A High-Affinity Fully Human Anti–IL-6 mAb, 1339, for the Treatment of Multiple Myeloma

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Abstract

Purpose: We investigated the in vitro and in vivo anti-multiple myeloma activity of monoclonal antibody (mAb) 1339, a high-affinity fully humanized anti-interleukin 6 mAb (immunoglobulin G1), alone and in combination with conventional and novel anti-multiple myeloma agents, as well as its effect on bone turnover.

Experimental Design: We examined the growth inhibitory effect of 1339 against multiple myeloma cell lines in the absence and in the presence of bone marrow stromal cells, alone or in combination with dexamethasone, bortezomib, perifosine, and Revlimid. Using the severe combined immunodeficient (SCID)–hu murine model of multiple myeloma, we also examined the effect of 1339 on multiple myeloma cell growth and multiple myeloma bone disease.

Results: mAb 1339 significantly inhibited growth of multiple myeloma cell in the presence of bone marrow stromal cell in vitro, associated with inhibition of phosphorylation of signal transducer and activator of transcription 3, extracellular signal-regulated kinase 1/2, and Akt. In addition, mAb 1339 enhanced cytotoxicity induced by dexamethasone, as well as bortezomib, lenalidomide, and perifosine, in a synergistic fashion. Importantly, mAb 1339 significantly enhanced growth inhibitory effects of dexamethasone in vivo in SCID-hu mouse model of multiple myeloma. mAb 1339 treatment also resulted in inhibition of osteoclastogenesis in vitro and bone remodeling in SCID-hu model.

Conclusions: Our data confirm in vitro and in vivo anti-multiple myeloma activity of, as well as inhibition of bone turnover by, fully humanized mAb 1339, as a single agent and in combination with conventional and novel agents, providing a rationale for its clinical evaluation in multiple myeloma. (Clin Cancer Res 2009;15(23):7144–52)

Interleukin 6 (IL-6) is a multifunctional cytokine regulating the immune response, the acute-phase response and bone metabolism (1). IL-6 belongs to a family of cytokines, which all act through receptor complexes containing the cytokine receptor subunit gp130 (2). Increased production of IL-6 has been implicated in the pathogenesis of several diseases, including autoimmune disorders, B-cell malignancies, and postmenopausal osteoporosis (3–5). In particular, the biological sequelae of IL-6 in the pathogenesis of multiple myeloma are well documented (6). Autocrine and paracrine IL-6 has been recognized to play a crucial role in growth and survival of multiple myeloma cells within the bone marrow milieu (7). In the bone marrow microenvironment, IL-6 is predominantly produced by bone marrow stromal cell, mediating multiple myeloma cell growth and preventing apoptotic cell death. IL-6 triggers at least three major signaling pathways: Ras/mitogen-activated protein (MAP)/extracellular signal-regulated kinase 1/2, and Akt. In addition, mAb 1339 enhanced cytotoxicity induced by dexamethasone, as well as bortezomib, lenalidomide, and perifosine, in a synergistic fashion. Importantly, mAb 1339 significantly enhanced growth inhibitory effects of dexamethasone in vivo in SCID-hu mouse model of multiple myeloma. mAb 1339 treatment also resulted in inhibition of osteoclastogenesis in vitro and bone remodeling in SCID-hu model.

Conclusions: Our data confirm in vitro and in vivo anti-multiple myeloma activity of, as well as inhibition of bone turnover by, fully humanized mAb 1339, as a single agent and in combination with conventional and novel agents, providing a rationale for its clinical evaluation in multiple myeloma. (Clin Cancer Res 2009;15(23):7144–52)
Translational Relevance

Interleukin 6 plays important role in multiple myeloma cell growth and survival within bone marrow milieu, making it an important therapeutic target in multiple myeloma. The preclinical studies presented here are designed to identify in vitro and in vivo efficacy of a fully human anti-interleukin 6 neutralizing antibody (1339) and have important implications for the therapy of multiple myeloma. Monoclonal antibody (mAb) 1339 is generated from the murine mAb, and the conversion to a fully humanized mAb could reduce immunogenicity and prolong half-life. In the present report, we describe the synergistic effect between mAb 1339 and conventional and novel agents, suggesting a potential clinical use of these combinations. In addition, we report in vitro and in vivo inhibition of bone turnover by mAb 1339, providing additional application in bone disease in myeloma. The data generated will help to extend this promising area of research and provide a basis for development of a clinical protocol in relapsed myeloma.

Materials and Methods

Cells. The IL-6–dependent multiple myeloma cell lines INA-6, provided by Dr. Edward Thompson (University of Texas Medical Branch), and XG1, provided by Dr. Bernard Klein, were cultured in RPMI 1640 (Mediatech) supplemented with 10% fetal bovine serum and 1 ng/ml rhIL-6 (R&D Systems). MM1S and MM1R multiple myeloma cell lines were provided by Dr. Steven Rosen (Northwestern University). U266 cells were obtained from the American Type Culture Collection. MM1S, MM1R, and U266 cell lines were cultured in RPMI 1640 supplemented with 10% fetal bovine serum. Bone marrow mononuclear cells and primary multiple myeloma cells were collected after obtaining informed consent using an Institutional Review Board (Dana-Farber Cancer Institute)–approved protocol. Cells were isolated and processed as previously described (18).

Reagents. The human 1339 mAb was generated by OPI ELISA Pharmacia in collaboration with Vaccinex. Then 1339 mAb has been licensed to Glaxo Smith Kline. 1339 has been designed using the murine B-E8 as template. mAb 1339 contains only a few residues of the variable antigen-binding region of the murine anti IL-6 antibody and the constant region of the human immunoglobulin G1k. Dexamethasone, Bortezomib, and lenalidomide were purchased. Perifosine was provided by Keryx Biopharmaceuticals.

Cell proliferation assay. Multiple myeloma cell proliferation was measured by [3H]thymidine (Perkin-Elmer) incorporation assay. Multiple myeloma cells (2 × 10⁴ cells per well) were cultured in 96-well plates (Costar) at 37°C for 24, 48, and 72 h, in the presence or absence of 1339 mAb. Cells were pulsed with [3H]thymidine (0.5 μCi per well) for 6 h and harvested, and radioactivity was counted using the LKB Betaplate scintillation counter (Wallac). In coculture experiments, multiple myeloma cells (2 × 10⁴ cells per well) were incubated in bone marrow stromal cell–coated 96-well plates (Costar) at 37°C for 24, 48, and 72 h, in the presence or absence of 1339 mAb. In the combination treatment experiments, cells were cultured with dexamethasone, bortezomib, perifosine, and Revlimid, in the absence or presence of 1339 mAb for 48 h. All experiments were carried out in triplicates.

Immunoblotting. Whole cell lysates were subjected SDS-PAGE using Prestac Gel (Bio-Rad Laboratories), transferred to a nitrocellulose membrane (Bio-Rad), and immunoblotted with anti-p–STAT3, anti-STAT3, anti-pERK (Santa Cruz Biotechnology), anti-ERK (Cell Signaling Technology), anti-pAkt (Cell Signaling Technology), or anti-Akt (Cell Signaling Technology) antibodies. After incubating with second antibody, membranes were developed by enhanced chemiluminescence (GE Healthcare).

Osteoclast differentiation assay. Human osteoclasts were generated from the nonadherent fraction of bone marrow mononuclear cells obtained from bone marrow aspirates of multiple myeloma patients after a 24-h culture period. The nonadherent fraction of bone marrow mononuclear cells were cultured in 96-well plates (5 × 10⁴ cells per

7 Unpublished data.
well) and stimulated with α-minimum essential medium (MEM) osteoclastic differentiation media containing 10% fetal bovine serum, 2% penicillin-streptomycin (Mediatech, Inc.), and 1% L-glutamine (Mediatech, Inc.), as well as 25 ng/mL of macrophage–colony-stimulating factor (R&D Systems) and 25 ng/mL of RANKL (PeproTech), in the presence or absence of 5 ng/mL of IL-6 (R&D Systems), and with or without 1 μg/mL of isotype control or mAb 1339. At the end of the culture period (7, 14, and 21 d), cells were fixed and stained for tartrate-resistant acid phosphatase, according to manufacturers’ guidelines (Takara Bio). Cells were observed and counted with a Nikon Eclipse TS 100 microscope, using a ×100 magnification.

SCID-hu mouse model. Six- to 8-wk-old male CB-17 SCID mice (Taconic) were housed and monitored in our Animal Research Facility. All experimental procedures and protocols had been approved by the Institutional Animal Care and Use Committee (VA Boston Healthcare System). Human fetal long bone grafts were s.c. implanted into SCID mice (SCID-hu), as previously described (19). Four weeks following bone implantation, 2.5 × 10⁶ INA-6 multiple myeloma cells were injected directly into the human bone implant. The level of soluble human IL-6 receptor in mice was used as marker of tumor burden. Mouse sera were serially monitored for soluble human IL-6 receptor levels by ELISA (R&D Systems, Inc.). After the first detection of soluble human IL-6 receptor, mice were injected with isotype control (100 μg per mouse once a week; n = 6), 1339 (100 μg per mouse once a week; n = 4), dexamethasone (1 mg/kg thrice a week; n = 4), and 1339 plus dexamethasone (n = 4). The pharmacokinetics of single (100 μg per mouse) i.p. administration of 1339 in SCID mice peripheral blood was measured by ELISA.

Micro-computed tomography and histologic analysis. One month after treatment with mAb 1339, bone chips were retrieved, fixed in freshly prepared 4% paraformaldehyde overnight, washed with 70% ethanol, and analyzed by micro-computed tomography and histologic examination. The samples were scanned at 18 μm with 300-ms integration time using micro-computed tomography imaging system (μCT-40, Scanco Medical), allowing us to look at the bone samples in three dimensions noninvasively (20, 21). Three-dimensional reconstructions were done after segmentation for qualitative assessment of treated and corresponding untreated bone. For the bone histology, specimens fixed in 4% paraformaldehyde were demineralization with 14% EDTA in PBS. The specimens were processed and embedded in paraffin, and 5-μm sections were prepared and stained with hematoxylin and eosin for histologic analysis. Sections were observed and photographed with a Nikon transmitted light microscope.

Statistical analysis. The statistical significance of differences between the individual and the combined treatments was analyzed using the t test; differences were considered significant when \( P \leq 0.05 \).

Results

mAb 1339 inhibits IL-6–dependent multiple myeloma cell growth. The human mAb 1339, designed using the murine B-E8 antibody as template, contains only few residues of the variable antigen-binding region of the murine anti–IL-6 antibody and the constant region of the human immunoglobulin G1k. We first compared the ability of mAb 1339 to inhibit multiple myeloma cell growth in comparison to various murine, chimeric, and humanized mAbs directed against IL-6 or IL-6 receptor (gp80 or gp130). We cultured INA-6 multiple myeloma cells in the presence of these mAbs, as well as isotype controls, at various concentrations. The effect on cell proliferation was assessed by [3H]thymidine uptake after 72 hours. As seen in Fig. 1A, mAbs had variable dose-dependent effect on INA-6 cell growth. For example, anti-gp130 mAb showed limited effect on
multiple myeloma cell growth, whereas anti-gp80 and anti-IL-6 murine, chimeric, and fully humanized mAb 1339 showed similar maximum anti-multiple myeloma activity. We next evaluated dose- and time-dependent activity of mAb 1339 on IL-6-dependent INA-6 and XG1 multiple myeloma cell lines. Multiple myeloma cells were cultured in the presence of different doses of mAb 1339 (0.1, 0.5, and 1 μg/mL), and cell proliferation was assessed by [H]thymidine uptake assay after 24, 48, and 72 hours. As seen in Fig. 1B, mAb 1339 induced dose- and time-dependent inhibition of proliferation of INA-6 and XG1 cell lines.

mAb 1339 overcomes the growth supportive effect of bone marrow stromal cell on multiple myeloma cells. We evaluated the ability of mAb 1339 to overcome the growth-promoting effect of bone marrow stromal cell on INA-6 and XG1. Multiple myeloma cell growth was measured at 24, 48, and 72 hours in the presence of varying concentrations of the antibody. As seen in Fig. 2A, mAb 1339 significantly inhibited the growth of INA-6 and XG1 cells in a dose-dependent fashion. We next examined whether mAb 1339 can affect bone marrow stromal cell–induced growth of multiple myeloma cell lines, which are not dependent on IL-6. MM1S, MM1R, and U266 cells were cultured for 48 hours in the presence of bone marrow stromal cell, with or without 1 μg/mL of mAb 1339. Similar to IL-6–dependent cell lines, the growth-promoting effects of bone marrow stromal cell on these multiple myeloma cell lines, as well as primary multiple myeloma cells, were significantly inhibited by mAb 1339 (Fig. 2B and C).

mAb 1339 inhibits STAT3, AKT, and ERK signaling pathways in MM1S cells. IL-6 mediates multiple myeloma proliferation, survival, and drug resistance through Raf/MAP/ERK kinase/MAP kinase, Janus-activated kinase/STAT3, and phosphoinositide 3-kinase/Akt pathways, respectively. To examine the effect of mAb 1339 on IL-6–induced signaling cascades, we cultured MM1S cells with mAb 1339 before treatment with exogenous IL-6 or bone marrow stromal cell culture supernatant. IL-6 (Fig. 3A) and bone marrow stromal cell culture supernatant (Fig. 3B) triggered STAT3, Akt, and ERK1/2 phosphorylation, which was completely abrogated by mAb 1339 in a dose-dependent fashion (0.1 and 1 μg/mL), confirming that mAb
1339–induced growth inhibition of multiple myeloma cells is associated with the blockade of IL-6 signaling cascades.

**mAb 1339 potentiates antmyeloma activity of conventional and novel agents.** Abrogation of IL-6 signaling increases the sensitivity of multiple myeloma cells to conventional and novel agents in the presence of bone marrow stromal cell. We next examined if 1339 mAb could enhance cytotoxicity induced by other therapeutic agents. INA-6, XG1, and MM1S cells were cultured with bone marrow stromal cells in the presence of dexamethasone (1 μmol/L), velcade (5 nmol/L), perifosine (2.5 μmol/L), or Revlimid (5 μmol/L), with or without mAb 1339 (1 μg/mL) for 48 hours, and cell proliferation was measured by [3H]thymidine uptake. Multiple myeloma cell coculture with bone marrow stromal cells almost completely abrogated dexamethasone-induced cytotoxicity, although this effect was less pronounced with other agents (data not shown). As seen in Fig. 4, combination of mAb 1339 with dexamethasone or other novel agents induced significantly higher inhibition of bone marrow stromal cell–induced multiple myeloma cell proliferation compared with antibody or other agents alone. For example, dexamethasone alone triggers 21% and 58% growth inhibition in INA-6 and MM1S cells, respectively, which was further enhanced to 60% and 76% inhibition in these cells, respectively (Fig. 4A). mAb 1339 similarly enhanced cytotoxicity induced by bortezomib (Fig. 4B), perifosine (Fig. 4C), and lenalidomide (Fig. 4D). These results indicate that the inhibition of IL-6 signaling can augment dexamethasone-, bortezomib-, perifosine-, and lenalidomide-induced cytotoxicity in multiple myeloma cells in the context of bone marrow stromal cells.

**mAb 1339 promotes multiple myeloma cell growth inhibition in a SCID-hu mouse model of multiple myeloma.** We next evaluated the in vivo effects of mAb 1339 on multiple myeloma cell growth using a SCID-hu murine model of human multiple myeloma (19). In this model, the human multiple myeloma cell line INA-6 is engrafted into a human fetal bone chip previously implanted in SCID mice (SCID-hu mice), and the level of soluble human IL-6 receptor produced by INA-6 cells in murine serum is used as a marker of tumor burden. We first determined the pharmacokinetics of single i.p. administration (100 μg per

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**Fig. 3.** 1339 inhibits STAT3, ERK1/2, and Akt signaling pathways. MM1S cells were incubated with IL-6 (5 ng/mL; 10 and 30 min; A) or with bone marrow stromal cell supernatant (30 min; B), in the absence or presence of 0.1 and 1 μg/mL of mAb 1339. Cells were harvested, and whole cell lysates were subjected to immunoblotting using the indicated antibodies. 1339 inhibits IL-6- and bone marrow stromal cell–induced activation of ERK1/2 and STAT3 pathway in multiple myeloma cells, whereas a relatively lesser effect was observed with the activation of AKT, as shown by densitometric quantitation of band intensity from Western blot (C). Data are means ± SD (n = 3) and are presented as fold change increase compared with control cells.
mouse) of 1339 in SCID mice. As shown in Fig. 5A, peak serum concentration (Cmax) of the mAb was observed after 24 hours, which was sustained up to 1 week. After the first detection of soluble human IL-6 receptor, mice were injected with isotype control (100 μg per mouse once a week; n = 6), mAb1339 (100 μg per mouse once a week; n = 4), dexamethasone (1 mg/kg thrice a week; n = 4), or 1339 plus dexamethasone (n = 4). As seen in Fig. 5B, mAb 1339 alone significantly inhibited multiple myeloma cells growth (P = 0.04), whereas in the dose and schedule used, dexamethasone alone had limited effect on multiple myeloma cell growth in SCID-hu mice (P = 0.07). However, the combination of mAb 1339 and dexamethasone had the greatest effect on multiple myeloma cell growth, which was significantly superior to dexamethasone or mAb 1339 alone.

**mAb 1339 preserves bone integrity in a SCID-hu mouse model of multiple myeloma.** IL-6 has been shown to play an important role in osteoclast differentiation and multiple myeloma bone disease by affecting bone turnover. To evaluate the effect of inhibition of IL-6 by 1339 on osteoclast differentiation, human osteoclasts were stimulated with osteoclast differentiation media, in the presence and absence of IL-6, with or without 1 μg/mL of isotype control or mAb 1339. Our results confirmed the promoting effect of IL-6 on osteoclast differentiation in a time-dependent manner, reaching the maximum effect after 14 days of stimulation (data not shown). As shown in Fig. 6A, 1339 was able to inhibit osteoclast differentiation and to neutralize the promoting effect of IL-6 on osteoclastogenesis (Fig. 6A). Next, to evaluate effect of 1339 on bone compartment in vivo, we did micro-computed tomography and bone histologic analysis on bone chips retrieved from SCID-hu mice after 1 month of treatment. Micro-computed tomography examination showed preserved human bone integrity (Fig. 6B), and histologic analysis by hematoxylin and eosin staining confirmed increased trabecular bone and decreased multiple myeloma cell number in the mAb-treated bones compared with isotype control–treated bone (Fig. 6C).

**Discussion**

IL-6 produced in the bone marrow microenvironment by stromal cells contributes significantly to multiple myeloma cell growth and survival. Patient-derived multiple myeloma cells and cell lines express IL-6 receptors and proliferate in vitro in response to IL-6 by activating major signaling cascades. Binding of IL-6 to its receptor induces phosphorylation of gp130, which subsequently activates Ras/MAP/ERK kinase/MAP kinase, Janus-activated kinase 2/STAT3, and phosphoinositide 3-kinase/Akt signaling cascades (22). These signaling cascades mediate multiple myeloma cell proliferation, survival, drug resistance, and migration, making IL-6 a promising therapeutic target in multiple myeloma.
myeloma. Importantly, IL-6 protects against apoptotic cell death induced by a variety of agents, including dexamethasone (22–25).

In the past, anti–IL-6 neutralizing mAbs have been shown to exert remarkable in vitro anti-multiple myeloma activity; however, their in vivo and clinical effectiveness remains unclear (13). For example, in a phase I study using a mouse-human chimeric monoclonal anti-IL6 antibody, none of the multiple myeloma patients achieved a response (26). However, two recent clinical studies on the anti–IL-6 mAb CNTO 328, one in combination with dexamethasone and another with bortezomib, have shown evidence of encouraging activity. The study in combination with bortezomib showed a trend for a better response rate and durability than would have been expected with bortezomib alone. These findings provide the rationale to now use the fully humanized mAb in combination studies in multiple myeloma. CNTO 328 has also been evaluated in phase I clinical trial in non-Hodgkin’s lymphoma, and Castleman disease besides multiple myeloma.

One of the major problems with mAb therapy is its immunogenicity, specifically defined as human anti-mouse antibody. To overcome this limitation, murine molecules are engineered to remove immunogenic murine content, which has been initially achieved by generation of mouse-human antibodies. Chimeric antibodies are composed of murine variable regions fused with human constant regions. Although with reduced immunogenicity and prolonged half-life, chimeric mAbs still contain a significant proportion (~35%) of antigenic mouse determinants, suggesting a possibility to generate human anti-mouse antibody. We therefore hypothesized that fully humanized antibody might be more efficient than chimeric antibodies in vivo.

mAb 1339 is a high-affinity fully human anti–IL-6 mAb (immunoglobulin G1) that was produced using murine elsilimomab mAb (also known as B-E8) as a template. BE-8 has been used clinically in hematological malignancies (13, 15–17). Unpublished in vitro studies have shown that 1339 shares biological properties with elsilimomab (B-E8), including affinity and epitope specificity. The conversion of the murine B-E8 mAb into a fully humanized mAb may result in improved therapeutic application due to reduced immunogenicity and prolonged half-life (15-20 days versus 3-4 days; ref. 27) by avoiding the need for daily injection of the mAb and increasing the concentration of circulating mAb in vivo.

Antitumor efficacy of mAb therapy may be due to a number of possible mechanisms, including antiproliferation through the blockage of growth pathways, intracellular signaling leading to apoptosis, enhanced down regulation and/or turnover of receptors, and promotion of immune responses such as antibody-dependent cell-mediated cytotoxicity (ADCC). mAb 1339 is a neutralizing antibody that directly binds to soluble IL-6, abrogating the growth promoting effects of the ligand; however, because it does not bind to tumor cells, it fails to induce ADCC in multiple myeloma (data not shown).

In this study, we show that mAb 1339 is able to inhibit multiple myeloma growth in the presence of exogenous IL-6 or when used in coculture experiments with bone marrow stromal cell, including non–IL-6–dependent multiple myeloma cell lines, as well as primary myeloma cells. The inhibition of multiple myeloma cell growth was associated with potent inhibition of STAT3 and ERK1/2 phosphorylation, confirming that mAb 1339–induced growth inhibition of multiple myeloma cells is associated with the blockade of IL-6 signaling cascades.

Because other cytokines/chemokines also can activate these signaling cascades in the bone marrow microenvironment, inhibition of individual cytokine may not totally inhibit myeloma cell growth and survival. For example, mAb 1339 is not able to completely block Akt phosphorylation in the context of bone marrow stromal cells because other cytokines (i.e., insulin-like growth factor-1, stromal cell–derived factor 1α, and vascular endothelial growth factor) also trigger the phosphoinositide 3-kinase/Akt pathway. We therefore examined and confirmed the ability of mAb 1339 to enhance cytotoxicity induced by conventional (dexamethasone) and novel (bortezomib, lenalidomide, and perifosine) agents.

Recently, Voorhees et al. (28) described the synergistic effect of CNTO 328 in combination with dexamethasone in a preclinical model of multiple myeloma in the presence of stroma. Although single-agent CNTO 328, had minimal apoptotic activity, CNTO 328 enhanced the bortezomib-mediated apoptotic activity against multiple myeloma cells, especially with added dexamethasone. We here show that mAb 1339 alone had inhibitory effect on multiple myeloma cell growth in vitro in the presence.
of bone marrow stromal cell and in vivo in a SCID-hu mouse model. Furthermore, mAb 1339 significantly increased the cytotoxicity of dexamethasone when used in combination in the murine model of human myeloma.

IL-6 has been shown as an osteoclast-activating factor required for human osteoclast precursor proliferation (10, 11, 29). The primary effect of IL-6 on osteoclast formation is to increase the pool of the early osteoclast precursors that in turn differentiate into mature osteoclasts, inducing bone resorption (12). Bone marrow levels of IL-6 have been correlated with bone turnover markers in myeloma. This increased osteoclast activity along with decreased osteoblast activity is responsible for bone lesions in multiple myeloma, which is observed in >80% of the patients. However, the precise role that IL-6 plays in osteoclast formation and myeloma bone disease remains to be defined (30). In our in vitro study, we have confirmed the osteoclast-promoting effect of IL-6. Our in vitro, as well as in vivo, observation confirms the biological significance of IL-6 on osteoclastogenesis and its role in myeloma bone disease. It also identified IL-6 as an important target to prevent or treat bone-related problems in myeloma.

In conclusion, our data show the anti-multiple myeloma activity of fully humanized mAb 1339 as a single agent and in combination with conventional and novel agents. More importantly, our study also indicates the use of 1339 to treat multiple myeloma–associated bone disease and provides evidences that the inhibition of the IL-6 signaling pathway could help to control tumor burden and bone disease.

Disclosure of Potential Conflicts of Interest

N. Munshi, commercial research grant, IDD Biotech.

References


Fig. 6. Effect of 1339 on osteoclastogenesis in vitro and bone remodeling in vivo. A, to evaluate the effect of inhibition of IL-6 by 1339 on osteoclast differentiation, human preosteoclasts were stimulated with osteoclast differentiation media, in the presence and absence of IL-6, with or without 1 μg/mL of isotype control or mAb 1339, for 7 d. At the end of the treatment period, cells were fixed, stained for tartrate-resistant acid phosphatase, and counted. Data are expressed as means ± SD and are presented as percentage change from control. B and C, to evaluate the effects of 1339 on the bone compartment, SCID-hu mice were injected with INA-6 cells into the implanted bone and were treated with isotype control or mAb 1339 after the first detection of tumor. One month after treatment, bone chips were retrieved and analyzed by micro-computed tomography and histologic examination. B, a qualitative assessment of images obtained from micro-computed tomography suggests resistance to osteolytic bone destruction by mAb 1339. C, hematoxylin and eosin staining showed increased bone tissue and decreased multiple myeloma cell number in the treated samples compared with controls. Original magnification, x100.
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