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# MYELOMA FOCUS

Newsletter of the

# MMRF

## Special Edition

### MMRF Reports from

Salamanca: IX<sup>th</sup> International Myeloma Workshop and from Chicago: ASCO

The Multiple Myeloma Research Foundation is proud to present this special edition newsletter that features highlights from recent key scientific sessions.



#### IX<sup>th</sup> International Myeloma Workshop

Salamanca, May 23-27

Over 1,000 clinicians and researchers attended this biennial workshop in the historic city of Salamanca. The primary aim of these workshops is to support continuing education and to serve as a forum for discussion on the scientific progress made in the experimental, clinical and therapeutic areas of Multiple Myeloma.

Special thanks to co-chairs Dr. Jesús San-Miguel (University of Salamanca Hospital) and Dr. Joan Bladé (Hospital Clinic, Barcelona), as well as the members of the workshop committees, for organizing this important meeting. The MMRF looks forward to the Xth International Workshop, which will be held in Sydney, Australia, in April 2005, and will be chaired by Dr. Douglas Joshua.

**Thank you to the sponsors of  
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#### American Society of Clinical Oncology (ASCO) 39<sup>th</sup> Annual Meeting

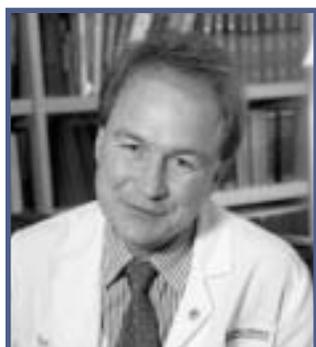
Chicago, IL, May 30-June 2

More than 25,000 cancer specialists from around the world attended the ASCO Annual Meeting, the premier educational and scientific event for oncology professionals, to discuss the latest advances in cancer care, treatment and prevention. Highlights of oral and poster presentations related to multiple myeloma from this extensive oncology meeting are discussed.



Hard at work in Salamanca  
(L-R): AQY, KA, SM, ??? and ???

# Novel Therapies in Clinical Trials



**Guest Editor  
Dr. Richardson**

## Velcade

The proteasome inhibitor Velcade (bortezomib, Millennium), formerly known as PS-341, was recently approved in the US for use in patients with relapsed or refractory myeloma who have received at least two prior therapies and have had disease progression on their most recent therapy. The approval was based primarily on the results of the Phase II SUMMIT trial, first presented at ASH 2002. In this

multi-center trial of 202 heavily pre-treated patients with relapsed and refractory myeloma, there was an overall response rate of 35% with Velcade therapy; 10% of patients had a complete response (CR) or near CR and 17% more had a partial response (PR). The most common side effects seen included nausea, diarrhea, fatigue, low platelet counts and neuropathy.

Pharmacogenomic analysis is helping to differentiate patients who responded from those who did not and will continue to be studied in future trials. Further analyses of data from the Phase II SUMMIT and CREST trials indicate that:

- At least 1 in 5 patients who received high-dose dex after they had not responded to, or relapsed after, Velcade alone had some benefit with the combination.
- The side effect profile in patients who were treated with Velcade for up to 18 months was similar to that seen in the first 6 months of treatment.
- Complete and partial response rates were independent of the number and type of prior treatments, as well as chromosome 13 deletion status, myeloma subtype and B<sub>2</sub>M levels.

The Phase III APEX trial is rapidly accruing patients with less advanced disease (progression after 1 to 3 prior lines of therapy) (see figure at right). See the MMRF's Clinical Trials Monitor [www.multiplemyeloma.org/clinical\\_trials/ctm/4.04.72.asp](http://www.multiplemyeloma.org/clinical_trials/ctm/4.04.72.asp) for more information about this trial

**Velcade Phase III APEX Trial**

- Multicenter/international at 66 sites ongoing
- 600 patients with relapsed and refractory myeloma

Velcade: (1.3 mg/m<sup>2</sup> twice/week x 2, 1 week off)

Versus

Dexamethasone:  
(40 mg/day; 4 days on, 4 days off x 3 odd cycles; 4 days x 1 on even cycles)

- Endpoint: Time to progression

Studies in the lab show Velcade to act synergistically with various types of chemotherapy. In addition, low doses of Velcade appear to restore chemosensitivity of resistant myeloma cell lines and to increase apoptosis. This has led to several combination therapy trials (see table below), including one evaluating low-dose Velcade and melphalan and another promising study using Velcade in combination with Doxil.

Drugs Being Evaluated in Combination with Velcade in Phase I and II Trials		
Drug	Patient Population	Preliminary Results
Doxil (liposomal doxorubicin)	Relapsed myeloma (n=23)	The majority of patients achieved a response or stable disease and the combinations were generally well tolerated
Melphalan	Relapsed/ refractory myeloma (n=15)	
Thalidomide	Myeloma resistant to, or relapsed from, autologous stem cell transplant or salvage therapy (n=20)	Previously reported that after two cycles of therapy, 60% of evaluable patients experienced at least a 25% reduction in M protein

Additional combination studies are planned, with conventional agents as well as other novel therapies. Velcade trials in newly diagnosed patients are also ongoing.

## IMiDs™

Immunomodulatory drugs (IMiDs, Celgene) are based on the structure and function of thalidomide. Recently reported preliminary results of the ongoing Phase II trial of CC5013 (Revimid™), which is being funded by an MMRF Program Grant, indicated an overall 54% response rate (≥25% reduction or better in M protein) in patients with relapsed or refractory myeloma. Side effects included low blood counts, diarrhea, fever, muscle cramps, neuropathy, constipation, rash and fatigue, but were generally mild. This large trial (over 100

patients) has just completed accrual. The Phase III trial comparing Revimid and dex in patients who have relapsed after one or more lines of therapy has started enrollment (see figure next page).

See the MMRF's Clinical Trials Monitor [www.multiplemyeloma.org/clinical\\_trials/ctm/4.04.86.asp](http://www.multiplemyeloma.org/clinical_trials/ctm/4.04.86.asp) for more information about this trial

# MYELOMA FOCUS

# Novel Therapies in Clinical Trials continued

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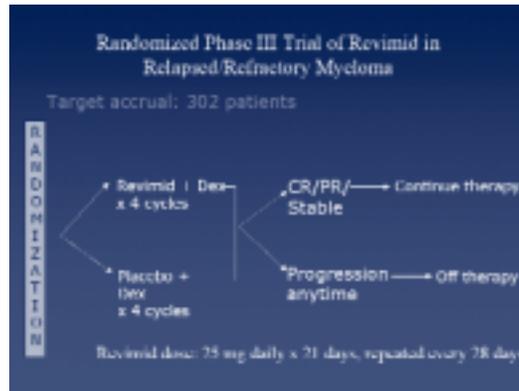
The information herein is not intended to replace the services of trained health professionals (or to be a substitute for medical advice.) You are advised to consult with your healthcare professional with regard to matters relating to your health, and in particular, regarding matters which may require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

An upcoming Phase II trial will evaluate Revimid alone with Revimid plus dex if Revimid alone is not successful in heavily pre-treated patients. Additional studies will evaluate Revimid in newly diagnosed patients and as maintenance therapy following stem cell transplant.

## Update on Other Promising Agents

Data from several studies suggest that arsenic trioxide (Trisenox®, Cell Therapeutics) produces consistent response rates in myeloma patients who have progressed despite standard or high-dose chemotherapy or other investigational agents, particularly when it is used in combination with other agents.

A Phase III study comparing dex alone with oblimersen sodium (Genasense™, G3139, Genta) in combination with dex in relapsed and refractory myeloma is nearing completion and two Phase II trials are providing encouraging preliminary results.



# Prognostic Factors

Patients with asymptomatic myeloma have a variable course of disease, with some patients remaining stable for a long period of time while others progress more rapidly. Various prognostic criteria for identifying patients at high risk who may benefit from early treatment have been proposed. Dr. Donna Weber and her colleagues at MD Anderson identified a number of individual factors that were linked to shortened time to progression in patients with asymptomatic disease. However, when the factors were looked at together, levels of M protein and immunoglobulin (Ig) type were best able to distinguish between low and high risk (see adjacent table). Magnetic resonance imaging (MRI) also provided

additional information; the presence of bone abnormalities on MRI indicated greater risk.

Similarly, Dr. Vincent Rajkumar of the Mayo Clinic presented data that identified M protein levels as the best predictor of progression in monoclonal gammopathy of undetermined significance (MGUS). Increased plasma cell labeling index (PCLI), which is an indicator of active myeloma cell growth, and increased numbers of plasma cells in the circulation were also identified as risk factors for progression of MGUS and asymptomatic myeloma.

Risk of Progression in Asymptomatic Myeloma	
Risk	M Protein and Ig type
Low	≤3 g/dL and IgG
Intermediate	>3 g/dL or IgA
High	>3 g/dL and IgA

# Novel Therapies in Preclinical Testing



**Guest Editor  
Dr. Mitsiades**

This is indeed a unique era in myeloma research with the wide variety of targeted therapies in preclinical testing. According to Dr. Kenneth Anderson (Dana-Farber), many of these agents target the myeloma cell in its bone marrow microenvironment (see figure right).

The most promising therapies, many of which are being investigated as a result of MMRF funding are described in the adjacent table. Several of these

agents target multiple pathways inside the tumor cell, reducing the ability of the cell to escape the effects of these drugs and potentially improving their efficacy.

## Progress in Immunotherapy

Stepwise improvements in immunotherapeutic strategies directed against myeloma continue to be made, further advancing the field. Dr. Freda Stevenson presented updated information on anti-idiotype DNA vaccines, one of which is being used to vaccinate donors of allogeneic stem cell transplants. The immune cells generated are transferred to the patient during DLI, circumventing the problem of immunosuppression common in myeloma patients.

Results of several preclinical studies of dendritic cell vaccines were presented, as well as a final report on a Phase I/II trial of Mylovenge™ idiotype-pulsed autologous dendritic cells (Dendreon). Mylovenge treatment induced idiotype-specific T cell immune responses in 43% of patients with advanced, refractory myeloma that correlated with improved time to disease progression. A small number of patients had minor responses or stable disease.

Other immunotherapies under investigation include idiotype-specific cytotoxic T cells and vaccibodies, which are recombinant immunoglobulin-type molecules that induce potent anti-idiotype responses. Microarray analysis has identified several cell proteins present in myeloma cells with abnormal cytogenetics and in relapsed disease as potential targets for immunotherapy.



## Promising Anti-Myeloma Therapies in Preclinical Testing

Compound	Description
17-AAG	Inhibits the activity of heat shock protein-90 (Hsp90), which plays an important role in the growth and survival of tumor cells; significantly prolonged survival in a mouse model of myeloma. Currently in Phase I trials sponsored by the NCI; a combination trial with Velcade is planned.
IGF-1 (insulin-like growth factor) receptor inhibitors	Are active against myeloma cells in the lab and in animal models. A number of these inhibitors, including agents under development by Novartis, are being evaluated in toxicology studies; Phase I trials are planned.
FGF-R3 inhibitors (Pfizer)	Inhibit the activity of FGF-R3, a receptor over-expressed in a subset of myeloma patients.
PTK787 (ZK 222584, Novartis)	Oral angiogenesis inhibitor that inhibits myeloma cell growth and overcomes drug resistance in the lab. A Phase II trial in relapsed or refractory myeloma should begin enrollment at Dana-Farber shortly.
Histone deacetylase (HDAC) inhibitors	HDAC inhibitors, such as SAHA (Aton) and LAQ842 (Novartis), induce apoptosis of myeloma cells in the lab. LAQ842 has also shown significant activity in a mouse model of myeloma and is in Phase I trials in hematologic cancers; a Phase I trial in myeloma is planned at Dana-Farber.

# Thalidomide

Thalidomide continues to be evaluated, alone and in combination, across the spectrum of myeloma disease. Results of over 60 studies were reported at Salamanca.

## Use in Relapsed and Refractory Disease

According to Dr. Meletios Dimopoulos (University of Athens), response to thalidomide are seen in 30% to 40% of patients with relapsed and refractory disease. The response rate can be improved to over 50% and more rapidly when dexamethasone is added (thal-dex). Dr. Raymond Alexanian (MD Anderson) noted that this enhanced effect is seen either when dex is initiated at the same time, or later when patients begin to relapse, and may allow reduction in the thal dose. In his opinion, thal-dex is an option when resistance to standard therapy is recognized.

## Use in Newly-diagnosed Myeloma

Thal-dex appears to be an active alternative to VAD (vincristine, doxorubicin and dex) for transplant induction therapy with response rates of approximately 65-70%. It is a promising therapy for newly diagnosed myeloma in patients who are candidates for stem cell transplantation. The results of a recently completed randomized trial will be available next year and will clarify the role of thal-dex as initial therapy for myeloma. Studies are also underway to identify strategies that can minimize the toxicities of thal-dex. Thal-dex may also be an alternative to melphalan and prednisone in patients who are not candidates for stem cell transplant, but more studies are needed. The recently reported efficacy of the thal as a single-agent in asymptomatic (smoldering/indolent) myeloma requires randomized studies.

AND YOU ARE GOING TO WANT TO ADD IN A FEW



Guest Editor  
Dr. Rajkumar

LINES TO REPLACE THE INFORMATION THAT WAS IN THE CHART -- THIS WAS A BIG SPACE SAVER!

## Use in Combination Therapy

Thalidomide is being investigated as part of combination therapy with a variety of agents, some of which are shown in the table below. These preliminary results are promising, but further studies and longer follow-up are necessary. Of particular importance is the issue of side effects with combination therapy, since the toxicity can increase with use of multiple drugs. The combination of thal and zoledronic acid (Zometa®, Novartis) is also being evaluated for efficacy in a Phase III trial in early asymptomatic patients, as well as part of various maintenance regimens.

## Dosing and Side Effects

Optimal thal dosing appears to be variable and side effects such as constipation, fatigue, sedation, rash, deep vein thrombosis (DVT, a serious disorder where blood clots form in the body) and neuropathy may require dose reductions. Therefore, therapy should be individualized for each patient to a dose that achieves response and is well tolerated.

Although patients with myeloma are at increased risk of DVT, this risk is increased further in patients receiving thal in combination with dex or chemotherapy. Dr. Zangari (University of Arkansas) reported that the risk of DVT in patients receiving thal plus doxorubicin -- containing chemotherapy appears to be higher in newly diagnosed patients. Data from several centers show that prophylactic anticoagulation may reduce this risk and patients may be able to continue thal treatment with proper anticoagulation. Further studies will help determine the most effective anticoagulation regimen.



MMRF Scientific Advisory Board Chairman Dr. Kenneth Anderson, of the Dana-Farber Cancer Institute, was presented with the **Waldenstrom Award for Myeloma Research** at the IXth International Workshop on Multiple Myeloma in Salamanca. This prestigious award, which has been in existence since 1989, is granted to an individual active in the field of myeloma who is considered exemplary by a committee of his or her peers.

# Transplantation Update

## Superiority of High-dose Therapy

Results of a recently published trial, as well as others presented at the meetings, establish high-dose chemotherapy with autologous stem cell transplantation (HDT/SCT) as a more effective first-line therapy than conventional chemotherapy for patients under the age of 65. These data confirm the results of the landmark IFM-90 trial.



Guest Editor  
Dr. Harousseau

Published results of the large British MRC VII trial, summarized by the author Dr. J. Anthony Child of the General Infirmary at Leeds, UK, indicate patients receiving HDT/SCT had higher rates of remission than those receiving conventional chemotherapy and longer survival (see table below). The benefit of HDT/SCT was particularly evident in patients with poor prognosis, indicated by high levels of beta-2 microglobulin (B<sub>2</sub>M).

Results of MRC VII Trial		
Treatment Arm	Remission Rate	Median Survival
HDT/SCT	44%	54 months
Conventional chemotherapy	8%	42 months

## Conditioning Regimens

A number of conditioning regimens in preparation for transplant are under investigation, including use of intermediate vs. high-dose melphalan, and the addition of dexamethasone and/or thalidomide. Dr. Mario Boccadoro (University of Torino, Italy) presented data suggesting that a regimen of repeated intermediate melphalan doses (100 mg/m<sup>2</sup>) prior to SCT is a suitable option for elderly patients aged 60 to 70 years of age, especially those who have other medical conditions.

Another way to strengthen the pretransplant regimen is the use of targeted skeletal radiation, such as Skeletal Targeted Radiotherapy (STR, NeoRx). Dr. William Bensinger (Fred Hutchinson Cancer Research Center, Seattle) presented data from the Phase I/II studies of STR in 83 patients that indicated an overall response rate of 64%. A randomized Phase III trial comparing high-dose melphalan alone and in combination with STR is planned, using a revised protocol designed to improve the safety of the regimen.

## Importance of Complete Remission

Several presentations highlighted the fact that the achievement of a complete response (CR) after HDT/SCT is associated with long-lasting disease control and prolonged survival. Based on data from 234 patients treated at MD Anderson, Dr. Raymond Alexanian reported that increased intensity of treatment and disease status had a major bearing on the achievement of a CR. However, the fact that a CR is achieved is most important, regardless of the method by which it is achieved.

## Single vs Double Transplants

The role of planned double (tandem) autologous stem cell transplants as a means to improve on the results of single transplants is still unclear. The recently reported final analysis of the IFM-94 trial, which was summarized by Dr. Michel Attal, demonstrated that tandem transplants provided significantly improved 7-year survival over single transplants in patients under the age of 60. The benefit was not observed until 4 years out.

Single Versus Double Transplant Studies	
Study	Preliminary Findings
HOVON 22 (Netherlands)	At 4 years, superior event-free survival (EFS) and time to progression (TTP) with double transplant but no effect on overall survival (OS)
MAG 95 (France)	No additional benefit of double transplant in patients under the age of 56 after an average follow-up of 53 months
Bologna 96 (Italy)	Significantly improved EFS and TTP with double transplants after a 3-year follow-up but no effect on OS
GMMG (Germany)	Final analysis expected in November 2003

However, other trials initiated in the 90s are not yet mature and preliminary results are inconclusive regarding the superiority of this highly demanding regimen (see table below). In addition, the designs of these studies vary, so comparisons are difficult.

Although several studies have demonstrated an advantage of performing a second transplant prior to relapse, data from a

continued next page

# Myeloma Genetics

It is becoming apparent that the path to myeloma is a multi-step process. According to Dr. Leif Bergsagel of Weill Medical College, Cornell University, myeloma arises because of genetic instability of a plasma cell. This is typically followed by translocations (swapping of portions of chromosomes) in the area of the chromosome that regulates antibody production, known as the IgH region. These IgH translocations turn on cancer genes (oncogenes) and appear to be an early immortalizing event since they are observed in patients with MGUS. In addition, these primary translocations appear to identify subgroups of patients with similar features and response to therapy.

Continued genetic instability and secondary translocations appear to lead to the progression to myeloma. According

#IgH Translocations	MGUS	Myeloma	Late-stage Myeloma	Myeloma Cell Lines
1	46%	55-66%	62%	92%
≥2	<5%	<5%	13%	50%
≥3	<1%	<1%	0%	13%

to Dr. Michael Kuehl of the NCI, the number of IgH translocations appears to increase as the disease progresses (see table above).

A number of laboratories are investigating the clinical implications of the various cytogenetic abnormalities present in myeloma. For example, patients with certain IgH translocations, such as t(4;14) and t(14;16), often have very aggressive disease while patients with t(11;14) often have a better prognosis. Dr. Bergsagel's lab has identified a group of patients that lacks primary IgH translocations and may represent a new molecular subtype of myeloma. These

patients express low levels of the cyclin D1 gene and appear to have a better prognosis. Dr. John Shaughnessy of the University of Arkansas noted that different patterns of gene expression, such as high levels of genes known as DKK1 and FRZB, are also associated with more severe myeloma bone disease.



**Guest Editor**  
**Dr. San-Miguel**  
reviewing **Myeloma Genetics,**  
**Progress in Immunology and**  
**Bone Disease Management**

## Transplantation Update continued

non-randomized study presented by Dr. Ray Powles of the Royal Marsden Hospital suggest that waiting until relapse provides similar results. IFM-94 data indicated that a planned second transplant was of most benefit to patients who did not achieve a CR following the first transplant, suggesting that patients who achieve a CR with the first transplant save the second transplant for relapse.

### Role of Allogeneic Transplants

The prospects for a molecular CR appear to be better following an allogeneic than autologous transplant due to the graft-versus-myeloma effect. However, the mortality rate seen with allografts-although improved in recent years-is still significantly higher than autografts due to graft-versus-host disease (GVHD), a serious and sometimes fatal condition occurring when donor cells attack the recipient's tissues. Dr. Gosta

Gahrton of the Karilinska Institute, Sweden noted that selection of patients based on prognostic factors and using gender-matched sibling donor transplants may help decrease overall mortality. The use of DLI to further mediate the graft-versus-myeloma effect is promising. Data reported by the HOVON group (Netherlands) indicate that 50% of patients who relapse following an allograft can achieve a response with DLI.

Because of the high mortality with allografts, the trend has been toward reduced intensity "mini" (nonmyeloablative) allogeneic transplants, often in combination with DLI. However, GVHD is also a serious complication of mini-transplants and use of this technique in myeloma requires further investigation to achieve the success and safety rates seen in other hematologic malignancies. In the future, the technique may extend the benefits of transplantation to more older individuals.



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## Bone Disease Management and Beyond

Intravenous bisphosphonates are recommended for all myeloma patients with evidence of bone disease. However, the bisphosphonate Zometa is currently being evaluated in a Phase I study in patients with MGUS and bone loss, who are therefore at high risk of disease progression, to determine its potential bone protective effect.

Studies suggest that bisphosphonates exhibit antitumor effects that may be

enhanced by steroids. As such, a Phase I trial has been initiated to explore the antimyeloma activity of higher doses of Zometa (up to 3-4 times the usual 4 mg dose).

<sup>153</sup>Samarium-EDTMP, a radioactive bisphosphonate, is reported to be a novel palliative approach to the treatment of symptomatic myeloma in elderly patients not eligible for further chemotherapy.



**Salamanca: IX<sup>th</sup> International Myeloma Workshop**  
**World wide collaboration to accelerate the search for a cure**

Top: International experts participate in myeloma workshop.  
Left: Drs Anderson, XXXX and San-Miguel