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REVIEW

# Recent advances in understanding multiple myeloma [version 1; referees: 4 approved]

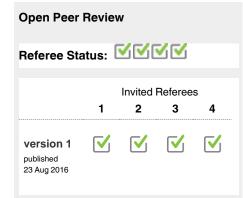Binod Dhakal[1], Saulius Girnius[2], Parameswaran Hari[1]

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## Abstract

There have been major recent advancements in the understanding and management of multiple myeloma. Diagnostic criteria have been revised and former ultra-high-risk smoldering multiple myeloma is now considered multiple myeloma in need of treatment. Understanding clonal progression, evolution, and tides not only has helped elucidate the disease behavior but might help expand therapeutic choices in order to select appropriate treatment for patients. Unprecedented response rates with modern triplet induction therapies containing proteasome inhibitor and immunomodulators have made this approach standard for initial treatment. The US Food and Drug Administration approved four new drugs (two targeted antibodies and two oral agents) in 2015 in relapsed/refractory multiple myeloma and these drugs along with the other already-available drugs have now increased the choices of regimens. Even drugs without single-agent activity, such as panobinostat and elotuzumab, have an important role, especially in the proteasome inhibitor refractory setting. Recent studies done in the context of novel agent induction suggest that high-dose therapy followed by autologous transplant continues to improve response rates and progression-free survival, thus underscoring their role in transplant-eligible patients. Evolving paradigms in the treatment of multiple myeloma include newer promising immune approaches, such as adoptive cellular therapies, vaccines, or antibody-based immune manipulations. Though multiple myeloma is still considered incurable, it is clear that with the improved understanding of disease biology and clonal architecture of relapse combined with the availability of multi-targeted approaches, we are ever closer to a lasting cure or transformation into indolent and long-lasting disease courses or both.

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|---|---|---|---|---|
|  | **1** | **2** | **3** | **4** |
| **version 1** published 23 Aug 2016 | ✓ | ✓ | ✓ | ✓ |

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## Introduction

Multiple myeloma (MM) is a clonal expansion of malignant plasma cells resulting in end organ damage, including lytic bone lesions, anemia, renal failure, or hypercalcemia. Both the understanding of MM and its management have evolved rapidly over recent years. Concomitant with the increasing incidence of MM to almost 30,000 patients annually in the US, mortality has trended down in the last decade, resulting in an increased prevalence of MM[1]. In 2015, four new drugs—the first two monoclonal antibodies and two oral agents—were approved by the US Food and Drug Administration (FDA). Importantly, these drugs have improved the outcomes in relapsed and heavily pre-treated patients.

## High-risk smoldering multiple myeloma

Smoldering MM (SMM) was traditionally defined on the basis of laboratory criteria—monoclonal (M) protein level of more than 3 g/dl or a clonal marrow plasmacytosis of more than 10%—and the absence of end organ damage. The ability to identify persons with SMM who are likely to progress rapidly to symptomatic MM has led to the revision of the criteria that define treatment initiation. Ultra-high-risk SMM patients with an 80% risk of progression to MM in 2 years are now considered in the updated criteria to have MM requiring treatment[2]. Currently, SMM is defined by the presence of serum M protein of at least 3 g/dl or 10 to 60% of clonal bone marrow plasma cells (or both) with no evidence of target organ damage, myeloma-defining events (MDEs), or amyloidosis[2]. Patients with high-risk SMM have a 25% risk of progression to MM in 2 years, whereas those with low risk have a 5% risk per year[3]. Multiple prognostic markers have been identified as surrogates for high-risk SMM[4–9]. Some of these include SMM with serum M protein of at least 3 g/dl, IgA isotype, involved/uninvolved free light chain ratio of at least 8 (but less than 100), bone marrow clonal plasma cells of 50 to 60%, t(4;14), del(17p), or 1q gain and Bence-Jones proteinuria. Management of high-risk SMM remains controversial after treatment with lenalidomide was shown to improve overall survival (OS) compared with a strategy of observation until target organ damage[10]. It is possible that SMM represents a curable stage of disease wherein early intervention approaches with limited toxicity may be curative and delay or avoid end organ damage provided that treatment does not lead to the outgrowth of more resistant clones. When compared with symptomatic MM, high-risk SMM can achieve a deeper response, as measured by minimal residual disease (MRD), with 11 out of 12 patients developing MRD negativity[11]. A longer follow-up is necessary to determine the duration of response, comparing it with the financial and physical burden of therapy. Thus, these treatments should be performed in clinical trials exploring the timing, the benefits, and the type of therapy in high-risk SMM.

## New criteria for multiple myeloma

The revised International Myeloma Working Group criteria for the diagnosis of MM requires, in addition to the presence of either 10% or more clonal plasma cells or a biopsy-proven plasmacytoma, one or more MDEs. MDE includes CRAB features (increased calcium level, renal dysfunction, anemia, and destructive bone lesions) and three specific biomarkers: (a) clonal plasma cells of at least 60%, (b) involved/uninvolved light chain ratio of at least 100, and (c) more than one focal lesion on magnetic resonance imaging. Each of these biomarkers was associated with an 80% risk of progression to symptomatic MM in 2 years in independent studies[4,7,8].

Staging of MM was recently updated to reflect the advances in treatment of MM as well as improved detection of high-risk disease. Revised-International Staging System (R-ISS) stage I disease includes ISS stage I with a normal lactate dehydrogenase (LDH) level and absence of high-risk cytogenetics (del(17p), t(4;14), or t(14;16)). R-ISS III includes ISS stage III with either high-risk cytogenetics or elevated LDH. R-ISS II includes all others. The 5-year OS rates were 82% in R-ISS I, 62% in R-ISS II, and 40% in R-ISS III[12].

## Clonal dominance

The initial event leading to malignant plasma cells occurs in the germinal center during isotype class switching and somatic hypermutation. These mutations are present in monoclonal gammopathies of unknown significance but are not sufficient for evolution to MM[13]. The progression to MM involves additional oncogenic events, including activation of oncogenes *K-Ras*, *N-Ras*, *FAM46C*, *MYC*, and *BRAF* and loss of function of *p53*, epigenetic changes with histone methylation/deacetylation, and genomic instability[14,15]. No one common driver mutation has been identified in MM, although recurrent variants have been identified. Deregulation of the RAS/MAPK, NF-κB pathway, and apoptotic response are involved, but only the inability for effective apoptotic response to DNA damage has prognostic value[15]. A second study confirmed that the presence of the aforementioned oncogenes did not influence OS or progression-free survival (PFS)[16]. In MM, at least four distinct evolutionary patterns can be discerned between initial treatment phase and subsequent relapses. The simplest situation is no change in the clonal and sub-clonal composition between various time points in the natural course of disease, which represents re-emergence of the original clonal plasma cell population at relapses. About one-third of patients in this group have stable genomes and are typically associated with hyperploidy and favorable outcomes. The other three scenarios include "either differential clonal response or clonal tides" where in sub-clones are identified at different time points, but their relative proportions change over time or linear clonal evolution where a new (previously undetectable) sub-clone emerges later or a branching evolution pattern corresponding to the emergence of new clones with the disappearance of old ones[16,17]. In these three groups, selective therapeutic pressures can suppress responsive clones, allowing resistant clones to become dominant. Persons with high-risk disease are more likely to exhibit linear evolution or clonal tides. Clones with inherent genomic instability, detected at low levels at diagnosis, may undergo further genomic shifts when exposed to DNA-damaging agents, emerging after multiple relapses as the fatal clone. Understanding the clonal evolution pattern will become increasingly relevant as therapeutic choices expand in order to select appropriate treatment for patients. Re-emergence of a previously sensitive sub-clone would warrant the use of the same combination therapy at relapse. Alternatively, the emergence under treatment-induced selection pressure of a newly dominant linearly evolved or pre-existing resistant sub-clone should lead to alternate drugs.

## Newer proteasome inhibitors

Two new proteasome inhibitors (PIs) have been approved in recent years: carfilzomib (K) and ixazomib (I). Carfilzomib is an intravenous, irreversible PI with impressive outcomes in both newly diagnosed MM and relapsed MM. In patients with early relapse (one to three prior regimens), when compared with lenalidomide and dexamethasone (RD), carfilzomib in combination with lenalidomide and dexamethasone (KRD) improved PFS (hazard ratio (HR) 0.69, $P = 0.0001$) and OS (HR 0.79, $P = 0.04$)[18]. In newly diagnosed patients, the KRD triplet had a response rate of 98%, a complete response rate of 56%, and MRD negativity rate by next-generation sequencing of 58%, and no discontinuation due to adverse events[11]. Benefits of carfilzomib include rapid time to response, excellent tolerability (15% discontinued due to adverse events), efficacy in high-risk disease, and the low rate of carfilzomib-induced peripheral neuropathy. Challenges with carfilzomib include twice-weekly intravenous administration, the risk for tumor lysis syndrome, and the possibility for cardiac events and dyspnea. One retrospective study identified that more than 20% of patients developed systolic heart failure or arrhythmias. Previous irradiation to the thoracic spine and concomitant administration of doxorubicin increased the risk for cardiac dysfunction[19]. To overcome these challenges, recent trials have demonstrated tolerability and response with escalated doses[20], whereas others are investigating efficacy of once-weekly dosing.

Ixazomib is an orally bioavailable, reversible PI with higher tissue distribution and a shorter dissociation half-life than bortezomib[21]. It has modest single-agent activity and response to bortezomib-exposed persons when combined with dexamethasone[22]. The combination of ixazomib with lenalidomide and dexamethasone (IRD) compared with RD shortened the time to response, improved the overall response rate, and increased median PFS (20.6 versus 14.7 months, HR 0.74, $P = 0.012$)[23]. Early signal also suggests that it may overcome the negative impact of cytogenetic alterations. Major toxicities include gastrointestinal (GI) toxicity, peripheral neuropathy, and cyclical thrombocytopenia. The tissue distribution and dissociation half-life have a theoretical benefit with extramedullary disease, although this has not yet been demonstrated in a clinical trial. Ixazomib can be used as the proteasome backbone for combination oral therapies, reducing the need for frequent infusion visits. IRD is being investigated in newly diagnosed, transplant-ineligible persons with MM in a multi-center clinical trial, but results are not yet available. The availability of an oral PI also increases the feasibility of oral PI-based maintenance/consolidation regimens after transplant. Although it has been approved by the FDA, European regulators are waiting for additional positive data.

## Immunomodulatory drug

Immunomodulatory drug (IMID) can bind cereblon on the E3 ubiquitin ligase complex, enhancing the ubiquitination and degradation of two zinc finger transcription factors[24,25]. Pomalidomide is an oral third-generation IMID approved for relapsed refractory MM after at least two prior regimens. In lenalidomide-refractory patients, including 75% who were dual refractory, the response rate for pomalidomide and weekly dexamethasone was 30% with a 4-month PFS[26]. In high-risk cytogenetics, patients with del(17p) had higher response rates, duration of response, and time to progression

than those with t(4;14)[27]. Pomalidomide is more effective earlier in the disease course[28], although approximately 40% of bortezomib- and lenalidomide-refractory patients can have a prolonged PFS[29]. Toxicities, including cytopenias, rash, and peripheral neuropathy, are unpredictable[30]. Unlike prior IMIDs, pomalidomide causes less endothelial stress and may be associated with lower rates of venous thromboembolic events, although patients should be on prophylactic anti-platelet therapy or anticoagulation[31]. Its limited toxicity allows for combination with PIs, cyclophosphamide, and monoclonal antibodies, improving its efficacy.

## Histone deacetylase inhibitor

Panobinostat, a pan-histone deacetylase inhibitor (HDAC), targets HDAC enzymes involved in the aggresome protein degradation pathway, working synergistically with PIs. In a heavily pre-treated patient population, including 73% who were bortezomib-refractory, the response rate of panobinostat, bortezomib, and dexamethasone was 35% with a 5.4-month PFS[32]. In bortezomib-refractory patients, the clinical benefit rate was better than 50% with a 4.2-month PFS. As high rates of GI distress and thrombocytopenia are seen with this agent, tolerability is a major impediment to its use and requires intense clinic/nursing support for continuous use. Dose interruptions occur in more than 50%, and relative dose intensity is only 73%. In a less heavily pre-treated population, response rates and PFS are improved, but the difficulty in maintaining dose intensity persists[33]. Nonetheless, panobinostat has a novel mechanism of action, is an oral agent, and continues to have an important role in the management of MM, especially in the PI-refractory setting.

## Monoclonal antibody

The FDA has recently approved two monoclonal antibodies in relapsed or refractory MM (RRMM) or both—elotuzumab and daratumumab—which target the signaling lymphocytic activation molecule F7 (SLAMF7) and CD38, respectively[34,35]. In a phase III trial of patients with RRMM, the addition of elotuzumab to RD significantly improved PFS (19.4 versus 14.9 months, $P < 0.001$)[35]. In addition, it improves the PFS of the subsequent therapy, suggesting a lasting effect on natural killer (NK) cells. Single-agent daratumumab produced a response rate of approximately 30% in heavily pre-treated patients and little toxicity other than infusion reactions[34]. Another CD38 antibody, isatuximab (SAR650984), has shown similar single-agent activity in RRMM but is not commercially available[36]. Both elotuzumab and daratumumab are being investigated in the front-line setting, and given the unprecedented single-agent activity, it is likely that daratumumab might be the backbone of MM treatment, akin to rituximab in B-cell lymphomas. Emerging data point to impressive responses for anti-CD38 antibodies in combination with IMIDs and PIs.

## Triplets at induction

When compared with doublets, triplet induction therapy containing a PI and an IMID results in a higher response rate and improved PFS and is preferred whenever possible in fit patients, especially given the synergism between these two drug classes[37,38]. A recent study has shown that bortezomib-lenalidomide and dexamethasone (VRD) has superior OS compared with RD[39]. Bortezomib-thalidomide and dexamethasone (VTD) has shown superior response rates than thalidomide and dexamethasone (TD) and bortezomib-dexamethasone

in randomized trials[37]. Bortezomib-cyclophosphamide and dexamethasone (VCD) was recently shown to have lower response rates than VTD[40] (Table 1). Although greater hematologic toxicity is seen in the former and peripheral neuropathy in the latter, the overall rate of grade 3/4 toxicity is similar, and individualization of therapy should dictate treatment decisions[41]. The second-generation PI carfilzomib in combination with lenalidomide and dexamethasone (KRD) has also shown excellent response rates in phase II trials[42], but additional data and regulatory approval are necessary prior to broader use. Conversely, lenalidomide-based triplets failed to show a PFS or OS benefit over lenalidomide-based doublets in an elderly population[43]. When compared with doublets, triplet therapies are associated with increased toxicity and usually longer PFS but not necessarily OS. The upfront use of the most active agents may limit treatment choices in future lines of therapy, possibly shortening the second and subsequent PFS periods. Given the prolonged survival in patients with myeloma as well as rapidly changing treatment modalities, this debate may be difficult to resolve.

### Triplets at first relapse

Management of RRMM remains controversial, although the field is moving toward combination triplet therapy at first relapse in fit patients. In the US, an abundance of second-line therapies are available, allowing individualization of therapy to both the patient and the disease. In older persons with RRMM, a geriatric assessment should be performed to determine a frailty score, evaluating the Katz Activities of Daily Living, the Lawton Instrumental Activity of Daily Living, and the Charlson Comorbidity Index[44]. Frail patients have shorter OS irrespectively of staging, treatment types, or physician-assessed performance status. Even when adjusted for International Staging System and chromosomal abnormalities, frail patients have shorter OS and PFS and higher rates of non-hematologic adverse events and treatment discontinuation and are likely to benefit from dose-adjusted therapy. Other validated frailty indexes evaluate similar factors as well as cytogenetics, renal function, and Karnofsky Performance Status[45].

The addition of a third drug to an IMID steroid combination improves response rates and PFS, although an OS benefit is not demonstrated consistently[18,35,46]. The addition of bortezomib (intravenous) to TD prolongs time to progression (HR 0.59, $P = 0.001$) in previously transplanted patients and results in a trend toward improved 24-month survival (71% versus 65%, $P = 0.093$)[46]. However, this population is not typical for the US, since only 20% were previously treated with bortezomib and 8% with thalidomide. Although VTD may have a limited role in the US, this study does illustrate the benefit of triplet therapy. The addition of carfilzomib to lenalidomide and dexamethasone improves not only response rates and PFS (HR 0.069, $P = 0.0001$) but also 24-month survival (HR 0.79, $P = 0.04$)[11]. The data from other recent trials of triplets in early relapsed disease, though clearly demonstrating PFS benefit, did not show an OS advantage.

### Which triplet to use

The choice of treatment at relapse is determined by the type, response, and duration of initial therapy as well as disease factors, patient factors, and patient preference. The ideal sequence of therapies is not known, but switching drug classes is likely beneficial, especially in higher-risk disease, given the evidence for clonal tides. For instance, if there is disease progression while on lenalidomide maintenance, a triplet containing lenalidomide would likely provide a suboptimal response. If available, carfilzomib/IMID triplet should be considered in aggressive relapses, given the excellent data with rapid induction of response and high rates of MRD negativity. Those who relapse following a short duration of remission after upfront therapy, including autologous stem cell transplant, or symptomatic relapses with significant clinical symptoms or disease relapse in high-risk cytogenetics are generally considered to be aggressive relapses. Elotuzumab-based treatment could be considered in individuals who are frail or have underlying cytopenias. An ixazomib-based regimen is an option if an oral regimen is desired and, based on early trends, may be considered, especially in del(17p) or extramedullary disease. A pomalidomide-based regimen could also be considered in del(17p). Panobinostat has a limited role in first relapse because of the toxicity profile unless used to restore PI sensitivity in those relapsing after prior PI regimens.

### Transplant still better

High-dose therapy followed by autologous stem cell transplantation (ASCT) was the standard of care for transplant-eligible patients

**Table 1. Triplet induction regimens and autologous stem cell transplantation studies in newly diagnosed multiple myeloma.**

| Regimen | Number of patients | Overall response rate | PFS | OS | Comments |
|---|---|---|---|---|---|
| VTD vs. TD[38] | 241 vs. 239 | 31% vs. 11% | NR | NR | NR |
| VTD vs. VCD[42] | 170 vs. 170 | 92.3% vs. 83.4% | NR | NR | NR |
| VRD vs. RD[40] | 242 vs. 232 | 71% vs. 63% | 43 vs. 31 months | NR vs. 63 months | Median OS/PFS |
| Conventional chemo vs. ASCT[48] | 100 vs. 100 | 81% vs. 22% | 28% vs. 10% | 52% vs. 12% | Pre-novel era; 5-year OS/PFS |
| ASCT vs. MPR[57] | 141 vs. 132 | NR | 54.7 vs. 37.4 months | 78.6% vs. 66.6% | Novel era PFS (median) OS (5-year) |

ASCT, autologous stem cell transplantation; MPR, melphalan/prednisone and revlimid; NR, not reported; OS, overall survival; PFS, progression-free survival; RD, lenalidomide and dexamethasone; TD, thalidomide and dexamethasone; VCD, bortezomib-cyclophosphamide and dexamethasone; VRD, bortezomib-lenalidomide and dexamethasone; VTD, bortezomib-thalidomide and dexamethasone.

before the era of novel agents. In pre-novel agent randomized trials, ASCT was uniformly associated with improved response rates and PFS, and about half of the studies showed an OS benefit and superior quality of life[47,48]. In one of the studies designed to address the question of early versus late ASCT[49], patients undergoing ASCT were found to have longer time without symptoms and treatment, and thus the patients with ASCT were found to have improved quality of life.

Given the unprecedented response rates with novel agents, the role of ASCT as front-line therapy has been questioned[50–52]. Novel agents have significantly improved the rate of complete response and MRD, both surrogates for improved survival[53,54]. The early versus late ASCT was investigated in a number of randomized trials[55,56], most recently in an international study conducted in the context of modern therapy with VRD induction, ASCT, and lenalidomide maintenance[57]. Superior OS benefit was seen in one study[56] whereas in the other two studies, early ASCT was found to have better PFS with no transplant-related deaths[55,57]. Maintenance therapy after ASCT is gaining increased acceptance. Two randomized trials demonstrated a PFS benefit to lenalidomide maintenance, but only the Cancer and Leukemia Group B (CALGB) trial demonstrated an OS benefit[58,59]. The difference in results could be explained by the use of two cycles of consolidation chemotherapy after ASCT and only one year of maintenance lenalidomide in the IFM (Intergroupe Francophone du Myelome) trial. In addition, the majority of subjects in the CALGB study, unlike the IFM trial, received a lenalidomide-based induction regimen. In addition, an unplanned subset analysis in the CALGB trial failed to show an OS benefit in those who did not receive a lenalidomide-based induction regimen. Likewise, bortezomib maintenance can improve PFS and possibly OS[60]. Further support for maintenance comes from the observation that maintenance lenalidomide, despite ASCT and consolidation therapy, can further deepen response, when measuring for MRD by flow[61]. Last, newer data demonstrate the benefit to continuous therapy. A meta-analysis of three trials, one of which included ASCT as part of consolidation, demonstrated improved PFS1, PFS2 (time to second progression of death), and OS with continuous therapy. In fact, a prolonged PFS1 did not reduce PFS2[62]. In conclusion, novel agent-based triplet induction, front-line early ASCT, and maintenance therapy remain the preferred strategy for transplant-eligible patients.

## Immunotherapy

The best-established immunotherapy in MM is allogeneic transplantation with a potent and often sustained graft-versus-myeloma (GVM) effect[63]. A series of prospective randomized studies, both in the US and Europe, explored the role of a tandem ASCT and reduced-intensity conditioning allogeneic stem cell transplants from a matched sibling or unrelated donor[64,65]. The results of these studies have been discordant, especially in the front-line treatment of MM[65–68]. Nonetheless, younger eligible patients with well-defined high-risk features should be considered for allogeneic transplant, especially within a clinical trial and early in the clinical course (front-line or first relapse). The risks of chronic graft-versus-host disease (cGVHD) and the need for long-term immunosuppression

remain major challenges. A number of studies suggest that immune therapy works in MM and these include demonstration of clinically meaningful GVM effect by donor lymphocyte infusions in patients relapsing after allogeneic transplant[69], complete remission after immunosuppression withdrawal[62], progression after allogeneic transplant, and the presence of cGVHD correlating with freedom from progression after allogeneic transplant[64].

A variety of novel post-ASCT or allogeneic transplant immunotherapeutic strategies are now being explored in MM. These include cellular approaches such as myeloma-specific T cells (via T-cell expansion), marrow-infiltrating lymphocytes[70], redirected T cells with chimeric antigen receptors[71,72], and tumor-based vaccines to induce myeloma-specific immunity in the context of enhanced antigen presentation[73]. A phase I/II study showed that adoptive transfer of tumor antigen vaccine-primed and co-stimulated T cells leads to augmented and accelerated cellular and humoral immune reconstitution, including antitumor immunity, after ASCT[74]. In another phase II trial, idiotype-pulsed antigen-presenting cells immunotherapeutic called APC8020 (Mylovenge), which was given after ASCT for MM, appeared to be associated with improved OS[75]. In a recent report, deep sustained response to anti-CD19 chimeric antigen receptor T cells was reported in a patient with relapsed/refractory disease[76]. Several promising antigenic targets have been identified for the development of anti-MM chimeric antigen receptors, such as B-cell maturation antigen, CD138, kappa light chains, and CS-1. Inhibitors of PD-1 and PDL-1 are being studied as a means of breaking down MM immune tolerance[71,77]. Though the anti-PD1 agent nivolumab was unimpressive[78], promising response rates were observed in combination with lenalidomide[79]. NK cell therapy has generated interest in the treatment of MM and a number of studies are exploring this option. These include modulation of NK activity using anti-KIR Ab IPH2101 (monoclonal antibody against inhibitory KIR on NK cells) to establish MM-specific immunity[80] safety and efficacy study of autologous-, allogeneic-, and cord-derived NK cells[81,82]. A clinical trial involving the haploidentical allo-stem cell transplant followed by planned NK cell infusion attempts to use donor-recipient KIR ligand mismatch and NK cell reactivity to facilitate long-term remission (NCT02100891). Another promising area is the use of tumor vaccine based on the study in which patients receiving a patient-specific dendritic cell/myeloma fusion vaccine demonstrated the expansion of MM-specific T cells as well as upgrading of response in a subgroup of patients[73]. A randomized phase II trial (BMT CTN 1401) with ASCT followed by lenalidomide maintenance with or without vaccination using the dendritic cell/myeloma fusion vaccine is currently accruing patients.

Hematopoietic cell transplantation provides an ideal platform for additional immune-based therapies. The recovery phase from ASCT (or other lymphodepleting therapy) represents a favorable platform for adoptive cellular therapy. The homeostatic lymphocyte proliferation following lymphopenia is a context in which immune checkpoint blockers may also be able to reverse MM-associated T-cell exhaustion[71,79]. Additionally, lymphopenia resulting from ASCT facilitates elimination of tolerogenic antigen-presenting cells and induces cytokine release that generates a more favorable

environment for adoptive T-cell therapy. Indirect evidence suggests that the immune system can contribute to the clinical benefits of ASCT (for example, those with early lymphoid recovery after ASCT have superior long-term outcomes)[83].

## Conclusions

Although MM has always been considered incurable, many investigators now believe that a significant fraction of patients currently undergoing therapy may be cured[84]. It is clear that with the improved understanding of disease biology and clonal architecture of relapse, combined with the availability of multi-targeted approaches, we are closer to a lasting cure than ever before. Nonetheless, many questions remain unanswered. Will the better understanding of myeloma biology guide the intensity of treatment, with high-risk disease necessitating aggressive therapy? With an increasing number of drug classes as well as new drugs in each class, the combination and sequencing of drugs are largely unresolved.

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1   **David Avigan**, Beth Israel Deaconess Medical Center & Harvard Medical School, Boston, Massachusetts, USA
    *Competing Interests:* No competing interests were disclosed.

2   **Qaiser Bashir**, Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA
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3   **Stefan Knop**, Wilhelm Sander Myeloma Unit, Division of Hematology and Medical Oncology, Wuerzburg University Medical Center, Wuerzburg, Germany
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4   **Monika Engelhardt**, Department of Hematology and Oncology, University of Freiburg Medical Center, Freiburg, Germany
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