ARTICLE TITLE: Understanding Biology to Tackle the Disease: Multiple Myeloma From Bench to Bedside, and Back

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After reading the article "Understanding Biology to Tackle the Disease: Multiple Myeloma from Bench to Bedside, and Back" the learner should be able to:
1. Describe the risk factors, clinical presentation, and diagnostic criteria for multiple myeloma and related plasma cell dyscrasias.
2. Discuss the recommended treatment options for patients with multiple myelomas and related plasma cell dyscrasias.
3. Summarize the molecular changes in multiple myelomas and related plasma cell dyscrasias that are most relevant to the development of new targeted therapies.

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Kenneth C. Anderson, MD reports personal fees from Celgene, Millennium, Gilead, Sanofi, and Bristol-Myers Squibb and ownership interests in Acetylon and Oncoprep during the conduct of the study.
Giada Bianchi, MD has nothing to disclose.

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Multiple myeloma (MM) is a cancer of antibody-producing plasma cells. The pathognomonic laboratory finding is a monoclonal immunoglobulin or free light chain in the serum and/or urine in association with bone marrow infiltration by malignant plasma cells. MM develops from a premalignant condition, monoclonal gammopathy of undetermined significance (MGUS), often via an intermediate stage termed smoldering multiple myeloma (SMM), which differs from active myeloma by the absence of disease-related end-organ damage. Unlike MGUS and SMM, active MM requires therapy. Over the past 6 decades, major advancements in the care of MM patients have occurred, in particular, the introduction of novel agents (ie, proteasome inhibitors, immunomodulatory agents) and the implementation of hematopoietic stem cell transplantation in suitable candidates. The effectiveness and good tolerability of novel agents allowed for their combined use in induction, consolidation, and maintenance therapy, resulting in deeper and more sustained clinical response and extended progression-free and overall survival. Previously a rapidly lethal cancer with few therapeutic options, MM is the hematologic cancer with the most novel US Food and Drug Administration-approved drugs in the past 15 years. These advances have resulted in more frequent long-term remissions, transforming MM into a chronic illness for many patients.

**Keywords:** multiple myeloma, monoclonal gammopathy of undetermined significance, smoldering multiple myeloma, microenvironment, hematopoietic stem cell transplant, proteasome inhibitors, immunomodulatory agents, molecularly targeted therapies

**Introduction**

**Epidemiology and Risk Factors**

Multiple myeloma (MM) is the second most common hematologic tumor and represents 2% of all newly diagnosed malignancies in the United States. Twenty-four thousand new MM cases and 11,000 MM-related deaths are estimated for the year 2014. MM is predominantly a disease of the elderly, with a median age at diagnosis of 69 years; incidence rates for males and females are 7.7 and 4.9 cases per 100,000 persons per year, respectively. Compared with whites, blacks are affected 2 to 3 times more frequently, while the disease is least common in Asians Americans/Pacific Islanders and intermediate for American Indians/Alaska Natives and Hispanics. Mortality rates are also 2-fold to 3-fold higher in blacks compared with whites at 7.9 per 100,000 men and 5.4 per 100,000 women versus 4.0 per 100,000 men and 2.5 per 100,000 women, respectively. The exact etiopathogenic mechanisms leading to MM are unknown, but several risk factors have been identified. In terms of environmental and occupational exposures, nuclear radiation and petroleum products are the only recognized risk factors, although epidemiologic studies strongly suggest other environmental exposures, including pesticides, given the higher incidence of MM in farmers and wood and leather manufacturers. A family history of monoclonal gammopathy of undetermined significance (MGUS), smoldering MM (SMM), MM, or other B-cell malignancies was recognized as a risk factor more than 50 years ago. Nonparametric and parametric linkage analyses in familial cases of MM and/or MGUS identified the 1q and 4q loci as the regions of interest for germline genetic mutations. ³
The hyperphosphorylated form of Paratarg-7 (P-7), a protein of unknown function, is inherited as an autosomal dominant trait in familial cases of MM and MGUS, suggesting a potential pathogenic role. Finally, as detailed below, a personal history of MGUS or SMM is a well-established risk factor for the development of MM.

Etiopathogenesis
It is believed that MM derives from the transformation of long-lived plasma cells (PCs), a subset of antibody-producing PCs that home to and survive in the bone marrow (BM) for years, contributing to immunologic memory. Antigenic profile analysis and sequencing of the immunoglobulin (Ig) variable region showed that MM cells (MMCs) evolve from a postgerminal center, common progenitor with early genetic mutations occurring at the pre-B stage, and later oncogenic events that take place at the PC stage (Fig. 1). MGUS consistently precedes MM with a 1% per year, life-long risk of cancerous transformation. The molecular bases underlying such malignant evolution have not yet been delineated.

Prognostic Algorithms of Evolution of MGUS and SMM to MM
Non-IgG Ig subtype, elevated monoclonal (M) protein, and an abnormal serum free light chain (sFLC) ratio have been identified as risk factors for the progression of MGUS to active MM. Multiparametric flow cytometric demonstration of an aberrant immunophenotype and/or DNA aneuploidy in the malignant clone have also been associated with increased risk in a predictive model of MGUS evolution to MM.

Based on retrospective data, the extent of BM infiltration, an M-protein spike (M spike) equal to or greater than 3 g/dL, and an abnormal sFLC ratio have been integrated into a predictive model of progression of SMM to active MM to aid in counseling and therapeutic decisions. More recently, an sFLC ratio of involved to noninvolved light chain equal to or greater than 100, peripheral blood circulating PCs
excess of $5 \times 10^6$/L and/or 5% per 100 cytoplasmic Ig-positive mononuclear cells, and BM infiltration exceeding 60% have been identified as risk factors for imminent (within 2–3 years) transformation of SMM to MM.15-17

Genetics and Clonal Evolution

MMCs are characterized by striking genomic complexity, suggesting that loss of function of genes involved in DNA replication fidelity and DNA repair is an early genetic event.18,19 About 50% to 60% of MM cases are hyperdiploid with trisomies in odd chromosomes (chromosomes 3, 5, 7, 9, 11, 15, 19, and 21). The initial genetic event in the nonhyperdiploid tumors is typically a translocation (t) between the Ig heavy-chain (IgH) locus on chromosome 14q32 and one of several oncogenes: fibroblast growth factor receptor 3 (FGFR3), multiple myeloma SET domain (MMSET), cyclin D1 and cyclin D3, MAF (v-maf avian musculoaponeurotic fibrosarcoma oncogene homolog), and MAFB. Secondary genetic events are typically activating mutations in pathways involved in proliferation, immortalization, and apoptosis resistance, such as MYC (v-myc avian myelocytomatosis viral oncogene homolog), K-RAS and N-RAS (Kirsten rat sarcoma [RAS] and neuroblastoma RAS viral [v-ras] oncogene homolog, respectively), BRAF (B-Raf proto-oncogene), PI3K (phosphatidylinositol-4,5-bisphosphate 3-kinase), and AKT (v-akt murine thymoma viral oncogene homolog); and/or deletion (del) of oncopressors, such as del(17p) involving the locus of TP53 (tumor protein 53). Genetic or nongenetic disruption of key regulators of PC differentiation, XBP-1 (X-box binding protein 1), PRDM1 (PR domain containing 1), and IRF-4 (interferon regulating factor 4), proved crucial for MM pathogenesis.20,21 While epigenetic changes in MM have been less well characterized, generalized gene hypomethylation is associated with the transition between MGUS and MM, whereas hypermethylation of specific target genes correlates with progression of MM into PC leukemia (Fig. 1).22

FIGURE 2. Clonal Evolution in Multiple Myeloma. This cartoon is a schematic representation of the clonal evolution of multiple myeloma (MM) over time under the pressure of changes in the microenvironment and exogenous stimuli, such as chemotherapy drugs. The size of each clone is proportional to its abundance in the pool of cancer cells. The 4 patterns of evolution described by Bolli et al23 are illustrated. The pink circles and squares inside blue ovals are mutations of the founder (F) clone, and the red shapes are mutations that were acquired de novo by the various subclones (S1, S2, S3, and S4). Genetic mutations tend to accumulate over time and upon disease progression, with increasing genomic complexity noted in the dominant (D) clone of the terminal, secondary, plasma cell (PC) leukemia stage.
Technological advances in genome analysis, in particular array comparative genomic hybridization (aCGH) and whole-genome and whole-exon sequencing (WGS and WES, respectively), have been instrumental in demonstrating clonal heterogeneity and clonal evolution in MM. Clonal heterogeneity was demonstrated in MM and its precursor conditions, MGUS, and SMM, with genetic complexity progressively increasing throughout the course of malignant transformation and peaking in the leukemic, terminal phase of the disease. Longitudinal follow-up of paired samples from patients with MM showed diverse patterns of clonal evolution over time (Fig. 2). In analogy with the Darwinian theory of evolution, both the genetic signature of the clone and the selective pressure of the
Histopathology and Molecular Pathology
A definitive diagnosis of clinically suspected MM requires the identification of an excess of monoclonal, malignant PCs in a tissue, typically the BM. Aberrant PCs can infiltrate serosa, skin, and parenchymal organs either as solitary extrasosseous plasmacytoma or as part of advanced stages of the disease characterized by malignant cells in the peripheral blood (PC leukemia). MMCs are large, round, or elliptical-shaped with abundant basophilic cytoplasm and an eccentrically located nucleus that has coarsely clumped chromatin. The Golgi apparatus is typically visible as a perinuclear hof (with lightly staining cytoplasm); and aberrant, binucleate, or multinucleate forms; mitotic figures; and prominent nucleoli are often detected (Fig. 3A–C). Under electron microscopy, MMCs show a large amount of endoplasmic reticulum (ER), reflective of abundant protein synthetic activity related to Ig production. Immunophenotypically, MMCs strongly express SDC1 (syndecan-1, also known as CD138) and monotypic light chain (either $\kappa$ or $\lambda$) (Fig. 3D, G, and H). In contrast to normal PCs, MMCs typically lack expression of CD19 (B-lymphocyte antigen CD19), CD27 (CD27 antigen), and CD45 (receptor-type tyrosine-protein phosphatase C), and they aberrantly express CD56 (also known as

### TABLE 1. Pathogenic Mechanisms Underlying the Most Common Presenting Symptoms and Signs of Multiple Myelomaa

| SIGNS AND SYMPTOMS                        | DIAGNOSTIC FINDINGS                        | PATHOGENIC MECHANISMS                                                                 |
|------------------------------------------|--------------------------------------------|--------------------------------------------------------------------------------------|
| Bone/back pain, cord compression, cauda equina | Lytic lesions, pathologic fractures         | Myelophthisis, solitary plasmacytoma, increased osteoclastogenesis, osteoblast inhibition |
| Fatigue, malaise                          | Anemia                                     | Myelophthisis, decreased EPO production, hemolysis                                  |
| Kidney injury                             | Light chain deposition, cast nephropathy, hypercalcaemia-induced vasocconstriction, AL amyloidosis, urate nephropathy |
| Hypercalcemia                             | OC/IB imbalance secondary to direct MM effect and BM cytokines                           |
| Hepatitis, liver failure                  | Amyloid deposition, MMC infiltration       |                                                                                      |
| Recurrent infections                      | Hypogammaglobulinemia, leucopenia          | Myelophthisis                                                                        |
| Encephalopathy                            | Hypercalcemia                              | Please see above                                                                      |
| Acute kidney injury                       | Please see above                           |                                                                                      |
| Elevated M spike, typically IgM; elevated serum viscosity | Hypercalcemia                              |                                                                                      |
| Peripheral neuropathy                     | Polyradiculopathy                          | AL amyloidosis, cryoglobulinemia type I, plasmacytoma                                |
| Headache, seizures, visual disturbances   | Elevated M spike, typically IgM; elevated serum viscosity | Hypercalcemia                                                                        |
| MMCs present in CSF, leptomeningeal enhancement on MRI | MM infiltration of CNS                        |                                                                                      |
| Cranial nerve paralysis                   | MMCs present in CSF, leptomeningeal enhancement on MRI | MM infiltration of CNS                                                               |
| Respiratory distress                      | Restrictive or dilated cardiomyopathy      | Cardiac AL amyloid                                                                   |
| Pleural effusions                         | MMC infiltration, plasmacytoma             |                                                                                      |
| Pulmonary edema                           | Hyperviscosity                             |                                                                                      |
| Pulmonary infiltrates                     | Pulmonary AL amyloidosis; plasmacytoma     |                                                                                      |
| Spontaneous bleeding, petechiae           | Elevated M spike, typically IgM; elevated serum viscosity | Hypercalcemia                                                                        |
| Thrombocytopenia                          | Myelophthis                               |                                                                                      |
| Purpura                                   | Cryoglobulin type I                        | Cryoglobulinemia type I                                                             |
| Abnormal sFLC, typically with monoclonal $\lambda$ light chain | AL amyloid                                  |                                                                                      |
| Acrocyanosis                              | Cryoglobulin type I                        | Cryoglobulinemia type I                                                             |

AL indicates amyloid light chain; BM, bone marrow; CNS, central nervous system; CSF, cerebrospinal fluid; EPO, erythropoietin; IgM, immunoglobulin M; M, monoclonal; MM, multiple myeloma; MMCs, multiple myeloma cells; MRI, magnetic resonance imaging; OB, osteoblast; OC, osteoclast; sFLC, serum free light chain. This table illustrates the most common presenting symptoms/signs reported by patients with newly diagnosed multiple myeloma with their correlated diagnostic findings and underlying pathogenic mechanisms. Reprinted with modifications from: Bianchi G, Ghobrial I. Does my patient with a serum monoclonal spike have multiple myeloma? Hematol Oncol Clin North Am. 2012;26:383-393 with permission from Elsevier; permission conveyed through Copyright Clearance Center Inc.
Clinical Presentation of MM and Related Dyscrasias

MM patients typically present with complaints of fatigue and unremitting bone pain. Other presenting symptoms and signs include recurrent infections, altered mental status, radiculopathy, purpura, and petechiae. All of these clinical features are the result of 1 or more of 3 pathogenic mechanisms: BM failure secondary to MMC infiltration, deposition/precipitation of monoclonal Ig or sFLC, and alteration in BM cytokines (Table 1). A diagnosis of MM requires the presence of end-organ failure exemplified by the CRAB acronym: hypercalcemia (C), renal failure (R), anemia (A), and/or bone disease (B) in the form of osteolytic lesions, pathologic fractures, or diffuse osteopenia (Table 2). Other MM-defining conditions are peripheral neuropathy, amyloid light chain (AL) amyloidosis, hyperviscosity syndrome, and recurrent infections. The clinical presentation of AL amyloidosis varies depending on organ involvement and can include heart failure secondary to restrictive or dilated cardiomyopathy, hepatic failure, gastrointestinal bleeding and/or diarrhea, nephrotic syndrome, and peripheral neuropathy. Hyperviscosity syndrome typically occurs in patients with IgM subtype MM, followed less often by the IgA and IgG3 subtypes, usually with paraproteinemia levels exceeding 5 g/dL. It manifests with cerebrovascular events, ocular signs, respiratory distress, and a tendency to bleed, and it is a true oncologic emergency requiring emergent plasmapheresis and cytoreductive therapy.

Work-Up and Diagnostic Criteria for MM and Related Dyscrasias

Multiple Myeloma
The diagnostic triad of MM is an M spike on serum and/or urine protein electrophoresis (SPEP and/or UPEP, respectively) or abnormal sFLC, the presence of a malignant PC population in the BM, and evidence of related organ or tissue impairment (ROTI) (CRAB criteria, hyperviscosity syndrome, AL amyloidosis, or recurrent infections). The diagnostic and staging studies in patients with suspected/confirmed MM are outlined in Table 3. Less than 1% of patients are diagnosed with true, nonsecretory MM; thus, an M spike on SPEP and/or UPEP and immunofixation...
and/or the presence of an abnormal sFLC ratio is the laboratory hallmark of MM. A bone survey inclusive of long bones and skull is specific, but not very sensitive, for MM-related bone disease, whereas positron emission tomography-computed tomography (PET-CT) and magnetic resonance imaging (MRI) are highly sensitive, but lack specificity, for the detection of radiographically occult lesions. Whole-body low-dose computed tomography (WBLDCT) has also been evaluated as an alternative imaging modality to skeletal survey. Compared with the latter, WBLDCT was more sensitive in identifying osteolytic lesions, often resulting in restaging (more frequently upstaging) of patients with MM. Although there is growing interest in using these imaging modalities for the early detection of MM-related bone disease, none of these have yet been embraced as part of the staging system of MM. Beyond early diagnosis, it has also been shown that PET-CT is a sensitive tool for the early assessment of treatment response and/or disease relapse after autologous stem cell transplant (ASCT). Fluorescence in situ hybridization and cytogenetics of BM MMCs should be obtained for risk stratification and treatment planning.

### Smoldering MM and MGUS

The absence of ROTI distinguishes SMM and MGUS from MM. SMM is characterized by a higher disease burden compared with MGUS, reflected in a greater M spike and/or BM infiltration by malignant PCs (Table 2). SMM has a cumulative risk of progression to MM of 70% at 15 years, and no therapy, with the exception of aminobisphosphonates, is recommended at present. In an effort to timely diagnose evolution to active MM, close medical follow-up with routine ambulatory visits and laboratory analysis is recommended for patients with SMM and MGUS. Ongoing trials are evaluating the effect of early treatment in high-risk SMM. While delayed progression to MM is anticipated and has been shown, it is critical to demonstrate that treatment has not selected a more malignant clone and that overall survival (OS) is also extended.

### Solitary Plasmacytoma

Solitary plasmacytoma represents 3% to 5% of cases of PC dyscrasia and is defined as a single area of malignant PC proliferation in a bone (osseous plasmacytoma) or in soft tissue (extraosseous plasmacytoma) in the absence of systemic symptoms and/or BM involvement. If either of these is present, then the plasmacytoma represents an extramedullary site of MM and typically warrants systemic chemotherapy. The majority of solitary plasmacytomas are successfully managed locally by surgical excision or radiation therapy, with a disease control rate of approximately 90%. However, between 30% and 50% of patients who are diagnosed with solitary plasmacytoma will develop MM within 5 years from diagnosis, particularly if they are elderly and have an osseous subtype.

### AL Amyloidosis

Periumbilical fat aspiration is indicated when AL amyloidosis is suspected. Amyloid protein displays the pathognomonic “apple-green” birefringence in samples viewed with polarized light microscopy after Congo red staining.

### PC Leukemia

The presence of circulating PCs in excess of $2 \times 10^9/L$ or 20% of leukocytes is diagnostic of PC leukemia, which is
further classified as primary when it occurs de novo (60% of cases) or secondary if it represents the leukemic transformation of advanced MM.

Staging and Prognostic Factors

Two staging systems exist for MM: the Durie-Salmon system, which was established in the mid-1970s to provide surrogate quantification of tumor burden, and the International Staging System (ISS), which stratifies patients into 3 groups based on levels of β2-microglobulin and serum albumin. With the introduction of novel agents, bortezomib, and immunomodulatory drugs (IMiDs), only the ISS has retained prognostic capability (Table 4).39,40 Adverse prognostic factors related to either patient or tumor characteristics are used to identify high-risk MM patients, who represent 15% to 20% of newly diagnosed individuals (Table 5).41 Host-related factors typically mandate a reduction in treatment intensity to avoid excessive toxicities, whereas tumor-related factors reflect biologic aggressiveness or high burden of disease.42

Among host-related factors, persistently impaired kidney function despite cytoreductive treatment is regarded as a poor prognostic factor for patients with MM.43 A serum creatinine level above 2 mg/dL has been used as a threshold to define kidney impairment.28 However, the serum creatinine level is influenced by age, race, and muscular mass, and it can often overestimate renal function, particularly in frail, elderly individuals. The estimated glomerular filtration rate (eGFR) based on the Modification of Diet in Renal Disease (MDRD) formula is a better surrogate of kidney function which can be further categorized into 5 stages according to the Kidney Disease Improving Global Outcomes classification.44,45 A lactate dehydrogenase (LDH) level above the higher limit of normal reflects high disease burden in MM and is associated with worse OS and progression-free survival (PFS) when combined with other factors.46 ISS and Durie-Salmon stage III disease is associated with a worse outcome.47

Treatment

The clinical application of 3 therapeutic strategies has profoundly altered the natural history of MM: melphalan and corticosteroid in the 1950s and 1960s, ASCT pioneered in the 1980s, and the proteasome inhibitor (PI) bortezomib and the IMiDs thalidomide and lenalidomide in the late 2000s.

**TABLE 4. Staging Systems for Multiple Myeloma**

| STAGE | DURIE-SALMON STAGINGa | ISS | OS ACCORDING TO ISS, mo |
|-------|-----------------------|-----|------------------------|
| I     | All of the following must be present: Hemoglobin >10 g/dL, serum calcium <12 mg/dL, absence of bone disease or solitary plasmacytoma, M protein <5 g/dL if IgG or <3 g/dL if IgA; and/or Bence-Jones proteinuria <4 g/24 h | Serum β2-microglobulin <3.5 mg/dL AND serum albumin ≥3.5 g/dL | 62 |
| II    | Meets criteria for neither stage I nor stage III | Meets criteria for neither stage I nor stage III | 44 |
| III   | One or more of the following must be present: hemoglobin <8.5 g/dL, serum calcium >12 mg/dL, extensive bone lesions, M protein >7 g/dL if IgG and >5 g/dL if IgA; and/or Bence-Jones proteinuria >12 g/24 h | Serum β2-microglobulin ≥5.5 mg/dL | 29 |

IgA indicates immunoglobulin A; IgG, immunoglobulin G; M protein, monoclonal protein; OS, overall survival; ISS, International Staging System; mo, months.

*pThis table compares the Durie-Salmon staging system with the ISS. Each stage is further subclassified as A (serum creatinine <2 mg/dL) or B (serum creatinine ≤2 mg/dL), depending on the serum creatinine level. Adapted from: Durie BG, Salmon SE. A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. Cancer. 1975;36:842-854.

**TABLE 5. Host-Related and Tumor-Related Adverse Prognostic Factors in Multiple Myeloma**

| Host-related factors | Tumor-related factors |
|---------------------|-----------------------|
| Impaired kidney function | Advanced stage (≥75 y) |
| Advanced age (>75 y) | High-risk cytogenetics |
| Poor performance status (ECOG >2) | - Translocations: t(4;14), t(14;16), t(14;20) |
| | - Deletions: del(17), del(17p) |
| | Nonhyperdiploid karyotype |
| | Primary plasma cell leukemia |
| | Adverse gene expression profile |
| | Elevated LDH |

Del indicates deletion; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; t, translocation.
1990s to early 2000s. Together with improvements in ancillary care of MM-related bone disease and immunoparesis, these interventions have resulted in a step-wise prolongation of OS from 1 to 2 years to the current 7 to 8 years and in a better quality of life. Although patients with adverse cytogenetics retain a worse prognosis irrespective of treatment strategies, aggressive upfront treatment with novel agents followed by single or double ASCT, consolidation, and maintenance significantly prolongs PFS and OS. When planning treatment for a patient with newly diagnosed MM, the first discriminating point is whether or not the patient is a candidate for ASCT, a judgment largely predicated on the likelihood of treatment-related morbidity and mortality based on performance status and comorbidities.

**Frontline Therapy for Transplant Candidates**

MM is the most common indication for ASCT in the United States. According to the Center for International Blood and Marrow Transplant Research, MM was the indication for transplant in 44% of all ASCTs performed during 2004 and 2005, with 25% of newly diagnosed MM patients undergoing ASCT in first remission. Unless contraindicated, patients younger than 65 years with limited comorbidities should undergo high-dose therapy followed by single or double ASCT, which will improve PFS and quality of life. Improved ancillary care, in particular prophylaxis and early treatment of post-ASCT infectious complications, has resulted in decreased treatment-related mortality, pushing the boundaries of age eligibility to younger than 75 years for otherwise fit individuals. Given that ASCT in first remission does not clearly prolong OS and that combination regimens with novel agents are progressively achieving more deep and durable responses with favorable side-effect profiles, studies are now reexamining the role and optimal timing of ASCT.

The use of alkylating agents, ie, melphalan, as induction therapy in transplant-eligible patients is discouraged because of the risk of compromising BM reserve, thus resulting in poor mobilization of hematopoietic stem cells. First-line treatment with double, triple, or quadruple combinations of novel agents as induction therapy achieves a response in the vast majority of patients, with rates of VGPR or better ranging between 60% and 75% for 3-drug regimens (Table 6). Clinical trials evaluating novel agents, in particular lenalidomide and bortezomib, as consolidation and maintenance after ASCT showed prolonged OS and PFS and an overall tolerable side-effect profile.

In randomized trials, bortezomib and/or lenalidomide plus dexamethasone have been shown to be effective initial treatments. RVD, bortezomib/thalidomide/dexamethasone (VTD), or cyclophosphamide/bortezomib/dexamethasone (CyBorD) achieved more frequent and deeper clinical responses compared with 2-drug combinations. In particular, bortezomib should be included as induction therapy in patients who have adverse cytogenetics, especially t(4;14), and those who present with renal failure because of its rapid effect in reducing tumor burden and paraproteinemia with no dose adjustment required. In contrast to bortezomib and thalidomide, lenalidomide requires dose adjustment based on the eGFR. In patients who have significant baseline peripheral neuropathy (PN) and low-risk disease, bortezomib might be omitted because of the risk of exacerbating PN, although subcutaneous administration of bortezomib drastically reduces the incidence of this side effect compared with intravenous injection.
Frontline Therapy for Nontransplant Candidates

Although melphalan can be used as frontline therapy in transplant-ineligible patients, novel agents have largely replaced it in the United States because of better side-effect profile and increased effectiveness.84 When feasible considering issues of availability, costs, and anticipated toxicities, novel agents should also be used as frontline therapy in transplant-ineligible patients. First-line options for transplant-ineligible patients with low-risk disease are either bortezomib or lenalidomide plus dexamethasone (Table 6).85 In combination with lenalidomide, low-dose dexamethasone improved both OS and the side-effect profile compared with high-dose dexamethasone, thus establishing low-dose dexamethasone as the preferred regimen.71,86 Triplet therapy, such as RVD or CyBorD, can be used either in full or at a reduced dose, depending on the patient’s performance status and comorbidities, especially in those with high-risk MM.78 As for transplant-eligible patients, maintenance therapy with lenalidomide for standard-risk disease or lenalidomide/bortezomib for high-risk disease is indicated to improve the depth of response and, ultimately, PFS and OS.73

US Food and Drug Administration-Approved Molecularly Targeted Therapies in MM

Over the past 15 years, 5 novel agents have been approved by the US Food and Drug Administration (FDA) for the treatment of MM, and another 7 agents are currently being evaluated in phase 3 clinical trials (Table 7).87 Major advantages of these novel compounds are their retained anti-MM efficacy in the context of the BM niche and their capacity to modulate the function of accessory cells important for MM pathogenesis, such as osteoclasts (OCs), osteoblasts (OBs), and immune cells (Fig. 4).88

**Immunomodulatory drugs**

Before it was rediscovered as an effective anti-MM agent, thalidomide was best known for its tragic teratogenic effects,
which were discovered after it had been marketed as an efficacious antiemetic in hyperemesis gravidarum in the late 1950s.\(^8^9\) Predicated on its antiangiogenic properties, a compassionate use trial of thalidomide in MM patients demonstrated its effectiveness in heavily pretreated, relapsed/refractory patients.\(^9^0\) Although the exact mechanisms of effectiveness of thalidomide and its more potent derivatives, lenalidomide and pomalidomide, were unclear, a major role for immunomodulation was postulated, hence the name of IMiDs.\(^9^1\) In 2010, Ito et al identified the molecular target of thalidomide-induced phocomelia: a component of an E3 ubiquitin-ligase complex named cereblon (CRBN).\(^9^2\) It has been recently discovered that binding of lenalidomide to CRBN and DNA binding protein 1 (DDB1), a different component of the E3 complex, is required for its anti-MM activity. This interaction causes activation of the ubiquitin ligase, resulting in proteasome-mediated degradation of the transcription factors Ikaros (IKZF1) and Aiolos (IKZF3).\(^9^3^,9^4\) Preclinical studies showed that IMiDs induced cell cycle arrest and caspase 8-mediated apoptosis, disrupted the interaction between MMCs and BM stromal cells (BMSCs), inhibited the secretion of tumorigenic cytokines, and elicited antitumor immunosurveillance through the activation of CD8-positive T lymphocytes and natural killer T cells and through the down-regulation of regulatory T cells.\(^9^1\) IMiDs proved highly effective against MM

| TABLE 7. Molecularly Targeted Therapies in Phase 3 Clinical Trials |
|-------------------------|---------------------------|------------------------|------------------------|
| DRUG CLASS | DRUG | TRIAL NAME | STUDY DESIGN | PRIMARY ENDPOINT | EXPECTED COMPLETION DATE |
| **PIs** | Ixazomib (MLN9708) | TOURMALINE-MM1 | Ixazomib/Len/Dex vs placebo/Len/Dex in R/R MM patients | PFS | June 2014 |
| | | C16014 | Ixazomib/Len/Dex vs placebo/Len/Dex in transplant- ineligible, newly diagnosed MM patients | PFS | June 2018 |
| | Oprozomib (ONX-0912) | OPZ007 | Oprozomib/Pom/Dex vs placebo/Pom/Dex in R/R MM patients | PFS | June 2016 |
| | Carfilzomib (PX-171) | ENDEAVOR | Carfilzomib/Dex vs Bor/Dex in relapsed MM patients | PFS | Jan 2016 |
| | | CLARION | Carfilzomib/Mel/Pred versus Bor/Mel/Pred in transplant- ineligible, newly diagnosed MM patients | PFS | April 2016 |
| | | ASPIRE | Carfilzomib/Len/Dex vs Len/Dex in R/R MM patients | PFS | Dec 2014 |
| | | FOCUS | Carfilzomib vs best supportive care in patients with R/R MM who have exhausted all therapeutic options | PFS | June 2014 |
| IMiDs | Pomalidomide (Pom) | NIMBUS | Pom/loDex vs high-dose Dex in patients with R/R MM | PFS | March 2013 |
| | | OPTIMISM | Pom/Bor/Dex vs Bor/Dex in patients with R/R MM | PFS | Jan 2015 |
| HDAC inhibitor | Panobinostat | PANORAMA-1 | Panobinostat/Bor/Dex vs placebo/Bor/Dex in patients with relapsed MM | PFS | Feb 2015 |
| Signaling inhibitors | Masitinib | AB06002 | Masitinib/Bor/Dex vs placebo/Bor/Dex as second-line therapy in patients with relapsing MM | PFS | April 2013 |
| | Aplidin | ADMYRE | Aplidin/Dex vs DEX alone in patients with R/R MM | PFS | June 2014 |
| MoAbs | Elotuzumab (Elo) | ELOQUENT-2 | Elo/Len/Dex vs placebo/Len/Dex in patients with R/R MM | PFS | Aug 2017 |
| | Daratumumab (DARA) | CR1036G3 | DARA/Len/Dex vs placebo/Len/Dex in patients with R/R MM | PFS | May 2017 |

Bor indicates bortezomib; Dex, dexamethasone; HDAC, histone deacetylase; IMiDs, immunomodulatory drugs; Len, lenalidomide; lo, low-dose; Mel, melphalan; MM, multiple myeloma; MoAbs, monoclonal antibodies; OS, overall survival; PFS, progression-free survival; PIs, proteasome inhibitors; Pred, prednisone; R/R, relapsed, refractory. Modified with permission from Orlowski RZ. Novel agents for multiple myeloma to overcome resistance in phase III clinical trials. Semin Oncol. 2013;40:634-651.\(^8^7\)
FIGURE 4. Activity of Novel Agents in the Context of the Bone Marrow Microenvironment. This cartoon represents the interaction of a multiple myeloma cell (MMC) (in light blue) with the bone marrow microenvironment and indicates the site of activity of molecularly targeted drugs. Arrows represent induction or stimulation, and stopped lines represent inhibition. Drugs in green boxes exert a stimulatory function, and drugs in red boxes have an inhibitory function. IMiDs indicates immunomodulatory drugs; NK-T cells, natural killer T cells; Treg, T-regulatory cells; WNT, wingless-type; CTLA4, cytotoxic T-lymphocyte-associated protein 4; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; TH17, T-helper 17 cell; IKZF1, Ikaros; IKZF3, Ikaros family zinc finger 3 (Aiolos); Ub, ubiquitin; BHQ-880, blocking antibody targeting DKK-1; IRE-1α, inositol-requiring enzyme 1α; STF-083010 and MKC-3946, inhibitors of IRE1α endoribonuclease activity; CRBN, cereblon; DDB1, DNA binding protein 1; BB10901, monoclonal antibody conjugated with the potent chemotherapeutic maytansine analog DM1; ER, endoplasmic reticulum; NPV-AUY922, synthetic resorcylic isoxazole amide inhibitor of heat-shock protein 90; MKW-2478, nonansamycin inhibitor of heat-shock protein 90; Pls, proteasome inhibitors; CD56, cluster of differentiation 56 (neural cell adhesion molecule); MIP-1α, macrophage inflammatory protein 1α; IL-6, interleukin 6; HDACs, histone deacetylases; HDACIs, histone deacetylase inhibitors; HSP90, heat-shock protein 90; DUB, deubiquitinating enzyme; B-AP15, specific inhibitor of deubiquitinating enzymes Uch37 and Usp14; P5091, inhibitor of the deubiquitylating enzyme Usp7; NF-κB, nuclear factor κB; PKC, protein kinase C; HIF-1α, heat-inducible factor 1α; MEK/ERK, mitogen-activated protein kinase (MEK)/extracellular regulated MAP kinase (ERK) kinase; BT062, monoclonal antibody conjugated with the potent chemotherapeutic maytansine analog DM4; RANK, receptor activator of nuclear factor κB; JAK/STAT3, Janus kinase/signal transducer and activator of transcription protein 3; AKT, v-akt murine thymoma viral oncogene homolog; JNK, c-JUN N terminal kinase; Ras/Raf, rat sarcoma viral oncogene/Raf proto-oncogene (serine/threonine kinase); RHO, rhodopsin; CD138, cluster of differentiation 138 (syndecan-1); PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; VEGF, vascular endothelial growth factor; TNFα, tumor necrosis factor α; VLA4, very late antigen 4; LFA-1, lymphocyte function-associated antigen 1; MUC-1, mucin 1; CS1, a surface molecule highly expressed by multiple myeloma cells; BMSC, bone marrow stromal cell.
and are typically used as first-line therapy in combination with bortezomib/dexamethasone. In MM, thalidomide is FDA approved as a first-line agent, and lenalidomide is approved as a second-line agent in combination with dexamethasone. Pomalidomide was granted accelerated approval as third-line therapy after bortezomib and lenalidomide based on the promising interim results from phase 3 trials in lenalidomide-refractory and/or bortezomib-refractory patients and pending results from a phase 3, multi-center, randomized, clinical trial in patients with refractory, relapsed MM comparing bortezomib/dexamethasone with pomalidomide (OPTIMISM or CC-4047-MM-007). Thalidomide, Revlimid, and Pomalyst are manufactured by Celgene Corporation (Summit, NJ). Category X signifies that studies in animals or humans have demonstrated fetal abnormalities, and/or there is positive evidence of human fetal risk based on adverse反应 data from investigational or marketing experience, and that the risks involved in use of the drug in pregnant women clearly outweigh potential benefits. The increased risk of VTE was observed in combination regimens, particularly those that included high-dose dexamethasone. The increased risk of second primary malignancy was observed particularly in combination with oral melphalan.

| VARIABLE | THALIDOMIDE (THALOMID) | LENALIDOMIDE (REVLIMID) | POMALIDOMIDE (POMALYST) |
|----------|------------------------|------------------------|------------------------|
| Route of administration | Oral | Oral | Oral |
| Renal dose adjustment | No | Yes | Unknown |
| FDA pregnancy category | X | X | X |
| Increased risk of VTE | Yes | Yes | Yes |
| Peripheral neuropathy | Yes | No | No |
| Other significant side effects | Somnolence, rash, constipation | Myelosuppression, fatigue, increased risk of second primary malignancies | Myelosuppression, fatigue, nausea, diarrhea |
| FDA-approved indication in MM | First line in combination with dexamethasone (2006) | Second line in combination with dexamethasone (2006) | Third line after bortezomib and an IMiD (2013) |

Preclinical studies proved that bortezomib, a boronate and reversible inhibitor of chymotrypsin-like activity, was effective against MM, prompting its rapid clinical development. Bortezomib received accelerated FDA approval to treat relapsed, refractory disease in 2003, as second-line therapy in 2005, and as a first-line treatment in 2008. It is now the backbone of the majority of upfront regimens in MM. Clinical trials showed that PN is a frequent and severe adverse effect of bortezomib. In the Assessment of Proteasome Inhibition for Extending Remissions (APEX) trial, PN was reported in 39% of patients, with 9% experiencing grade 3 or greater PN requiring dose reduction or schedule modification. In two-thirds of patients, neuropathy resolved or improved significantly 3 to 4 months after discontinuation of therapy. Pre-existing PN was the only identified risk factor, while the molecular signature profile appeared to suggest a different pattern of gene expression in patients who developed bortezomib-related neuropathy versus controls. Importantly, weekly rather than twice weekly treatment and subcutaneous administration of bortezomib have markedly decreased the incidence of PN without modifying the effectiveness of the treatment. Nevertheless, de novo or
acquired resistance to bortezomib remains a major problem, thus prompting the development of second-generation PIs characterized by higher potency, improved pharmacokinetics, or broader activity on the 3 catalytic subunits (Table 9). Carfilzomib is an epoxy ketone PI that irreversibly inhibits the chymotrypsin-like activity of the proteasome.106 An open-label, single-arm, phase 2 study in relapsed/refractory MM showed an overall response rate (ORR) of 23.7% and a median OS of 15.6 months in patients who received carfilzomib, prompting its FDA approval as third-line therapy after bortezomib and at least 1 IMiD.107 Similar to bortezomib, carfilzomib was shown to at least partially overcome the negative prognosis of adverse cytogenetics.108 PN was observed in only 12.4% of patients and was mostly grade 1 and 2, thus making carfilzomib a valid alternative for patients who were unable to tolerate bortezomib; however, several patients experienced carfilzomib-related congestive heart failure, cardiac arrest, and myocardial infarction.107

Several molecular mechanisms have been shown to mediate cytotoxicity of bortezomib against MMCs, including caspase 8-mediated and caspase 9-mediated apoptosis; induction of terminal unfolded protein response (UPR), heat–shock response (HSR), and proteotoxicity; inhibition of the canonical nuclear factor κB (NF-κB) pathway; and cell cycle arrest. Like lenalidomide, bortezomib was shown to disrupt MMC-BMSC interaction, thereby interrupting prosurvival and drug resistance, and to positively impact bone metabolism by inducing apoptosis of OCs and enhancing osteoblastogenesis.109-111

### Maintenance Therapy
The limited side effects and sustained activity of novel agents prompted their use as consolidation and maintenance therapy with the goal of prolonging PFS and possibly OS. Both IMiDs and bortezomib, alone or in combination, have been evaluated as maintenance therapy in clinical trials. In transplant–ineligible patients, the use of lenalidomide as maintenance after melphalan/prednisone/lenalidomide (MPR) induction significantly prolonged PFS from 14 to 31 months, but it did not affect OS.73 However, quality of life was improved for the patients who received maintenance.73,84 Bortezomib/thalidomide (VT) maintenance after bortezomib/melphalan/prednisone/thalidomide (VMPT) induction improved ORR and PFS, but OS was unchanged because of a higher incidence of severe adverse events, particularly neutropenia and cardiac events.112

In transplant–eligible patients, maintenance with lenalidomide improved quality of life, PFS, and OS.113 Overall, the benefits of such prolonged treatment appear to outweigh the small, but statistically significant, increased incidence of secondary malignancies observed in patients treated with lenalidomide.114 While thalidomide was similarly beneficial when used as maintenance post-ASCT, post-hoc analysis of multiple trials based on cytogenetics revealed a decreased OS for patients harboring high-risk cytogenetics, particularly del(17), who received prolonged treatment with thalidomide.115-117 Bortezomib alone or in combination with lenalidomide is a well-accepted maintenance regimen post-ASCT. This combination maintenance is promising even in high-risk MM.118 A phase 3 study evaluating bortezomib-based induction and maintenance post-ASCT clearly demonstrated that prolonged treatment with bortezomib is feasible, tolerated, and results in improved PFS and OS; however, the independent effect of maintenance cannot be assessed from that study.67

### Reduced-Intensity Allogeneic Hematopoietic Stem Cell Transplant
Allogeneic hematopoietic stem cell transplant (HSCT) was anticipated to improve the outcome of patients with MM based on the prolonged survival and decreased relapse rate observed in patients after syngeneic transplantation compared with ASCT, consistent with the graft-versus-
myeloma effect. However, the 40% treatment-related mortality rate observed in early trials implementing myeloablative transplant appeared to outweigh the prolonged PFS and OS observed in some patients. Improvement in the prevention and treatment of graft-versus-host disease (GVHD) and infectious complications, as well as the introduction of reduced-intensity conditioning, have improved treatment-related mortality without compromising the graft-versus-myeloma effect. A recent meta-analysis that included over 1900 patients from 6 different trials compared tandem ASCT with ASCT followed by human leukocyte antigen (HLA)-matched, reduced-intensity conditioning (RIC) allogeneic transplant and showed no clear benefit for the latter. However, a potential long-term benefit of allogeneic HSCT might have been underestimated because of the short follow-up of the largest studies included in that analysis. The use of diverse conditioning and GVHD prophylaxis regimens also might have impacted the results. Importantly, induction chemotherapy did not include novel agents, likely impacting the depth of response pretransplant, an important prognostic factor for survival.

Because the value of allogeneic HSCT remains unclear and the treatment-related mortality is substantial, this procedure should only be used in high-risk, fit patients with MM in the context of clinical trials. Improvement in the prevention and treatment of postallo geneic transplant complications, particularly GVHD and infections, as well as the use of novel agents in induction, consolidation, and maintenance therapy, might modify this recommendation.

Investigational Molecularly Targeted Therapies

Myeloma drugs used as first-line treatment can be effective in case of disease recurrence when a considerable amount of time has elapsed since their last use and/or when incorporated into different combination regimens. However, concurrent comorbidities, decreased BM reserve, and higher incidence and severity of adverse events generally limit therapeutic success; and, eventually, resistance develops. A deeper understanding of the role of the BM microenvironment and the pathogenetic role of a functional ubiquitin–proteasome system (UPS), along with the clinical application of genome sequencing, have helped inform the design of novel therapies, including molecularly targeted drugs. The most advanced are summarized in Table 7, and their targets are outlined in Figure 4.

**Drugs affecting protein synthesis, folding, and degradation**

Through a variety of environmental perturbations, eukaryotic cells maintain a tight homeostatic control via a series of stress-response pathways, including the UPR and HSR pathways. These same pathways can activate apoptosis when stress is overwhelming; ie, the activating transcription factor 6 (ATF6) and inositol-requiring enzyme 1z (IRE-1z)/XBP-1 branches of the UPR induce transcription of chaperones and genes involved in red-ox balance, lipid biosynthesis, and ER-associated degradation to cope with the increased load of misfolded proteins. The eukaryotic translation initiation factor 2z (eIF2z) kinase 3 (PERK)/ATF4 pathway initially suppresses protein translation through phosphorylation of eIF2z to decrease the load of misfolded proteins, but it eventually leads to CCAAT–enhancer–binding protein (C/EBP) homologous protein (CHOP)-mediated apoptosis.

The rapid accumulation of proteins targeted for degradation, such as polyubiquitinated proteins, recently has been recognized as a cellular stress for secretory cells such as PCs, and apoptosis secondary to proteotoxicity ensues when the coping systems are overwhelmed. The sustained protein synthesis of MMCs, together with their profound sensitivity to PIIs, suggests that targeting the UPS is a promising novel therapeutic strategy in MM. Predicated on this hypothesis, inhibitors of deubiquitinating enzymes (DUBs) and a combination of PI and histone deacetylase 6 (HDAC6) therapies have been developed. DUBs are a large family of enzymes whose function is the removal of ubiquitin moieties from protein substrates before they can bind to the 20S core of the proteasome for degradation. As such, they play a major role in several key cellular functions, including proliferation, proteolysis, and apoptosis; therefore, they represent a promising target for cancer therapy. Two DUB inhibitors have been successfully evaluated in preclinical MM studies and are now moving to clinical development. HDAC6 is a class II, microtubule-associated HDAC that recently was proved to shuttle misfolded protein to the aggresomes, which are subcellular organelles whose function is the collection, confinement, and eventual degradation of polyubiquitinated proteins.

Treatment with bortezomib induces compensatory aggresome formation in vitro, and blockade of both proteasome degradation and aggresome formation with PI and HDAC6 inhibitor was synergistic in inducing MM cytotoxicity. The HDAC6–selective inhibitor ACY-1215 (ricolinostat) showed a good therapeutic index and promising activity in phase 1/2 trials in combination with bortezomib/dexamethasone or lenalidomide/dexamethasone.

STF-083010 and MKC-3946, 2 inhibitors of the endonuclease activity of IRE-1z, have been developed with the goal of targeting XBP-1 and its substrates regulating both PC differentiation and the UPR. Forced expression of spliced XBP-1 in precursor B cells was sufficient to cause MM–like disease in a murine model, and the serum XBP-1 level is an adverse prognostic factor in patients with MM. Both inhibitors were active in vitro and in animal models and thus represent promising drugs for clinical development.

Inhibitors of the molecular chaperone heat-shock protein 90 (HSP90) were developed in an
attempt to broadly target its client proteins, including several oncogenes. However, the clinical development of both inhibitors has been challenging because of severe toxicities, particularly hepatotoxicity and lack of activity as single agents. NVP-AUY922 (VER52296) and KW-2478, 2 resorcinol-derived HSP90 inhibitors, are currently in phase 1/2 clinical trials in combination with bortezomib. Inhibitors of prosurvival signaling pathways

Signaling pathways related to proliferation, survival, and drug resistance are often hyperactivated in cancers, including MM, and have been the focus of molecular therapeutic development. Among these, AKT and JUN (jun proto-oncogene) have been effectively targeted in MM. AKT is constitutively phosphorylated in MMCs, thereby activating downstream pathways, including mechanistic target of rapamycin (mTOR) and NF-κB, mediating increased proliferation and apoptosis resistance. Certain stimuli, such as interaction with BMSCs and exposure to bortezomib, further induce AKT activation. Perifosine, a small-molecule inhibitor of AKT, is cytotoxic against MM alone and synergizes with bortezomib and DNA-damaging agents in vitro. Its molecular mechanisms of effectiveness include induction of c-JUN N terminal kinase (JNK) and down-regulation of AKT activation. Certain stimuli, such as interaction with BMSCs and exposure to bortezomib, further induce AKT activation. Perifosine, a small-molecule inhibitor of AKT, is cytotoxic against MM alone and synergizes with bortezomib and DNA-damaging agents in vitro. Its molecular mechanisms of effectiveness include induction of c-JUN N terminal kinase (JNK) and down-regulation of AKT activation. A phase 2 study of perifosine with bortezomib with or without dexamethasone produced clinical responses in 32% of bortezomib-refractory patients and 65% of bortezomib-relapsed patients; although this agent is not undergoing further development, the study did validate Akt as a novel therapeutic target in MM. Activation of p38 (mitogen-activated protein kinase) and JNK signaling mediates plitidepsin (aplidin) activity against MM. The limited activity of this marine-derived molecule observed in a phase 2 trial (ORR, 13%) was significantly improved by the addition of dexamethasone (ORR, 22%), and a phase 3 study of plitidepsin/dexamethasone is ongoing.

Masitinib (AB1010), a broad-spectrum tyrosine kinase inhibitor, is also being evaluated in a phase 3 clinical trial in combination with bortezomib/dexamethasone. Its effectiveness is predicated on the role of the tyrosine kinases c-Kit, platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor 3 (FGFR3), and Lyn in MM proliferation and survival. The class I HDAC inhibitor panobinostat (LBH-589) and the class I and IIb HDAC inhibitor vorinostat (SAHA) are also in clinical development in MM. HDACs are frequently overexpressed in cancer and have a crucial role in epigenetic control of gene expression and in modulating cellular processes, such as cell cycle and protein degradation.

Vorinostat produced a modest but statistically significant benefit in PFS when combined with bortezomib and/or lenalidomide; however, adverse events were severe, including thrombocytopenia, fatigue, and diarrhea. Similar side effects were noted in patients who received panobinostat in combination with bortezomib (phase 1b) or bortezomib/dexamethasone (phase 2). The ORR was 73.3% in the former study and 34.5% in the latter, inclusive of responses in bortezomib-refractory patients. A recent phase 3 trial of panobinostat with bortezomib showed that the combination achieved a 4-month PFS advantage, but one-third of patients discontinued therapy because of adverse events.

Basic research investigating the biology of MM has identified additional putative molecular targets for MM therapy. Among these are Bruton tyrosine kinase (BTK) and bromodomain 4, which mediate osteoclastogenesis and chromatin modification, respectively. Inhibitors of both molecules are currently under evaluation in clinical trials in MM.

Drugs specifically targeting the BM microenvironment

Among the molecularly targeted therapies in clinical development, AMD3100 (plerixafor) and TH-302 were designed to target MMCs in the context of the BM microenvironment. The former is a selective stromal cell-derived factor 1α (SDF-1α) antagonist that blocks the maladaptive homing and re trafficking of MMCs to the BM niche and synergizes with both bortezomib and conventional chemotherapeutic agents in mouse models. The latter is a prodrug that is activated only in hypoxic environments such as the BM, and it inhibits MMC proliferation and neoangiogenesis in animal models. Both drugs are currently in phase 1/2 clinical trials in combination with bortezomib (plerixafor) or bortezomib/dexamethasone (TH-302).

BHQ-880 is a blocking antibody that targets Dickkopf-1 (DKK-1), a molecule that is highly expressed in the BM microenvironment of MM patients and is involved in the inhibition of osteoblastogenesis and osteoblast (OB) activity. By restoring OB function, BHQ-880 was shown to cause MM growth inhibition in preclinical models, and it is currently being evaluated in phase 1/2 clinical trials both alone and in combination with the bisphosphonate zoledronic acid.

Monoclonal antibodies

Among targeted therapies in phase 3 trials are 2 monoclonal antibodies (MoAbs): elotuzumab (ELO) and daratumumab (DARA). The former is a humanized IgG1 antibody against CS1, a surface molecule highly expressed by MMCs whose function is still elusive. ELO showed no anti-MM activity as single agent but remarkably achieved an ORR greater than 80% in a phase 1/2 trial in combination with low-dose dexamethasone, prompting a phase 3 study of this combination. The molecular target of DARA is CD38, a transmembrane glycoprotein frequently
expressed by MMCs and other B-cell lineage cancers. DARA mediates its anti-MM activity via antibody-dependent and complement-dependent cytotoxicity and direct induction of growth arrest.\(^{159}\) In contrast to ELO, DARA has single-agent activity and is currently being evaluated alone and in combination with IMiDs and PIs in phase 3 trials.\(^{160}\)

BT062 and BB10901 are 2 MoAbs conjugated with a potent chemotherapeutic agent, DM4 and DM1, respectively. The former targets CD138, and the latter targets CD56, in both cases selectively delivering drugs to MMCs. Both agents are in phase 1 clinical evaluation as single agents or in combination with low-dose dexamethasone.

**Immune therapies**

Immune tolerance and anergy are thought to play a major role in MM progression and recurrence, as evidenced by the benefit of graft versus myeloma noted in allogeneic transplant. Several strategies have been attempted to increase autologous immunosurveillance, particularly post-ASCT in the setting of minimal disease burden. These include vaccination against MM-specific peptides and the use of dendritic cell–MMC fusion vaccination alone or in combination with IMiDs.\(^{161}\)

Cytoxic T-cell activation typically requires the simultaneous presence of 2 signals: the first through engagement of the T-cell receptor (TCR) with an appropriately presented antigen, and the second transmitted by a TCR coreceptor with stimulatory function.\(^{162}\) Conversely, TCR coreceptors with inhibitory function, such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death 1 (PD-1), are crucial to down-regulate and terminate the activity of cytotoxic T cells.

A feature shared by several malignancies, including MM, is the overexpression of programmed death ligand 1 (PD-L1), the ligand of PD-1, which results in cancer-induced immunologic tolerance.\(^{163}\) As in other malignancies, BM-resident T cells derived from MM patients were found to overexpress PD-1. Based on these findings and the successful clinical trials with antibodies against PD-1 and PD-L1 in solid cancers, these antibodies are entering clinical trials in MM, either alone or in combination with vaccination strategies post-ASCT.\(^{164-166}\)

**Ancillary Therapy**

Myeloma-related bone disease is the major determinant of poor quality of life and decreased performance status in patients with MM. The majority (80%-90%) of patients with MM will develop MM-related bone disease over the course of their illness, ranging from osteopenia to pathologic fractures. The monthly, intravenous administration of the aminobisphosphonate pamidronate was shown to decrease skeletal-related events (pathologic fractures, cord compression, need for orthopedic surgery or radiotherapy) in a large, double-blind study that enrolled patients with Durie-Salmon stage III MM who presented with at least 1 bone lesion.\(^{167}\) Along with diminished complications, treatment with pamidronate improved symptoms related to bone disease, performance status, and overall quality of life. Pamidronate largely has been replaced by zoledronic acid, a related bisphosphonate with higher potency that requires shorter infusion time (15 minutes vs 4 hours) and has an incidence of acute nephrotoxicity comparable to that of clodronic acid, a first-generation, orally bioavailable bisphosphonate (5.2% for zoledronic acid vs 5.7% for clodronic acid, at 2 years), allowing its use in patients with mild to moderate renal failure.\(^{168}\) Direct antitumoral activity of nitrogen-containing bisphosphonates (pamidronate and zoledronic acid) was reported in a preclinical model of MM and in patients with breast cancer, suggesting that targeting the OB/OC imbalance results in anticaner activity.\(^{169,170}\)

Predicated on these results, a phase 3, randomized, prospective clinical trial was launched comparing zoledronic acid with an orally available bisphosphonate, clodronate, in MM. That trial revealed improved OS in the patients who received zoledronic acid, providing the first clinical evidence of its anti-MM activity.\(^{171}\)

Currently, bisphosphonates are indicated for all MM patients receiving therapy, especially if presenting with bone lesions, and should be considered in patients with SMM, particularly in the context of clinical trials. The duration of bisphosphonate therapy is not well defined and is largely a matter of balancing its efficacy versus the risk of significant side effects, including osteonecrosis of the jaw, which is reported in approximately 4% to 11% of MM patients who receive long-term treatment with either zoledronic acid or pamidronate.\(^{172,173}\) It is advised to continue aminobisphosphonate therapy in patients who have active disease and to consider discontinuation for patients in complete remission or for those who attain a VGPR.\(^{174}\) Meticulous dental care with at least annual examination and close monitoring of renal function are recommended for patients receiving high-dose bisphosphonates because of the risk of bisphosphonate-related osteonecrosis of the jaw and renal failure.\(^{168}\) For patients with moderate or severe kidney impairment, the receptor activator of NF-κB ligand (RANKL) inhibitor denosumab can be used in place of bisphosphonates.\(^{175}\)

Prophylactic anticoagulation is recommended for patients who are receiving combination therapy that includes an IMiD given the excess incidence of venous thromboembolic events noted in clinical trials. Depending on the presence or absence of patient-related risk factors for venous stasis, either aspirin, low-molecular-weight heparin, or warfarin are accepted forms of anticoagulation.\(^{176}\) Two forms of contraception should be used in patients receiving IMiDs given the proven (thalidomide) or anticipated (lenalidomide,
pomalidomide) severe teratogenicity of these compounds. Prophylactic antiviral therapy is recommended for patients who are treated with bortezomib and other PIAs due to the high incidence of varicella zoster virus reactivation noted in the APEX trial. The Changing Landscape of MM Natural History The paradigm of MM as an invariably rapidly fatal cancer has changed because of the introduction of novel agents and ASCT as well as improvements in ancillary therapies. Novel drugs and more effective treatment of MM-related bone disease have resulted in improved quality of life and performance status. Genomic and epigenomic studies are ongoing to help personalize treatment and identify additional novel molecular targets of therapy. Given the pace of approval of therapies in MM over the past 10 years, there is a realistic hope that MM will soon become a chronic disease in the majority of patients, with curative potential for some. The close interplay between bench research and bedside observations remains the key to advance diagnosis, prognosis, and therapy to improve patient outcome.

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