New Strategies in the Treatment of Multiple Myeloma
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Abstract
Multiple myeloma is the second most common hematologic malignancy affecting terminally differentiated plasma cells. Although high-dose chemotherapy and autologous stem cell transplantation have improved survival in younger patients, the natural history of multiple myeloma has been changed with the availability of six new agents approved in the past 10 years (thalidomide, bortezomib, lenalidomide, liposomal doxorubicin, carfilzomib, and pomalidomide). Despite this significant improvement in the overall outcome, multiple myeloma remains incurable in the majority of patients, prompting a continued search for additional therapeutic options. Extensive molecular and genomic characterization of multiple myeloma cells in their bone marrow milieu, which affects myeloma cell growth and survival, has provided a number of novel drugable targets and pathways. Perturbation of protein catabolism at multiple levels has become an important target in multiple myeloma. Similarly, improvements in monoclonal antibody generation and vaccine development, along with identification of a number of cell surface and cellular targets, have led to the development of various strategies, including antibodies and antibody–drug conjugates that are under investigation preclinically and in early clinical studies. We propose that eventually, molecularly informed multiagent combination therapies will be required to eliminate the multiple myeloma cell clone for long-term disease control.

Background
Multiple myeloma is characterized by excess bone marrow plasma cells in association with monoclonal protein in the blood and/or urine, often associated with bone destruction, anemia, hypercalcemia, and renal dysfunction. It affected 21,700 new individuals in the United States in 2012, with a prevalence of 71,213 total patients, and 10,710 patients died from the disease. Fifty years ago, the advent of melphalan and prednisone extended patient median survival to 2 to 3 years, and high-dose therapy followed by stem cell rescue has prolonged median survival to 4 to 5 years. Increasing awareness of the role of the bone marrow in supporting growth, survival, and drug resistance of multiple myeloma cells, along with concomitant development of novel agents to overcome cell adhesion–mediated drug resistance to conventional therapies, has transformed the treatment paradigm in multiple myeloma. Specifically, the proteasome inhibitor, bortezomib, and immunomodulatory drugs, thalidomide and lenalidomide, have formed the framework for multiple new treatment options for newly diagnosed and relapsed/refractory multiple myeloma as well as maintenance therapy. Most importantly, median survival has increased to more than 7 years as a direct result (1). Parallel advances in the genomics of multiple myeloma have defined additional disease heterogeneity and complexity as well as providing the rationale for personalized single-agent and combination therapies.

On the Horizon
Going forward, the major translational research focus in multiple myeloma is in 4 main areas: development of novel agents targeting the multiple myeloma cell in the bone marrow microenvironment, development of immune (vaccine and adoptive immunotherapy) strategies, development of rationally based combination therapies, and use of genomics for improved classification and personalized therapy.

Targeting protein catabolism
Normal cellular homeostasis is maintained by a balanced regulation of protein synthesis and degradation. The ubiquitin proteasome system (UPS) is a nonlysosomal intraacellular protein degradation pathway mediated via proteasome holoenzymes, ubiquitin ligases, and deubiquitylating enzymes (DUB; ref. 2). Deregulation of the UPS pathway is linked to the pathogenesis of various human diseases, including multiple myeloma, and therefore inhibitors of UPS pathways either at the level of proteasomal or ubiquitylating/deubiquitylating enzymes offer great promise as a novel therapeutic strategy (Fig. 1). We and others have characterized targeting of the UPS using our in vitro and in vivo models of the multiple myeloma cell in the bone marrow milieu, specifically elucidating the molecular and
cellular mechanisms whereby proteasome inhibitors target tumor cells, host–tumor interactions, and the bone marrow microenvironment to overcome conventional drug resistance. Our preclinical and clinical studies led to the U.S. Food and Drug Administration (FDA) approval of bortezomib for relapsed/refractory and newly diagnosed multiple myeloma. Although bortezomib represents a major advance, not all patients respond and those that respond, relapse. More recent studies have therefore defined mechanisms of resistance to proteasome inhibitors and strategies to overcome them, including second-generation proteasome inhibitors and scientifically informed combination therapies.

**Novel proteasome inhibitors.** Second-generation proteasome inhibitors differ qualitatively and quantitatively from bortezomib in their pattern of proteasome inhibition and can overcome bortezomib resistance in preclinical models. Carfilzomib, a recently approved agent for relapsed multiple myeloma that is an epoxyketone that irreversibly and covalently binds to the chymotryptic site of the proteasome, resulting in increased extent and duration of inhibition compared with bortezomib (3, 4). In relapsed and bortezomib-refractory multiple myeloma, phase I/II clinical trials have shown 20% single-agent responses lasting 8 months, with prolongation of survival to 15 months and lack of neuropathy (5–7). In bortezomib-naïve patients, response rates are at least doubled, and combination trials of carfilzomib with lenalidomide and dexamethasone show a remarkable extent and frequency of response both in relapsed and in newly diagnosed multiple myeloma. Another second-generation proteasome inhibitor, marizomib, blocked chymotryptic-, trypsin-, and caspase-like proteasome activities and overcame bortezomib resistance in preclinical models. Ongoing clinical studies have defined the dose and schedule and early signs of efficacy (8). MLN9708 is an oral boron-containing proteasome inhibitor that has a shorter proteasome dissociation half-life than bortezomib, with improved pharmacokinetics and antitumor activity both in vitro and in vivo (9, 10). Already, MLN9708 has shown single-agent clinical activity in relapsed refractory multiple myeloma as well as high-response rates when it was combined with lenalidomide and dexamethasone in an all-oral regimen to treat newly diagnosed multiple myeloma.

**Deubiquitylating enzyme inhibitors.** Bortezomib has validated targeting protein homeostasis as an effective therapeutic strategy in multiple myeloma. More recent efforts have focused on discovery and development of small-molecule inhibitors of DUBs, another major component of UPS.
Our studies show increased expression and activity of the DUB USP7 in multiple myeloma cells versus normal plasma cells, and that its inhibition by P5091 triggers ubiquitylation and degradation of HDM2, thereby activating p53 and p21 signaling and triggering apoptosis. Importantly, blocking UPS in this manner upstream of the proteasome can overcome bortezomib resistance.

Inhibitors of aggresome pathway. Recent studies have identified the aggresome pathway as an alternative system for polyubiquitylated protein degradation and shown that histone deacetylase 6 (HDAC6) binds to both polyubiquitylated proteins and dynein motors, thereby acting to shuttle protein complexes to aggresomes (11). We have led both preclinical studies and clinical trials combining broad type 1 and 2 HDAC inhibitors vorinostat or panobinostat to block aggresomal pathway with the proteasome inhibitor bortezomib to overcome bortezomib resistance (12, 13). In an international phase III clinical trial, the combination of vorinostat and bortezomib was superior to bortezomib and placebo in relapsed and refractory multiple myeloma, with overall response rates of 54% versus 41%, respectively \( (P < 0.0001) \). The progression-free survival (PFS) and time to progression were prolonged in the combination arm compared with the bortezomib alone cohort, with PFS HR reduction of 23% \( (P = 0.01) \). However, the actual PFS difference was only 7.63 versus 6.83 months, owing at least in part to the side effect profile of diarrhea, fatigue, and thrombocytopenia attendant to combined therapy. A clinical grade prototype selective HDAC6 inhibitor, ACY 1215, has rapidly been translated from the bench to the bedside and is now under evaluation as a single agent as well as in combination with bortezomib to achieve dual blockade of proteasomal and aggresomal protein degradation, with a more favorable therapeutic index (14).

Immune manipulations

Immune dysfunction with decreased humoral and cellular responses and related risk of infection is a hallmark of multiple myeloma. This suppressed immune function permits continued growth of tumor cells. Dysregulation of various components of T-helper (T\(_{H1}\)) cells has recently been described, including decreased T\(_{H1}\) responses with IFN-γ production, increased suppressor responses by T\(_{H2}\) cells, and dysfunctional T-regulatory cells (15), and increased T\(_{H17}\) cells with associated cytokines [interleukin (IL)-17, IL-21, IL-22, and IL-23], which both promote tumor cell growth and bone disease and suppress immune function (16). Similarly, plasmacytoid dendritic cells are abnormal in multiple myeloma because they do not trigger normal effector cell function as well as promote tumor cell growth and drug resistance (17). Strategies to overcome these mechanisms of immune suppression for clinical application include anti–IL-17 monoclonal antibody (mAb), anti–IL-6 mAb, anti–PD1 mAb, CpG oligonucleotides, and immunomodulatory agents (18).

Immunomodulatory agents. Thalidomide, lenalidomide, and pomalidomide are immunomodulatory agents, which directly target multiple myeloma cells, abrogate binding of multiple myeloma cells in bone marrow, inhibit constitutive and multiple myeloma cell binding–induced transcription and secretion of cytokines, inhibit angiogenesis, and modulate T-cell, natural killer (NK)-cell, NK T-cell, and dendritic cell functions (19–24). Thalidomide and lenalidomide have been incorporated into the treatment paradigm of newly diagnosed and relapsed multiple myeloma as well as maintenance therapy. Pomalidomide, the more potent drug in this class, has shown promising results in phase I and II studies and was recently approved for relapsed multiple myeloma (25–28). Pomalidomide with low-dose dexamethasone has achieved 30% to 40% durable responses even in patients whose multiple myeloma is resistant to both lenalidomide and bortezomib, and this agent is currently under evaluation in combination clinical trials with proteasome inhibitors.

Monoclonal antibodies. mAb-Based therapies function by stimulating antibody–dependent cell-mediated cytoxicity (ADCC) or complement-dependent cytotoxicity (CDC) mediated by NK or T cells, blocking growth or survival signaling molecules by inhibiting ligand or its binding to receptors, stimulating apoptosis signaling cascades, and/or specifically delivering chemotherapeutic agents or toxins to multiple myeloma cells (29). Numerous mAb-based strategies have been preclinically and clinically evaluated in multiple myeloma. One of the most promising mAbs is elotuzumab, which targets CS1, an antigen highly and uniformly expressed at the gene and protein level in multiple myeloma cells of patients (30). Elotuzumab mediates ADCC in preclinical models, and a derived clinical trial of single-agent elotuzumab in relapsed refractory multiple myeloma achieved stable disease. Importantly, our laboratory studies showed that ADCC activity of elotuzumab against multiple myeloma cells was enhanced by lenalidomide, which in turn translated to phase I/II trials of lenalidomide, elotuzumab, and dexamethasone. Remarkably, this combination achieved 82% response in relapsed multiple myeloma, and after a median follow-up of 16.4 months, the median time to progression was not reached (31), providing the framework for an ongoing phase III trial of lenalidomide, elotuzumab, and dexamethasone versus lenalidomide and dexamethasone in relapsed multiple myeloma.

A number of other mAbs targeting multiple myeloma cells or its bone marrow environment have progressed to phase I/II studies. These include daratumumab, a humanized mAb targeting CD38 that induces ADCC and CDC, modulates enzymatic activation, and induces apoptosis by crosslinking CD38 (32). A preliminary phase I/II investigation of this mAb in heavily pretreated multiple myeloma showed clinical benefit in 18 of 29 patients, including 5 partial responses. BT062, an anti–CD138 mAb conjugated to mytansinoid DM4, selectively triggered apoptosis in multiple myeloma cells in preclinical models (33). In phase I/II trials, preliminary evidence of clinical benefit has been observed. mAbs targeting cytokines, including siltuximab targeting IL-6 (34), BHZ880 targeting DKK1 (35), tabalumab targeting B-cell...
activating factor (BAFF; ref. 36), and denosumab, a fully human monoclonal antibody that inhibits receptor activator of nuclear factor-κ B ligand (RANKL; ref. 37), also have promise as treatments of both multiple myeloma and related bone disease. Combination of tabalumab and bortezomib has shown interesting activity in a phase I/II study. The stage of clinical development of additional mAbs in multiple myeloma is shown in Table 1.

Vaccination strategies. On the basis of the success of allogeneic transplantation in achieving long-term disease-free survival as well as graft-versus-multiple myeloma responses following donor lymphocyte infusions, other immunotherapeutic approaches are being evaluated to treat multiple myeloma. An emerging focus has been to augment autologous anti–multiple myeloma immune responses using both dendritic cell–based (38) as well as protein and peptide-based vaccination approaches. A dendritic cell/multiple myeloma cell fusion vaccination has shown induction of humoral and cellular immune response in patients after transplant (39), and its clinical benefit will be evaluated in a clinical trial. Anti-PD-1 mAb has also been investigated in clinical trials as a means to restore immune function and prolong clinical response after transplant. To overcome the complexity of cell-based vaccination and to fulfill the need to produce individual patient-specific vaccines, tumor-associated antigen-specific protein or peptide-based vaccinations are also being investigated in multiple myeloma. One of the best-studied target antigens is idiotype protein, the immunoglobulin produced by multiple myeloma cells. Although clinically meaningful immunologic responses and antitumor effects after idiotype protein vaccination have been reported in lymphoma, direct evidence of clinical benefit in multiple myeloma is lacking (18). Other multiple myeloma-associated antigen targets for vaccines include Sp17, MAGE-1, NY-ESO, Xbp-1, CD138, DKK-1, and CS1, which are commonly tested first in the context of HLA-A2+ patients (40–46). Moreover, peptide cocktails from several antigens have been pooled for vaccination to expand the breadth and potency of response (47). The task ahead is to evaluate these vaccine approaches in appropriate clinical settings early in the disease course or in the setting of minimal residual disease, and to couple them with strategies to overcome mechanisms of immunoparesis (19) as a means to induce more robust clinically significant immune responses.

Promising novel targets

BET bromodomains. Gene regulation is fundamentally governed by reversible, noncovalent assembly of macromolecules. The ε-N-acetylation of lysine residues on

<table>
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<tr>
<th>Target</th>
<th>Agent</th>
<th>Clinical study phase</th>
<th>Single agent (S)/combination (C)</th>
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<tr>
<td>Activin A</td>
<td>Sotatercept</td>
<td>I/II</td>
<td>S</td>
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<td>BAFF</td>
<td>Tabalumab (mAb)</td>
<td>I/II</td>
<td>S, C (lenalidomide)</td>
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<td>CD38</td>
<td>Daratumumab</td>
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<td>CD40</td>
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<td>CD56</td>
<td>huN901-D1M1 (mAb)</td>
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<td>CD74</td>
<td>Milatuzumab</td>
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<td>CD138</td>
<td>BT062 (mAb-DM4)</td>
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<td>CS1</td>
<td>Eliotuzumab</td>
<td>II/III</td>
<td>S, C (lenalidomide, bortezomib)</td>
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<td>CXCR3</td>
<td>Plerixafor</td>
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<td>DKK-1</td>
<td>BHQ-880 (mAb)</td>
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<td>FGF, PDGF</td>
<td>Dovitinib</td>
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<td>HM1.24</td>
<td>anti-HM1.24 (mAb)</td>
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<td>S</td>
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<td>IGF-1/R</td>
<td>CP-751,871 (mAb)</td>
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<td>EM164 (mAb)</td>
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<td>IPH101</td>
<td>I/II</td>
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<td>AR20.5 (mAb)</td>
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<td>S</td>
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<td>VEGF/R</td>
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<td>Vandetanib (ZD6474)</td>
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histone tails (Kac) is associated with an open chromatin architecture and transcriptional activation. Context-specific molecular recognition of acetyl-lysine is principally mediated by bromodomains. Therefore, bromodomain-containing proteins are of substantial biologic interest, both as components of transcription factor complexes and determinants of epigenetic memory. The bromodomain and extra-terminal (BET)-family (BRD2, BRD3, BRD4, and BRD7) is defined by a common domain architecture comprising 2 N-terminal bromodomains that share a high level of sequence conservation and a more divergent C-terminal recruitment domain. Recent research has established a compelling rationale for targeting bromodomains in cancer (48), in particular, BRD4 in multiple myeloma (49). BRD4 is a critical mediator of transcriptional elongation, recruiting the transcription elongation factor complex (P-TEFb). Knockdown of BRD4 in proliferating cells leads to G1 arrest and apoptosis, associated with decreased expression of genes important for mitotic progression and survival. The mechanistic link between transcriptional elongation, BRD4, and the c-Myc oncogenic transcription factor provided the rationale for BRD4 inhibition in multiple myeloma (49). JQ1, the first chemically optimized potent and selective inhibitor of BET bromodomains, showed efficacy in preclinical models of multiple myeloma (50). Specifically, JQ1 leads to depletion of the c-Myc oncoprotein and downregulation of the c-Myc transcriptional program, leading to cell-cycle arrest and tumor cell senescence both in vitro and in vivo. Clinical trials of BRD4 inhibitors therefore represent a new potential therapeutic modality for multiple myeloma.

**MMSET.** MMSET is a multiple myeloma oncogene identified at the t(4;14) translocation breakpoint present in approximately 15% of multiple myeloma (51). Microarray analysis showed that all patients harboring the t(4;14) rearrangement overexpressed MMSET (52). MMSET contains several potential functional motifs, including a SET (Suvar 3-9, Enhancer-of-zeste, Trithorax) domain with histone methyltransferase activity. Like other SET-domain-containing proteins, MMSET can methylate histones, thereby leading to changes in gene expression. Methylation of histone 3 lysine tail residue 36 is associated with the activation of gene transcription in multiple myeloma (53, 54). Overexpression of MMSET in multiple myeloma cells has profound effects on gene expression and cell growth, which requires the enzymatic function of the SET domain. Because MMSET plays a critical role in pathogenesis of t(4;14) multiple myeloma, it represents a novel therapeutic target amenable to blockade with small molecules.

**BTK.** Bruton’s tyrosine kinase (Btk), a nonreceptor tyrosine kinase, plays a key role in normal B-cell function through activation of the B-cell antigen receptor signaling pathway. Btk also plays a major role in osteoclastogenesis and osteoclast maturation by modulating the activity of NFATc1, the major transcriptional factor activated following RANKL stimulation. Its potential role in the multiple myeloma cell and its microenvironment has therefore recently been evaluated. Btk knockdown confirmed the role of Btk activation in the bone marrow milieu in promoting multiple myeloma cell growth, survival, and interaction with other bone marrow stromal components, as well as multiple myeloma-induced bone lysis (55). Importantly, an oral and selective Btk inhibitor ibrutinib blocked RANKL/M-CSF-induced phosphorylation of Btk and downstream PLCγ2 in osteoclasts, thereby abrogating TRAP5b and bone resorption activity, as well as decreasing secretion of multiple cytokines and chemokines from osteoclasts and bone marrow stromal cells. It also blocked multiple myeloma cell growth and survival triggered by IL-6 or coculture with bone marrow stromal cells or osteoclasts in vitro. In addition, in vivo activity of ibrutinib against multiple myeloma cells and multiple myeloma cell–induced osteolysis has been shown in the severe combined immunodeficient (SCID)-hu model of human multiple myeloma in mice. These functional sequelae of Btk activation mediating osteolysis and growth of multiple myeloma cells have provided the basis for ongoing phase I/II clinical trials of ibrutinib in multiple myeloma.

**Synergistic combination therapies**

The success rate of phase III randomized clinical trials in oncology has been very low, but in multiple myeloma, we have informed the design of combination clinical trials based upon additive or synergistic cytotoxicity, as well as on overcoming drug resistance, in preclinical models. For example, pegylated doxorubicin with bortezomib, based upon inhibition of DNA-damage repair by bortezomib in preclinical studies, showed efficacy in a phase III trial and is now FDA approved. Enhanced efficacy of immunomodulatory drugs thalidomide and lenalidomide with corticosteroids in preclinical models provided the framework for their clinical evaluation and ultimate FDA approval in combination. Recent studies have validated a number of targets the inhibition of which can sensitize or overcome resistance to bortezomib in vitro, including inhibitors of HDAC (56, 57), aurora kinase A (58), Akt (59), HSP 90 (60, 61), BAFF (36, 62), and cyclin-dependent kinase 5 (63), and combination clinical trials are ongoing. Perhaps, the most active combination to date is that of lenalidomide, bortezomib, and dexamethasone, which preclinically triggers dual apoptotic signaling and clinically can achieve responses in nearly two thirds of patients whose multiple myeloma is resistant to either lenalidomide or bortezomib alone (64). Importantly, this combination as initial therapy in a phase II study has led to a report of 100% overall response, with three quarters very good partial responses and nearly half complete responses, including molecular complete responses (65). Indeed, we are currently evaluating the role of high-dose melphalan and stem cell transplantation in the context of this unprecedented extent and frequency of response. These studies show rapid translation of preclinical leads from the bench to the bedside and clinical trials, which have improved the practice of medicine in multiple myeloma.
Development of personalized medicine in multiple myeloma

Comprehensive oncogenomic analysis has identified numerous complex genetic and epigenetic alterations in multiple myeloma. Some of these recurrent and highly focal amplifications and deletions in the multiple myeloma genome have now been identified at an early stage of plasma cell disorder (66), including monoclonal gammopathy of undetermined significance and smoldering multiple myeloma, with further evolution associated with progression to active multiple myeloma (67). Importantly, an integrated analysis of genomic data has identified candidates resident within the regions of genomic alterations predicted to be involved in multiple myeloma pathogenesis and progression. The biologic behavior and clinical outcome in multiple myeloma are dependent on these molecular determinants, which are also attractive therapeutic targets. Although FISH-identified t(4;14), t(14;16), and del(17p13) have been considered to portend poor prognosis (68), more recent single-nucleotide polymorphism array analysis in 192 uniformly treated patients identified amp(1q23.3), amp(5q31.3), and del(12p13.31) as the most powerful independent adverse prognostic markers (P < 0.0001; ref. 69). The data obtained from extensive analysis of patient samples with annotated clinical outcome have now provided insight into the molecular mechanism of disease behavior, helped develop sensitive prognostic models, identified novel therapeutic targets, provided the framework for the development of molecularly based therapies, and eventually will help develop individualized therapy (70) to improve outcomes with reduced toxicity. Importantly, our study and those of others profiling DNA, mRNA, microRNA, and spliced RNA (67), as well as proteomics and whole-genome sequencing (71), have shown remarkable complexity in multiple myeloma even at diagnosis, with further genomic evolution ultimately leading to relapse of disease. It therefore seems, as in the models of childhood acute lymphoblastic leukemia and other curable cancers or infectious diseases, such as tuberculosis and HIV, that combination therapies will be needed. Specifically, targeted combination therapy regimens directed at those genetic abnormalities present, as well as those known to confer development of resistance, will be needed from the outset to treat newly diagnosed multiple myeloma. For example, with a backbone of combinations containing proteasome inhibitors, immunomodulatory agents, and steroids, additional agents can be added on the basis of patient-specific genomic abnormalities, such as an activated Ras/Raf pathway, p53 abnormality, MMSET, or specific HDAC upregulation. Then, maintenance therapies such as lenalidomide or newer agents under investigation may prolong response. The parallel development of assays for minimal residual disease, including PCR for patient-specific immunoglobulin gene rearrangements or the use of multiparameter flow cytometry, can in turn inform the need for and duration of maintenance treatment strategies. Ultimately, prolonged disease-free survival and cure are on the horizon in multiple myeloma.

Disclosure of Potential Conflicts of Interest

N.C. Munshi has an ownership interest (including patents) in Oncopep and is a consultant/advisory board member of Celgene, Millennium, Onyx, and Merck. K.C. Anderson has an ownership interest (including patents) and is a scientific founder of Acetylon, a scientific founder of Oncopep, and a consultant/advisory board member of Celgene, Millennium, Onyx, and Merck.

The Editor-in-Chief of Clinical Cancer Research (K.C. Anderson) is an author of this article. In keeping with the AACR’s Editorial Policy, the paper was peer reviewed and a member of the AACR’s Publications Committee identified an editor from another AACR journal to oversee the review process.

Authors’ Contributions
Conception and design: N.C. Munshi, K.C. Anderson
Development of methodology: N.C. Munshi, K.C. Anderson
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): K.C. Anderson
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): N.C. Munshi, K.C. Anderson
Writing, review, and/or revision of the manuscript: N.C. Munshi, K.C. Anderson
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): N.C. Munshi, K.C. Anderson

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