Multiple myeloma (MM) is an example of a disease that has seen rapid bench-to-bedside translation of novel agents targeting the tumor in its microenvironment, with clinical trials ultimately leading to FDA approval. Remarkably, 16 new treatments for MM have been approved in the past 12 years, including 7 new FDA-approved treatments in 2015 alone (Table 1). As a direct result, the median survival of patients with MM has already been extended 3- to 4-fold, with significant additional benefit expected from recent therapies. How do these advances impact the current and future practice of medicine in MM?

The availability of novel oral therapies that are effective and well-tolerated has allowed for multiple clinical protocols evaluating novel agents in earlier stages of MM than ever before. Traditionally, within the spectrum of plasma cell disorders extending from monoclonal gammopathy of undetermined significance (MGUS) to smoldering MM (SMM) to active MM, patients with bone marrow plasmacytosis and monoclonal protein are often diagnosed with active MM when they have already developed clinical sequelae. These sequelae include hypercalcemia, renal dysfunction, anemia, and bone disease (CRAB), and recurrent infections, hyperviscosity, and neuropathy. Now, however, we have the ability to diagnose patients before the development of these clinical sequelae, and to evaluate the ability of novel therapies to delay or even prevent the development of these complications.

Based on retrospective studies, the International Myeloma Working Group (IMWG) has determined that patients with more than 60% bone marrow plasmacytosis, more than 100-fold free light chain ratio, or more than one bone lesion on PET/CT or MRI scanning, even in the absence of CRAB features, are at high short-term risk of developing active MM. The IMWG therefore now includes them as patients with active MM in whom therapy is indicated. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for MM has incorporated this new definition as well. This has major potential implications for changing the natural history of MM, because it extends the definition of active MM to a broader patient population.

Moreover, multiple ongoing clinical trials in SMM are evaluating the ability of novel targeted and immune therapies to delay or prevent development of CRAB and other features of MM. For example, immune strategies, including immunomodulatory drugs (IMiDs), monoclonal antibodies (MoAbs), checkpoint inhibitors, histone deacetylase (HDAC) 6 inhibitors, and/or cellular therapies used in this SMM population may have the ability to induce long-lasting autologous memory anti-MM immunity. Given that the immune system is potent, selective, and adaptable, such a memory anti-MM response may be able to overcome the ongoing genetic

### Table 1. Novel FDA-Approved Agents in Myeloma

<table>
<thead>
<tr>
<th>Agents</th>
<th>Class/Mechanism of Action</th>
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<tbody>
<tr>
<td>Bortezomib, carfilzomib, ixazomib</td>
<td>Proteasome inhibitors</td>
</tr>
<tr>
<td>Lenalidomide, pomalidomide</td>
<td>Immunomodulatory drugs</td>
</tr>
<tr>
<td>Panobinostat</td>
<td>Histone deacetylase inhibitor</td>
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<tr>
<td>Elotuzumab, daratumumab</td>
<td>Monoclonal antibodies</td>
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between the ‘ Lines

Anderson

and epigenetic events underlying progression and relapse of disease. Clinical and regulatory strategies have already derived clinical trials evaluating the ability of these and other treatments to delay or prevent development of complications, while not selecting for a more aggressive disease course and shorter overall survival after CRAB features do develop. Preventing active MM with earlier intervention is now a realistic goal.

Myeloma is genetically and epigenetically very heterogeneous—with extensive and ongoing DNA damage and multiple clones at presentation—and probably represents many separate diseases. Prognostication for patients has to date has been based on the International Staging System (ISS), predicting outcome predicated on universally available serum β2 microglobulin and albumen, and fluorescence in situ hybridization (FISH) studies of MM cells. The IMWG has refined the ISS to now include serum lactate dehydrogenase and high-risk chromosomal abnormalities defined by FISH, and this refined ISS is now incorporated into the NCCN Guidelines as well.

As we develop novel effective therapies going forward, it is essential to establish such uniform up-to-date criteria to define relative utility of treatments and outcomes in patient subsets. For example, high-risk MM defined by t(4;14) translocation can now be effectively treated with proteasome inhibitors (PIs), and immune therapies such as MoAbs can elicit responses even in the context of 17p deletion.

Multiple efforts are ongoing to further define disease heterogeneity and ultimately inform precision medicine in MM therapy based on genetic/epigenetic profiling. Given the degree of inherent and ongoing genetic instability, clonal evolution, and DNA damage in MM, combinations of targeted therapies will probably be needed both to target current abnormalities and to prevent the development of changes underlying resistance and leading to relapse. Importantly, in MM as in other diseases, the advent of effective immune therapies now requires new criteria for response, which may ultimately include assessment for restoration of immune repertoire in the host.

Progress in the treatment of MM to date has primarily been due to the development of 2 novel classes of agents, PIs and IMiDs. PIs block the breakdown of misfolded proteins in MM, thereby triggering tumor cell apoptosis, and have multiple other effects on both tumor and accessory cells (eg, inducing apoptosis of osteoclasts). The prototype boronic acid PI bortezomib has been combined with the IMiD lenalidomide and dexamethasone (RVD); this triplet therapy achieves high extent and frequency of response in newly diagnosed MM, including minimal residual disease (MRD) negativity, and is superior to lenalidomide and dexamethasone (RD). Triplet therapy, either with RVD or cyclophosphamide/bortezomib/dexamethasone, is the NCCN recommended option for newly diagnosed MM. The remarkable efficacy of bortezomib has led to the development of the second-generation PI carfilzomib, an epoxy ketone with increased extent and duration of proteasome inhibition without attendant neuropathy.

More recently, an oral boronic acid–based PI, ixazomib, was developed. Ixazomib is taken only once weekly and has a favorable side-effect profile. Carfilzomib and ixazomib are now incorporated into the NCCN Guidelines, both as single agents and in combination with lenalidomide and dexamethasone, based on phase I/II and III trials in relapsed MM. Moreover, carfilzomib and ixazomib are included as options for treatment of newly diagnosed MM due to high overall extent and frequency of response when either one—as was true for bortezomib—is used in a triple combination treatment with lenalidomide and dexamethasone. Excitingly, these triplets, with or without high-dose therapy and autologous stem cell transplantation, are showing high extent and frequency of response, including MRD negativity.
Ongoing studies are comparing multicolor flow cytometry versus gene sequencing to assess MRD in marrow. Each can detect 1 MM cell in 10^6 normal bone marrow cells. PET/CT imaging is similarly being evaluated to detect extramedullary MRD. Many clinical trials already include MRD as an end point. These trials will help clinicians determine the optimal technique to measure MRD and its clinical and regulatory utility. For example, can clinical decisions be informed by MRD status; that is, can maintenance be discontinued in patients with MRD-negative disease? From a regulatory point of view, it is urgent to define MRD and other biomarkers that can be assessed early and predict for long-term benefit, in order to allow for rational design of clinical trials leading to rapid new drug development and registration.

The benefits of novel therapies now allow for high rates of durable responses in patients with relapsed MM as well. Novel agents included in the NCCN Guidelines include the MoAbs elotuzumab and daratumumab. Daratumumab, but not elotuzumab, has clinical activity as a single agent, and both have enhanced activity when coupled with IMiDs. They are the first immune therapies in MM and are active even in the traditionally high-risk 17p deletion subset. As noted previously, combination immune therapies incorporating IMiDs, MoAbs, checkpoint inhibitors, vaccines, HDAC6 inhibitors, and cellular therapies will rapidly build on the MoAb–IMiD foundation and are highly likely to transform the natural history of MM, especially when used in earlier stages of disease.

Finally, what is the future treatment and outcome in MM? I think that there are 3 “Achilles’ heels,” or vulnerabilities, to target in novel approaches to build on current progress.

First, the use of PIs has validated blocking protein degradation as an effective treatment strategy in MM. Already the combination of the HDAC inhibitor panobinostat with bortezomib to block aggresomal and proteasomal protein degradation, respectively, has been FDA-approved and incorporated into the NCCN Guidelines to treat relapsed MM. Ongoing efforts are targeting the ubiquitin proteasome cascade at other sites; that is, targeting de-ubiquitinating agents to overcome PI resistance. In addition, more selective HDAC6 inhibitors have been developed to improve both efficacy and tolerability. Finally, the IMiDs thalidomide, lenalidomide, and pomalidomide bind to the cereblon ubiquitin 3 ligase complex in MM cells, leading to the degradation of critical hallmark downstream substrates. Ongoing efforts are developing other novel agents that target cereblon and other ubiquitin 3 ligase complexes to selectively target oncogenic substrates for degradation in MM and other cancers.

The immune approaches of IMiDs, MoAbs, checkpoint inhibitors, vaccines, HDAC6 inhibitors, and cellular therapies offer great potential to overcome the immune suppression that is a hallmark of MM and that predisposes patients to infections, a common cause of morbidity and mortality. We now know that T cells with anti-MM activity can be stimulated with IMiDs, checkpoint inhibitors, and/or HDAC6 inhibitors, with the potential of inducing persistent long-term memory anti-MM immunity.

Finally, at diagnosis, MM often shows extensive genetic heterogeneity, DNA damage, and multiple clones, with ongoing DNA damage underlying development of resistance and disease relapse. Although targeting multiple signaling pathways with combinations of targeted therapies is under evaluation in clinical trials, another approach is to exploit and target the phenotype conferred by this extensive intrinsic and ongoing genetic and epigenetic damage. Recent examples in our ongoing translational efforts include development of novel agents that can restore death signaling in MM cells with extensive gene damage; block replicative
stress response while increasing reactive oxygen species, thereby overwhelming MM cells; and target more than one node in an aberrant circuit or loop in MM signaling to enhance response.

The recent progress in MM is remarkable, and we are poised to transform the natural history of this disease. The NCCN Guidelines for MM rapidly incorporate evidence-based advances, thereby assuring awareness and access to these treatments by patients and caregivers alike.