MULTIPLE MYELOMA RESEARCH FOUNDATION

MYELOMA FOCUS

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Accelerating the Search for a Cure

INSIDE THIS ISSUE

Novel Therapies Pages 2-3

Thalidomide Page 4

Transplantation Page 5

Myeloma Bone Disease Page 6

Gene Expression Profiling Page 7

Agents in Early Development Page 8

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SPECIAL EDITION

THE MMRF REPORTS FROM

The American Society of Hematology (ASH) Meeting in Philadelphia

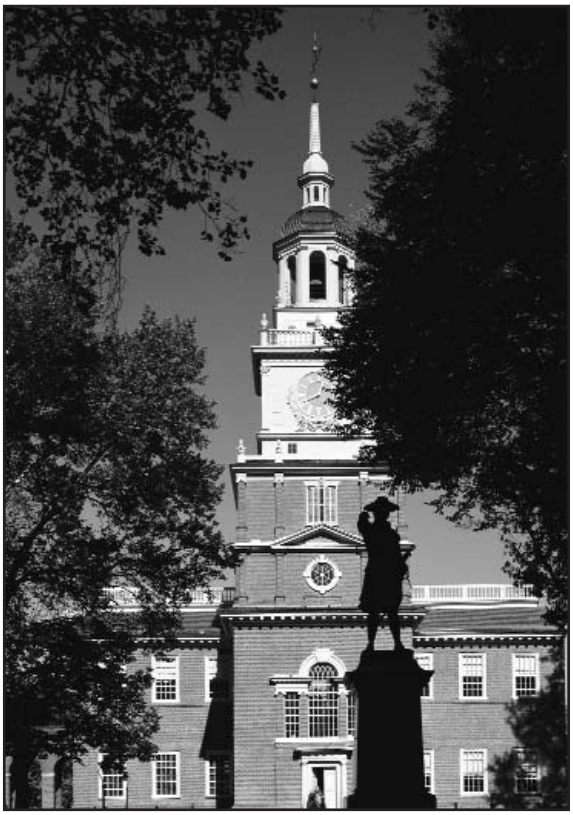
The Multiple Myeloma Research Foundation (MMRF) is pleased to present this special edition newsletter reporting from the 44th Annual Meeting of the American Society of Hematology (ASH). Encouraging results of several key clinical trials, as well as cutting-edge research findings from around the world were presented in Philadelphia, PA at the meeting held December 6-10.

THE TOP NEWS FROM THE MEETING INCLUDED:

- Final results of the Phase II SUMMIT trial of Velcade™ (bortezomib, formerly PS-341, Millennium) in 202 patients with advanced relapsed and refractory myeloma, which indicated an overall response rate of 35% and demonstrable clinical benefits. Altogether, 59% of patients experienced a response or achieved stable disease with the proteasome inhibitor, which was generally well tolerated (page 2).

- Preliminary results of the Phase II trial of the immunomodulatory drug Revimid™ (CC-5013, Celgene) in relapsed or refractory myeloma, which showed an overall 54% response rate in the 46 patients evaluated to date. In the study, 85% of these patients experienced a reduction or stabilization in their M protein, without the side effects commonly seen with thalidomide (page 3).

- Updated results of the IFM-94 study, which showed that although response rates were similar with single and double autologous stem cell transplants in patients with previously untreated myeloma in this study, double transplants offered improved survival at 7 years over single transplants (page 5).



- Results from trials of other therapies in late-stage development, such as Trisenox® (Cell Therapeutics) and Genasense™ (Genta) as well as data on thalidomide (Celgene), promising combination therapies and agents in preclinical development were presented. Important new insights into myeloma bone disease and myeloma genetics were also highlighted.

Novel Therapies

This is a very exciting time in myeloma research -- there are a wide variety of novel agents showing promise in clinical trials and in preclinical models.

The MMRF thanks K. Anderson, MD of the Dana-Farber Cancer Institute for his role as Guest Editor on the following Novel Therapies report.

Velcade (PS-341)

Final results of the Phase II SUMMIT trial of Velcade in patients with advanced relapsed and refractory myeloma showed an impressive 35% overall response rate and 59% of patients experienced a response or stable disease.

In the study, 202 patients who had received an average of six previous therapies received Velcade (1.3 mg/m^2) twice a week for 2 weeks with 1 week off for up to 24 weeks. Dexamethasone was permitted if there was a suboptimal response. Responses were assessed using the rigorous Bladé criteria (see table below).

Bladé Criteria: Select Criteria for Determination of Response

Response	M Protein	% Plasma Cells in Bone Marrow	Skeletal Disease (on x-ray)
Complete response (CR)	100% ↓and IF neg†	<5%	Stable
Partial response (PR)	≥50% ↓	N/A	Stable
Minimal response (MR)	≥25% ↓	N/A	Stable
Stable disease (SD)	Not meeting criteria for MR or PD		
Progressive disease (PD)	>25%↑	>25%↑	New bone lesions or ↑ in size

*Includes two assessments performed 6 weeks apart. Responses must have lasted at least 6 weeks.
†IF = immunofixation (a sensitive test for trace amounts of M protein)

Responses to Velcade in evaluable patients are presented in the table to the right. The median duration of response was 12 months and the median overall survival was 16.4 months. Most importantly, these responses were clinically meaningful; patients experienced increased levels of hemoglobin and immunoglobulins, as well as improved performance status and quality of life. In addition, 17% of patients who did not respond to Velcade alone improved their response with the addition of dexamethasone.

Velcade was generally well tolerated and adverse events were predictable and manageable. The most commonly reported events were gastrointestinal-related, and there was some neuropathy and low platelet counts reported, primarily in patients starting with these conditions.

Results of a smaller, similarly designed Phase II trial of Velcade in 54 patients with earlier stage disease (relapsed or refractory myeloma after initial therapy) were also impressive. In the CREST study, overall responses of 30% and 50% were seen at the two doses tested (1.0 or 1.3 mg/m^2, respectively). Complete responses were seen in 4% of patients in both dose groups.

The Phase III APEX trial of Velcade in relapsed and refractory myeloma is underway. This study will enroll 600 patients at 66 centers worldwide and will compare Velcade (1.3 mg/m2, same schedule as above) with high-dose dexamethasone. Earlier this year, Velcade was granted fast-track status by the FDA and Millennium plans to file a New Drug Application in 2003. Velcade is also being evaluated in combination with other agents.

Response To Velcade Alone in the SUMMIT Trial

Response (Bladé criteria)	Percent Patients
Complete Response (IF neg)	4%
Complete Response (IF pos)*	6%
Partial Response	17%
Minimal Response	8%
Overall response	**35%**
Stable Disease	24%

*100% reduction in M protein but still detectable by IF

Visit Clinical Trials Monitor (CTM) on the MMRF's web site, www.multiplemyeloma.org, for more information on this and other Velcade trials.

Novel Therapies

Revimid (CC-5013)

Preliminary results of the Phase II trial of Revimid in 70 patients with relapsed or refractory disease confirmed earlier reports of efficacy. Of the 46 patients who could be evaluated, there was an overall 54% response rate and 39 patients (85%) experienced a reduction or stabilization in their M protein.

In this study, two oral dose regimens were evaluated: 15 mg twice a day or 30 mg once a day for 3 weeks, followed by 1 week rest. Dexamethasone could be added if the response was suboptimal. Response rates are reported in the table below.

Response Rates: Phase II Trial of Revimid Alone

Dose	# patients	Response (Bladé criteria)		
		CR	PR	MR
15 mg 2x daily	23	0	22%	43%
30 mg once daily	23	9%	13%	22%
Both doses	**46**	**4%**	**17%**	**33%**
Overall response	**46**	**54%**		

It was noteworthy that five of seven patients who did not respond to the Revimid did so after dexamethasone was added, raising the total number of patients who achieved a response or stable disease to 96%. Overall, Revimid was well tolerated and there was no significant neuropathy, constipation or sleepiness. Patients tolerated the 30-mg once-daily dose slightly better than the 15-mg twice-daily dose, where there were more reports of low blood cell counts.

A Phase III trial of Revimid in patients with relapsed and refractory myeloma is set to begin in early 2003. A total of 302 patients will be enrolled at 50 sites worldwide. The trial will compare Revimid and dexamethasone against dexamethasone alone. Visit Clinical Trials Monitor (CTM) on the MMRF's web site www.multiplemyeloma.org, for more information on this trial. Additional trials are planned.

Other Agents in Late-Stage Trials

Promising results from other late-stage clinical trials were reported. Studies of Trisenox® (arsenic trioxide, Cell Therapeutics) alone or in combination with vitamin C or chemotherapy suggest that the agent produces clinically relevant responses in the majority of cases of chemotherapy-resistant myeloma. A summary of recent findings in myeloma is shown below. Several Phase II studies of Trisenox, alone or in combination with other agents, in patients with recurrent or refractory myeloma are ongoing.

Recent Trisenox Trials in Myeloma

Investigator	Regimen	Objective Response	Stable Disease
Hussein	Trisenox + Vitamin C	10/21 (48%)	8/21 (38%)
Lee	Trisenox	2/6 (33%)	4/6 (67%)
Berenson	Trisenox	2/7 (29%)	1/7 (14%)
Berenson	Trisenox + Vitamin C + Chemo.	4/6 (67%)	1/6 (17%)

The Bcl-2 antisense agent Genasense™ (Genta) may be useful in resistant myeloma. Preliminary results indicate that 3 of 5 patients who had progressed on VAD (vincristine, adriamycin, and high-dose dexamethasone) responded to the combination of Genasense and VAD. One additional patient had stable disease. Other than fatigue, side effects were no different than those expected with VAD. This finding of "resistance reversal" supports the ongoing Phase III trial of Genasense with high-dose dexamethasone in refractory or relapsed myeloma.

Promising Combination Therapies

Because various anti-myeloma agents act in different ways, it is likely that combination therapy will offer the best chance for improved responses. A variety of combinations are already showing promising results:

- Thalidomide and Velcade in myeloma resistant to salvage therapy post-autologous transplant
- Velcade and Doxil® (liposomal doxorubicin, Ortho-Biotech) in refractory myeloma
- Velcade plus doxorubicin or melphalan in the laboratory
- Thalidomide plus Doxil, vincristine, and dexamethasone (DVd-T) in relapsed/refractory disease

Thalidomide: A Wide Spectrum of Activity

The MMRF thanks D. Weber, MD of the MD Anderson Cancer Center for her role as Guest Editor on the following Thalidomide report.

Data regarding thalidomide usage as a single agent or in combination with other therapies in myeloma was presented (see Novel Therapies section for more information on combination therapies). These findings demonstrate that thalidomide is increasingly being used across the entire spectrum of myeloma disease.

Thalidomide As Initial Therapy

Thalidomide may be useful as initial therapy for asymptomatic myeloma and may delay progression to symptomatic disease. In a study at the Mayo Clinic involving 31 patients with smoldering or indolent myeloma, 34% experienced at least a 50% reduction in M protein with thalidomide therapy. This significant activity in early stage disease warrants confirmation in randomized trials.

Thalidomide As Maintenance Therapy

Thalidomide also appears to enhance survival when used as post-transplant maintenance therapy. When used alone or in combination with interferon, thalidomide (100-400 mg/day) significantly improved overall survival following autologous stem cell transplantation. Further randomized trials will help confirm these findings.

Thalidomide In Later Stage Patients

Long-term follow-up of patients receiving thalidomide for advanced and refractory myeloma indicates that thalidomide is highly beneficial in this patient population. Superior survival rates are seen in patients with good prognostic factors (absence of chromosome abnormalities and low beta-2 microglobulin).

Results reported from an Italian study of low-dose thalidomide in combination with dexamethasone are among the first to demonstrate that thal-dex is an effective salvage treatment for advanced myeloma and improves survival. Thal-dex, in this study, resulted in rates of response and event-free survival that were equivalent to conventional chemotherapy (see table below). However, thal-dex offered significantly improved overall survival, was not myelotoxic, postponed the need for chemotherapy, and delayed the occurrence of resistant disease.

Salvage Treatment for Advanced Myeloma

	Thal-dex	Conventional Chemotherapy
Response (50% - 100% ↓ in M protein)	52%	45%
Median progression-free survival	12 months	11 months
Median overall survival	27 months	19 months ($p<0.05$)

In a US Phase II study to determine the effect of dose on response and tolerability, thalidomide was also shown to be active in relapsed myeloma following stem cell transplantation. An overall response rate of 54% was seen in patients receiving 200 to 600 mg/day of thalidomide. Optimal thalidomide dosing appears to be variable and needs to be individualized to a dose that is both well tolerated and effective for the patient.

Management of Clotting

There have been some reports of clotting (thrombotic/embolic) events in patients receiving thal-dex. According to a study conducted at MD Anderson, it appears that these events may be related to certain predisposing patient factors. Data from the MD Anderson study, as well as from the Total Therapy II Trial, demonstrate a decrease in thrombotic and embolic events with therapeutic doses of anticoagulation.

Ongoing Studies

Thalidomide is currently being evaluated as part of combination therapy in patients with smoldering/indolent myeloma, newly-diagnosed disease, and relapsed/refractory myeloma. Celgene will begin a Phase III registration trial in 2003 of thal-dex in newly diagnosed patients. Visit Clinical Trials Monitor (CTM) on the MMRF's web site, www.multiplemyeloma.org, for more information on this and other thalidomide trials.

Transplantation Update

Double Transplants Offer Improved Survival

Updated results of the IFM-94 study comparing single versus double autologous transplants in 399 patients under the age of 60 with previously untreated myeloma report improved survival at 7 years with double transplants, despite similar response rates with both procedures. The probabilities of event-free and overall survival with double transplants were double that seen with single transplants (see figures below).

The relative merit of double transplant has yet to be determined. Other studies of shorter duration have not shown additional benefit with a second transplant; however, apparent differences may not appear until 4 years following transplant. So we eagerly anticipate further confirmatory studies.

Right now, it appears that patients who benefit most from double transplants are those who do not achieve a good response (defined as a 90% reduction in M protein) after the first transplant.

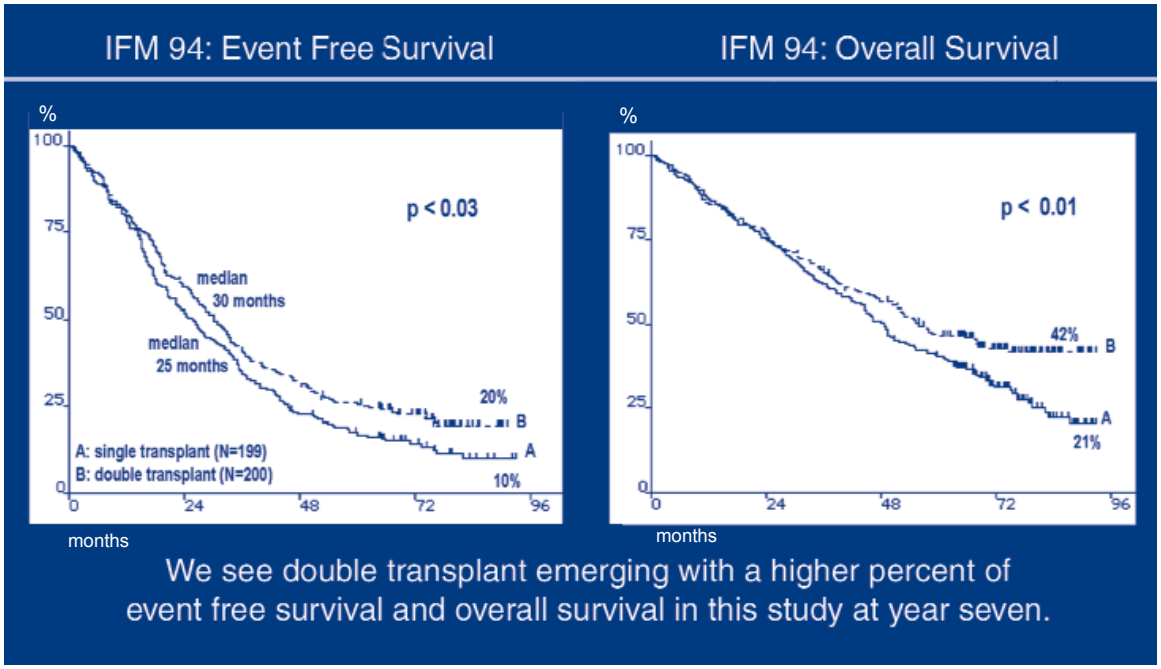
The MMRF thanks
J.L. Harousseau, MD
University Hospital,
Nantes, France
for his role as Guest Editor on the following Transplantation report.

There does not appear to be a significant difference in response rates between single and double transplants in patients who have a good response after transplant. In autologous transplants, the result of induction therapy appears to be an important factor in the overall outcome following the transplant.

However, because patients with poor prognostic factors respond poorly to double transplants, these patients may be good candidates for allogeneic transplants, including mini (non-myeloablative) transplants that involve lower-dose chemotherapy/radiation rather than a high-dose regimen, or a clinical trial with a novel agent.

One such mini-transplant approach -- an autologous transplant followed by a mini-allogeneic transplant -- appears to be a feasible option for myeloma and may allow the benefits of an allogeneic transplant with less toxicity. Preliminary results of an ongoing Italian multicenter trial involving patients up to 65 years of age with newly diagnosed myeloma show a high rate of sustained complete responses due to the beneficial graft-versus-myeloma effects, confirming an earlier report of the efficacy of the procedure by the Seattle Consortium.

The results of transplantation need to be improved. The future of transplantation may involve the use of novel agents to improve the results of induction therapy, as well as to maintain response after transplant.



Biology of Myeloma Bone Disease

The MMRF thanks D. Roodman, MD, PhD
University of Pittsburgh Cancer Institute
for his role as Guest Editor on the following Myeloma Bone Disease report.

Bone disease is the most devastating complication of myeloma, occurring in 80% or more of patients. There exists a "vicious cycle" between myeloma cells and bone-destroying osteoclasts whereby tumor cells secrete factors that increase the activity of osteoclasts and osteoclasts in turn secrete factors that promote tumor cell growth.

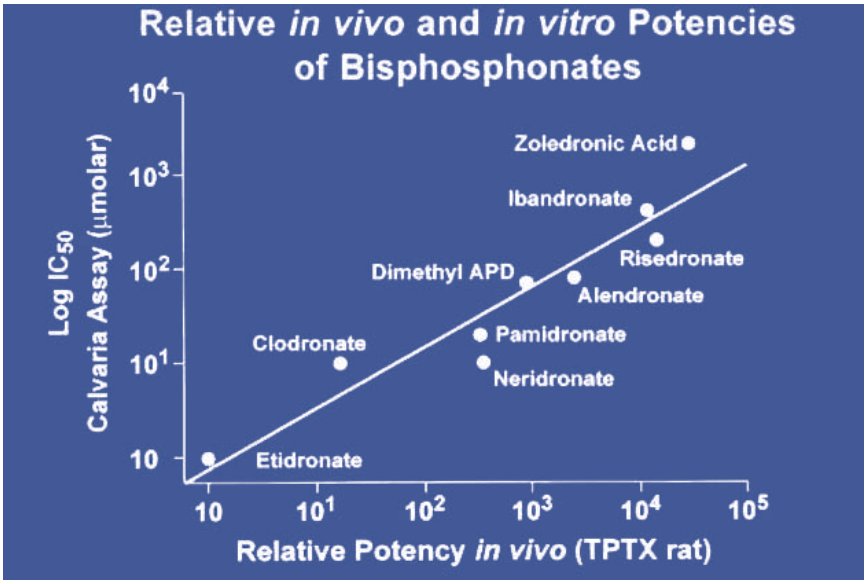
Bisphosphonates have significantly improved the outlook for patients with myeloma, reducing the incidence of skeletal-related events -- new bone lesions, fractures and surgery or radiotherapy to bone -- by about half. Aredia® and Zometa® (pamidronate and zoledronic acid, Novartis) are highly effective bisphosphonates. Both are equally effective, but Zometa is more potent and convenient due to the shorter infusion time (15 minutes vs. 2 hours). Both appear to be equally safe as long as they are not infused in a shorter time period than indicated. Because kidney function may be affected by bisphosphonates, patients' creatinine levels should be measured prior to administration of these agents. Because there is limited data with use of Zometa in patients with kidney failure, such patients should receive Aredia.

Bisphosphonates may have a therapeutic potential in myeloma beyond treating bone lesions. Zometa was reported to have direct anti-myeloma activity in an animal model of plasmacytoma.

New Agents in Development

Insight into myeloma bone disease has identified new targets for therapy. RANK ligand (RANKL) plays a major role in the development and activity of osteoclasts and myeloma cells induce its expression. Agents that block the expression of RANKL are promising candidates for myeloma bone disease. Two such agents include osteoprotegerin (OPG), a natural inhibitor of RANKL, and RANK-Fc, an engineered inhibitor of RANKL that acts in a similar way to OPG. Both inhibit bone destruction and decrease tumor burden in animal models of myeloma. In a Phase I study in patients with myeloma or breast cancer, OPG reduced bone resorption.

Another factor that appears to be involved in myeloma bone disease is macrophage inflammatory protein-1a (MIP-1a). Blocking the activity of this factor has also been shown to reduce both tumor burden and bone destruction in animal models of myeloma.



The MMRF wishes to express thanks and gratitude to these sponsors who made sure that this up-to-date and critically important medical information reaches patients and members of the healthcare community. Their support has made this special edition newsletter possible.

Celgene CTI Genta Millennium Novartis

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The information herein is not intended to replace the services of trained health professionals (or to be a substitute for medical advice.) You are advised to consult with your healthcare professional with regard to matters relating to your health, and in particular, regarding matters which may require diagnosis or medical attention.

Gene Expression Profiling

Gene expression profiling (GEP) is rapidly becoming a useful diagnostic and prognostic tool in the clinical management of myeloma and is providing new insights into the biology of the disease.

The MMRF thanks J. Shaughnessy, PhD
University of Arkansas for Medical Sciences
for his role as Guest Editor on the following GEP report.

GEP To Identify Risk and Prognosis

Microarray technology allows us to look at the expression of 35,000 genes in a single patient at the same time. These genetic profiles can then be used to stratify patients into different risk groups based on their relationship to known clinical parameters linked to prognosis.

There are gene expression patterns that differentiate normal plasma cells and myeloma cells. From these studies it is also apparent that monoclonal gammopathy of undermined significance (MGUS) has gene expression profiles that are indistinguishable from myeloma, suggesting that MGUS has all the features of malignancy. Gene expression profiling has also identified four different subgroups of myeloma. These subgroups appear to range from less aggressive (MGUS-like) to more aggressive disease (similar to myeloma cell lines that represent advanced-stage disease) and will likely need to be treated accordingly. Myeloma cells have distinct genetic profiles that distinguish them from normal plasma cells. Profiles of myeloma cells range from MGUS-like to those resembling myeloma cell lines.

GEP To Identify Treatment

Microarray technology may eventually be able to classify patients and custom-tailor their therapy based on how they are expected to respond. In fact, a trial investigating the potential of linking specific genetic profiles to response to particular therapies is now underway.

Chromosomal Abnormalities in Myeloma

Genetic studies are further delineating chromosome abnormalities in myeloma and their prognostic significance. For example, chromosome abnormalities, especially of chromosome 13, were firmly linked to poor prognosis after double autologous transplantation based on a median follow-up of almost 10 years of patients in the Total Therapy I trial (Arkansas). Another study of double transplants conducted at Arkansas indicate that chromosome abnormalities also appear to have adverse prognostic implications not only when present at diagnosis, but especially when they persist following initial therapy and prior to the first of two autologous transplants. Other studies have looked into a specific chromosomal abnormality, the 4;14 translocation, as a predictor of poor survival and have identified the resultant activation of the MMSET oncogene as an important factor in initiation and progression of myeloma.

Studies such as these show that routine cytogenetic analysis at the time of diagnosis is important for early recognition of high-risk myeloma. These high-risk patients should be considered for alternative therapies that may have a greater chance of success.

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New Agents in Development

While much of this newsletter is an update on therapies in trial, the results of preclinical studies of a variety of new agents are also encouraging. The table to the right provides information on these agents.

Visit the MMRF's web site to view the web cast from this year's ASH meeting. The site offers audio interviews with the most notable doctors and researchers in myeloma, who presented at ASH this year. Key slides, abstracts and transcripts from these presentations are available for you to download. The most promising news and highlights are available at **www.multiplemyeloma.org**

Agents in Early Development for Myeloma

AGENT	DESCRIPTION
Agents targeting circuits within the cell that allow growth and survival	
Farnesyl transferase inhibitors (FTIs)	FTIs induce apoptosis of myeloma cells in the lab and prevent their growth in response to IL-6.
Histone deacetylase (HDAC) inhibitors	These agents, such as SAHA and LAQ842 (Novartis), induce apoptosis of myeloma cells in the lab; LAQ842 has also shown significant activity in a mouse model of myeloma.
Heat shock protein (Hsp) inhibitors	Hsps promote cell survival and growth. 17-AAG, an Hsp inhibitor, prolongs survival in a mouse model of myeloma and is being evaluated in clinical trials in various cancers; phase II trials are planned.
Agents targeting cell surface receptors involved in drug resistance	
Insulin-like growth factor (IGF) receptor inhibitors	IGFs stimulate growth of myeloma cells and protect them from apoptosis. Inhibitors of the IGF receptor, such as ADW (Novartis), block these actions.
Agents targeting tumor cell interactions with the microenvironment	
(LPAAT)-b inhibitors	These agents induce apoptosis of myeloma cells. Several agents in this class developed by Cell Therapeutics are being investigated.