About the International Myeloma Foundation

Founded in 1990, the International Myeloma Foundation (IMF) is the oldest and largest myeloma-specific charity in the world. With more than 350,000 members in 140 countries, the IMF serves myeloma patients, family members, and the medical community. The IMF provides a wide range of programs in the areas of Research, Education, Support, and Advocacy:

**RESEARCH** The IMF is the leader in globally collaborative myeloma research. The IMF supports lab-based research and has awarded over 100 grants to top junior and senior researchers since 1995. In addition, the IMF brings together the world’s leading experts in the most successful and unique way through the International Myeloma Working Group (IMWG), which is publishing in prestigious medical journals, charting the course to a cure, mentoring the next generation of innovative investigators, and improving lives through better care.

**EDUCATION** The IMF’s educational Patient & Family Seminars, Medical Center Workshops, and Regional Community Workshops are held around the world. These meetings provide up-to-date information presented by leading myeloma specialists and researchers directly to myeloma patients and their families. Our library of more than 100 publications, for patients and caregivers as well as for healthcare professionals, is updated annually and available free of charge. Publications are available in more than 20 languages.

**SUPPORT** Our toll-free InfoLine at 800-452-CURE (2873) is staffed by coordinators who answer questions and provide support and information via phone and email to thousands of families each year. The IMF sustains a network of more than 150 support groups and offers training for the hundreds of dedicated patients, caregivers, and nurses who volunteer to lead these groups in their communities.

**ADVOCACY** The IMF Advocacy program trains and supports concerned individuals to advocate on health issues that affect the myeloma community. Working both at the state and federal level, the IMF leads two coalitions to advocate for parity in insurance coverage. Thousands of IMF-trained advocates make a positive impact each year on issues critical to the myeloma community.

Learn more about the way the IMF is helping to improve the quality of life of myeloma patients while working toward prevention and a cure. Contact us at 800-452-CURE (2873) or 818-487-7455, or visit myeloma.org.

Improving Lives Finding the Cure
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**Introduction**

The IMF *Concise Review of the Disease and Treatment Options* is an overview of myeloma, with a discussion of pathophysiology, clinical features, and treatment options. We hope that the information will be helpful to both healthcare professionals and patients.

**What is myeloma?**

Myeloma is a cancer of the plasma cells in the bone marrow. Myeloma is synonymous with “multiple myeloma” and “plasma cell myeloma.” The malignant plasma cells (see Figure 1), or myeloma cells, accumulate in the bone marrow. The major features of myeloma result from the abnormal accumulation of myeloma cells within the bone marrow, causing:

- Disruption of normal bone marrow function reflected by anemia and/or low white counts or platelet counts.
- Destruction and invasion of bone and surrounding areas of bone marrow involvement.
- Production and release of monoclonal protein from the myeloma cells into the blood stream and/or into the urine.
- Reduction of normal immune function, reflected by reduced levels of normal immunoglobulins and increased susceptibility to infection. Infection is also more likely if the white blood cell count is low.

Plasmacytomas are localized tumors composed of plasma cells, which can grow inside bone (intra-medullary) or outside bone (extra-medullary or soft-tissue). When there are multiple plasmacytomas inside or outside bone, this condition is also called multiple myeloma. When patients with myeloma have disease outside the bone marrow, this is called “extra medullary disease” (EMD).

**Production of monoclonal protein by myeloma cells**

The characteristic property of myeloma cells is the production and secretion (release) of monoclonal protein into the blood and/or urine. The amount of monoclonal protein produced by myeloma cells varies considerably from patient to patient. In assessing myeloma, it is very important to know if a patient’s myeloma cells are high producers or low producers or non-secretors (with no protein released into the blood or urine). Once the relationship between the protein level and the amount of myeloma in the bone marrow is known, it is possible to interpret and understand the relationship between a particular protein level and the myeloma tumor burden. Monoclonal protein is also called M-protein, M-component, myeloma protein, paraprotein, protein spike, or M-spike. The monoclonal protein is called a spike because of the way it appears on protein electrophoresis, a laboratory technique used to separate and identify proteins (see Figure 2).

The monoclonal protein is an immunoglobulin or a component/fragment of an immunoglobulin. Figure 3 illustrates...
the structure of a normal immunoglobulin molecule. In myeloma cells, mutations have occurred in the genes responsible for immunoglobulin production. Myeloma proteins therefore have an abnormal amino acid sequence and protein structure. Typically, the normal antibody function of the immunoglobulin is lost, and the three-dimensional structure of the molecule may be abnormal.

Increased production of abnormal immunoglobulin has a number of consequences:

- **Excess monoclonal protein accumulates** in the bloodstream and/or is excreted in the urine.
- **The abnormal monoclonal molecules can adhere** to each other and/or to other tissues such as blood cells, blood vessel walls, and other blood components. This can reduce blood flow and circulation, causing hyperviscosity syndrome (*discussed in text*).
- **More light chains are produced** than are needed to combine with the heavy chains to create a whole immunoglobulin molecule. These excess light chains are called Bence Jones proteins (*see “Annotated history” section*). Free Bence Jones proteins have a molecular weight of 22,000 daltons and are small enough to pass freely into the urine.
- **The abnormal monoclonal proteins can also have a wide range of other properties** including:
  - Binding to normal blood clotting factors, resulting in increased bleeding tendency, enhanced blood clotting, or phlebitis (inflammation of the veins).
  - Binding to nerves to cause neuropathy or to circulating hormones to cause metabolic dysfunction.
- **Free Bence Jones proteins can also adhere** to each other and/or to other tissue (just as the whole immunoglobulin molecule can). In this case the end result is either:
  1. **AL Amyloidosis** – A disease in which the Bence Jones light chains (usually lambda) are cross-linked in a highly symmetric “beta-pleated” fashion and become deposited in tissue around the body, including, for example, kidney, nerves, and heart tissue; or
  2. **Light Chain Deposition Disease (LCDD)** – Light chains (usually kappa) are deposited in a more haphazard fashion, but most selectively in small blood vessels of the eyes and kidneys; or
  3. **Monoclonal Immunoglobulin Deposition Disease (MIDD)** – A disease caused by deposition of fragments of heavy chains, light chains, or both heavy and light chains.

It is important to be aware that routine blood testing can give very strange results because of “stickiness” or hyperviscosity of myeloma blood samples in automated chemical analyzers and/or because of interference with chemical reactions.
Annotated history

Dr. Henry Bence Jones was the first to investigate a strange protein in the urine of a patient with myeloma. What caught his attention was a urine protein that dissolved upon boiling, but re-precipitated on cooling: These are called “Bence Jones” light chains. This patient also had a strange bone disease that we now call multiple myeloma. The following is a brief annotated summary of progress in research and treatment for myeloma and related diseases from that time forward.

1844–1850
First case descriptions of myeloma referred to as “mollities and fragilitas ossium” (soft and fragile bones). The first documented patient, Thomas Alexander McBean, was diagnosed in 1845 by W Macintyre in London. The unusual urine problem he discovered was fully investigated by H Bence Jones, who published his findings in 1848. In 1846, J Dalrymple, a surgeon, determined that the diseased bones contained cells subsequently shown to be plasma cells. W Macintyre published the full details of this case of Bence Jones myeloma in 1850. S Solly published a similar case of myeloma (Sarah Newbury) in 1844, but without any detailed urine studies.

1873
J von Rustizky introduced the term “multiple myeloma” to designate the presence of multiple plasma cell lesions in bone.

1889
O Kahler published a detailed clinical description of multiple myeloma, “Kahler’s disease.”

1890
S Ramon y Cajal provided the first accurate microscopic description of plasma cells.

1900
JH Wright discovered that myeloma cells are plasma cells.

1903
FP Weber noted that lytic lesions, then known as myeloma bone disease, are detectable using X-rays.

1909
FP Weber suggested that plasma cells in the bone marrow cause the myeloma bone destruction.

1930s
The routine diagnosis of myeloma remained difficult until the 1930s, when bone marrow aspirates were first used on a larger scale. The development of the ultracentrifuge and serum/urine protein electrophoresis improved both screening and diagnosis.

1953
Immunoelectrophoresis allowed exact identification of the monoclonal myeloma proteins. Immunofixation has since been introduced as a more sensitive method.

1956
L Korngold and R Lipari noted that Bence Jones proteins are related to normal serum gamma globulin as well as abnormal serum proteins. In their honor, the two types of Bence Jones proteins are called kappa (ĸ) and lambda (λ).

1958
Discovery of sarcolysin in the USSR. From this, melphalan (Alkeran®) was derived. For the first time, treatment was possible.

1961
JG Waldenström emphasized the importance of the differentiation between monoclonal and polyclonal gammopathies. He associated IgM monoclonal proteins with macroglobulinemia as distinct from myeloma.

1962
First report of successful treatment of myeloma with melphalan by DE Bergsagel.

1964
First report of successful treatment of myeloma with cyclophosphamide (Cytoxan®) by DR Korst. Results with cyclophosphamide proved to be similar to results with melphalan.

1969
Melphalan combined with prednisone was shown by R Alexanian to produce better results than melphalan alone.

1975
Durie-Salmon Staging System for myeloma introduced. Patients classified to assess benefits of chemotherapy at different disease stages (I, II, III, A or B).
1976–1992
Various combinations of chemotherapy agents tried, including the M2 regimen (VBMCP), VMCP-VBAP, and ABCM, with some indication of superiority versus MP. However, in 1992, a comparative meta-analysis (WM Gregory) showed equivalent results for all combinations.

1979–1980
Labeling index (growth fraction analysis) first introduced as a test in myeloma and related diseases. Plateau phase of myeloma, defined as stable remission for ≥ 6 months, identified. Plateau phase is a period when the growth fraction (LI%) of residual bone marrow plasma cells is zero.

1982
Twin transplants performed by A Fefer and EF Osserman as treatment for myeloma.

1983
First use of serum β2 microglobulin as a prognostic test (R Bataille, JA Child, and B Durie).

1984
B Barlogie and R Alexanian introduce VAD (vincristine + Adriamycin® + dexamethasone) chemotherapy.

1984–1986
First reports of allogeneic transplants in myeloma by various investigators.

1986–1996
Large numbers of studies evaluating high-dose therapy with autologous bone marrow or stem cell rescue by various investigators. Both single (TJ McElwain) and double (B Barlogie) transplant procedures introduced.

1996
- First randomized study indicating possible benefit of high-dose therapy with bone marrow transplant support versus standard chemotherapy (M Attal on behalf of IFM group).
- Randomized study of the bisphosphonate pamidronate (Aredia®) versus placebo indicates reduction in bone problems (“skeletal related events”).

1997
Evidence that viruses may be involved in triggering myeloma. Myeloma more common in patients with HIV and hepatitis C. Human herpes virus-8 (HHV-8) found in bone marrow dendritic cells. RNA found in blood with specificity for SV40 cancer-causing simian (monkey) virus.

1998
- Continued research on the role of high-dose chemotherapy with autologous and allogeneic transplant. The magnitude of benefit and patient population(s) likely to benefit remain uncertain. Transplant performed as part of initial (induction) therapy is shown to produce results similar to transplant done at first relapse.
- Chromosome 13 deletions shown to be poor prognostic factor for transplantation as well as some other therapies.
- New study reconfirms prednisone as a helpful maintenance therapy with prolongation of remission. Alpha interferon also shown again to have some benefit in prolonging remission.

1999
- Thalidomide shown to be an effective anti-myeloma therapy in patients with relapsing/refractory disease.
- Mini-allogeneic transplant introduced as less toxic method to achieve a graft-versus-myeloma effect.
- Randomized French study shows no major benefit of double autologous transplant versus single transplant.
- Longer-term follow-up shows that Aredia treatment continued for two years is helpful.

2000
For the first time, there are several promising new approaches for myeloma therapy. New clinical trials include thalidomide analogues (e.g., lenalidomide or Revlimid®), long-acting Adriamycin analogues (e.g., pegylated doxorubicin or Doxil®), arsenic trioxide (Trisenox®), anti-angiogenesis agents (e.g., VEGF tyrosine kinase inhibitor), agents to block cell adhesion, and proteasome inhibitors (e.g., bortezomib or Velcade®).

2001
New classification system proposed for myeloma and related diseases.

2002
- Evidence of efficacy of new agents in clinical trials including Velcade (phase III, Millennium) and Revlimid (phase III, Celgene).
Thalidomide combined with dexamethasone as frontline therapy for myeloma produces response rate of approximately 70%.

In the United Kingdom, Medical Research Council (MRC) reports autotransplant results at American Society of Hematology (ASH) annual meeting. Overall benefit noted, especially for patients with high serum β2 microglobulin (> 7.5 mg/L).

2003

Bortezomib (PS-341 or Velcade) is approved in the United States by the Food and Drug Administration (FDA) as treatment for relapsed myeloma following at least two prior therapies.

MRC autotransplant results provide the second randomized data set indicating benefit of autotransplant versus standard-dose chemotherapy.

Results of Intergroupe Francophone du Myélome (IFM) study comparing single with double transplant shows overall benefit with the double transplant after more than four years of follow-up. However, no apparent added benefit is shown for patients already in complete remission with the first transplant.

Little Rock group (J Shaugnessy/B Barlogie) shows that bone disease in myeloma is associated with production of a particular protein called DKK-1.

2004

Results of an ECOG randomized trial comparing thalidomide plus dexamethasone versus dexamethasone alone for previously untreated myeloma indicate a 59% response rate with the combination versus 41% with dexamethasone alone (ECOG Criteria).

Results of a multi-institutional randomized trial comparing Velcade with dexamethasone show superiority of Velcade.

Early results with Velcade in the frontline setting show excellent results: 83% response rate with Velcade + dexamethasone and 94% with Velcade + Adriamycin + dexamethasone and the ability to harvest stem cells with successful transplantation and engraftment.

New myeloma staging system introduced, the International Staging System (ISS).

2005

Two large phase III trials show that lenalidomide plus dexamethasone is superior to dexamethasone alone in relapsed myeloma (time to progression > 15 months versus five months).

Velcade receives full FDA approval for treatment of patients with myeloma after one prior therapy.

International Staging System (ISS), developed by the International Myeloma Working Group (IMWG) of the International Myeloma Foundation (IMF), is published.

Numerous new agents in early development.

Addition of thalidomide to standard melphalan + prednisone regimen shows remarkable added benefit. Several upfront trials are ongoing.

2006

New response criteria for assessing treatment benefit are developed and published.

Lenalidomide (Revlimid) receives FDA approval for treatment of myeloma in combination with dexamethasone in patients who have received at least one prior therapy.

Numerous new agents continue to be developed.

2007

FDA accepts a supplemental NDA for use of Velcade plus Doxil to treat relapsed or refractory myeloma in patients who have not previously received Velcade and have received at least one prior therapy.

Combination thalidomide + dexamethasone plus Doxil compared with thalidomide + dexamethasone in a phase III trial for newly diagnosed myeloma.

2008

Thalidomide approved by the European Medicines Agency (EMA) as part of the MPT regimen (melphalan + prednisone + thalidomide) for frontline therapy.

Velcade approved by the FDA as part of the VMP regimen (Velcade + melphalan + prednisone) for frontline therapy.

Many new drugs in development and trials ongoing. The second-generation proteasome inhibitor carfilzomib (PR-171, which later became known by its brand name Kyprolis®) shows promise in early trials.
FDA approves plerixafor (Mozobil®) in combination with G-CSF for collection of stem cells for autologous transplantation in patients with myeloma.

**2009**
- Development of new drugs continues, including encouraging results from trials of second-generation proteasome inhibitors carfilzomib and NP-0052; HDAC inhibitors vorinostat and panobinostat; HSP-90 disrupter tanespimycin; monoclonal antibody elotuzumab; and third-generation immunomodulatory drug (IMiD®) pomalidomide (which later became known by its brand name Pomalyst®).
- IMWG analysis shows cytogenetic and FISH abnormalities combined with ISS stage are prognostic; some novel therapies overcome poor risk factors.
- Positive results with CyBorD induction therapy for newly diagnosed myeloma.
- IMWG publishes guidelines for serum free light chain analysis as well as consensus statement and guidelines for imaging techniques in the diagnosis and monitoring of myeloma.
- Several publications by O Landgren support genetic features in pathogenesis of monoclonal gammopathy of undetermined significance (MGUS), and BM Weiss demonstrates that an MGUS precedes myeloma in most patients.

**2010**
- FDA approves a risk evaluation and mitigation strategy (REMS) to ensure the safe use of erythropoiesis-stimulating agents (ESAs), which may promote tumor growth, shorten survival, and increase the risk of cardiovascular adverse events.
- Preliminary identification of erythropoietin (Epo) receptors on myeloma cells.
- Development of new drugs continues, including more encouraging results from trials of second-generation proteasome inhibitor carfilzomib; HDAC inhibitors vorinostat and panobinostat; monoclonal antibody elotuzumab; and third-generation IMiD pomalidomide.
- Several studies suggest a role for lenalidomide maintenance therapy.
- Frontline therapy with novel agents may be as effective as transplantation in eligible patients.
- Zoledronic acid (Zometa®) may have an anti-myeloma effect; effective dental hygiene has reduced occurrence of osteonecrosis of the jaw (ONJ).
- S Rajkumar demonstrates superiority of lenalidomide plus low-dose dexamethasone over lenalidomide plus standard-dose dexamethasone in ECOG E4A03 trial.
- P Richardson publishes positive results with induction therapy for newly diagnosed myeloma with RVD (Revlimid + Velcade + dexamethasone).
- IMWG publishes consensus statement on allogeneic transplant, recommending that it be done for myeloma patients only within the context of a clinical trial.

**2011**
- Approval of subcutaneous (SQ) administration of Velcade based on international phase III trial led by P Moreau (IFM group).
- J San Miguel and O Landgren articulate the need to redefine asymptomatic or smoldering multiple myeloma (SMM) and to treat high-risk SMM.
- A Palumbo publishes new paradigm for the treatment of older patients.
- O Landgren and National Cancer Institute (NCI) team demonstrate higher incidence of MDS and AML among patients with MGUS.
- CAFE study demonstrates that balloon kyphoplasty is superior to non-surgical approaches in management of painful vertebral compression fractures.
- Complete response (CR) after stem cell transplant determined to be a “central prognostic factor” by Spanish Myeloma Group (GEMM).
- Italian group demonstrates correlation of CR with long-term PFS and OS in elderly patients treated with novel agents.
- IMWG publishes guidelines for the treatment of patients who are candidates for autologous stem cell transplant.

**2012**
- Carfilzomib (Kyprolis) receives FDA approval for the treatment of patients with myeloma who have had at least two prior therapies, including bortezomib and an IMiD, and demonstrated disease progression on or within 60 days of the last therapy.
IMWG publishes data on progression and survival after treatment with IMiDs and bortezomib, and establishes a benchmark of 9-month median OS.

IMWG publishes consensus statement on plasma cell leukemia, including diagnostic requirements, response criteria, and treatment recommendations.

4-drug EVOLUTION study with bortezomib, dexamethasone, cyclophosphamide, and lenalidomide demonstrates no benefit and more toxicity than 3-drug regimens VCD and VRD.

M Faham presents paper on detection of circulating myeloma cells in the peripheral blood of 93% of the patients tested with high-throughput sequencing of DNA and RNA.

Studies of carfilzomib in combination therapies (KCyD, KRD, KTD, KCyTD) and of pomalidomide in combination therapies (Pd, PKD, PCyPred, BiaxinPD, PCyD, PVDd) demonstrate their efficacy as “platform” drugs.

First studies of oral proteasome inhibitors, MLN9708 (ixazomib) and ONX0912 (oprozomib).

First studies of anti-CD 38 monoclonal antibody, daratumumab, demonstrate single-agent activity.

2013

Pomalidomide (Pomalyst) receives FDA approval for patients with myeloma who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy.

First studies presented of anti-CD monoclonal antibody, SAR650984, demonstrate single-agent activity.

MV Mateos et al. publish results of trial comparing lenalidomide plus dexamethasone versus observation in high-risk SMM. Time to progression (TTP) and overall survival (OS) significantly longer in the lenalidomide + dexamethasone arm.

IFM’s FIRST trial demonstrates superiority of continuous lenalidomide + dexamethasone over MPT or lenalidomide + dexamethasone for 18 months, laying the groundwork for later EMA approval of frontline lenalidomide.

Combination of bortezomib, dexamethasone, and HDAC inhibitor panobinostat for relapsed/refractory myeloma improves progression-free survival over bortezomib + dexamethasone.

Two studies determine that progression of SMM to active disease is significantly different based on the underlying cytogenetic subtype of the disease.

B Paiva et al. publish an immunophenotypic algorithm to identify newly diagnosed myeloma with an MGUS-like signature and long-term disease control.

A Dispenzieri et al. reclassify highest-risk SMM as active MM requiring treatment.

2014

A Palumbo publishes meta-analysis of second primary malignancies with lenalidomide therapy and identifies increased risk with combination of melphalan + lenalidomide, but not with lenalidomide + cyclophosphamide or lenalidomide + dexamethasone.

MT Drake et al. find that cortical bone micro-architecture is weakened in MGUS patients compared to age-matched controls.

New methods of minimal residual disease (MRD) detection by multiparameter flow cytometry and deep sequencing provide higher sensitivity in quantifying response to treatment.

A Palumbo et al. determine that continuous therapy improves PFS1, PFS2, and OS over fixed-duration therapy.

Hevylite® test approved by FDA for use in IgA and IgG myeloma.

SJ Russell publishes proof of principle on systemic oncolytic virotherapy with measles virus.

IMWG publishes updated criteria for the diagnosis of myeloma, defining ultra-high-risk SMM as myeloma.

2015

FDA and EMA approve lenalidomide (Revlimid) in the frontline setting based on the FIRST trial, with caveats about harvesting stem cells after only four cycles of therapy, careful monitoring of blood counts, and risk of SPMs in the post-transplant setting.

IMWG publishes report on geriatric assessment tool developed by A Palumbo et al.
■ IMWG publishes consensus statement on the role of MRI in the management of patients with myeloma.
■ IMWG publishes consensus recommendations for the uniform reporting of clinical trials.
■ IMWG publishes revised International Staging System (R-ISS) for multiple myeloma (see Table 4).
■ IMWG jointly publishes consensus statement on salvage hematopoietic cell transplantation in patients with relapsed multiple myeloma (with ASBMT, ESBMT, and BMTCTN).
■ FDA approves panobinostat (Farydak®) in combination with bortezomib and dexamethasone for the treatment of patients with multiple myeloma who have received at least two prior regimens, including bortezomib and an IMiD.
■ In November, FDA approves three new drugs for the treatment of relapsed disease: daratumumab (Darzalex®), the first monoclonal antibody for the treatment of myeloma, followed by ixazomib (Ninlaro®), the first oral proteasome inhibitor, and elotuzumab (Empliciti®), an immunostimulatory monoclonal antibody. Both of the latter are indicated in combination with lenalidomide and dexamethasone.

2016
■ IMWG publishes Gene signature combinations improve prognostic stratification of multiple myeloma patients.
■ IMWG publishes Recommendations for management of relapsed multiple myeloma.
■ IMWG publishes Recommendations for the diagnosis and management of myeloma-related renal impairment.

■ IMWG publishes Consensus criteria for response and minimal residual disease assessment in multiple myeloma.
■ In October, sponsored by the IMF’s Black Swan Research Initiative® (BSRI®), the iStopMM® study launches in Iceland under the direction of principal investigator S Kristinsson. All consenting citizens over the age of 40 (approximately 140,000 people) are screened for MGUS, SMM, and myeloma. Those with myeloma are treated; those with MGUS and SMM are monitored and invited to participate in a randomized clinical trial to prevent the onset of myeloma.
■ In November, FDA approves daratumumab in combination with lenalidomide + dexamethasone (based on the POLLUX study) or in combination with bortezomib + dexamethasone (based on the CASTOR study) for the treatment of patients who have had at least one prior therapy.
■ BMT CTN StaMINA study presented at ASH demonstrates equal PFS and OS at 38 months follow-up for each of three approaches to upfront transplant: (1) ASCT followed by lenalidomide maintenance, (2) tandem ASCT followed by lenalidomide maintenance, and (3) ASCT plus four cycles of VRD consolidation followed by lenalidomide maintenance.

2017
■ B Durie et al. publish results of the randomized phase III SWOG 0777 clinical trial in Lancet, comparing VRD to RD in newly diagnosed myeloma patients ineligible for ASCT. Study demonstrates superiority of triplet therapy combining a proteasome inhibitor and an immunomodulatory agent.

Epidemiology
There are more than 100,000 people in the United States currently living with myeloma. According to the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute (NCI), myeloma represents 1.8% of all new cancer cases. Approximately 30,330 Americans were diagnosed with myeloma in 2016, and an estimated 12,650 people died from the disease. Myeloma is more common in men than women (male:female ratio is 1.44:1) and among individuals of African-American descent.

The incidence of myeloma rises with age and varies from country to country from a low of < 1/100,000 in China to approximately 4/100,000 in most industrialized Western countries. Better diagnostic techniques and the higher average age of the general population may, in part, explain the rising incidence over the last several decades. A trend toward more frequent myeloma in patients under age 55 implies important environmental causative factors in the past 60 years.
Several recent studies have evaluated the causation of, or predisposition to, myeloma, MGUS, and related disorders. Environmental or work-related exposures to toxic chemicals are definite causal factors. Firefighters, other first responders, and individuals in a variety of other occupations with toxic exposure such as farmers and farm workers, as well as individuals who are obese, are at increased risk of myeloma. Eating seafood contaminated with heavy metals and/or chemicals may be a risk factor for myeloma. Other medical conditions including immune system disorders and infections can be underlying and/or trigger factors. Several studies are focused on the genetic risk factors for myeloma.

**Pathophysiology**

The uncontrolled growth of myeloma cells has many consequences, including:

- skeletal destruction;
- bone marrow failure;
- increased plasma volume and viscosity;
- suppression of normal immunoglobulin production;
- renal insufficiency.

Nonetheless, the disease can remain asymptomatic for many years, as noted in the discussion of MGUS. In the symptomatic phase, the most common presenting complaint is bone pain. The serum and/or urine M-protein is elevated and typically rising at the time of diagnosis. (Please note: “M” is used for Monoclonal, Myeloma, Monoclonal immunoglobulin, and M-component.)
These are not quite identical, but are used synonymously.) The overall pattern of disease phases for patients with myeloma is illustrated in Figure 4. It is important to note that there can be multiple periods of response and remission. The pathophysiology of myeloma is summarized in Table 2 in schematic form.

### Bone disease

Ever since the first recognition of myeloma in 1844, there has been awareness of an unusual and unique type of bone disease. It has taken until quite recently to determine the mechanisms involved. The first clue was that both myeloma cells and increased numbers of osteoclasts are present at sites of bone destruction. Understanding of the mechanisms has evolved from the observation that myeloma cells produce osteoclast-activating factors (OAFs) to the identification of local cytokines such as IL-1β, IL-6, and TNF-α and -β; chemokines such as MIP-α, and cell-cell adhesion processes involving β3 integrin, all of which are involved in producing increased numbers and activity of osteoclasts. A substance called RANK ligand (RANKL) has been identified as a critical mediator of osteoclast activation. Many details of the mechanisms of bone disease in myeloma are now understood. Several targets for treatment approaches have been identified.

Besides activation of osteoclasts, the other characteristic feature of myeloma bone disease is inhibition of osteoblasts, which are responsible for new bone production and bone healing. “Coupling” between osteoclast and osteoblast function is responsible for normal bone remodeling and repair. The mechanisms responsible for “un-coupling” in myeloma are also under investigation. An important new observation is that the cholesterol-lowering statins (HMG-CoA reductase inhibitors, e.g., Lipitor®, Mevacor®) can enhance osteoblast activity and promote bone healing. Both bortezomib and lenalidomide have been shown to promote bone healing in addition to exerting potent anti-myeloma activity. Studies to further investigate the benefit of several new bone therapies are ongoing.

### Table 2. Schema of pathophysiology

<table>
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<th>Skeletal Findings</th>
<th>• Solitary or multiple osteolytic lesions</th>
<th>• Diffuse osteoporosis (osteopenia)</th>
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<tr>
<td>Associated Effects of Bone Destruction</td>
<td>• Elevated serum calcium</td>
<td>• Bone fractures</td>
</tr>
<tr>
<td></td>
<td>• Hypercalciuria (calcium increase in urine)</td>
<td>• Loss of height (vertebral collapse)</td>
</tr>
<tr>
<td>Extramedullary (extraskeletal) Myeloma</td>
<td>• Soft tissue involvement, mostly common in head/neck area (e.g., nasopharynx); also in liver, kidney, and other soft tissue sites including skin</td>
<td></td>
</tr>
<tr>
<td>Peripheral Blood</td>
<td>• Anemia</td>
<td>• Circulating monoclonal B lymphocytes (precursors of myeloma cells)</td>
</tr>
<tr>
<td></td>
<td>• Abnormal clotting</td>
<td>• Plasma cell leukemia</td>
</tr>
<tr>
<td></td>
<td>• Leukopenia</td>
<td>• Circulating plasma cells</td>
</tr>
<tr>
<td>Plasma Protein Changes</td>
<td>• Hyperproteinnemia (elevated protein)</td>
<td>• Narrowed anion gap (low serum sodium)</td>
</tr>
<tr>
<td></td>
<td>• Hypervolemia (expanded volume)</td>
<td>• Elevated serum β2-microglobulin</td>
</tr>
<tr>
<td></td>
<td>• Monoclonal immunoglobulins (IgG, IgA, IgD, IgE, IgM or light chains only)</td>
<td>• Decreased serum albumin</td>
</tr>
<tr>
<td></td>
<td>• Tubular dysfunction with acidosis</td>
<td>• Elevated serum IL-6 and C-reactive protein (CRP)</td>
</tr>
<tr>
<td></td>
<td>(Fanconi syndrome)</td>
<td></td>
</tr>
<tr>
<td>Kidney Abnormalities</td>
<td>• Proteinuria, casts without leukocytes or erythrocytes</td>
<td>• Uremia (kidney failure)</td>
</tr>
<tr>
<td></td>
<td>• Tubular dysfunction with acidosis</td>
<td>• Amyloidosis or light chain deposition disease and renal dysfunction</td>
</tr>
<tr>
<td></td>
<td>(Fanconi syndrome)</td>
<td></td>
</tr>
</tbody>
</table>
**Anemia**

Anemia is a characteristic feature of myeloma. Although simple physical displacement of marrow red blood cell precursors is undoubtedly a factor, the specific inhibition of red cell production by micro-environmental cytokine and adhesion molecule effects is a more functional explanation. Two research teams have described the involvement of hepcidin (a peptide hormone that controls iron regulation) in anemia caused by myeloma. Their research was based on the hypothesis that interleukin-6 (IL-6) and certain bone morphogenetic proteins (BMPs), cytokines produced in myeloma, are also known to be regulators of hepcidin. Improvement in anemia thus occurs with successful treatment of the myeloma. Recombinant Epo (e.g., Epogen® or Procrit®) should be used with caution in the light of reports of the association of Epo with increased tumor growth and reduced survival in patients with cancer and the identification of Epo receptors on myeloma cells.

**Kidney dysfunction**

Impairment of kidney function is a common complication in patients with myeloma. However, this does not mean that every patient will have this problem. In some patients, myeloma proteins, especially Bence Jones light chains, cause renal injury by a variety of mechanisms ranging from tubular damage resulting from large accumulations of precipitated light chains, to effects of myeloma proteins deposited as amyloid, to selective tubular damage resulting in the metabolic effects of an entity called Fanconi syndrome. Fanconi syndrome is a type of selective kidney tubular damage with leakage of amino acids and phosphates into the urine, which can in turn cause metabolic bone disease.

Other important factors related to kidney dysfunction in myeloma patients are increased levels of calcium and/or uric acid, infection, and the effects of drugs such as nephrotoxic antibiotics, non-steroidal anti-inflammatory drugs (NSAIDS), or contrast agents or dyes used for diagnostic studies. An important observation is the potentially toxic effect of gadolinium-based contrast agents used with MRI. Patients with kidney problems should discuss the use of gadolinium with their physicians. Awareness of potential kidney damage and maintaining sufficient fluid intake are especially important for patients with myeloma to help avert the damaging effects of these various factors.

**Other organ dysfunction**

Myeloma cells can accumulate in bone marrow and/or in a variety of tissue sites and produce a broad range of potential complications.

- **Neurologic effects** – Nerve tissue is often affected in myeloma patients either by the direct antibody effects of myeloma proteins against nerves (e.g., myelin sheaths) or by deposition of amyloid fibrils on nerves, thus impairing function. These effects result in peripheral neuropathies that must be distinguished from other causes of neuropathy such as diabetes mellitus or from primary nerve disorders such as multiple sclerosis, Parkinson’s disease, and many others. Because of myeloma patients’ susceptibility to infection, viral infections of nerve tissue are quite common, most particularly varicella zoster (shingles), herpes zoster (cold sores), Epstein-Barr virus (mononucleosis), or cytomegalovirus, which may result in Bell’s Palsy (partial facial paralysis) or other complications.

- **Plasmacytomas** – Both in bone and in soft tissue, plasmacytomas can result in compression or displacement of nerves, the spinal cord, or even brain tissue. These pressure effects often represent a medical emergency and require immediate treatment with high doses of corticosteroids, radiation therapy, or neurosurgery.

- **Infections** – The predisposition to infections is perhaps the single most characteristic feature of myeloma patients besides the strong tendency for bone disease. The mechanisms responsible for infection susceptibility are not fully understood. The presence of active myeloma in
the bone marrow results in impairment of normal immune function, including inhibition of normal antibody production (reflected by hypogammaglobulinemia), impaired T-lymphocyte function, and activated but aberrant monocyte/macrophage function. Some studies indicate that a factor issuing from the activated macrophages both enhances the activity of the myeloma and inhibits normal immunoglobulin production and T-lymphocyte function.

Myeloma patients are susceptible to both viral infections and infections with “encapsulated” bacteria such as pneumococcus. However, in the face of neutropenia and the effects of high-dose chemotherapy, and with the added local effects of implanted catheters (e.g., Hickman and Groshon catheters or PICC lines), the whole range of bacterial, fungal, and opportunistic infections can occur in patients with myeloma undergoing therapy.

**In summary, key aspects of infections in myeloma patients are:**

- **Reduced immunity** because of myeloma
- **Low white blood cell counts** because of myeloma build-up in bone marrow and/or the impact of treatment.

**Infection, or any question of infection, should not be ignored.** Prompt review is required to assess the need for immediate antibiotic and/or antiviral therapy. Many patients learn to have therapy on hand for any emergency.

**Types of myeloma**

The type of monoclonal protein produced varies from patient to patient. The most common is IgG and the least common is IgE. Table 3 shows the percentages of different types of myeloma. Each type is associated with slightly different patterns of disease. For example, IgA myeloma is more commonly associated with disease outside bone (extramedullary disease), whereas IgD myeloma is more commonly associated with plasma cell leukemia and renal damage.

**Clinical symptoms**

About 70% of patients with myeloma present with pain of varying intensity, often in the lower back or ribs. Sudden severe pain can be a sign of fracture or collapse of a vertebral body. General malaise and vague complaints are frequent. Significant weight loss is rare.

Both neutropenia and hypogammaglobulinemia (immunoparessis) increase the likelihood of infections. Although pneumococcal pneumonia is the classic infection associated with myeloma at presentation, other bacteria, such as streptococci and staphylococci, are now frequently isolated. Haemophilus infection and herpes zoster infections also occur.

Hypercalcemia, historically found in 30% of patients at diagnosis, causes tiredness, thirst, and nausea. Precipitation of calcium salts can result in deterioration of kidney function. Of note, in recent years the incidence of hypercalcemia in newly diagnosed patients has dropped to 10%–15%, most likely because of earlier diagnosis. In Latin America and some parts of Asia where late diagnosis is common, hypercalcemia remains more common.

**Table 3. Types of monoclonal protein (%)**

<table>
<thead>
<tr>
<th>Type of Monoclonal Paraprotein</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum</td>
<td>75%</td>
</tr>
<tr>
<td>Urine (Bence Jones or light chains only)</td>
<td>11%</td>
</tr>
<tr>
<td>Two or more monoclonal paraproteins</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Heavy chains (G or A) only</td>
<td>&lt;1</td>
</tr>
<tr>
<td>No monoclonal paraprotein</td>
<td>1</td>
</tr>
<tr>
<td>IgM (rarely myeloma, typically associated with Waldenström’s macroglobulemia)</td>
<td>12%</td>
</tr>
</tbody>
</table>

*This includes different types of MGUS and myeloma as well as Waldenström’s macroglobulemia.*

Source: Data on 1,827 myeloma patients collected and analyzed by W Pruzanski and MA Ogryzlo, 1970.
Hyperviscosity resulting from high myeloma protein levels can cause problems such as bruising, nose bleeding, hazy vision, headaches, gastrointestinal bleeding, sleepiness, and a variety of ischemic neurological symptoms caused by reduced blood and oxygen supply to the nerve tissue. Hyperviscosity occurs in < 10% of patients with myeloma and in about 50% of patients with Waldenström’s macroglobulinemia (all of whom have IgM paraprotein or M-component). Increased bleeding is often exacerbated by thrombocytopenia as well as by binding of monoclonal proteins to clotting factors and/or platelets.

Neurologic involvement can result in specific problems depending on the location of affected nerves. Particularly common problems are spinal cord compression, meningitis, and carpal tunnel syndrome. Although the first two are due to plasma cell tumor formation or infiltration, carpal tunnel syndrome is usually due to amyloid deposition (deposition of Bence Jones proteins in a special beta-pleated form).

**Staging and prognostic factors**

Prognosis in myeloma is determined by both the number and specific properties of myeloma cells in a given patient. These specific properties include the growth rate of myeloma cells, the production rate of monoclonal proteins, and the production or non-production of various cytokines and chemicals that damage or significantly impair other tissues, organs, or bodily functions. In 1975, the Durie-Salmon Staging System was developed, bringing together the major clinical parameters in correlation with measured myeloma cell mass (the total number of myeloma cells in the body). In 2005, a new staging system was developed by the IMF-sponsored IMWG. Clinical and laboratory data were gathered on 10,750 previously untreated symptomatic myeloma patients from 17 institutions, including sites in North America, Europe, and Asia. Potential prognostic factors were evaluated using a variety of statistical techniques. Serum β2 microglobulin (Sβ2M), serum albumin, platelet count, serum creatinine, and age emerged as powerful predictors of survival and were then further analyzed.

A combination of serum β2 microglobulin and serum albumin provided the most powerful, simple, and reproducible three-stage classification. The ISS was further validated by demonstrating effectiveness in patients in North America, Europe, and Asia; in patients younger and older than age 65 years; with standard therapy or auto transplant; and in comparison with the Durie-Salmon Staging System. In August 2015 the IMWG published the Revised International Staging System (R-ISS) for multiple myeloma in order to incorporate two further prognostic factors: genetic risk as assessed by FISH and level of LDH (see Table 4).

Myeloma can be classified based upon genetic risk using molecular fluorescence in situ hybridization (FISH) and cytogenetic abnormalities identified in bone marrow myeloma cells. Such classification can have important implications for treatment. Higher-risk disease is defined as the presence of any one of the following genetic mutations: t(4;14), t(14;16), t(14;20), deletion of 17p by FISH, or deletion of chromosome 13 or hypodiploidy by conventional metaphase cytogenetics. It is crucial to be aware that treatment selection is very much influenced by genetic risk. For example, the presence of t(4;14), which has been noted as a poor risk factor in the past, has largely been overcome with the use of Velcade (bortezomib) combination regimens. There is also a positive impact of lenalidomide-containing regimens in patients with t(4;14) in several Revlimid trials. A report from the IFM group indicated that the presence of t(14;16) was also no longer a predictive prognostic factor in their trials, while IFM findings published in February 2015 indicate that in early relapse, Pomalyst is an effective treatment for those with deletion 17p. New and better risk classification systems are being developed and evaluated with the expectation that it will be possible to offer treatment selection based upon documented treatment outcomes with new combination approaches.
One such new risk classification system is microarray-based gene expression profiling (GEP), which has been used to assess risk in myeloma patients both at diagnosis and at relapse. Approximately 15% of newly diagnosed patients assessed with GEP in clinical trials have shown a high-risk GEP signature. Such patients have shorter durations of complete remission, event-free survival, and OS. While GEP has the potential to further refine risk prognosis beyond standard cytogenetics (karyotyping) and FISH, its use is currently limited by the lack of a uniform platform across many centers in the world and by widespread unavailability.

**Definition of clinical response**

The IMWG uniform response criteria are recommended to classify response to treatment (see Table 5). Improvements in M-component must be associated with evidence of clinical improvement (such as reduced bone pain and/or improved red blood cell counts). It is important to keep in mind that a higher percent regression does not automatically confer longer survival. When there is residual disease, the characteristics of the remaining drug-resistant myeloma cells determine the outcome. These remaining myeloma cells may, or often may not, have any tendency for immediate regrowth (relapse). If there is no regrowth, this is what is called “plateau phase”: residual, but stable disease. The fraction of resistant myeloma cells is primarily dependent upon the intrinsic molecular features of the individual myeloma and the pre-treatment tumor burden or stage. Responding patients go from a high-risk status to a lower-risk status until, ideally, no signs of myeloma are left, or they reach a stable plateau phase, but with measurable residual disease. The time required to reach the plateau phase is variable, ranging from three to six months (rapid response), to 12 to 18 months (slow response). (See Figure 4.)

As treatment has improved, it has become more important to assess response to treatment as accurately as possible. Besides the depth of response, which is indicated by PR (≥ 50% improvement), VGPR (≥ 90%), or CR (100% reduction in monoclonal protein) (see Table 5), one must now consider even deeper responses as well as duration of response. With the increasing efficacy of new treatments, the importance of accurately assessing response to treatment has become even more critical.

---

**Table 4. Standard Risk Factors for Multiple Myeloma and the R-ISS**

<table>
<thead>
<tr>
<th>PROGNOSTIC FACTOR</th>
<th>CRITERIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISS Stage</td>
<td>Serum ß2-microglobulin &lt; 3.5 mg/L, serum albumin ≥ 3.5 g/dL</td>
</tr>
<tr>
<td></td>
<td>Not ISS stage I or III</td>
</tr>
<tr>
<td></td>
<td>Serum ß2-microglobulin ≥ 5.5 mg/L</td>
</tr>
<tr>
<td>CA by iFISH</td>
<td>High Risk</td>
</tr>
<tr>
<td></td>
<td>Standard Risk</td>
</tr>
<tr>
<td>LDH</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>High</td>
</tr>
</tbody>
</table>

**A new model for risk stratification for multiple myeloma**

<table>
<thead>
<tr>
<th>R-ISS Stage</th>
<th>PROGNOSTIC FACTOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>ISS stage I and standard-risk CA by iFISH and normal LDH</td>
</tr>
<tr>
<td>II</td>
<td>Not R-ISS stage I or III</td>
</tr>
<tr>
<td>III</td>
<td>ISS stage III and either high-risk CA by iFISH or high LDH</td>
</tr>
</tbody>
</table>

Abbreviations: CA, chromosomal abnormalities; iFISH, interphase fluorescence in situ hybridization; ISS, International Staging System; LDH, lactate dehydrogenase; R-ISS, Revised International Staging System.
**Table 5. IMWG criteria for response assessment including criteria for minimal residual disease**

<table>
<thead>
<tr>
<th><strong>IMWG MRD criteria (requires a complete response as defined below)</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sustained MRD-negative</strong></td>
<td>MRD (minimal residual disease) negativity in the marrow – NGF (next-generation flow), or NGS (next-generation sequencing), or both – and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD-negative at 5 years)</td>
</tr>
<tr>
<td><strong>Flow MRD-negative</strong></td>
<td>Absence of phenotypically aberrant clonal plasma cells by NGF on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10⁵ nucleated cells or higher</td>
</tr>
<tr>
<td><strong>Sequencing MRD-negative</strong></td>
<td>Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the LymphoSIGHT platform (or validated equivalent method) with a minimum sensitivity of 1 in 10⁵ nucleated cells or higher</td>
</tr>
<tr>
<td><strong>Imaging-positive MRD-negative</strong></td>
<td>MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less mediastinal blood pool SUV (maximum standardized uptake value) or decrease to less than that of surrounding normal tissue</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Standard IMWG response criteria</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stringent complete response</strong></td>
<td>Complete response as defined below plus normal FLC ratio and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤ 4:1 or ≥ 1:2 for κ and λ patients, respectively, after counting ≥ 100 plasma cells)</td>
</tr>
<tr>
<td><strong>Complete response</strong></td>
<td>Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and &lt; 5% plasma cells in bone marrow aspirates</td>
</tr>
<tr>
<td><strong>Very good partial response</strong></td>
<td>Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M-protein plus urine M-protein level &lt; 100 mg per 24 h</td>
</tr>
<tr>
<td><strong>Partial response</strong></td>
<td>≥ 50% reduction of serum M-protein plus reduction in 24 h urinary M-protein by ≥ 90% or to &lt; 200 mg per 24 h; If the serum and urine M-protein are unmeasurable, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria; If serum and urine M-protein are unmeasurable, and serum-free light assay is also unmeasurable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was ≥ 30%. In addition to these criteria, if present at baseline, a ≥50% reduction in the SPD (sum of the products of the maximal perpendicular diameters of measured lesions) of soft tissue plasmacytomas is also required</td>
</tr>
<tr>
<td><strong>Minimal response</strong></td>
<td>≥25% but ≤49% reduction of serum M-protein and reduction in 24-h urine M-protein by 50%—89%. In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size (SPD) of soft tissue plasmacytomas is also required</td>
</tr>
<tr>
<td><strong>Stable disease</strong></td>
<td>Not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates. Not meeting criteria for complete response, very good partial response, partial response, minimal response, or progressive disease</td>
</tr>
</tbody>
</table>

*(Table 5 continues on next page)*
### Standard IMWG response criteria (continued)

#### Progressive disease

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase of 25% from lowest confirmed response value in one or more of the following criteria:</td>
<td>Serum M-protein (absolute increase must be $\geq 0.5$ g/dL);</td>
</tr>
<tr>
<td></td>
<td>Serum M-protein increase $\geq 1$ g/dL, if the lowest M component was $\geq 5$ g/dL;</td>
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<tr>
<td></td>
<td>Urine M-protein (absolute increase must be $\geq 200$ mg/24 h);</td>
</tr>
<tr>
<td></td>
<td>In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be $&gt;$ 10 mg/dL);</td>
</tr>
<tr>
<td></td>
<td>In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be $\geq 10%$);</td>
</tr>
<tr>
<td></td>
<td>Appearance of a new lesion(s), $\geq 50%$ increase from nadir in SPD of $&gt; 1$ lesion, or $\geq 50%$ increase in the longest diameter of a previous lesion $&gt; 1$ cm in short axis;</td>
</tr>
<tr>
<td></td>
<td>$\geq 50%$ increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease</td>
</tr>
</tbody>
</table>

#### Clinical Relapse

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical relapse requires one or more of the following criteria:</td>
<td>Direct indicators of increasing disease and/or end organ dysfunction (CRAB features) related to the underlying clonal plasma-cell proliferative disorder. It is not used in calculation of time to progression or progression-free survival but is listed as something that can be reported optionally or for use in clinical practice;</td>
</tr>
<tr>
<td></td>
<td>Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression);</td>
</tr>
<tr>
<td></td>
<td>Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and $\geq 1$ cm) increase as measured serially by the SPD of the measurable lesion;</td>
</tr>
<tr>
<td></td>
<td>Hypercalcemia ($&gt; 11$ mg/dL);</td>
</tr>
<tr>
<td></td>
<td>Decrease in hemoglobin of $\geq 2$ g/dL not related to therapy or other non-myeloma-related conditions;</td>
</tr>
<tr>
<td></td>
<td>Rise in serum creatinine by $2$ mg/dL or more from the start of the therapy and attributable to myeloma;</td>
</tr>
<tr>
<td></td>
<td>Hyperviscosity related to serum paraprotein</td>
</tr>
</tbody>
</table>

#### Relapse from complete response (to be used only if the end point is disease-free survival)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any one or more of the following criteria:</td>
<td>Reappearance of serum or urine M-protein by immunofixation or electrophoresis;</td>
</tr>
<tr>
<td></td>
<td>Development of $\geq 5%$ plasma cells in the bone marrow;</td>
</tr>
<tr>
<td></td>
<td>Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia)</td>
</tr>
</tbody>
</table>

#### Relapse from MRD negative (to be used only if the end point is disease-free survival)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any one or more of the following criteria:</td>
<td>Loss of MRD negative state (evidence of clonal plasma cells on NGF or NGS, or positive imaging study for recurrence of myeloma);</td>
</tr>
<tr>
<td></td>
<td>Reappearance of serum or urine M-protein by immunofixation or electrophoresis;</td>
</tr>
<tr>
<td></td>
<td>Development of $\geq 5%$ clonal plasma cells in the bone marrow;</td>
</tr>
<tr>
<td></td>
<td>Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia)</td>
</tr>
</tbody>
</table>

combination therapies, it is now necessary to add the terms “minimal residual disease (MRD)” and “MRD-negative” to the response criteria, concepts that were previously unattainable and unmeasurable in myeloma. Minimal disease levels are now not only possible to achieve, but are verifiable with next-generation sequencing and next-generation flow, a highly sensitive and specific new type of flow cytometry performed on bone marrow that was developed at the University of Salamanca, Spain. The FDA has endorsed this new 8-color flow test as the standard means to measure depth of response in US-based myeloma clinical trials. In addition, another sensitive new test, the heavy + light chain isotype (Hevylite®) assay, will be incorporated into response criteria as a blood marker of low-level disease activity. In July 2016, *Lancet Oncology* published *International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma*.

Important terms are:
- **TTP** – Time To Progression: the time from start of treatment until relapse occurs.
- **PFS** – Progression-Free Survival: the length of survival during which the patient is still in remission*.
  - **PFS1** – As defined by A Palumbo, the time from the start of therapy to the occurrence of first relapse.
  - **PFS2** – The time from start of therapy to the occurrence of second relapse, incorporating the duration of both first and second remissions.

*Remission is generally considered to be at least a partial response (PR, ≥ 50% improvement) which lasts for at least 6 months.

**Treatment**

**Exclude MGUS or asymptomatic myeloma**

The first and most important decision is to determine if treatment is required. Patients with MGUS and standard- or low-risk asymptomatic or smoldering multiple myeloma (see Table 1) should be observed closely rather than treated. There are currently many clinical trials using various therapeutic regimens to treat high-risk smoldering myeloma and several trials that are attempting to determine if it is possible to enhance the immune regulation of early myeloma or reduce the likelihood of disease activation.

Of note are two completed studies: The Spanish group’s (PETHEMA) trial for high-risk SMM in which patients were either observed or treated with lenalidomide and dexamethasone, and the NCI study of carfilzomib, lenalidomide, and dexamethasone for patients with high-risk SMM. In the Spanish trial, disease progression was delayed and OS at a median of six years was significantly improved among patients who were treated with lenalidomide and low-dose dexamethasone as compared to those who were observed. In the NCI pilot study, which was presented at ASH 2014, the combination of carfilzomib, lenalidomide, and dexamethasone in the 12 enrolled patients resulted in a 100% complete response rate over the course of the study. Moreover, 11 of the 12 patients who responded have maintained their MRD negativity. They are being followed to assess the duration of their MRD-negative status.

A large, ongoing, combined ECOG/SWOG trial was started in 2010, in which patients with high-risk SMM are randomized to lenalidomide versus placebo. Many other trials are now available for patients with high-risk SMM, some of which incorporate experimental agents. There is as yet, however, no universally accepted definition of what constitutes high-risk SMM. The criteria for high-risk SMM vary from trial to trial, making it difficult to standardize a definition.

As part of its Black Swan Research Initiative®, the IMF is supporting two clinical trials dubbed “Cure Trials” to treat patients with high-risk smoldering myeloma. These studies will treat asymptomatic
disease early and aggressively in an attempt to reach sustained MRD negativity and cure before clonal evolution and end organ damage occur. The CESAR trial is enrolling patients in Spain. The US trial, ASPIRE, based at Mayo Clinic (Rochester, Minnesota), which began accruing patients in 2017.

**New diagnostic criteria**

The IMWG published *Updated Criteria for the Diagnosis of Myeloma* (SV Rajkumar et al. *The Lancet*) in order to accurately identify “the subset of patients with smoldering multiple myeloma and biological malignancy who are at imminent risk of developing CRAB features.” The validated criteria for “ultra-high-risk” SMM, now defined as active myeloma, are:

- At least 60% plasmacellularity of bone marrow.
- A ratio of involved to uninvolved free light chains of at least 100.
- Two or more focal lesions > 5 mm on MRI.

Because these criteria have individually been proven to carry an 80% or greater risk of progression to active disease within 18 months to two years, any one of them is considered a “myeloma-defining event.” Thus, asymptomatic patients with any of these criteria should be considered to have early active myeloma and should be treated, not merely observed. This is a major paradigm shift in myeloma, as previous wisdom held that all asymptomatic patients be observed until one or more of the CRAB criteria were manifest. Because there are now treatment tools available to prevent disease progression and potentially to cure myeloma before it causes end-organ damage, it is now imperative to intervene in cases of early active disease.

Specific anti-myeloma treatment is recommended when active myeloma has developed, as reflected by an increasing M-component and/or emerging or imminent clinical problems or “CRAB” features (See Table 1). Problems sufficient to require treatment include bone destruction (lytic lesions and/or osteoporosis), renal insufficiency, progressive reduction in blood counts (e.g., anemia, neutropenia), elevated blood calcium, nerve damage, or other significant organ or tissue damage caused by myeloma or myeloma protein. These indications for the need to start treatment can be summarized as CRAB features: Calcium elevation, Renal problems, Anemia, or Bone issues. The overall goals of treatment are to address specific problems and to achieve general control of the disease. A summary of types of treatments is provided in Table 6.

**Table 6. Myeloma treatment options**

| 1. | Induction therapy |
| 2. | High-dose chemotherapy with hematopoietic stem cell transplant |
| 3. | Conservative use of radiation to preserve bone marrow |
| 4. | Maintenance therapy |
| 5. | Supportive care: |
| Anti-viral therapy | Brace/corset |
| Bisphosphonates | Kypholasty/vertebroplasty |
| Growth factors | Exercise |
| Antibiotics | Emergency care |
| (e.g., dialysis, plasmapheresis, surgery, radiation) |
| 6. | Management of drug-resistant or refractory disease |
| 7. | Novel and experimental therapies: |
| Immunomodulatory drugs | Farydak® (panobinostat); HDAC inhibitor ACY-241 in clinical trials |
| Thalomid® (thalidomide), Revlimid® (lenalidomide), Pomalyst® (pomalidomide) | Immunotherapies pembrolizumab, pidilizumab, lambrolizumab, CAR T cells in clinical trials |
| Approved injectable proteasome inhibitors | Monoclonal antibodies Darzalex® (daratumumab) and Empliciti® (elotuzumab); isatuximab (SAR650984) and siltuximab in clinical trials |
| Velcade® (bortezomib) and Kyprolis® (carfilzomib), and oral proteasome inhibitor Ninlaro® (ixazomib); oral proteasome inhibitors oprozomib and marizomib in clinical trials | Pan-tumor suppressor gene promoter selinexor in clinical trials |

myeloma.org
Treatment overview

Please see the History section for an overview of the evolution of currently used treatments. Since melphalan was first introduced in 1962, various combination chemotherapy regimens have been utilized and attempts have been made to improve outcomes using high-dose chemotherapy regimens with bone marrow transplant (BMT) or peripheral blood stem cell transplant (PBSCT). In the standard type of BMT or PBSCT, the “transplant” is a “rescue” with normal bone marrow stem cells after the stem cells in the body have been destroyed by high-dose chemotherapy (usually melphalan).

In the 1980s and 1990s, high-dose melphalan with stem cell rescue was one of the few techniques available to reduce myeloma tumor burden and achieve better outcomes. With the introduction of thalidomide for myeloma treatment in 1997, the options for treatment expanded. Complete responses could be achieved with a simple oral agent. Additional novel agents followed soon after: first bortezomib in 2003, then lenalidomide in 2005, carfilzomib in 2012, pomalidomide (2013), panobinostat (2015), and in rapid succession in November 2015, daratumumab, ixazomib, and elotuzumab. The addition of these new agents to the myeloma armamentarium has left practitioners somewhat at a loss as to best combinations and sequencing. What has become increasingly clear, however, is that no single therapy is likely to be effective for every myeloma patient, nor is any single agent likely to achieve a cure on its own. Rather, the combination approach that attacks myeloma cells with multiple drugs through multiple pathways has thus far demonstrated superior efficacy. This concept was amply demonstrated by the long-awaited results of the SWOG S0777 multi-center trial, which were presented at ASH 2015 and published in The Lancet in January 2017. This trial compared Velcade + Revlimid + dexamethasone (VRD) to Revlimid + dexamethasone (Rd) in newly diagnosed patients who were not candidates for transplant. The data demonstrated that PFS and OS were a year longer with VRD than with Rd. These data firmly establish the superiority of triplet frontline therapy and confirm the efficacy of the combination of a proteasome inhibitor and an immunomodulatory drug.

There is no simple answer to the question of “the best” treatment options available today. Fortunately, there are numerous regimens that can produce very deep and durable responses (remissions lasting ≥ 2 years) and improved OS. The best choice for each patient depends upon individual factors such as age, stage, genetic features, kidney status, comorbidities, cost, and of course, personal preference.

Myeloma patients must be aware of the need for careful discussions with their physicians about treatment choices.

Options for patients who are not candidates for stem cell transplant

The approach to frontline treatment has changed substantially with the introduction of the novel agents thalidomide, bortezomib, lenalidomide, and carfilzomib. Selection of frontline therapy should be tailored to the patient’s fitness status and to the presence or absence of kidney disease, peripheral neuropathy, and high-risk genetic mutations. At the present time, almost all patients in the US receive induction therapy that includes at least one novel agent. A recent registry survey showed that Revlimid + dexamethasone and Velcade-based combinations are used in approximately equal numbers in the frontline setting. The thalidomide + dexamethasone combination is now less frequently used, primarily because of the availability of next-generation IMiDs and their relatively favorable side effects profile in contrast to thalidomide-related adverse events that include thrombosis, fatigue, cytopenia, and peripheral neuropathy.
The 2017 NCCN Guidelines for treatment of patients who are not candidates for high-dose therapy with stem cell transplant include, in category 1, Velcade + Revlimid + dexamethasone (VRD) and Revlimid + low-dose dexamethasone (Rd). The 2013 publication of the IFM’s three-arm FIRST trial comparing continuous Revlimid + dexamethasone therapy to fixed-dose Revlimid + dexamethasone and to MPT not only led to the 2015 FDA and EMA approvals of frontline Revlimid + dexamethasone, but demonstrated the superiority of continuous therapy with Revlimid over fixed-dose Revlimid or MPT.

The International Myeloma Working Group consensus statement for the management, treatment, and supportive care of patients with myeloma not eligible for standard autologous stem cell transplantation (A Palumbo et al. JCO January 13, 2014) recommends that these older and sometimes frailer patients be treated according to their fitness level. Geriatric assessment predicts survival and toxicities in elderly myeloma: an International Myeloma Working Group report (A Palumbo et al. Blood January 27, 2015) is a geriatric assessment tool developed to assess comorbidities and cognitive and physical status. The tool predicts mortality and the risk of toxicity in elderly myeloma patients, the better to tailor therapy appropriately. The guidelines recommend that while it is usually preferable to treat the elderly frail patient with a two-drug regimen (Velcade + dexamethasone or Revlimid + dexamethasone), fit, newly diagnosed patients who are not eligible for transplant should be treated with three-drug regimens such as RVD or its variant, reduced-dose “VRD lite”; CyBorD (cyclophosphamide + bortezomib + dexamethasone); and more commonly outside the US, CTD (cyclophosphamide + thalidomide + dexamethasone) or VMP (Velcade + melphalan + prednisone). (See Table 7.)

At the 2014 and 2015 annual meetings of ASH, MV Mateos from the Salamanca group presented data demonstrating that for non-transplant-eligible patients, VMP and Rd can be given either sequentially or alternatively, with equivalent outcomes for either approach.

If stem cell harvest is planned

A basic caveat for transplant-eligible patients is the avoidance of melphalan-containing induction regimens, since melphalan can damage bone marrow. Older age (> 70 years) is not an absolute deterrent to stem cell transplant. Whether or not autologous transplant is an appropriate option must be discussed with each patient on an individual basis, taking into account fitness, genetic risk factors, family and work considerations, and personal preference.

It has become an open question whether auto transplant as a part of first-line treatment is required or whether it can be offered as an option at first relapse or later. We await the final results of three definitive phase III clinical trials that will answer this question. The data from a phase II IFM study of VRD induction followed by upfront high-dose therapy with autologous stem cell transplant, VRD consolidation, and one year of Revlimid maintenance demonstrated a further 20% increase in depth of response after transplant beyond that achieved with induction VRD (M Roussel et al. JCO July 2014). Given this and other data on upfront transplant,
it is reasonable to proceed with the transplant as part of frontline therapy for transplant-eligible patients while awaiting definitive phase III trial results. Follow-up data from the IFM 2009 trial comparing VRD with and without upfront transplant (tracked as far as December 2016), demonstrate improved PFS but no difference in overall survival.

The approach to frontline or induction therapy prior to stem cell harvest and high-dose therapy with stem cell rescue has evolved and changed considerably over the last two decades. The former standard induction regimen has now been supplanted by more effective combination regimens with less toxicity. The version 3.2017 NCCN “preferred regimens” in category 1 for primary therapy of transplant candidates include PAD (PS-341/bortezomib + doxorubicin + dexamethasone) and VRD (Velcade + Revlimid + dexamethasone). “Other regimens” with an NCCN category 1 rating are VD (Velcade + dexamethasone), VTD (Velcade + thalidomide + dexamethasone), and Rd (Revlimid + dexamethasone). Stem cell harvesting following Revlimid + dexamethasone may require a growth factor plus cyclophosphamide or plerixafor, as opposed to growth factor alone.

Other regimens listed by the NCCN with lower levels of evidence include CyBorD (cyclophosphamide + bortezomib + dexamethasone), KRD (Kyprolis + Revlimid + dexamethasone), and IRD (ixazomib + Revlimid + dexamethasone). The current consensus is that three-drug combination therapies are recommended as induction prior to ASCT.

Caveats for various induction options
Three-drug regimens can produce rapid responses and have high response rates.

- Regimens containing lenalidomide and dexamethasone carry an increased risk of blood clots (deep vein thrombosis, DVT) and require prophylactic aspirin or other anticoagulant treatment. Patients receiving induction therapy prior to ASCT with a lenalidomide-containing regimen should have their stem cells mobilized and harvested after no more than four cycles of therapy.
- Neuropathy is a concern with the thalidomide- and Velcade-containing regimens. Supplements such as the amino acids L-carnitine and L-glutamine and vitamins B6 and B12 may offer some neuroprotection. A new mRNA test is in development that would identify myeloma patients at risk for bortezomib-induced peripheral neuropathy, thus guiding treatment selection ahead of time.
- The incidence of peripheral neuropathy has been demonstrated to be significantly less with subcutaneous Velcade than with IV administration.
- Bortezomib and ixazomib, and to a lesser degree carfilzomib, increase susceptibility to herpes zoster infection (shingles). Patients taking Velcade and ixazomib should be given prophylactic antiviral therapy; prophylactic antiviral therapy should be considered for patients taking carfilzomib who have a prior history of herpes zoster infection.

It is a challenge to select the best treatment for each patient. One must consider the early risks of treatment, responses and length of remission, DVT and neuropathy risks, convenience, and costs. Presence of genetic high-risk features and/or renal compromise may sway the choice toward Velcade combinations. Open dialogue to discuss the “pros and cons” is crucial.

Table 8. Induction therapy options for transplant-eligible patients

<table>
<thead>
<tr>
<th>Velcade-based triple therapy</th>
<th>Kyprolis-based triple therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Velcade + Cytoxan + dexamethasone (VCD or CyBorD)</td>
<td>Kyprolis + Cytoxan + dexamethasone (KCD)</td>
</tr>
<tr>
<td>Velcade + Revlimid + dexamethasone (VRD or RVD)</td>
<td>Kyprolis + Revlimid + dexamethasone (KRD)</td>
</tr>
<tr>
<td>Velcade + thalidomide + dexamethasone (VTD)</td>
<td>Kyprolis + thalidomide + dexamethasone (KTD)</td>
</tr>
<tr>
<td>Velcade + Adriamycin + dexamethasone (PAD)</td>
<td>Other</td>
</tr>
</tbody>
</table>
Transplantation

High-dose therapy (HDT) with autologous stem cell transplantation (ASCT)

- The role of autologous transplantation has been extensively reviewed, and remains a topic under investigation in both the upfront and relapse, or salvage, settings.

- HDT with autologous stem cell transplantation has been shown to improve both response rates and survival in patients with myeloma. However, this approach is not curative. With the introduction of novel combination therapies in addition to ASCT, some investigators are introducing the notion that a subgroup of patients (“good risk”) may have extended survival and may achieve “functional cure” (defined as complete remission for ≥ 4 years).

- Complete remission rates with HDT as a planned part of frontline therapy can now be ≥ 90% with new pre- and post-transplant strategies, with PFS rates extending to four years.

- At ASH 2015, M Attal (University of Toulouse, France) presented the French data from the IFM/DFCI 2009 phase III clinical trial of VRD with upfront ASCT versus VRD with no or delayed ASCT in newly diagnosed, transplant-eligible patients. As of early 2017, the OS curves at four years follow-up remain overlapping, despite improved PFS and MRD negativity among patients in the transplant arm. OS follow-up is ongoing.

- Morbidity and mortality – With current growth factor, antibiotic, and other supportive care, the procedure-related mortality with HDT is very low: < 5%. The majority of centers use intravenous high-dose melphalan alone at a dose of 200 mg/m² as the preparative regimen.

Current Recommendations

HDT with autologous stem cell support should be recommended as part of the frontline therapy for eligible newly diagnosed patients with symptomatic myeloma.

- The standard conditioning regimen is melphalan 200 mg/m². Total body irradiation is not recommended.

- Stem cell purging is not recommended because of added expense without additional clinical benefit.

- Peripheral blood stem cells are recommended over bone marrow because of ease of collection and more rapid engraftment.

- The pre-transplant regimens are discussed above.

Role of auto transplantation at time of first relapse

Part of the decision process for autotransplant involves knowledge of the impact of waiting, with a view to transplant at relapse. Until definitive overall survival data are available in the IFM/DFCI trial for patients who had upfront, delayed, or no transplant, each patient and his or her physician must evaluate the relative risks and benefits of proceeding with, delaying, or foregoing transplant. Quality of life becomes an important consideration. On the one hand, if transplant is not performed as a planned primary strategy, then typically additional therapy, including maintenance, is required, with corresponding toxicity and side effects. On the other hand, the major impact of the transplant is deferred, which for some patients is a better personal choice.

Harvesting and storing stem cells for later use

There is a strong reluctance in many centers to harvest stem cells without a clear plan for use, typically immediate use. This reluctance arises from protocol priorities, cost/utilization constraints for harvesting and storage, as well as numerous other factors. Nonetheless, many patients request
and want their stem cells harvested, even though they may not be enthusiastic about immediate high-dose therapy.

Current Recommendations

- Harvesting with storage for future use is recommended with review on a case-by-case basis.
- There is medical and scientific rationale for saving stem cells for later use.
- Delayed transplant is a viable treatment option.
- A second transplant at relapse is a viable option, especially if a remission of > 2 years has occurred following a first transplant. *(See discussion of “double” transplantation.)*

Table 9. Most commonly used chemotherapy drugs

<table>
<thead>
<tr>
<th>DRUG NAME</th>
<th>OTHER TREATMENT NAME</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melphalan <em>(M)</em>*</td>
<td>Alkeran* (by mouth or IV)</td>
<td>Best single agent for treatment</td>
</tr>
<tr>
<td>Cyclophosphamide <em>(C or CY)</em>*</td>
<td>Cytoxan* (by mouth or IV)</td>
<td>Similar efficacy to M but with more GI and GU toxicity and less bone marrow stem cell injury</td>
</tr>
<tr>
<td>Prednisone <em>(P)</em>*</td>
<td>Prednisolone* (similar) (usually by mouth)</td>
<td>Directly active, works well with M, C, and B. Does not produce suppression of bone marrow</td>
</tr>
<tr>
<td>Dexamethasone <em>(D)</em>*</td>
<td>Decadron* (by mouth or IV)</td>
<td>Similar to prednisone but more potent; more severe side effects</td>
</tr>
<tr>
<td>Melphalan* (M)**</td>
<td>Alkeran* (by mouth or IV)</td>
<td>Best single agent for treatment</td>
</tr>
<tr>
<td>Cyclophosphamide <em>(C or CY)</em>*</td>
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<tr>
<td>Dexamethasone <em>(D)</em>*</td>
<td>Decadron* (by mouth or IV)</td>
<td>Similar to prednisone but more potent; more severe side effects</td>
</tr>
</tbody>
</table>

Novel Agents

<table>
<thead>
<tr>
<th>DRUG NAME</th>
<th>OTHER TREATMENT NAME</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pegylated, liposomal doxorubicin*</td>
<td>Doxil* (IV)</td>
<td>In combination, promising activity, less toxicity than A</td>
</tr>
<tr>
<td>Bortezomib <em>(B, V, or P)</em>*</td>
<td>Velcade* (IV)</td>
<td>Directly active, used alone or in combination</td>
</tr>
<tr>
<td>Daratumumab</td>
<td>Darzalex*</td>
<td>Approved for use as a single agent in patients who have had at least 3 lines of therapy</td>
</tr>
<tr>
<td>Elotuzumab</td>
<td>Empliciti®</td>
<td>Approved for use in combination with len/dex in patients who have had 1–3 prior lines of therapy</td>
</tr>
<tr>
<td>Ixazomib</td>
<td>Ninlaro®</td>
<td>Approved for use in combination with len + dex in patients who have had 1 prior therapy</td>
</tr>
<tr>
<td>Thalidomide <em>(T)</em>*</td>
<td>Thalomid* (by mouth)</td>
<td>Directly active, approved for use in combination with dexamethasone, used in other combinations</td>
</tr>
<tr>
<td>Lenalidomide <em>(R or L)</em>*</td>
<td>Revlimid® (by mouth)</td>
<td>Directly active, approved for use in combination with dexamethasone, used in other combinations</td>
</tr>
<tr>
<td>Carfilzomib</td>
<td>Kyprolis® (IV)</td>
<td>Directly active, used alone or in combination</td>
</tr>
<tr>
<td>Pomalidomide</td>
<td>Pomalyst® (by mouth)</td>
<td>Directly active, used alone or in combination</td>
</tr>
<tr>
<td>Panobinostat</td>
<td>Farydak® (by mouth)</td>
<td>Approved for use in combination with bortezomib and dexamethasone</td>
</tr>
</tbody>
</table>

*Alkylating agents  **Common abbreviation
The role of double or tandem transplantation

- At present the added benefit of double or tandem transplantation versus a single autologous transplant is unclear.
- The results with planned primary tandem transplant (Total Therapy 1, 2, 3, 4, and 5 at the University of Arkansas) have been good. The median overall survival has been 68 months, with some sub-groups having even longer survival. Total Therapy 3, which incorporates the use of Velcade, appears to offer earlier response and increased response rates, although patients with high-risk factors, including older age, higher LDH, abnormal cytogenetics, or advanced disease, are not as likely to achieve extended benefit.
- Comparative studies, including the French randomized studies, have shown benefit predominantly for a subgroup of patients (those who are not in VGPR or CR).

Current Recommendations

- At the present time, planned tandem transplant continues to be a clinical trial option and should be carried out at centers specialized in this approach. A planned second transplant can be considered in patients achieving < VGPR with a first auto transplant.
- A second transplant in a patient who has responded well with a first transplant and relapsed after > 2 years is a helpful and viable option.
- Saving and storing enough stem cells for a second or additional transplant, if appropriate, is strongly recommended.

The role of allogeneic transplantation

- Despite medical improvements over the past two decades, full allogeneic transplant, even with a perfectly matched sibling donor, is a high-risk procedure in the management of myeloma. The initial treatment-related morbidity and mortality is high. Even at centers with the greatest experience, and in the best risk settings, initial mortality is at least 15% to 20%. In other centers, 20% to 30% or higher mortality is frequently reported. The pulmonary complications are usually the most critical for patients with myeloma.
- The potential advantages of allogeneic transplantation are myeloma-free stem cells and graft-versus-myeloma effect. But, despite these factors, long-term cure is rare. Relapse continues at a rate of approximately 7% per year with long-term follow-up. Graft-versus-host disease (GVHD) can also be an ongoing problem, requiring therapy and reducing quality of life.
- The graft-versus-myeloma effect can be enhanced by using donor lymphocyte infusions and has been clinically beneficial in some cases.
- Long-term follow-up data published in Sweden by G Gharton et al. in 2013 demonstrated that “long-term outcome in patients with multiple myeloma was better with auto/reduced-intensity conditioning (RIC) allo as compared with auto only, and the auto/RICallo approach seemed to overcome the poor prognostic impact of del(13) observed after autologous transplantation. Follow-up longer than five years is necessary for correct interpretation of the value of auto/RICallo in multiple myeloma.”

Current Recommendations

- Conventional full-match allogeneic transplantation is rarely recommended as a primary strategy because the risks are too high.
“Mini” (or RIC, reduced-intensity conditioning) allogeneic transplantation is only recommended in a clinical trial setting. There has been increasing interest in the upfront use of allogeneic transplant for high-risk patients.

Identical twin or “syngeneic” transplantation is a rare option, which is a safe procedure with good outcome and is recommended as a consideration when an identical twin is available.

Radiation

Radiation therapy is an important modality of treatment for myeloma.

For patients with severe local problems such as bone destruction, severe pain, and/or pressure on nerves or the spinal cord, local radiation can be dramatically effective. The major disadvantage is that radiation therapy permanently damages normal bone marrow stem cells in the area of treatment. Wide-field radiation encompassing large amounts of normal bone marrow should be avoided. A general strategy is to rely on systemic chemotherapy to achieve overall disease control, limiting the use of local radiation therapy to areas with particular problems.

Maintenance therapy

Immunomodulatory drugs – In 2012, three randomized placebo-controlled trials reported a significant prolongation of progression-free survival with Revlimid as maintenance therapy for

<table>
<thead>
<tr>
<th>Table 10. High-Dose Therapy (HDT)</th>
</tr>
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<tbody>
<tr>
<td><strong>TRANSPLANT TYPE</strong></td>
</tr>
</tbody>
</table>
| Single Autologous | • 50% excellent remissions  
• At least as good as standard therapy regarding overall survival and probably better for patients with high Sβ2M  
• Basis for strategies to produce true remission or long-term cure  
• New preparative regimens may produce true complete remission | • Relapse pattern similar to standard chemotherapy  
• More toxic and expensive  
• Patients who decisively benefit from transplant not clearly identified  
• Maintenance therapy may still be required/recommended |
| Double Autologous | • 2002 update of French data indicates survival benefit for subset of patients not in CR or VGPR  
• Excellent results with tandem transplant (see text) | • Role of double versus single still unclear  
• Much more toxic and expensive versus single  
• No survival benefit if in CR or VGPR after first transplant |
| Traditional Allogeneic | • No risk of contamination of marrow/stem cells with myeloma  
• Possible graft-versus-myeloma effect to prolong remission | • Even for HLA identical siblings, significant risk of early complications and even death  
• Risk of complications unpredictable  
• Restricted to age < 55  
• More toxic and expensive versus autologous |
| Reduced-intensity conditioning (RIC) allogeneic transplant or “Mini-Allo” | • Less toxic form of allo  
• Preparative chemotherapy usually well tolerated  
• Results in anti-myeloma immune graft | • Still produces graft-versus-host disease  
• Full benefits still unclear  
• Risk of initial mortality approximately 17%  
• Not recommended for myeloma patients outside the context of a clinical trial |
| Identical Twin | • No risk of myeloma contamination in transplanted cells  
• Much less risky than allogeneic transplant | • No graft-versus-myeloma effect  
• Need identical twin < 55 |
myeloma. Two of these trials looked at post-transplant maintenance, and the third trial evaluated Revlimid as maintenance following standard melphalan-based therapy. The US CALGB study’s (P McCarthy et al.) initial results demonstrated that lenalidomide at a dose of 10 mg per day for 21 out of 28 days doubles time to progression compared with placebo when given to patients with stable disease or better after high-dose melphalan and ASCT. Follow-up data from that trial demonstrated that lenalidomide maintenance also increases overall survival. An international meta-analysis of all three trials presented by P McCarthy at the American Society of Clinical Oncology (ASCO) meeting in June 2016 demonstrated that continuous lenalidomide following autologous stem cell transplantation improved overall survival in these patients. The benefit in overall survival was consistent across subgroups.

Balanced against the favorable data on maintenance with lenalidomide is the low but increased risk of a second malignancy. A follow-up study by A Palumbo of the Italian group determined that lenalidomide alone does not increase the risk of second malignancy, but that the combination of melphalan and lenalidomide, two agents that can take a toll on the bone marrow, does. We await the results of several additional maintenance trials with approved and experimental agents.

A 2012 meta-analysis of patients receiving thalidomide maintenance therapy demonstrated that patients had marginally better overall survival. Thalidomide maintenance, however, increases the risk of venous thrombosis and peripheral neuropathy.

**Velcade** – The Dutch-Belgian/German randomized phase III clinical trial, known as HOVON-65/GMMG-HD4, comparing PAD plus bortezomib maintenance to VAD plus thalidomide maintenance was published in August 2012. Not only did Velcade result in improved PFS and OS, but its use as maintenance therapy administered on an every-other-week schedule was well tolerated and resulted in additional responses. Initial results also indicated benefit in patients with the deletion 17p poor-risk FISH genetic feature.

**Supportive care**

**Bisphosphonates** – Bisphosphonates are a class of chemicals that bind to the surface of damaged bones in patients with myeloma. This binding inhibits ongoing bone destruction and can improve the chances of bone healing and recovery of bone density and strength. A randomized study utilizing the bisphosphonate pamidronate (Aredia) showed particular benefit in patients responding to ongoing chemotherapy (see Figure 5). The IMWG’s 2013 recommendations for the treatment of myeloma-related bone disease state that bisphosphonate therapy should be considered in all patients receiving first-line anti-myeloma therapy, regardless of the presence of osteolytic bone lesions on conventional radiography. Other bisphosphonates available include clodronate (Bonefos®), an oral formulation in use in Europe for the treatment of myeloma bone disease, and zoledronic acid (Zometa), approved in the US and Europe as treatment of both hypercalcemia and bone disease. Several new therapies to prevent myeloma-related bone loss are in clinical trials, including denosumab, a monoclonal antibody to RANK ligand, BHQ880, an anti-DKK1 monoclonal antibody, and sotatercept (ACE-011), a fusion protein that stimulates bone growth.
Several concerns have emerged related to chronic bisphosphonate use. Two of these, kidney damage and osteonecrosis of the jaw (ONJ) are addressed in detail in the IMF publication *Understanding Bisphosphonate Therapy*. Both conditions are fortunately relatively uncommon, but awareness of these potential problems is the key to prevention. Kidney function must be serially monitored (especially serum creatinine before each treatment dose), particularly with Zometa use. If the serum creatinine increases by 0.5 to 1.0 mg/dL, dose and/or schedule adjustments for Aredia or Zometa may be required. For Zometa, one of the simplest adjustments is to extend the infusion time from 15 minutes to 30–45 minutes, which reduces the risk of renal impairment.

An American Academy of Oral Medicine position paper on the management of bisphosphonate-related ONJ (BONJ) was originally published in *The Journal of the American Dental Association* in December 2005 and has been updated several times, most recently in a 2014 position paper entitled *Medication-Related Osteonecrosis of the Jaw – 2014 Update*. The first recommendation is prevention of medicine-related ONJ through regular dental check-ups. If a problem is found, referral to an expert (i.e., an oral surgeon) is strongly recommended. Any major jaw surgery must be avoided until consultation has been sought. Dental extractions should be avoided until full consultation has been obtained as well. Infection may require antibiotic therapy. In recent years, the incidence of ONJ appears to have decreased dramatically in the wake of greater awareness of the problem and attention to dental hygiene before and after initiating bisphosphonate therapy.

However, additional concerns have emerged with long-term use of bisphosphonates. Although atypical (subtrochanteric) fractures of the femur are rare, there is data that establishes an association with five or more years of bisphosphonate treatment with their occurrence. In October 2010, the FDA added subtrochanteric fracture of the femur to the “Precautions and Warnings” section of the package inserts for all bisphosphonates. Two recent publications discuss the possible association between oral bisphosphonates and cancer of the esophagus. Using the same database, one group did not find an association (CR Cardwell et al.), whereas the other group reported an increased risk (JR Green et al.). These findings require further examination.

The IMWG’s 2013 recommendations state that for patients in CR or VGPR, the optimal duration of bisphosphonate therapy is not clear; bisphosphonates should be administered for at least 12 months and up to 24 months, and then at the physician’s discretion. For patients who have active disease, who have not achieved a response, or who have threatening bone disease beyond two years, bisphosphonate therapy can be decreased to every three months. The most current guidelines on the role of bisphosphonates in myeloma from the American Society of Clinical Oncology (ASCO) (R Kyle et al. *JCO* 2007) recommend treating for two years, then considering discontinuation of bisphosphonates for patients whose disease is responsive or stable. Continued use of bisphosphonates should be at the discretion of the physician.

**Antibiotics** – Infections are a common and recurrent problem in patients with myeloma. A careful strategy for infection management is required. Antibiotic therapy should be instituted immediately if active infection is suspected. Use of preventive or prophylactic antibiotics with recurrent infection is controversial. A comparative study (URCC/ECOG, DH Vesole et al.) presented at ASH 2010 concluded that “the use of prophylactic antibiotics did not decrease the incidence of serious infection (> grade 3 and/or hospitalization) nor of any infection within the first two months of treatment.” Based on this study, the authors recommend that antibiotics should not be mandated in the first two months of treatment, but should be considered on a case-by-case basis. The continuation of prophylactic antibiotics can increase the chance of antibiotic resistance, but it can also reduce the chance of recurrent infectious complications. The use of high-dose gammaglobulin therapy may be required in patients with acute and severe recurrent infections. GM-CSF may be helpful in
improving the white blood cell levels in an effort to overcome infectious complications. The use of G-CSF or GM-CSF is helpful in the recovery phase following bone marrow or stem cell transplantation. G-CSF and GM-CSF are also used in harvesting stem cells.

**Antivirals** – An increased incidence of herpes zoster (shingles) has been observed in some patient populations with myeloma (but not other malignancies) who are treated with bortezomib or ixazomib. Therefore, prophylactic antiviral therapy should be considered with bortezomib and ixazomib therapy. While the carfilzomib package insert states that only 2% of the patients in clinical trials developed shingles, it is generally recommended that patients receiving carfilzomib receive antiviral prophylaxis as well if they have a history of prior herpes zoster infection. Myeloma patients are cautioned not to get the shingles (Zostavax®) vaccine, as it is a live virus that poses a significant risk to those who are immunocompromised.

**Management of relapsing or refractory disease**

As illustrated in the pathophysiology section, a frequent problem in myeloma is the relapse that occurs following a one- to three-year remission. Although maintenance therapy may be useful in prolonging the initial remission period, the relapse, which supervenes inevitably, requires re-induction therapy. The following is an overall strategy for the management of relapsing disease.

If first relapse occurs after a remission of at least six months to one year, the first strategy is to consider re-utilizing the therapy that produced the remission in the first place. NCCN guidelines state that “if the relapse occurs greater than six months after completion of the initial primary therapy, patients may be retreated with the same primary regimen.” Approximately 50% of patients will experience a second remission with the same therapy that produced the first. This is particularly true for patients whose disease is in remission for more than one year following the initial induction attempt. As an example, a patient who received Revlimid + low-dose dexamethasone and whose myeloma has gone into remission for two years can again receive Rd therapy. If remission has lasted less than six months, some alternative therapy will usually be required. This is also the case if relapse has occurred following a second or third use of the original induction therapy. Adding a third drug to the regimen is an important consideration in this setting. (See Figure 6.)

**Velcade (bortezomib)** plays a crucial role as a platform on which to base combination therapies for relapse (VR, VRD, VCD, etc.). In August, 2014, based on the international phase II RETRIEVE trial, Velcade was approved in the US for the retreatment of adult patients with myeloma who had previously responded to Velcade therapy and relapsed at least six months following completion of that therapy.

**Kyprolis (carfilzomib)** has been evaluated alone and as a backbone drug in combination therapy trials for relapse therapy. It has demonstrated safety and efficacy in such combination therapies as KCyD, KRD, KTD, and KCyTD, all of which were presented at ASH in 2012. Final results of the ASPIRE trial comparing Kyprolis + Revlimid + dexamethasone to Revlimid + dexamethasone in relapsed
myeloma were presented at the 2014 annual ASH meeting, demonstrating the superiority of KRD over RD. Results of the ENDEAVOR trial comparing Kyprolis + dexamethasone to Velcade + dexamethasone in myeloma patients who had had from one to three prior therapies were released in March 2015 and demonstrated that patients who were in the Kyprolis + dexamethasone arm had double the progression-free survival of patients in the Velcade + dexamethasone arm (18.7 versus 9.4 months). Final analysis of this trial, and of other trials going forward with Kyprolis, will have to determine whether the higher-than-approved dose of Kyprolis in the ENDEAVOR trial and the number of patients in the trial who had had previous Velcade significantly influenced the results. The results of the phase I carfilzomib + pomalidomide + dexamethasone trial in relapsed/refractory myeloma were published in Blood in November 2015. The data showed that the combination was well tolerated and highly active, with a 50% response rate (PR or better) in highly pretreated patients.

**Pomalyst (pomalidomide)** has also demonstrated its value in the relapse setting in multiple combination therapy trials (PD, PVD, PCyPred, BiaxinPD, PCyD, KPD). Encouraging recent news from the IFM was published in Blood in February 2015, indicating that patients with early relapsed/refractory myeloma who have high-risk deletions 17p and/or t(4;14) show improved PFS and OS with Pomalyst + low-dose dexamethasone.

The 2015 approvals of panobinostat, daratumumab, ixazomib, and elotuzumab provide new options for the treatment of patients with relapsed disease. The optimal sequencing and combining of therapies remains to be sorted out. Of the newly approved therapies, only **Darzalex (daratumumab)** has shown single-agent activity and may be administered as monotherapy to patients who have received at least three prior therapies, including a proteasome inhibitor and an immunomodulatory agent, or are double-refractory. Recent results of the CASTOR (daratumumab + bortezomib + dexamethasone in patients who have had at least one prior therapy) and POLLUX (daratumumab + lenalidomide + dexamethasone in patients with relapsed or refractory myeloma) studies, as well as the results of other ongoing trials with daratumumab in various disease settings, have broadened the approved indications for daratumumab. Panobinostat was approved in combination with bortezomib and dexamethasone for patients who have had at least two prior regimens, including bortezomib and an immunomodulatory drug; ixazomib and elotuzumab were approved in combination with lenalidomide and dexamethasone, the former for patients who have had one prior therapy, and the latter for patients who have had one to three prior therapies. Issues of cost, value, and access to expensive combination therapies with these new drugs remain to be sorted out.

**Other options** – It is important to keep in mind that a variety of single and combination chemotherapy protocols are available for the management of relapsing and refractory disease. Depending upon the exact problem, a variety of interventions may be possible. For example, if relapse is associated with the development of one or two bone lesions, radiation to the site(s) of bone involvement may be a satisfactory way to manage the relapse. If overall relapse has occurred, dexamethasone as a single agent can be very useful in achieving overall control of the disease. The use of dexamethasone is attractive because it can be given by mouth and does not cause significant side effects such as hair loss or reduction in peripheral blood count values.

Another important point is that relapse following high-dose therapy with transplant has, in many cases, a pattern similar to relapse following more standard approaches. Second and sometimes third remissions can be achieved following relapse after bone marrow transplantation. Whether a second high-dose therapy with transplant is the most appropriate strategy, as opposed to some other approach, is currently unclear and must be based upon individual patient considerations.
Given the continuing rapid rate of development of new therapies for myeloma, as well as investigation of new combinations of existing and new agents, treatment in the context of clinical trials can be an option for patients with relapsed myeloma.

A full range of supportive care is crucial for the management of myeloma. When first diagnosed, a number of emergency procedures may be required, including dialysis, plasmapheresis, surgery, and radiation to reduce pressure on a nerve, the spinal cord, or other crucial organ. The management of pain is essential for the initial care of patients with myeloma. This can be difficult until initial disease control is achieved. There is no reason for patients with myeloma to have major ongoing pain with the range of new drugs and strategies available. There can be reluctance on the part of the patient and/or the physician to implement full pain control procedures because of concerns about addiction. Control of pain should always be the first priority. A brace or corset can help stabilize the spine or other areas, reducing movement and pain. Moderate exercise is also important in recovering bone strength and mobility and can help in overall pain reduction.

**New and emerging therapies**

Many new treatments and combination therapies are available in the setting of clinical trials. Clinical trial phases are listed in Table 12. The emergence of immunotherapy has created a new paradigm in cancer treatment; immuno-oncology agents currently in clinical trials for myeloma include monoclonal antibodies, tumor suppressor gene stimulators, CAR T-cell therapies, engineered dendritic cells, oncolytic virotherapies, and checkpoint inhibitors. Patients are encouraged to check

<table>
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<tr>
<th>Blood Tests</th>
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<tbody>
<tr>
<td>• Routine blood counts</td>
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<td>• Chemistry panel</td>
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<tr>
<td>• Liver function tests</td>
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<tr>
<td>• Myeloma protein measurements <em>(serum protein electrophoresis plus quantitative immunoglobulins)</em></td>
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<tr>
<td>• Serum Free Light Chain Assays <em>(Freelite®)</em></td>
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<td>• Heavy/Light Chain Assay <em>(Hevylite®)</em></td>
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<td>• Serum β2 microglobulin</td>
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<td>• C-reactive protein</td>
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<td>• Peripheral blood labeling index (LI)</td>
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<td>• Serum erythropoietin level</td>
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<th>Urine</th>
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<tr>
<td>• Routine urinalysis</td>
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<tr>
<td>• 24-hour urine for measurement of total protein, electrophoresis, and immunoelectrophoresis</td>
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<tr>
<td>• 24-hour urine for creatinine clearance if serum creatinine elevated</td>
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<tr>
<th>Bone Evaluation</th>
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<tr>
<td>• Skeletal survey by X-ray</td>
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<tr>
<td>• MRI/CT scan for special problems</td>
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<tr>
<td>• Whole body FDG/PET scan if disease status unclear</td>
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<tr>
<td>• Bone density measurement <em>(DEXA scan)</em> as baseline and to assess benefit of bisphosphonates</td>
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<th>Bone Marrow</th>
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<tr>
<td>• Aspiration and biopsy for diagnosis and periodic monitoring</td>
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<tr>
<td>• Special testing to assess prognosis looking for multiple potential karyotypic and FISH abnormalities (number of chromosomes, translocations, deletions — e.g., FISH 13q-, t[4;14], 1q21, etc.)</td>
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<th>Other Testing (special circumstances)</th>
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<tr>
<td>• Amyloidosis</td>
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<tr>
<td>• Neuropathy</td>
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<td>• Renal or infectious complications</td>
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**Table 11. Tests required to monitor therapy responses**
with their physicians regarding the availability of new clinical trials. For questions or concerns, the IMF is available via email at TheIMF@myeloma.org or by calling 800-452-CURE (2873), toll-free in the United States and Canada, or 818-487-7455 from other parts of the world. The Myeloma Matrix 2.0: Smart Patients, the IMF search tool that lists all drugs currently in clinical trials for myeloma, is available with ongoing updates on the IMF website at matrix.myeloma.org. Good summaries of new therapies are presented in the IMF reports from ASH, ASCO, EHA, and IMWG. These summaries are available online at myeloma.org or by calling the IMF.

**Recommended reading**

**2017**

**2016**

**2015**
- Palumbo A, et al. Revised ISS for myeloma: a report from the IMWG. *JCO* 2015

**2014**
- Ocio E, et al. New drugs and novel mechanisms of action in 2013: a report from the IMWG. *Leukemia* 2014
- Palumbo A, et al. IMWG consensus: management, treatment, and supportive care of patients with myeloma not eligible for standard ASCT. *JCO* 2014

**2013**

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**Table 12. Clinical trial phases**

<table>
<thead>
<tr>
<th>Phase</th>
<th>Description</th>
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<tbody>
<tr>
<td>I</td>
<td>Early testing to assess dosing, tolerance, and toxicity in patients</td>
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<tr>
<td>II</td>
<td>Further testing to evaluate how effective treatment is at the dose and schedule selected</td>
</tr>
<tr>
<td>III</td>
<td>Comparison of the new treatment with prior treatment(s) to determine if the new treatment is superior</td>
</tr>
<tr>
<td>IV</td>
<td>Usually carried out after FDA approval to assess cost-effectiveness, quality of life impact, and other comparative issues</td>
</tr>
</tbody>
</table>
• Ludwig H, et al. IMWG recommendations for global myeloma care. *Leukemia* 2013


• Terpos E, et al. IMWG recommendations for the treatment of myeloma-related bone disease. *JCO* 2013

2012


2011


• Cavo M, et al. IMWG consensus approach to the treatment of myeloma patients who are candidates for ASCT. *Blood* 2011


• Kumar S, et al. Risk of progression and survival in myeloma relapsing after therapy with IMiDs and bortezomib. *Leukemia* 2011


2010


• Kyle R, et al. MGUS and SMM: Risk factors for progression and guidelines for monitoring and management. *Leukemia* 2010

• Lokhorst H, et al. IMWG consensus statement regarding the current status of allogeneic SCT for myeloma. *JCO* 2010

• Ludwig H, et al. Survival and years of life lost in different age cohorts of patients with myeloma. *JCO* 2010

• Terpos E, et al. The use of biochemical markers of bone remodeling in myeloma. *Leukemia* 2010

2009

• Durie B, et al. Genetic polymorphisms of EPHX1, Gsk3b, TNFSF8 and myeloma cell DKK-1 expression linked to bone disease. *Leukemia* 2009


2008


• Ludwig H, et al. myeloma in patients younger than age 50 years presents with more favorable features. *Blood* 2008


2007


2006

One of the most daunting aspects of being diagnosed with multiple myeloma is learning about – and understanding – an unfamiliar disease that is quite complicated. From diagnosis to long-term survival, the 10 Steps to Better Care® will guide you through the myeloma journey:

1. Know what you’re dealing with. Get the correct diagnosis.
2. Tests you really need.
3. Initial treatment options.
4. Supportive care and how to get it.
5. Transplant: Do you need one?
6. Response Assessment: Is treatment working?
7. Consolidation and/or maintenance.
9. Relapse: Do you need a change in treatment?

Visit 10steps.myeloma.org to gain a better understanding of the disease and diagnosis, and proceed through the steps to learn the best tests, treatments, supportive care, and clinical trials currently available.

As always, the International Myeloma Foundation (IMF) urges you to discuss all medical issues thoroughly with your doctor. The IMF is here to equip you with the tools to understand and better manage your myeloma. Visit the IMF website at myeloma.org or call the IMF InfoLine at 800-452-CURE (2873) or 818-487-7455 to speak with our trained information specialists about your questions or concerns. The IMF is here to help.