

# Multiple Myeloma:

Treatment Options for Refractory or Relapsed Disease

## MULTIPLE MYELOMA: THE BASICS

### Prevalence and Incidence

An estimated 19,920 new cases of multiple myeloma will occur in the United States in 2008. Of these, about 11,190 will be in men and about 8,730 in women. Multiple myeloma is slightly more common among men than women, and almost twice as common among blacks as among whites. The average age at diagnosis is 65 to 70 years.

### Survival Rates

About 10,690 Americans are expected to die of multiple myeloma in 2008. As of 2006, the 5-year relative survival rate for multiple myeloma was approximately 34%. Survival is higher in younger people and lower in the elderly, according to the American Cancer Society. Of course, 5-year survival rates are based on patients diagnosed and initially treated more than 5 years ago prior to that report. Recent improvements in treatment may result in a more favorable outlook for recently diagnosed patients.

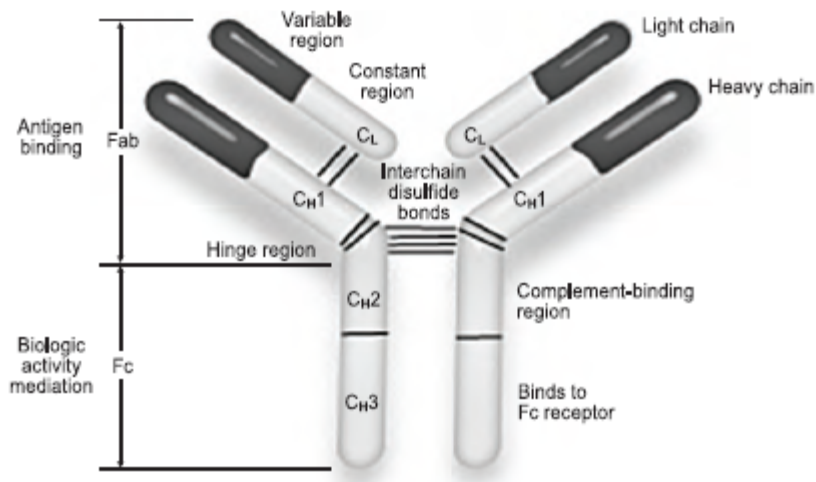
### Definition

Multiple myeloma (myeloma or plasma cell myeloma) is a cancer of the plasma cells in the bone marrow. Normally,  $\leq 5\%$  of bone marrow cells are plasma cells; in multiple myeloma that level is elevated. There are different clones of plasma cells in the bone marrow, which make the numerous types of immunoglobulins (antibodies) needed for the immune system. In myeloma, the cancerous plasma cells are monoclonal and overcrowd the bone marrow, causing some of the complications associated with the disease. These abnormal cancerous plasma cells make a similar immunoglobulin (monoclonal immunoglobulin, also called an M-protein). This can be of any type: IgG, IgA, IgD or IgE; IgG is, however, most common. Sometimes the cancerous plasma cells secrete only the light chains of the immunoglobulin, which are called monoclonal kappa and lambda light chains or Bence Jones proteins. Overall, approximately 70% of patients with myeloma will have elevated IgG, 20% IgA, and 5%-10% light chains only (Bence Jones protein). About 1% will have IgD, IgE, IgM or

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nonsecretory disease (cancerous plasma cells that do not secrete immunoglobulin). About 30% of the time there is an imbalance in the production of light and heavy chains resulting in excess light chains along with the monoclonal antibody.



### Immunoglobulin Molecular Structure

#### Clinical Presentation

The clinical presentation of multiple myeloma is variable; approximately 30% of patients are asymptomatic at diagnosis. In these cases the diagnosis is usually made because a healthcare practitioner notices an elevated protein on routine blood tests and follows up. The clinical findings suggesting a possibility of multiple myeloma include:

#### *Bone Disease*

Generalized bone loss throughout the body and lytic bone lesions are seen. Bone pain is a common finding in multiple myeloma, often from vertebral compression fractures. The bone marrow microenvironment and the myeloma cells produce many factors that promote the proliferation of myeloma cells and bone loss. These include growth factors such as vascular endothelial growth factor (VEGF), tumor necrosis factor (TNF), and interleukin 6 (IL-6), among others.

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### *Hypercalcemia*

About 20% of patients will have hypercalcemia upon presentation. Hypercalcemia can cause nausea, confusion, constipation, polyuria, and fatigue.

### *Anemia*

About 60% of patients will have anemia at the time of diagnosis; most will develop it eventually. It can cause fatigue and weakness. The anemia is caused to some degree by crowding out of the normal cells, but there is also inhibition of red blood cell production by various cytokines. Sometimes neutropenia can also occur, and paradoxically platelets may be elevated or lowered.

### *Renal Insufficiency*

Kidney disease is commonly associated with multiple myeloma. Renal impairment is present at diagnosis in approximately 20% to 25% of patients with multiple myeloma, with another 20% developing it later in the disease process. The abnormal proteins from the myeloma cells can cause a kidney damage through a variety of mechanisms.

Hypercalcemia can contribute to kidney disease, as well.

### *Infections*

Recurrent infections are common in patients with multiple myeloma. Patients with multiple myeloma have approximately a 15-fold increase in the risk of infections, particularly pneumonia. Patients with multiple myeloma are more susceptible to bacterial infections, especially from encapsulated microorganisms, such as pneumococcus, as well as viral infections. In multiple myeloma, the patient has an excess of one particular immunoglobulin that does not fight infection and levels of normal immunoglobulin are often suppressed. In addition, the abnormal plasma cells in the bone marrow can crowd out the normally functional white blood cells. All of the mechanisms for immune dysfunction are not fully elucidated.

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### *Venous Thromboembolism*

Patients with multiple myeloma are at a high risk of developing venous thromboembolism (VTE). This risk is increased by several of the agents used to treat it such as thalidomide and lenalidomide. Prophylaxis may be appropriate for certain patients and the possibility of VTE should be kept in mind when taking care of myeloma patients.

### *Hyperviscosity*

Hyperviscosity is less common than the above disease characteristics. If blood levels of immunoglobulin are very high, blood viscosity may increase. This can cause mental status changes due to the sludging of the blood and decreased cerebral blood flow. Retinal hemorrhages, mucosal bleeding, and cardiopulmonary symptoms, such as shortness of breath and chest pain, may occur. If severe, hyperviscosity can be a medical emergency requiring prompt attention.

## **Diagnosis**

### **Initial work-up**

If multiple myeloma is suspected, the initial work-up should include:

- CBC
- Chemistry, including calcium, BUN, and creatinine
- Serum protein electrophoresis and immunofixation
- Quantitative immunoglobulin levels
- 24-hour urine protein electrophoresis and immunofixation

If a monoclonal protein is detected, a bone marrow aspirate and biopsy should be performed and sent for pathological examination to assess the amount of plasma cells, as well as for chromosomal studies and flow cytometry.

The *quantitative immunoglobulin test* will show if there is an increase in any particular type of immunoglobulin, but it does not determine if immunoglobulin is monoclonal. It

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could be polyclonal, meaning having many different kinds of antibodies, although they are of the same class. Polyclonal gammopathy is not caused by myeloma and it may be normal or related to processes such as infection or inflammation.

*Electrophoresis* is an essential test in the work up of myeloma. Electrophoresis will identify if the elevated antibody level is monoclonal or polyclonal. If there is an increase in a monoclonal protein, it is seen as a spike on the electrophoresis, called an *M spike*.

About 1% of patients will have nonsecreting myeloma, that is, no monoclonal protein is found in the blood or urine. Yet, they have multiple myeloma as evidenced by increased plasma cells in the bone marrow. This is not common, but if multiple myeloma is suspected and no monoclonal protein is identified, a bone marrow biopsy may be justified.

In addition to these tests, a *skeletal survey* is done to look for the lytic bone lesions. A bone scan is not used because of the poor isotope uptake in lytic lesions. Areas of bone abnormality, in particular spinal lesions, may need to be examined with magnetic resonance imaging (MRI). Spinal lesions sometimes cause spinal cord compression. The potential for spinal cord compression must always be kept in mind when caring for patients with multiple myeloma.

After a diagnosis is made, other tests are used to help determine prognosis including: *B<sub>2</sub> microglobulin*, lactate dehydrogenase (*LDH*), *albumin*, and *C-reactive protein*. An elevated level of *B<sub>2</sub> microglobulin*, *LDH*, and *C-reactive protein*, and a low level of serum albumin are all markers of a poor prognosis. Another test, called a *plasma cell labeling index* (*PCLI*), indicates the proportion of plasma cells proliferating. In general, a lower percentage of proliferating cells indicates the potential for longer survival.

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### Genetics and Prognosis

Certain chromosomal abnormalities are associated with prognosis in multiple myeloma.

- A translocation between chromosome 4 and 14 (t(4;14)), translocation between chromosome 14 and 16 (t(14;16)), or deletions in chromosome 13 are poor prognostic factors in myeloma. Patients with these abnormalities are considered high risk.
- Translocations between chromosomes 11 and 14 (t(11;14)) may be associated with an improved survival. (NCCN Guidelines v.2.2008) (Stewart 2008)

Consensus guidelines from the Mayo Clinic note their strong belief in dividing patients into “high-risk” and “low-risk” groups to guide therapy. These can be accessed at [www.msmart.org](http://www.msmart.org) and are shown below. However, this is not universally accepted and the NCCN guidelines state that not enough data exist to determine how prognostic factors should affect therapeutic decisions.

One goal of multiple myeloma therapy, as is for many cancers, is to individualize treatments. A current challenge is to better develop criteria to determine who will benefit most from a particular therapy.

Mayo Clinic Classification of Active Multiple Myeloma	
High Risk (25%)	Standard Risk (75%)*
FISH: <ul style="list-style-type: none"> <li>➤ Del 17 p</li> <li>➤ t(4:14)*</li> <li>➤ t(14;16)</li> </ul>	All others including: <ul style="list-style-type: none"> <li>➤ Hyperdiploid</li> <li>➤ t(11;14)</li> <li>➤ 6(6;14)</li> </ul>
Cytogenetic deletion 13	
Cytogenetic hypodiploidy	
PCLI ≥3%	
*Patients with t(4;14), b2M <4 mg/L, and Hb ≥10 g/dL may have intermediate-risk disease	

Source: [www.msmart.org](http://www.msmart.org)

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## Criteria for the Diagnosis and Classification of Plasma Cell Disorders

### MGUS

If a monoclonal protein is found and the patient has <10% plasma cells in the bone marrow, no symptoms, and no related organ or tissue impairment, the patient is said to have a monoclonal gammopathy of unknown significance (MGUS). These patients require only periodic monitoring of the protein levels to check for progression; annually is usually sufficient. About 1% of these patients per year will develop multiple myeloma.

### Plasmacytoma

A plasmacytoma is a tumor of plasma cells. They can originate from the bone (osseous) or from soft tissue (extra-osseous). Tissue biopsy of the tumor is necessary for the diagnosis of plasmacytoma. Plasmacytomas may occur along with more widespread disease or without evidence of multiple myeloma elsewhere in the body. Patients in whom a solitary plasmacytoma is suspected must be evaluated very carefully to be certain that they do not have bone marrow disease. Patients with solitary plasmacytomas are not treated systemically, but receive local therapy for the plasmacytoma. Surgical resection and/or radiation therapy for extra-osseous and radiation for osseous plasmacytomas is indicated. After treatment the patient must be monitored for disappearance of the plasmacytoma-producing M protein. Monitoring is carried out initially every 4 weeks, then longer if the protein disappears. Patients can have recurrence of the plasmacytoma or recur systemically; therefore, continued monitoring is needed. However, unlike multiple myeloma, they can be cured.

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Patients with multiple myeloma are first classified as having asymptomatic (formerly called *smoldering*) or symptomatic (*active*) disease.

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Multiple Myeloma Classifications	
Asymptomatic Myeloma (Smoldering)	Symptomatic Myeloma (Active)
	Requires the addition of one or more of the following to the M protein and plasma cells:
<ul style="list-style-type: none"> <li>• Serum M protein &gt; to 3.0 g/dL <i>and/or</i></li> <li>• Bone marrow clonal plasma cells ≥10%</li> </ul>	<ul style="list-style-type: none"> <li>• Bone disease (lytic lesions or osteoporosis or osteopenia with compression fractures)</li> </ul>
<ul style="list-style-type: none"> <li>• No symptoms</li> </ul>	<ul style="list-style-type: none"> <li>• Increased calcium (&gt;11.5 g/dL)</li> </ul>
<ul style="list-style-type: none"> <li>• No related tissue or organ impairment or symptoms</li> </ul>	<ul style="list-style-type: none"> <li>• Anemia (hemoglobin, &lt;10 g/dL or 2 g &lt; normal)</li> </ul>
	<ul style="list-style-type: none"> <li>• Renal insufficiency (serum creatinine &gt;2 mg/dL)</li> </ul>

The acronym CRAB can be used to remember the characteristics of symptomatic myeloma: **C**alcium increased, **R**enal insufficiency, **A**nemia, **B**one lesions.

## Staging

Patients with active multiple myeloma are staged further. Two staging systems are used. The *Durie-Salmon Staging* system has been in use for more than 30 years; a simpler staging system, the *International Staging System (ISS)*, has been shown to be very sensitive in predicting prognosis and, therefore, guiding treatment of multiple myeloma.

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Staging of Multiple Myeloma		
Stage	Durie-Salmon	ISS
I	All of the following:	Beta <sub>2</sub> microglobulin: <3.5 mg/L
	• Hemoglobin: >10 g/dL	Serum albumin: ≥3.5 g/dL
	• Serum calcium: ≥ 12 mg/dL	
	• Normal skeletal survey or solitary plasmacytoma only	
• Low M protein <ul style="list-style-type: none"> <li>▪ IgG: &lt;5 g/dL</li> <li>▪ IgA: &lt;3 g/dL</li> <li>▪ Bence Jones protein: &lt;4 g/24h</li> </ul>		
II	Neither stage I nor stage III	Neither stage I nor stage III
III	One or more of the following:	Beta <sub>2</sub> -microglobulin: >5.5 mg/L
	• Hemoglobin: <8.5 g/dL	
	• Serum calcium: >12 mg/dL	
	• ≥3 lytic bone lesions	
• High M protein <ul style="list-style-type: none"> <li>• IgG: &gt;7 g/dL</li> <li>• IgA: &gt;5 g/dL</li> <li>• Bence Jones protein: &gt;12 g/24h</li> </ul>		

Durie-Salmon subclassification:

A: Normal renal function (serum creatinine level: <2.0 mg/dL)

B: Abnormal renal function (serum creatinine level: ≥2.0 mg/dL)

## Treatment

Patients with Stage I or asymptomatic myeloma do not require immediate treatment.

They should be monitored every three to six months for progression. This group of patients can do well for extended periods. Clinicians can explore possible clinical trials for early disease management; however, treatment outside a trial is not indicated. If a patient progresses to a Stage II or beyond, systemic treatment is indicated.

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#### **Supportive Care**

Patients with multiple myeloma have systemic disease. Therefore, they require close monitoring of organ function and meticulous supportive care. Serum calcium levels, as well as renal function and hemoglobin levels, must be watched carefully. The risk of spinal cord compression and hyperviscosity should be considered when evaluating symptoms.

#### *Bone Disease*

Bisphosphonates are recommended for patients with bone disease, including osteopenia. In general, bisphosphonates are not used for stage I disease and are not recommended in asymptomatic disease. A clinical trial employing early use of bisphosphonates may be an option.

Before starting bisphosphonate therapy, patients should have a dental examination and then watched closely for the development of osteonecrosis of the jaw. Renal function must be followed closely, as well. Bisphosphonates had been used indefinitely. At present, it is usually recommended that the duration be modified based on disease activity. For example, patients with a good response to systemic therapy and no active bone disease should stop bisphosphonate therapy at one year. Patients with a less-than-partial response should continue bisphosphonate therapy for two years. If active bone disease is still present at two years, decisions concerning duration of therapy should be made on an individual basis. The duration of bisphosphonate therapy is not universally agreed upon, but is an important subject with the availability of more effective therapy for multiple myeloma.

Patients with bone disease may need an orthopedic consultation if they have an impending fracture or symptomatic vertebral compression fracture. Kyphoplasty or vertebroplasty may be indicated for the vertebral lesions.

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#### *Infection*

Prompt evaluation of fever or any sign of infection and institution of appropriate antimicrobials are essential. Patients with recurring life-threatening infection may be considered for intravenous immunoglobulin therapy. Also, vaccinations such as pneumococcal vaccine polyvalent (Pneumovax<sup>®</sup> 23) and influenza vaccine should be considered. Further, some patients receive high-dose corticosteroids as part of their systemic treatment, compounding the risk of infection. These patients should likely receive *Pneumocystis carinii*, herpes zoster, and fungal prophylaxis.

#### *Renal Insufficiency*

Renal insufficiency is part of the multiple myeloma disease process. Bisphosphonates can increase the risk of renal insufficiency. As part of the management of multiple myeloma, patients undergo many scans. Therefore, careful consideration should be given to the risks for renal disease when ordering contrast. Intravenous contrast should be avoided. In general, recommendations are to avoid nonsteroidal anti-inflammatory drugs (NSAIDs), as well.

#### **Initial Treatment**

Autologous stem cell transplant is considered standard therapy for multiple myeloma in patients who are well enough. When beginning therapy, one should first decide whether the patient is a transplant candidate. There are no strict criteria for transplant eligibility, as older age and renal insufficiency are not absolute contraindications to transplant. Comorbidities and performance status are the main factors to consider. The patients who are transplant candidates first receive induction therapy. The preferable regimen is one that does not include alkylating agents, which can damage stem cells. The NCCN Guidelines show numerous acceptable regimens for these patients.

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<b>NCCN PRIMARY INDUCTON THERAPY FOR TRANSPLANT CANDIDATES</b>
• Bortezomib/dexamethasone
• Bortezomib/doxorubicin/dexamethasone
• Bortezomib/lenalidomide/dexamethasone
• Bortezomib/thalidomide/dexamethasone
• Dexamethasone
• Liposomal doxorubicin/vincristine/dexamethasone
• Lenalidomide/dexamethasone
• Thalidomide/dexamethasone

Available at [http://www.nccn.org/professionals/physician\\_gls/PDF/myeloma.pdf](http://www.nccn.org/professionals/physician_gls/PDF/myeloma.pdf)

Dexamethasone alone is a standard induction regimen; however, the novel agents thalidomide, bortezomib, and lenalidomide are being used in various combinations as induction therapy with increasing frequency. The reader is referred to the NCCN multiple myeloma guidelines for a summary of the data behind potential regimens (available at [http://www.nccn.org/professionals/physician\\_gls/PDF/myeloma.pdf](http://www.nccn.org/professionals/physician_gls/PDF/myeloma.pdf)).

The same regimens are acceptable for patients not eligible for transplants plus a few additional choices because stem cell damage is not of such a concern. Again, the reader is referred to the NCCN guidelines for a summary of data behind potential regimens.

<b>NCCN PRIMARY INDUCTON THERAPY FOR NON TRANSPLANT CANDIDATES</b>
• Dexamethasone
• Lenalidomide/low-dose dexamethasone
• Liposomal doxorubicin/vincristine/dexamethasone
• Melphalan/prednisone
• Melphalan/prednisone/bortezomib
• Melphalan/prednisone/thalidomide
• Thalidomide/dexamethasone
• Vincristine/doxorubicin/dexamethasone

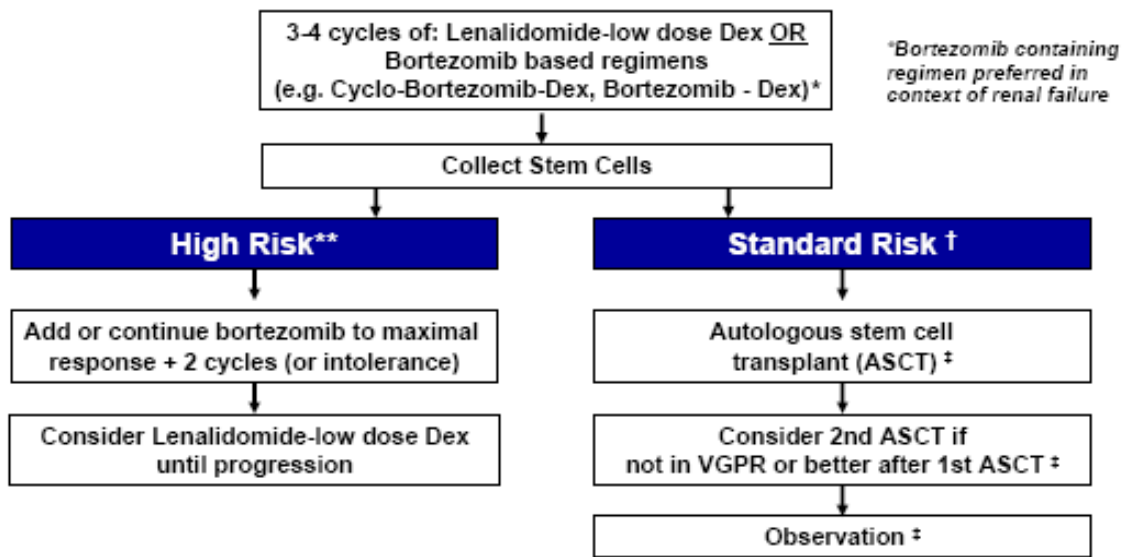
Available at [http://www.nccn.org/professionals/physician\\_gls/PDF/myeloma.pdf](http://www.nccn.org/professionals/physician_gls/PDF/myeloma.pdf)

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The Mayo Clinic consensus guidelines use prognostic data to stratify and guide treatment accordingly. These are not incorporated into NCCN guidelines. However, as the understanding of the biology of multiple myeloma increases, it is increasingly recognized that the disease is heterogeneous. Better stratification of patients with therapy individualized for their disease is a major goal, though not yet incorporated into standard practice.

### mSMART – Off-Study Transplant Eligible



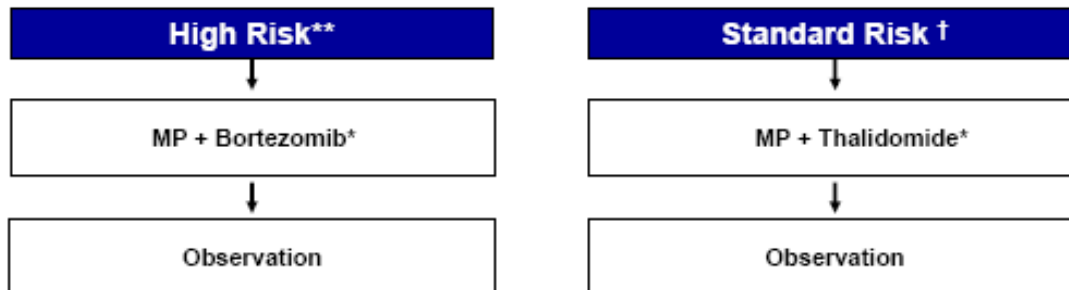
\*\* Consider clinical trials, including allogeneic approaches in selected younger patients

† If transplant deferred continue induction as tolerated  
‡ For patients not in VGPR or better after ASCT, consider Thalidomide to maximum response as tolerated

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## mSMART – Off-Study *Transplant Ineligible*



*\* In patients in whom administration of thalidomide or bortezomib is of concern, consider MP or Rd*

MP (melphalan/prednisone)

Rd (lenalidomide/dexamethasone)

[www.msmart.org](http://www.msmart.org)

### Response Criteria

It is important to assess the response to the treatment of multiple myeloma in order to make further management decisions.

#### International Myeloma Working Group Uniform Response Criteria

sCR, stringent complete response

- CR as below plus normal free light chain ratio and absence of clonal cells in marrow by immunohistochemistry or immunofluorescence

CR, complete response

- Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and  $\leq 5\%$  plasma cell in bone marrow

VGPR, very good partial response

- Serum and urine M-protein detectable by immunofixation but not on electrophoresis or  $\geq 90\%$  reduction in serum M-protein plus urine M-protein level 100 mg/24 hours

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PR, partial response

- $\geq 50\%$  reduction of serum M-protein and reduction in 24h urinary M-protein by  $\geq 90\%$  or to  $< 200$  mg/24 h
- If only free light chains are involved, a  $\geq 50\%$  decrease in the difference between involved and uninvolved free light chain levels is required in place of the M-protein criteria
- In nonsecretory disease  $\geq 50\%$  decrease in plasma cells in the bone marrow is required

SD, stable disease

- Not meeting criteria for sCR, CR, VGPR, PR, or progressive disease. (See definition of progressive disease in the WebEx module: *Multiple Myeloma: Treatment Options for Refractory or Relapsed Disease*)

### Maintenance Therapy

Several studies indicate that maintenance therapy with thalidomide may be beneficial after autologous stem cell transplant. Concern exists, however, about the side effects this may cause and their effects on both quality of life and subsequent therapy. For example, the neuropathy associated with thalidomide can be significant. Bortezomib can also cause neuropathy. Therefore, if thalidomide maintenance therapy has left a patient with significant neuropathy, this may limit the ability to administer bortezomib as a subsequent therapy. Lenalidomide and bortezomib are also under study as maintenance therapy.

### Relapsed Disease

Please see the accompanying continuing education WebEx presentation discussing the recognition and treatment of recurrent or relapsed multiple myeloma. This presentation also contains examination of several case studies.

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### Recommended Reading

Multiple Myeloma: Cancer of the Bone Marrow Concise Review of the Disease and Treatment Options. International Myeloma Foundation 2008/2009 edition available at: [http://myeloma.org/pdfs/cr08-eng\\_f1web.pdf](http://myeloma.org/pdfs/cr08-eng_f1web.pdf)

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