cells, while expression of CD138 on MM cells is significantly higher than on normal plasma cells. Some additional normal tissue expression is observed, with IHC staining of epithelia of several organs, weak staining of some endothelial cells, and renal tubule expression noted.

Tassone et al. first described the potential of tumor targeting with an anti-CD138 antibody-maytansinoid conjugate using the murine parent of the antibody (B-B4) found in BT062. Treatment of CD138-positive cells with B-B4-DM1 significantly decreased cell survival in a dose-dependent manner while B-B4 antibody alone had little activity. Little cytotoxicity was observed with B-B4-DM1 against CD138-positive cells, although these cells were equally sensitive to the unconjugated maytansinoid DM1, demonstrating that the activity of B-B4-DM1 was dependent on targeting CD138. Anti-tumor activity of B-B4-DM1 was evaluated in MM xenograft studies in mice. Marked tumor regressions were observed upon treatment with B-B4-DM1 in subcutaneous MM models as measured by tumor volume or by fluorescent imaging of green fluorescent protein-expressing adhesion of CD56+ MM cell lines and patient MM cells to bone marrow stromal cells (BMSCs), which is known to protect MM cells from drug-induced cytotoxicity, did not protect against the specific cytotoxicity of IMGN901. Treatment with IMGN901 in a human MM tumor xenograft model in immune-compromised mice showed that the immunoconjugate was effective in both a minimal and bulky disease setting, whereas the unmodified huN901 antibody and a non-binding control conjugate were not active in the MM model.

The clinical evaluation of IMGN901 was initiated with a Phase 1 study in patients with relapsed or relapsed/refractory MM who failed at least one prior therapy, and have CD56+ MM (clinicaltrials.gov identifier NCT00346255). Eligible patients receive an intravenous infusion of IMGN901 on two consecutive weeks every three weeks. Objectives for the study include determination of the maximum tolerated dose (MTD), the dose-limiting toxicities (DLTs) and pharmacokinetics of increasing doses of IMGN901. Preliminary results were reported most recently at the American Society of Hematology meeting in December 2008. Nineteen patients had received IMGN901 at the time of data cutoff ranging in dose level from 40 to 140 mg/m². One patient experienced a DLT (grade 3 fatigue) at the 140 mg/m² dose level, with no patients having clinically significant myelosuppression or hypersensitivity reactions. In addition, no immune response to the immunoconjugate has been detected. Maximal plasma concentrations of IMGN901 generally increased with dose with an elimination half-life of the immunoconjugate ranging between 16–24 hours. Notably, the half-life of the huN901 antibody

Figure 1. Schematic representation of antibody-maytansinoid conjugates, IMGN901 and BT062.

BT062

The antibody-maytansinoid conjugate BT062 in development by Biotest AG targets CD138, a primary diagnostic marker for multiple myeloma. Immunohistochemical (IHC) and flow cytometric analysis of patient MM cells has shown that CD138 is expressed in a vast majority of cases. Within the hematopoietic compartment, CD138 expression is restricted to normal plasma cells, with no expression on hematopoietic stem cells, while expression of CD138 on MM cells is significantly higher than on normal plasma cells. Some additional normal tissue expression is observed, with IHC staining of epithelia of several organs, weak staining of some endothelial cells, and renal tubule expression noted.

Tassone et al. first described the potential of tumor targeting with an anti-CD138 antibody-maytansinoid conjugate using the murine parent of the antibody (B-B4) found in BT062. Treatment of CD138-positive cells with B-B4-DM1 significantly decreased cell survival in a dose-dependent manner while B-B4 antibody alone had little activity. Little cytotoxicity was observed with B-B4-DM1 against CD138-positive cells, although these cells were equally sensitive to the unconjugated maytansinoid DM1, demonstrating that the activity of B-B4-DM1 was dependent on targeting CD138. Anti-tumor activity of B-B4-DM1 was evaluated in MM xenograft studies in mice. Marked tumor regressions were observed upon treatment with B-B4-DM1 in subcutaneous MM models as measured by tumor volume or by fluorescent imaging of green fluorescent protein-expressing

adhesion of CD56+ MM cell lines and patient MM cells to bone marrow stromal cells (BMSCs), which is known to protect MM cells from drug-induced cytotoxicity, did not protect against the specific cytotoxicity of IMGN901. Treatment with IMGN901 in a human MM tumor xenograft model in immune-compromised mice showed that the immunoconjugate was effective in both a minimal and bulky disease setting, whereas the unmodified huN901 antibody and a non-binding control conjugate were not active in the MM model.

The clinical evaluation of IMGN901 was initiated with a Phase 1 study in patients with relapsed or relapsed/refractory MM who failed at least one prior therapy, and have CD56+ MM (clinicaltrials.gov identifier NCT00346255). Eligible patients receive an intravenous infusion of IMGN901 on two consecutive weeks every three weeks. Objectives for the study include determination of the maximum tolerated dose (MTD), the dose-limiting toxicities (DLTs) and pharmacokinetics of increasing doses of IMGN901. Preliminary results were reported most recently at the American Society of Hematology meeting in December 2008. Nineteen patients had received IMGN901 at the time of data cutoff ranging in dose level from 40 to 140 mg/m². One patient experienced a DLT (grade 3 fatigue) at the 140 mg/m² dose level, with no patients having clinically significant myelosuppression or hypersensitivity reactions. In addition, no immune response to the immunoconjugate has been detected. Maximal plasma concentrations of IMGN901 generally increased with dose with an elimination half-life of the immunoconjugate ranging between 16–24 hours. Notably, the half-life of the huN901 antibody

Figure 1. Schematic representation of antibody-maytansinoid conjugates, IMGN901 and BT062.

BT062

The antibody-maytansinoid conjugate BT062 in development by Biotest AG targets CD138, a primary diagnostic marker for multiple myeloma. Immunohistochemical (IHC) and flow cytometric analysis of patient MM cells has shown that CD138 is expressed in a vast majority of cases. Within the hematopoietic compartment, CD138 expression is restricted to normal plasma cells, with no expression on hematopoietic stem cells, while expression of CD138 on MM cells is significantly higher than on normal plasma cells. Some additional normal tissue expression is observed, with IHC staining of epithelia of several organs, weak staining of some endothelial cells, and renal tubule expression noted.

Tassone et al. first described the potential of tumor targeting with an anti-CD138 antibody-maytansinoid conjugate using the murine parent of the antibody (B-B4) found in BT062. Treatment of CD138-positive cells with B-B4-DM1 significantly decreased cell survival in a dose-dependent manner while B-B4 antibody alone had little activity. Little cytotoxicity was observed with B-B4-DM1 against CD138-positive cells, although these cells were equally sensitive to the unconjugated maytansinoid DM1, demonstrating that the activity of B-B4-DM1 was dependent on targeting CD138. Anti-tumor activity of B-B4-DM1 was evaluated in MM xenograft studies in mice. Marked tumor regressions were observed upon treatment with B-B4-DM1 in subcutaneous MM models as measured by tumor volume or by fluorescent imaging of green fluorescent protein-expressing

adhesion of CD56+ MM cell lines and patient MM cells to bone marrow stromal cells (BMSCs), which is known to protect MM cells from drug-induced cytotoxicity, did not protect against the specific cytotoxicity of IMGN901. Treatment with IMGN901 in a human MM tumor xenograft model in immune-compromised mice showed that the immunoconjugate was effective in both a minimal and bulky disease setting, whereas the unmodified huN901 antibody and a non-binding control conjugate were not active in the MM model.

The clinical evaluation of IMGN901 was initiated with a Phase 1 study in patients with relapsed or relapsed/refractory MM who failed at least one prior therapy, and have CD56+ MM (clinicaltrials.gov identifier NCT00346255). Eligible patients receive an intravenous infusion of IMGN901 on two consecutive weeks every three weeks. Objectives for the study include determination of the maximum tolerated dose (MTD), the dose-limiting toxicities (DLTs) and pharmacokinetics of increasing doses of IMGN901. Preliminary results were reported most recently at the American Society of Hematology meeting in December 2008. Nineteen patients had received IMGN901 at the time of data cutoff ranging in dose level from 40 to 140 mg/m². One patient experienced a DLT (grade 3 fatigue) at the 140 mg/m² dose level, with no patients having clinically significant myelosuppression or hypersensitivity reactions. In addition, no immune response to the immunoconjugate has been detected. Maximal plasma concentrations of IMGN901 generally increased with dose with an elimination half-life of the immunoconjugate ranging between 16–24 hours. Notably, the half-life of the huN901 antibody
tumors. The anti-tumor activity of B-B4-DM1 was confirmed in a SCID-hu model of human MM, where patient MM cells proliferate in a human bone chip microenvironment.

In addition to targeting a different antigen, BT062 differs from IMGN901 in the cytotoxic maytansinoid moiety (i.e., DM4 instead of DM1) and the nature of the disulfide linkage that joins the cytotoxic maytansinoid to the antibody.35 The clearance of IMGN901 is primarily antigen-dependent due to CD56 expression on NK cells, and thus the mono-hindered disulfide linkage (with a single methyl group proximal to the disulfide bond; Fig. 1) used in IMGN901 provides for an immunoconjugate that is stable during its circulation in plasma. In the case of BT062, the more hindered disulfide linkage (two methyl groups proximal to the disulfide bond; Fig. 1) offers the possibility for increased immunoconjugate exposure since the linkage is less susceptible to disulfide exchange reactions. Indeed, BT062, with its more hindered disulfide linkage, was more efficacious in mouse MM xenograft studies than the version with a less hindered disulfide linkage.31 The anti-CD138 antibody component of BT062 (nBT062) is a murine/human IgG4 chimeric form of B-B4. Ikeda et al.31 confirmed that, like B-B4-DM1, BT062 shows potent and CD138-dependent cytotoxicity toward CD138-positive MM cells in vitro and in vivo, and further demonstrated that BT062 anti-tumor activity is not affected by drug-resistance factors such as IL-6 and IGF-1, or CAM-DR.

While experiments using excess free nBT062 show that the cytotoxicity of BT062 requires specific binding to CD138, antibody-maytansinoid conjugates similar to BT062 have been shown to have potent cell killing effects not only on antigen-positive cells, but also on antigen-negative cells that are in close proximity to the tumor cells.35 Importantly, this bystander killing requires the presence of antigen-positive cells. The local release of potent maytansinoid moieties from target cells and uptake into nearby non-target cells is the proposed mechanism for this activity. Such bystander activity was demonstrated for BT062 in mixed cultures of antigen-positive and antigen-negative tumor cells growing in co-culture in round-bottomed wells,31 and may have an important impact on BT062 efficacy through eradication of tumor cells that heterogeneously express CD138 or disruption of the tumor microenvironment by elimination of tumor stromal cells. A multi-center Phase 1 dose escalation clinical study of BT062 in subjects with relapsed or relapsed/refractory multiple myeloma is currently underway (Clinicaltrials.gov identifier NCT00723359).

Conclusion

The search for new treatments to improve outcomes for MM patients has led to the development of novel antibody-based therapies currently undergoing clinical evaluation. Two antibody-maytansinoid conjugates, IMGN901 and BT062, have demonstrated potent anti-myeloma activity in preclinical studies and early clinical data is encouraging.

Acknowledgements

R.L. and K.W. are employees of ImmunoGen, Inc.

References

1. Cancer Facts and Figures. American Cancer Society, Inc. 2008.
2. Attal M, Harousseau JL, Stoppa AM, Sotto JJ, Fuzibet JG, Rossi JF, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Français du Myelome. N Engl J Med 1996; 335:91-7.
3. Child JA, Morgan GJ, Davies FE, Owen RG, Bell SE, Hawkins K, et al. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. N Engl J Med 2003; 348:1875-83.
4. Kumar SK, Rajkumar SV, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, et al. Improved survival in multiple myeloma and the impact of novel therapies. Blood 2008; 111:2516-20.
5. Mitsiades CS, Hideshima T, Chauban D, McMillin DW, Klippel S, Laubach JP, et al. Emerging treatments for multiple myeloma: beyond immunomodulatory drugs and bortezomib. Semin Hematol 2009; 46:166-75.
6. Stein R, Smith MR, Chen S, Zalazhi, Goldberg DM. Combining mirlatumumab with bortezomib, doxorubicin or dexamethasone improves responses in multiple myeloma cells. Clin Cancer Res 2009; 15:2508-17.
7. Lejeune PDJ, Mayo MF, Whitman K, Johnson RJ, Allen CA, McClain YV, Garrett LM, Hoffman K, et al. Antibody-maytansinoid conjugates are activated in targeted cancer cells by lysosomal degradation and linker-dependent intracellular processing. Cancer Res 2006; 66:4426-33.
8. Lewis Phillips GD, Li G, Dugger DL, Crocker LM, Parsons KL, Mai E, et al. Targeting HER2-positive breast cancer with trastuzumab-DM1, an antibody-cytotoxic drug conjugate. Cancer Res 2008; 68:9280-90.
9. Hewish M, Chau I, Cunningham D. Insulin-like growth factor 1 receptor targeted therapeutics: novel compounds and novel treatment strategies for cancer medicine. Recent Pat Anticancer Drug Discov 2009; 4:54-72.
10. Qiang J, Du X, Chan Y, Chan P, Li H, Wu P, et al. Antibody-dependently targeted killing of FGFR3 in bladder carcinoma and 4(14)-positive multiple myeloma in mice. J Clin Invest 2009; 119:1216-29.
11. Lambert JM. Drug-conjugated monoclonal antibodies for the treatment of cancer. Curr Opin Pharmacol 2005; 5:543-9.
12. Senter PD. Potent antibody drug conjugates for cancer therapy. Curr Opin Chem Biol 2009; 13:235-44.
13. Stasi R. Gemtuzumab ozogamicin: an anti-CD33 immunoconjugate for the treatment of acute myeloid leukemia. Expert Opin Biol Ther 2008; 8:527-40.
14. Brosi PF, Beitz J, Chen G, Chen XH, Duffy E, Kieffer L, et al. Approval summary: gemtuzumab ozogamicin in relapsed acute myeloid leukemia. Clin Cancer Res 2001; 7:1490-6.
15. Chari RV. Targeted cancer therapy: specifying efficacy to cytotoxic drugs. Acc Chem Res 2008; 41:98-107.
16. Erickson HK, Park PU, Widdison WC, Kovrun YV, Garrett LM, Hoffman K, et al. Antibody-maytansinoid conjugates are activated in targeted cancer cells by lysosomal degradation and linker-dependent intracellular processing. Cancer Res 2006; 66:4426-33.
17. Lewisa GD, Gil G, Dugger DL, Crocker LM, Parsons KL, Mai E, et al. Targeting HER2-positive breast cancer with trastuzumab-DM1, an antibody-cytotoxic drug conjugate. Cancer Res 2008; 68:9280-90.
18. Thiery JP, Brackenbury R, Rutishauser U, Edelman GM. Adhesion among neural cells of the chick embryo II. Purification and characterization of a cell adhesion molecule from neural retina. J Biol Chem 1977; 252:6841-5.
19. Griffin JD, Herend T, Beveridge R, Schlossman SF. Characterization of an antigen expressed by human natural killer cells. J Immunol 1985; 130:2974-91.
20. Patel K, Moore SE, Dickson G, Rossell RJ, Beverley PC, Kenmeh J, et al. Neural cell adhesion molecule (NCAM) is the antigen recognized by monoclonal antibodies of similar specificity in small-cell lung carcinoma and neuroblastoma. Int J Cancer 1989; 44:573-8.
21. Ohishi Y, Kaku T, Oya M, Kobayashi H, Wake N, Tsuneyoshi M. CD56 expression in ovarian granulosacell tumors, and its diagnostic utility and pitfalls. Gynecol Oncol 2007; 107:30-8.
22. Lantos LL, Le AM, Givin CI, Loken MR, Phillips JH. The relationship of CD16 (Leu-11) and Leu-19 (NKH-1) antigen expression on human peripheral blood NK cells and cytotoxic T lymphocytes. J Immunol 1986; 136:4480-6.
23. Harada H, Kawano MM, Huang N, Harada Y, Iwato K, et al. Phenotypic difference of normal plasma cells from mature myeloma cells. Blood 1995; 81:2658-63.
24. Tassone P, Gozzini A, Goldmacher V, Shammas MA, Whitman KR, Carrasco DR, et al. In vitro and in vivo activity of the maytansinoid immunoconjugate huN901-N2-deacetyl-N2-(3-mercaptop-1-oxo-2-propyl)-maytansine against CD56-positive multiple myeloma cells. Cancer Res 2004; 64:4629-36.
25. Rawstron AC, Owen RG, Davies FE, Johnson RJ, Jones RA, Richards SJ, et al. Circulating plasma cells in multiple myeloma: characterization and correlation with disease stage. Br J Haematol 1997; 97:46-55.
26. Sahara N, Takeshita A, Shigeno K, Fujisawa S, Takeshita K, Naito K, et al. Clinicopathological and prognostic characteristics of CD56-negative multiple myeloma. Br J Haematol 2002; 117:882-5.

27. Ely SA, Knowles DM. Expression of CD56/neural cell adhesion molecule correlates with the presence of lytic bone lesions in multiple myeloma and distinguishes myeloma from monoclonal gammopathy of undetermined significance and lymphomas with plasmacytoid differentiation. Am J Pathol 2002; 160:1209-9.

28. Chanan-Khan AA, Gharibo M, Jagannath S, Munshi NC, Anderson KC, DePaolo D, et al. Phase I Study of IMGN901 in Patients with Relapsed and Refractory CD56-Positive Multiple Myeloma. ASH Annual Meeting Abstracts 2008; 112:3689.

29. Lutz R, Ab O, Foley K, Goldmacher V, Whiteman K, Xie H, et al. Efficacy of the huN901-DM1 conjugate in combination with antineoplastic agents against multiple myeloma cells in preclinical studies. AACR Meeting Abstracts 2007; 2007:5577.

30. Whiteman K, Ab O, Bartle L, Foley K, Goldmacher V, Lutz R. Efficacy of IMGN901 (huN901-DM1) in combination with bortezomib and lenalidomide against multiple myeloma cells in preclinical studies. AACR Meeting Abstracts 2008; 2008:2146.

31. Ikeda H, Hideshima T, Fulciniti M, Lutz RJ, Yasui H, Okawa Y, et al. The monoclonal antibody nBT062 conjugated to cytotoxic Maytansinoids has selective cytotoxicity against CD138-positive multiple myeloma cells in vitro and in vivo. Clin Cancer Res 2009; 15:4628-37.

32. Wijdenes J, Vooijs WC, Clement C, Post J, Morard F, Vira N, et al. A plasmocyte selective monoclonal antibody (B-B4) recognizes syndecan-1. Br J Haematol 1996; 94:318-23.

33. Chilosi M, Adami F, Lestani M, Montagna L, Cimarosto L, Semenzato G, et al. CD138/syndecan-1: a useful immunohistochemical marker of normal and neoplastic plasma cells on routine trephine bone marrow biopsies. Mod Pathol 1999; 12:1101-6.

34. Tassone P, Goldmacher VS, Neri P, Gozzini A, Shammas MA, Whiteman KR, et al. Cytotoxic activity of the maytansinoid immunoconjugate B-B4-DM1 against CD138·multiple myeloma cells. Blood 2004; 104:3688-96.

35. Kowtun YV, Audette CA, Ye Y, Xie H, Ruberri MF, Phimney SJ, et al. Antibody-drug conjugates designed to eradicate tumors with homogeneous and heterogeneous expression of the target antigen. Cancer Res 2006; 66:3214-21.