

## Promising therapies in multiple myeloma

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### Introduction

Progress in medical research has enhanced our understanding of tumor biology, delineated genetic and molecular mechanisms of tumor growth and survival, and defined the impact of the microenvironment in cancer pathogenesis. As a consequence of these advances, cancers deemed rapidly fatal only a few decades ago can now be treated effectively, with prolonged survival in an increasing proportion of patients. This is particularly true for multiple myeloma (MM), in which the introduction of drugs targeting the tumor in its microenvironment, such as the proteasome inhibitor bortezomib and the immunomodulatory drugs (IMiDs) thalidomide and lenalidomide, into initial, consolidation, maintenance, and salvage therapies has markedly improved patient outcome. In this perspective, we discuss the most promising therapies to even further improve MM treatment, with a focus on drugs inhibiting the ubiquitin-proteasome pathway; histone deacetylase (HDAC) inhibitors (HDACi); immune therapies including IMiDs, monoclonal antibodies (mAbs), immune checkpoint inhibitors, agents targeting accessory plasmacytoid dendritic cells (pDCs), vaccines, and chimeric antigen receptor–engineered T (CAR-T) cells; drugs targeting tumor cell homing to, and exploiting hypoxia in, the bone marrow (BM) microenvironment; molecularly targeted therapies against kinesin spindle protein (KSP), v-akt murine thymoma viral oncogene homolog 1 (AKT), exportin 1 (XPO1), cyclin-dependent kinases (CDKs), bromodomain and extraterminal (BET) bromodomain 4, and serine/threonine kinase 4 (STK4); as well as delineating the impact of genomics on MM therapy. These advances in understanding the biology of MM will allow for earlier treatment of patients using rationally informed combination therapies with curative potential.

### Where do we stand with MM treatment?

Melphalan plus prednisone treatment of MM was introduced in the 1960s and achieved median survival of 2 to 3 years.<sup>1</sup> High-dose IV melphalan followed by autologous hematopoietic stem cell transplant (ASCT) was pioneered in the 1970s, with the first randomized trial of high-dose chemotherapy followed by ASCT vs conventional chemotherapy showing a 5-year overall survival (OS) rate of 52% vs 12%, respectively, in the 1990s.<sup>2</sup> Remarkably, over the last decade, the introduction of novel agents targeting MM in the context of the BM microenvironment has transformed the MM treatment paradigm and markedly improved patient outcome.<sup>3</sup> Landmark studies of the IMiDs thalidomide and lenalidomide and the proteasome inhibitor (PI) bortezomib provided the basis for rapid US Food and Drug Administration (FDA) approval of these treatments for patients with MM.<sup>4-6</sup> Incorporation of combination novel agents into the ASCT algorithm as induction, consolidation, and maintenance therapy has resulted in

unprecedented overall response rates (ORRs) and a threefold increase in OS.<sup>7</sup> In this perspective, we focus on the targeted therapies that, in our view, hold the greatest potential to even further improve on this progress (Table 1 outlines investigational agents in advanced clinical development).

### Drugs targeting the ubiquitin-proteasome system

In preclinical studies, bortezomib, the first-in-class boronic acid inhibitor of the CT-L activity of the proteasome and immunoproteasome, inhibits cell cycle progression, growth, and DNA damage repair in MM cells (MMCs), as well as induces caspase-8- and caspase-9-mediated apoptosis, terminal UPR, proteotoxic stress, and heat shock protein response.<sup>8-10</sup> In addition, it targets the BM microenvironment, evidenced by its antiosteoclast, antiangiogenesis, and proosteoblast activities.<sup>11,12</sup> Preclinical studies moved rapidly to phase 1, 2, and 3 clinical trials that demonstrated durable responses to bortezomib and provided the basis for its FDA approval in all stages of MM management.<sup>5,13,14</sup> Together with IMiDs and dexamethasone, bortezomib is now integrated as frontline therapy in the majority of MM patients, with ORRs as high as 100% with lenalidomide/bortezomib/dexamethasone, demonstrating the powerful synergy of using both PIs and IMiDs in combination.<sup>7,15</sup> The relative inconvenience of parenteral administration, peripheral neuropathy attendant to IV (vs subcutaneous) bortezomib administration, and the emergence of resistance has since stimulated the development of second-generation PIs with improved pharmacodynamics and more potent and/or broader activity against proteasome catalytic subunits, as well as the potential for oral administration.

Carfilzomib, an epoxyketone irreversible inhibitor of the CT-L proteasome activity, was approved by the FDA for treatment of relapsed MM refractory to bortezomib and exposed to an IMiD, based on a 23.7% ORR and a median progression-free survival (PFS) of 3.7 months.<sup>16</sup> In bortezomib-naïve patients, carfilzomib combined with low-dose dexamethasone achieved a 52.2% ORR in patients treated with the 27 mg/m<sup>2</sup> dose, and median PFS was not reached at the time the trial was reported.<sup>17</sup> When compared to the 41% ORR achieved with single-agent bortezomib in the Assessment of Proteasome Inhibition for Extending Remissions (APEX) trial, these data suggest that carfilzomib may be more effective than bortezomib.<sup>13,18</sup> Indeed, interim analysis of the ENDEAVOR trial (NCT01568866, a randomized, open-label, phase 3 study of carfilzomib plus dexamethasone vs bortezomib plus dexamethasone in patients with relapsed multiple myeloma) showed that carfilzomib/dexamethasone

achieved a PFS of 18.7 months vs 9.4 months for bortezomib/dexamethasone in largely bortezomib-pretreated patients. However, increased toxicities were also noted in this study, including renal and cardiopulmonary side effects at the higher dose of carfilzomib used (56 mg/m<sup>2</sup>). The recently completed phase 3 randomized ASPIRE trial compared carfilzomib/lenalidomide/dexamethasone (KRd) to lenalidomide/dexamethasone (Rd) in relapsed or in RRMM and showed a 26.3- vs 17.6-month PFS, respectively ( $P < .0001$ ), which was associated with an increase in overall and extent of response to KRd. Importantly, there were no major differences in adverse events in either cohort, with the exception of hypertension, dyspnea, and deep venous thrombosis, all of which were higher with KRd. Encouragingly, as a frontline therapy, this triple combination achieved a 98% ORR, with a 62% near complete response (nCR) rate or better, and an estimated PFS rate at 2 years of 92% at a median follow-up of 13 months.<sup>19</sup> Importantly, this combination can achieve molecular complete responses (CRs) without attendant neuropathy, but again, some caution is warranted because both venous thrombosis and significant shortness of breath (possibly due to diastolic dysfunction) were noted in some patients in this study.<sup>19</sup> Randomized trials are now underway comparing KRd to lenalidomide/bortezomib/dexamethasone in newly diagnosed patients, and results of these studies are awaited with great interest.

Ixazomib (MLN9708) is a reversible, orally bioavailable boronic acid based inhibitor of the CT-L activity of the 20S proteasome.<sup>20</sup> It triggers both caspase-8- and caspase-9-mediated apoptosis, upregulates p53 and p21, induces terminal UPR, and can overcome bortezomib resistance in preclinical studies.<sup>20</sup> It also induces tumor-suppressor microRNA 33b, with associated downregulation of the oncogene PIM-1.<sup>21</sup> As a single agent, weekly oral ixazomib achieved an 18% ORR in RRMM, including bortezomib-resistant MM, and was also active when given twice weekly in more heavily pretreated patients.<sup>22,23</sup> It is well tolerated, with low rates of peripheral neuropathy and treatment discontinuation. Remarkably, in a phase 1/2 study, the combination of ixazomib/Rd achieved a 90% ORR, with a 59% very good partial response rate or better in NDMM.<sup>24</sup> Moreover, maintenance therapy with ixazomib, given as 1 tablet weekly, was well tolerated and further improved response.<sup>25</sup> Ixazomib/Rd is being compared to Rd in 2 phase 3 clinical trials in RRMM (NCT01564537, TOURMALINE-MM1) and NDMM (NCT01850524, TOURMALINE-MM2). At the first interim analysis for patients enrolled in the TOURMALINE1 trial in RRMM, the primary end point of PFS extension with ixazomib/Rd vs Rd has been reached. This opportunity to use an all oral and well-tolerated regimen combining IMiDs and PIs both as salvage and especially as induction therapy is a major advance, as is the opportunity to use oral PI in maintenance treatment, which has particular promise in older patients in whom favorable tolerability is a premium.

Oprozomib (ONX 0912, PR-047), an orally bioavailable carfilzomib analog, is cytotoxic in preclinical MM models, including against bortezomib-resistant patient MMCs, and triggers synergistic cytotoxicity with lenalidomide and HDACs.<sup>26</sup> Similar to bortezomib and carfilzomib, it also has a bone anabolic effect in preclinical models.<sup>27</sup> Oprozomib achieved a 33% to 37% ORR in RRMM, including bortezomib- and carfilzomib-refractory MM (NCT01416428).<sup>28</sup> However, 20% of patients experienced severe (grade 3 or higher) gastrointestinal side effects, including 2 patients with fatal outcome. Preliminary results from a phase 1b/2 study of oprozomib/dexamethasone in RRMM showed a 42% ORR, with improved tolerability (NCT01832727), and phase 1/2 studies of oprozomib/dexamethasone plus IMiDs or cyclophosphamide in RRMM are ongoing.<sup>29</sup>

To determine whether inhibition of all 3 proteolytic subunits of the proteasome can overcome bortezomib resistance, the panproteasome inhibitor marizomib (NPI-0052) is currently being evaluated in clinical trials.<sup>30</sup> Twice-weekly marizomib in combination with dexamethasone achieved a 19% ORR, even in bortezomib-, carfilzomib-, lenalidomide-, and pomalidomide-refractory MM.<sup>31</sup> Based on preclinical studies demonstrating synergistic cytotoxicity of marizomib and pomalidomide/dexamethasone, a phase 1 trial of this combination in RRMM is now ongoing (NCT02103335).<sup>32</sup>

Access to the 20S proteolytic core of the proteasome requires the concerted activity of the 19S regulatory particles (RPs), which control gate opening and access to the core, along with deubiquitinating enzymes, which remove ubiquitin from target proteins prior to their degradation.<sup>33,34</sup> The 19S ubiquitin receptor RPN13, as well as the deubiquitinating enzymes ubiquitin-specific peptidase (USP)7 and USP14/ubiquitin carboxyl-terminal hydrolase L5 (UCHL5), are upregulated in MM cell lines (MMCLs) and patient MMCs; conversely, knockdown of these targets decreases MM viability.<sup>35-37</sup> RA190, P5091, and B-AP15 are small-molecule inhibitors of RPN13, USP7, and USP14/UCHL5, respectively. All are enzyme-specific inhibitors and are cytotoxic in vitro and in vivo against MMCLs and patient MMCs, including bortezomib-resistant MMCs.<sup>37</sup> Culture of MMCs with BM stromal cells does not overcome the cytotoxic effect of these therapies, which trigger synergistic MM cytotoxicity when combined with IMiDs, bortezomib, and the HDACi vorinostat.<sup>35,38</sup> Importantly, these agents block the ubiquitin-proteasome system (UPS) upstream of the proteasome, thereby causing accumulation of polyubiquitinated proteins without blocking the proteasome; they overcome PI resistance and trigger activation of intrinsic and extrinsic apoptotic pathways in a p53-independent fashion. The first USP14/UCHL5 inhibitor B-AP15 clinical trial for RRMM in humans is beginning soon, and will further validate the UPS as a therapeutic target in MM and assess whether targeting UPS upstream of the proteasome can overcome clinical PI resistance (Figure 1, section A).

## HDACs

HDACs are multifunction enzymes with distinct structure and target specificities that mediate epigenetic silencing of gene expression, thereby modulating key cellular processes, including proliferation, migration, and survival (Figure 1, section D).<sup>39</sup> HDACis, therefore, represent a promising targeted therapy in oncology. In MM, a particular rationale for use of HDACis is their role in disrupting aggresomal protein degradation. Combining bortezomib and HDACis to simultaneously block the proteasome and aggresome, respectively, triggers synergistic cytotoxicity and overcomes bortezomib resistance in preclinical studies.<sup>40</sup> Based on this data, the phase 3 Vantage 088 trial in RRMM compared bortezomib alone or in combination with the class I and IIb HDACi vorinostat.<sup>41</sup> Although combination therapy achieved a 54% ORR vs a 41% ORR for bortezomib alone ( $P < .0001$ ), there was only a modest prolongation in PFS (7.6 vs 6.8 months, respectively;  $P = .01$ ), primarily due to diarrhea, fatigue, and thrombocytopenia leading to increased discontinuation of treatment in the combination arm.<sup>41</sup> In contrast, a phase 1 trial of vorinostat in combination with Rd in RRMM achieved a 47% partial response (PR) rate and was better tolerated, but the therapeutic index remained narrow.<sup>42</sup> A phase 3 clinical trial of bortezomib with or without the pan-HDACi panobinostat achieved a 4-month prolongation of PFS with combination vs bortezomib-alone treatment (12 vs 8 months;  $P < .0001$ ); moreover, 28% vs 16% of patients achieved nCR or better ( $P = .00006$ ). Based on

**Table 1. Promising investigational agents in advanced clinical development in MM**

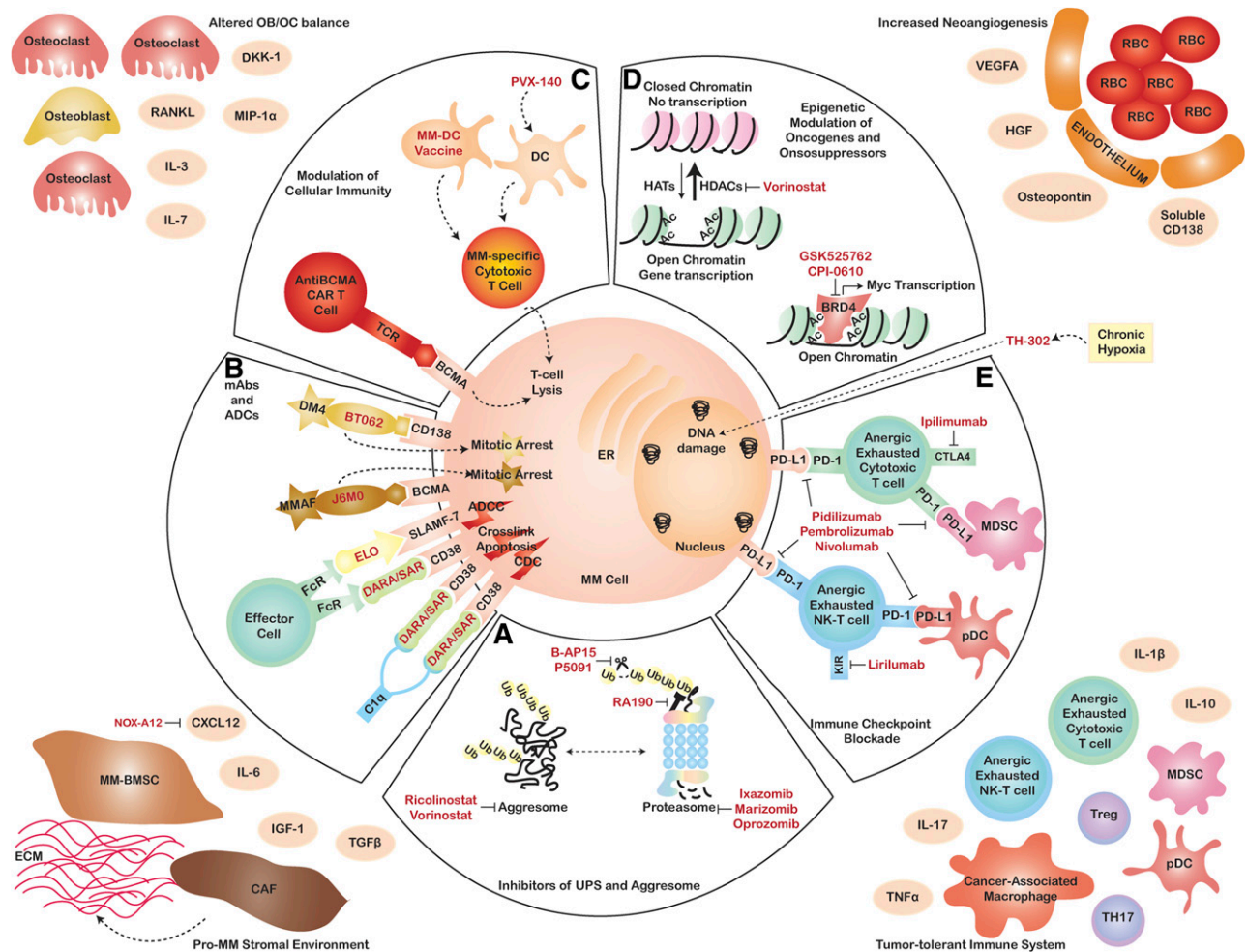
Drug class	Drug name	Relevant pharmacokinetic/ pharmacodynamic properties	Mechanisms of effectiveness	Most advanced phase of development	Study design
PI	Ixazomib (MLN9708)	Orally bioavailable, reversible, boronate-based inhibitor of CT-L proteasome activity	PolyUb protein accumulation Caspase-8- and caspase-9-mediated apoptosis p53 and p21 upregulation Terminal UPR induction miR33b upregulation PIM1 downregulation	Phase 3	Ixazomib/Len/Dex vs placebo/Len/Dex in RRRM Ixazomib/Len/Dex vs placebo/Len/Dex in transplant-ineligible NDMM
	Marizomib (NPI-0052)	Orally bioavailable, irreversible, $\beta$ -lactone- $\gamma$ -lactam inhibitor of CT-L, T-L, and C-L proteasome activities	PolyUb protein accumulation Caspase-8- and caspase-9-mediated apoptosis	Phase 1	Marizomib/Pom/Dex in RRRM
HDACi	Oprozomib (ONX 0912, PR-047)	Orally bioavailable, irreversible epoxyketone inhibitor of CT-L proteasome activity	PolyUb protein accumulation	Phase 1b/2	Oprozomib/Dex in RRRM
	Vorinostat (SAHA)	Small molecule class III HDACi	Caspase-8- and caspase-9-mediated apoptosis p21 and p53 upregulation Rb dephosphorylation BID cleavage Calpain activation	Phase 3	Oprozomib in RRRM Vorinostat/Bort vs Bort alone in RRRM
	Ricolinostat	Orally bioavailable, small-molecule HDAC6 inhibitor	Caspase-8- and caspase-9-mediated apoptosis Terminal UPR induction PolyUb protein accumulation Aggresome disruption	Phase 1/2	Ricolinostat/Len/Dex in RR MM Ricolinostat/Bort/Dex in RRRM Ricolinostat/Pom/Dex in RRRM
	Elo	Anti-SLAMF7 humanized mAb	ADCC Enhanced NK function	Phase 3	Elo/Len/Dex vs placebo/Len/Dex in NDMM
	Dara	Anti-CD38 human mAb	Cross-linking-mediated cytotoxicity ADCC CDC ADCP	Phase 3	Dara/Len/Dex vs placebo/Len/Dex in RRRM Dara/Bort/Dex vs placebo/Bort/Dex in RRRM
	Sar	Anti-CD38 humanized IgG1 mAb	Homotypic aggregation-mediated cytotoxicity ADCC CDC	Phase 1	Sar/Len/Dex in RRRM Sar/Pom/Dex in RRRM
	Indatuximab ravtansine (BT062)	Chimeric, anti-CD138-conjugated maytansinoid DM4	Maytansinoid DM4 released intracellularly upon CD138-mAb internalization Tubulin polymerization inhibition leading to cell cycle arrest and apoptosis	Phase 1/2	Indatuximab ravtansine/Len/Dex in RRRM
	J6M0-mcMMAF (GSK2857916)	Humanized and atucosylated anti-BCMA-conjugated monomethyl auristatin F	Monomethyl auristatin F released intracellularly upon BCMA-mAb internalization Tubulin polymerization inhibition leading to cell cycle arrest and apoptosis Blockade of BAFF- and APRIL-induced NF- $\kappa$ B activation	Phase 1	Dose escalation of J6M0-mcMMAF in RRRM

The table summarizes the most salient properties of novel agents in advanced clinical development.

ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; APRIL, a proliferation-inducing ligand; BAFF, B-cell activating factor; BCMA, B-cell maturation antigen; Bort, bortezomib; Carl, carfilzomib; CDC, complement-dependent cytotoxicity; C-L, caspase-like; CRM-1, chromosome region maintenance 1; CT-L, chymotrypsin-like; CXCL, chemokine (CXC motif) ligand; Dara, daratumumab; DC, dendritic cell; Dex, dexamethasone; Dox, doxorubicin; Elo, elotuzumab; Ig, immunoglobulin; IL, interleukin; Len, lenalidomide; MCL-1, myeloid leukemia cell 1; miR, microRNA; MMC, MM cell; NDMM, newly diagnosed MM; NF, nuclear factor; NK, natural killer; PD-1, programmed cell death 1; PolyUb, polyubiquitinated; Pom, pomalidomide; RR, relapsed and refractory; R/R, relapsed and refractory; RRRM, relapsed and refractory MM; SAHA, suberoylanilide hydroxamic acid; Sar, SAR650984; SMM, smoldering MM; T-L, trypsin-like; UPR, unfolded protein response; XBP-1, X-box binding protein 1.

**Table 1. (continued)**

Drug class	Drug name	Relevant pharmacokinetic/ pharmacodynamic properties	Mechanisms of effectiveness	Most advanced phase of development	Study design	
Immune therapies	Pembrolizumab (MK-3475)	Humanized, anti-PD-1 mAb	Increased anti-MM T, NK, and NK-T cell-mediated cytotoxicity	Phase 1/2	Pembrolizumab + Len post-ASCT	
	Pidilizumab (CT-011)	Humanized, anti-PD-1 mAb	Increased anti-MM T, NK and NK-T-mediated cytotoxicity	Phase 1/2	Pembrolizumab + Pom/Dex in RRMM Pidilizumab + Len in RRMM	
	Nivolumab (BMS936558) P VX-410	Human IgG4 anti-PD-1 mAb XBP-1-, CD138-, and SLAMF7-derived peptide vaccine targeting HLA2-restricted antigen-presenting cells	Increased T, NK, and NK-T antitumor cytotoxicity Expansion and activation of MM-specific T cells	Phase 1 Phase 1	Nivolumab ± ipilimumab or lirinumab in R/RRMM P VX-410 alone or in combination with Len in SMM	
BM-targeting therapies	MM-DC vaccine	Chemically fused autologous MIMCs and DCs targeting CD4 <sup>+</sup> and CD8 <sup>+</sup> T cells	Anti-MM humoral and cytotoxic response	Phase 2	MM-DC vaccine alone or in combination with pidilizumab post-ASCT	
	Anti-BCMA CAR-T cells	Anti-BCMA CAR-T cells	Specific, anti-MM T-cell response	Phase 1	Anti-BCMA CAR-T cells in RRMM	
Molecularly targeted therapies	TH-302	Hypoxia-activated DNA alkylator prodrug	Genotoxic damage	Phase 1/2	TH-302/Bort/Dex in RRMM	
	NOX-A12	CXCL12 pegylated mirror-image L-oligonucleotide	CXCL12/CXCR4 signaling inhibition	Phase 2a	NOX-A12/Bort/Dex in RRMM	
	Filanesib (ARRY-520)	KSP inhibitor	Mitotic arrest	Phase 2	Filanesib alone or in combination with Carf/Dex in RRMM	
	Selinexor (KPT-330)	CRM-1 inhibitor	Apoptosis Cell cycle arrest	Phase 1/2	Selinexor/Dex Selinexor/liposomal Dox/Dex Selinexor/Pom/Dex Selinexor/Bort/Dex	
	GSK2141795 Afuresentib (GSK2110183)	Akt inhibitors	Mcl-1 inhibition NF-κB inhibition IL-6 pro-MM effect inhibition	Phase 2	Selinexor/Carf/Dex in RRMM GSK2141795 + trametinib in RRMM GSK2110183 in PI-refractory MM	
	Dinaciclib (SCH 727965)	Inhibitor of CDK 1, 2, 5 and 9	UPR induction Apoptosis	Phase 2	Dinaciclib in RRMM	
	GSK525762 CPI-0610	BET bromodomain small molecule inhibitor	Inhibition of nuclear localization of spliced XBP-1 p53 accumulation MCL-1 downregulation Myc downregulation	Phase 1	GSK525762 in relapsed and refractory hematologic malignancies CPI-0610 in RRMM	
	<p>The table summarizes the most salient properties of novel agents in advanced clinical development.</p> <p>ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; APRIL, a proliferation-inducing ligand; BAFF, B-cell maturation antigen; Bort, bortezomib; Carf, carfilizomib; CDC, complement-dependent cytotoxicity; C-L, caspase-like; CRM-1, chromosome region maintenance 1; CT-L, chymotrypsin-like; CXCL, chemokine (CXC motif) ligand; Dara, daratumumab; DC, dendritic cell; Dex, dexamethasone; Dox, doxorubicin; Elo, elotuzumab; Ig, immunoglobulin; IL, interleukin; Len, lenalidomide; MCL-1, myeloid leukemia cell 1; miR, microRNA; MMC, MM cell; NDMM, newly diagnosed MM; NF, nuclear factor; NK, natural killer; PD-1, programmed cell death 1; PolyUb, polyubiquitinated; Pom, pomalidomide; RR, relapsed and refractory; R/R, relapsed or refractory; RRMM, relapsed and refractory MM; SAHA, suberoylanilide hydroxamic acid; Sar, SAR650984; SMM, smoldering MM; T-L, trypsin-like; UPR, unfolded protein response; XBP-1, X-box binding protein 1.</p>					



**Figure 1. Multimodality targeting of MM in the context of the BM microenvironment.** In the center is the MMC (in light pink), with nuclear clumped chromatin and endoplasmic reticulum (ER). The surrounding 5 sections each represent a different modality of anti-MM therapy, with investigational agents outlined in red. In section A is the UPS, closely interacting with the aggresome pathway. Deubiquitinating enzymes USP7 and USP14/UCHL5 are symbolized by a scissors and the 19S ubiquitin (Ub) receptor RPN13 as a receptor associated with the proteasome cap. Section B contains the monoclonal antibodies mAbs daratumumab (DARA) and SAR650984 (SAR), targeting CD38, as well as elotuzumab (ELO), targeting SLAMF-7, which mediate CDC, direct cytotoxicity from cross-linking, and ADCC. The antibody-drug conjugates (ADCs) indatuximab ravtansine (BT062) and J6M0-mcMMAF (J6M0) target CD138 and BCMA, respectively. Both toxins cause mitotic arrest and apoptosis after being released intracellularly upon internalization of the ADC-target complex and lysosomal lysis. Section C represents several strategies for modulation of cytotoxic immunity. In red is an anti-BCMA CAR-T cell; in orange is an MM-specific cytotoxic T cell activated via direct interaction with MM-DC vaccine or with autologous DC presenting peptides from the PVX-140 vaccine. Two different strategies to modulate epigenetic control of oncosuppressor and oncogene expression are outlined in section D. Nucleosomes are represented as spheres (histones) wrapped in a black thread (DNA). Open nucleosomes with acetylated (Ac) sites are green, whereas closed chromatin structure is pink. The BET bromodomain 4 protein (BRD4) is represented as a red trapezoid, binding to acetylated nucleosomes and inducing *Myc* transcription. Section E contains a representation of immune checkpoint blockade, with cytotoxic T and NK-T cells represented in green and blue, respectively. PD-1 and its ligand PD-L1 are represented as complementary transmembrane structures on effector cells and target cells (MMCs, myeloid-derived suppressor cells [MDSCs], and pDCs), respectively. Cytotoxic T-lymphocyte-associated protein 4 (CTLA4) and killer cell immunoglobulin-like receptor (KIR) are also pictured on effector cells. Outside the sections, TH-302 hypoxia-activated alkylating agent and NOX-A12 CXCL12 inhibitor are represented. In the 4 corners are key cellular and noncellular elements of the BM niche that contribute to MM pathogenesis: excess of osteoclasts (OC) compared to osteoblasts (OB; upper left corner); increased neoangiogenesis (upper right corner); tumor-tolerant immune system (lower right corner); and cancer-associated fibroblasts (CAF) responsible for the secretion of a pro-MM extracellular matrix (ECM), and MM-associated BM stromal cells (BMSC; lower left corner). Relevant cytokines in the BM milieu are represented as orange ovals. FcR, Fc receptor; HATs, histone acetylases; HGF, hepatocyte growth factor; MIP-1 $\alpha$ , macrophage inflammatory protein 1 $\alpha$ ; PD-L1, programmed cell death ligand 1; RANKL, receptor activator of NF- $\kappa$ B ligand; RBC, red blood cell; TCR, T-cell receptor; TGF $\beta$ , transforming growth factor  $\beta$ ; TH17, T helper 17 cells; TNF $\alpha$ , tumor necrosis factor  $\alpha$ ; Treg, regulatory T cell; VEGFA, vascular endothelial growth factor A.

these results, panobinostat in combination with bortezomib and dexamethasone was recently FDA approved as a third-line therapy in MM patients previously exposed to bortezomib and IMiDs. A 34.5% ORR to this combination was observed in a multicenter phase 2 trial in bortezomib-resistant RRMM patients, including patients with high-risk cytogenetics, which further supports its clinical activity in this setting.<sup>43,44</sup> As with vorinostat, however, the side-effect profile observed in the phase 3 study led to discontinuation of treatment in 34% of combination-treated vs 17% of bortezomib-treated patients,

highlighting the need for more selective HDACI approaches with potential for an improved therapeutic index.<sup>44</sup>

In this context, HDAC6 plays a key role in aggresomal protein degradation because it binds to misfolded proteins on the one hand and to the dynein motility complex on the other, thereby shuttling polyubiquitinated proteins to the aggresome/lysosome for degradation.<sup>45</sup> Ricolinostat (ACY-1215) is a specific orally bioavailable HDAC6 inhibitor that is cytotoxic against MMCs and synergizes with bortezomib and Rd in vitro.<sup>46</sup> A phase 1b study of ricolinostat

plus bortezomib/dexamethasone in RRMM showed a 45% ORR and a 29% ORR in bortezomib-refractory MM (NCT01323751).<sup>47</sup> Importantly, preclinical studies showed that ricolinostat with IMiDs downregulates MYC and triggers synergistic cytotoxicity.<sup>48</sup> A phase 1b trial of ricolinostat plus Rd in RRMM achieved a 64% ORR, including 85% in lenalidomide-sensitive and 50% in lenalidomide-refractory MM patients (NCT01583283).<sup>49</sup> Importantly, there were no grade 3 or 4 adverse events when ricolinostat was combined with either PIs or IMiDs, and clinical trials of ricolinostat in combination with pomalidomide daily for 21 days in RRMM are ongoing. Lastly, preclinical studies are further evaluating other isoform-selective HDACs targeting HDACs relevant for MM growth and proliferation. For example, HDAC3 knockdown triggers MM cytotoxicity and apoptosis, and HDAC3 selective inhibitor BG45 is active, alone or with bortezomib, in MM preclinical models.<sup>50</sup> Thus, isoform-selective oral HDACs may improve tolerability, allowing for their future clinical evaluation in combination with targeted and immune therapies.

## Immune therapies

### IMiDs

The rationale for using thalidomide, the first-in-class IMiD, in MM was its antiangiogenic properties.<sup>4</sup> However, the immunomodulatory effect of thalidomide and its more potent derivatives, lenalidomide and pomalidomide, was soon recognized as a major determinant of their anti-MM activity.<sup>51</sup> IMiDs are now incorporated into therapies for RRMM and NDMM due to a series of FDA approvals based on their remarkable clinical activity.<sup>6,52,53</sup> Moreover, maintenance therapy with lenalidomide has achieved improvement in PFS in both transplant-eligible and -ineligible patients, and incorporation of bortezomib into maintenance confers benefit even in high-risk disease.<sup>54-56</sup> Importantly, both the FDA and the European Commission approved continuous Rd for treatment of transplant-ineligible NDMM patients based on the results of the FIRST trial, which compared continuous Rd vs Rd for 72 weeks vs melphalan/prednisone/thalidomide (MPT) for 72 weeks.<sup>53</sup> Patients treated with continuous Rd achieved a PFS of 25.5 months vs 20.7 and 21.2 months for limited Rd and MPT, respectively ( $P < .001$ ); the 4-year OS rate was 59% vs 56% and 51%, respectively. Importantly, there was a decreased incidence of hematologic and neurologic adverse events and of second primary hematologic cancers in patients treated with continuous Rd compared to MPT, further supporting continuous Rd as a first-line MM therapy in this setting.

Mechanisms of action of IMiDs include caspase-8-mediated apoptosis; abrogation of MMC binding to BM stromal cells; modulation of cytokine secretion; upregulation of T, NK, and NK-T cells; and downregulation of regulatory T cells.<sup>57</sup> Most recently, the E3 ubiquitin ligase cereblon has been identified as the molecular target of lenalidomide.<sup>58,59</sup> Binding of lenalidomide to cereblon causes proteasome-dependent degradation of Ikaros family zinc finger proteins 1 and 3, which in turn mediates both MM cytotoxic and immune effects of IMiDs. Ongoing research is focusing not only on identifying biomarkers predictive of lenalidomide sensitivity but also on designing novel IMiDs based on the IMiD binding site to cereblon.<sup>60</sup> Moreover, efforts are attempting to delineate the mechanism of synergy underlying IMiD/PI combination therapy, because *in vitro* data indicate that an intact UPS is required for IMiD activity.<sup>59</sup> PIs may only partially inhibit the proteasome at therapeutic concentrations, allowing degradation

of certain substrates such as the Ikaros protein; alternatively, the polyubiquitinated Ikaros proteins could act as dominant negative, impairing the physiologic function of their nonubiquitinated counterpart.<sup>59</sup> These efforts will allow for rational, next-generation combination therapies.

Importantly, predicated on their immunostimulatory effects, IMiDs enhance activities of immune therapies including mAbs, checkpoint inhibitors, and vaccines, providing the framework for combination clinical trials.<sup>61</sup> Our group has long supported the theory that the malignant microenvironment is a necessary pathogenic element in MM, and we believe that disrupting this key interaction via immune therapy will prove vital to improving treatment outcome for MM patients (Figure 1).

### mAbs

Elotuzumab is a fully humanized mAb directed against the glycoprotein SLAM family member 7 (SLAMF-7), which is highly expressed on the cell surface of MMCLs and patient MMCs.<sup>62</sup> Elotuzumab triggers ADCC and enhances NK cell function against MMCs. As a single agent, it achieved stable disease in the setting of RRMM. Predicated on preclinical studies showing that lenalidomide augmented ADCC, a phase 2 study of elotuzumab with Rd in patients with RRMM, including patients with high-risk disease, achieved a 92% ORR and PFS of 32.5 months.<sup>63,64</sup> Phase 3 studies of this combination vs Rd in patients with NDMM (NCT01335399, ELOQUENT-1) and RRMM (NCT01239797, ELOQUENT-2) are ongoing.

The target of the mAb daratumumab is CD38, a transmembrane protein expressed on MM and activated immune cells, hematopoietic progenitor cells, and endothelial cells. The anti-MM effect of daratumumab is both direct, due to inhibition of enzymatic activity and apoptotic signaling triggered via cross-linking on the MM cell surface; and immune-mediated via ADCC, complement-dependent cytotoxicity, and antibody-dependent cellular phagocytosis (Figure 1, section B).<sup>65,66</sup> Preliminary studies showed very promising single-agent activity, with a 31% ORR in heavily pretreated RRMM, leading to designation of breakthrough status by the FDA and a strong rationale for combination approaches.<sup>67</sup> Specifically, as with elotuzumab, the addition of Rd to daratumumab significantly increased depth of response to a 75% PR rate or better in RRMM.<sup>68</sup> Phase 3 trials of daratumumab with Rd or bortezomib/dexamethasone in RRMM are currently accruing (NCT02076009 and NCT02136134, respectively); and a phase 3 study of daratumumab/Rd in NDMM is planned (NCT02252172). Similar results have been observed with another CD38 mAb, SAR650984, with responses even in carfilzomib- and pomalidomide-resistant MM.<sup>69</sup>

Indatuximab ravtansine (BT062) is an antibody-drug conjugate comprising anti-CD138 mAb targeting syndecan1 (CD138) coupled to the potent maytansinoid DM4 toxin.<sup>70</sup> Upon internalization of the CD138-antibody-drug conjugate complex and lysosome-mediated proteolysis, DM4 is released and inhibits tubulin polymerization, resulting in cell cycle arrest and apoptosis.<sup>71</sup> In a phase 1/2 trial in combination with Rd, indatuximab ravtansine achieved a 78% ORR, including responses in bortezomib- and lenalidomide-refractory MM (NCT01638936).<sup>72</sup> J6M0-mcMMAF (GSK2857916) is a humanized, afucosylated mAb directed against BCMA conjugated via a non-cleavable linker to the antimetabolic agent monomethyl auristatin F. The latter is released intracellularly via a mechanism similar to DM4 for BT062, and induces cell cycle arrest and apoptosis. Because BCMA is the receptor for B-cell activating factor and a proliferation-inducing ligand, J6M0-mcMMAF also blocks B-cell activating factor- and a proliferation-inducing ligand-induced nuclear factor  $\kappa$ B activation.<sup>73</sup>

A phase I study of J6M0-mcMMAF in RRMM is now ongoing (NCT02064387).

Additional preclinical and clinical studies are evaluating mAbs directed against antigens expressed on MMCs such as CD40, CD54 (also known as intercellular adhesion molecule 1), CD56, and GM2 ganglioside; as well as the anti-vascular endothelial growth factor A (VEGF-A) mAb bevacizumab.

### Immune checkpoint blockade

Cancer immune escape due to tumor-induced NK- and T-cell anergy/exhaustion has emerged as an important determinant of cancer progression and/or recurrence.<sup>74</sup> In MM, the importance of host antitumor immunity is evidenced by long-term molecular CR observed post-allogeneic hematopoietic stem cell transplant due to ongoing graft-versus-MM effect.<sup>75</sup> Most recently, mAbs to block the inhibitory interaction of PD-1 on T or NK cells with its ligand PD-L1 on tumor cells or tumor-promoting accessory cells have achieved remarkable responses in both solid tumors and hematologic malignancies.<sup>74,76</sup>

In MM, tumor cells, pDCs, and myeloid-derived suppressor cells all express PD-L1, whereas BM-resident cytotoxic T, NK, and NK-T cells express PD-1.<sup>77,78</sup> Our preclinical *in vitro* and *ex vivo* studies showed that blockade of PD-1/PD-L1 inhibits accessory cell (pDC or myeloid-derived suppressor cell)-induced MM proliferation and survival while triggering host T- and NK-cell anti-MM cytotoxicity. Moreover, these effects can be markedly enhanced by lenalidomide, suggesting the utility of combination immune therapies.

There are multiple checkpoint inhibitor clinical trials ongoing or planned in MM. A phase 2 study of the humanized anti-PD-1 mAb pembrolizumab (MK-3475) with lenalidomide post-ASCT (NCT02331368) and a phase 1/2 study of pembrolizumab plus pomalidomide/dexamethasone in RRMM (NCT02289222) are ongoing. The humanized anti-PD-1 mAb pidilizumab (CT-011) is being evaluated in combination with vaccination post-ASCT (NCT01067287), as well as with lenalidomide in RRMM patients (NCT02077959). The fully human immunoglobulin G4 anti-PD-1 antibody nivolumab (BMS936558), alone or in combination with the CTLA4-blocking antibody ipilimumab or the killer cell immunoglobulin-like receptor-blocking antibody lirilumab, is being evaluated in a phase I clinical trial in relapsed or refractory hematologic malignancies, including MM (NCT01592370) (Figure 1, section E). Future trials will combine checkpoint inhibitors, mAbs, vaccinations, and/or IMiDs in an attempt to further enhance autologous, selective anti-MM memory immunity and achieve durable clinical responses. Importantly, the potency, selectivity, and adaptability of the immune response may allow for effective host anti-MM immunity, even in the setting of ongoing genomic evolution, thereby preventing disease relapse.

### Vaccines

Vaccination against cancer-specific antigens represents a promising strategy to modulate patient antitumor immune response, particularly in the settings of early-stage or minimal residual disease. For example, we are vaccinating patients with SMM with the goal of delaying their progression to active disease. The vaccine (PVX-410) consists of a cocktail of HLA-A2-specific peptides derived from X-box binding protein 1, CD138, and SLAMF-7 MM antigens, which can trigger HLA-restricted expansion and activation of MM-specific T cells. Ongoing studies are combining PVX-410 with lenalidomide and with anti-PD-1 to further enhance MM-specific immune responses (NCT01718899).<sup>79</sup>

An alternative approach involves vaccination of patients with their own tumor cells fused to autologous DCs (MM-DC fusion vaccine) (Figure 1, section C). In a phase I trial in RRMM, we have shown that MM-DC fusion vaccination triggers both humoral and cellular anti-MM responses, associated with 70% stable disease.<sup>80</sup> Excitingly, MM-DC vaccination post-ASCT achieved a 78% very good partial response rate and a 47% CR or nCR rate, with responses improving from PR to CR/nCR after 100 days posttransplant in 24% of patients, suggesting its utility to treat minimal residual disease.<sup>81</sup> A phase 2 randomized clinical trial of post-ASCT maintenance using lenalidomide with or without MM-DC vaccination is opening soon. Decreased regulatory-T cell function and minimal disease state posttransplant suggest that this setting is optimal for vaccination; again, the goal is to enhance vaccine-induced long-term autologous anti-MM memory immunity by combining vaccination with lenalidomide or anti-PD-1 antibodies, or both.

### pDCs

pDCs are increased in MM BM and promote tumor cell proliferation, survival, and drug resistance; moreover, they also fail to trigger host antitumor immune response.<sup>82</sup> Either cytosine-phosphate-guanosine (CpG) oligodeoxynucleotide A or C792 (a cytosine guanine dinucleotide oligodeoxynucleotide C acting as a Toll-like receptor 9 agonist) can mature MM pDCs, thereby restoring their immunostimulatory ability while abrogating their pro-MM activities.<sup>83</sup> Clinical trials of Toll-like receptor 7 agonist are planned to test the therapeutic benefit of solely targeting immune accessory cells, because these agents have no direct anti-MM activity. Importantly, because PD-L1 is expressed on pDCs, checkpoint inhibitor therapy can also abrogate the functional sequelae of pDCs in MM.<sup>78</sup>

### Modulation of cellular anti-MM immune surveillance

CD19-directed CAR-T cells have achieved remarkable responses in relapsed and refractory chronic lymphocytic leukemia, non-Hodgkin lymphoma, and acute lymphoblastic leukemia.<sup>84,85</sup> CAR-T cells directed against CD38 and SLAMF-7 are in preclinical development in MM, whereas CAR-T cells against BCMA are already being evaluated in a phase I clinical trial (NCT02215967) (Figure 1, section C).<sup>86</sup> The opportunity here is for dramatic tumor cell reduction, even in high-risk, refractory MM; moreover, use of lenalidomide and/or checkpoint inhibitors post-CAR-T cell therapy may allow for persistence of cancer immune surveillance by avoiding T-cell exhaustion.

Bispecific T-cell engagers (BiTEs) are composed of 2 single-chain variable fragments connected by a linker.<sup>87</sup> BiTEs redirect anticancer immunity by binding to a T cell-specific antigen (typically CD3) with 1 fragment and to a cancer-specific epitope with the other fragment, thus juxtaposing the effector and cancer cells. The CD3-CD19 BiTE blinatumomab was granted FDA approval based on a 43% CR rate in relapsed or refractory B cell-precursor acute lymphoblastic leukemia.<sup>88</sup> CD3-CD38 BiTEs are in preclinical development for MM.

## Novel therapies directly targeting the BM microenvironment

MMCs establish a bidirectional prosurvival relationship with both cellular and noncellular elements of the BM milieu and can co-opt the function of BM accessory cells to create a permissive microenvironment for their growth and survival (Figure 1; 4 corners).<sup>89</sup> Therefore,

directly targeting the BM microenvironment represents a novel strategy to indirectly abrogate MM growth and survival.

### CXCL12/CXCR4 axis inhibitors

CXCL12, also known as SDF-1 $\alpha$ , mediates trafficking and homing of MMCs to the BM microenvironment.<sup>90</sup> Plerixafor, an inhibitor of the CXCL12 ligand CXCR4, is used for mobilization of normal BM hematopoietic stem cells for ASCT and has been tested as an anti-MM therapy, predicated on mobilizing MMCs from their protective BM milieu.<sup>91,92</sup> Inhibition of CXCL12 using NOX-A12 (olaptosed pegol), a high-affinity anti-SDF-1 $\alpha$  pegylated mirror-image L-oligonucleotide, triggers MM cytotoxicity in preclinical studies.<sup>93</sup> In a phase 2a trial in RRMM, combination NOX-A12/bortezomib/dexamethasone achieved a PFS of 6.5 months and a 73% ORR, even in high-risk and/or bortezomib-refractory patients.<sup>94</sup> The regimen was well tolerated, and this combination is now entering phase 3 trials.

### Exploiting hypoxia against MM

The BM microenvironment in MM is hypoxic, and hypoxia inducible factor 1 $\alpha$  is upregulated in patient MMCs.<sup>95</sup> Moreover, hypoxia is a driver of epithelial to mesenchymal transition in MMCs, thereby promoting their dissemination.<sup>96</sup> TH-302 is a DNA alkylator prodrug selectively activated under hypoxic conditions, which triggers MM cytotoxicity, alone and with bortezomib, in preclinical models.<sup>97</sup> A phase 1/2 study of TH-302 with dexamethasone/bortezomib showed no dose-limiting toxicity at the recommended phase 2 dose, with 29% and 50% ORRs in the phase 1 and 2 cohorts, respectively.<sup>98</sup> Exploiting MMC vulnerability due to hypoxia may therefore allow for selective tumor cytotoxicity and a favorable therapeutic index.

## Promising targeted therapies

Predicated on preclinical studies, a number of signaling molecules have been identified as potential molecular targets of MM therapy. Inhibitors of aurora kinase A and B, KSP XPO1 (also known as chromosome region maintenance 1 [CRM-1]) AKT, and CDKs are among those in promising early-phase clinical trials.<sup>99</sup> The KSP inhibitor filanesib (ARRY-520) causes apoptosis in MM and is being evaluated in RRMM, alone (NCT02092922 and NCT00821249, phase II) or in combination with bortezomib/dexamethasone (NCT01248923, phase I) or carfilzomib/dexamethasone (NCT01372540 and NCT01989325, phase I and II, respectively).<sup>100</sup> Because this agent is highly bound in serum to  $\alpha$ 1-acid glycoprotein, its activity is enhanced in patients with low  $\alpha$ 1-acid glycoprotein levels.<sup>101</sup> Selinexor (KPT-330), an inhibitor of the nuclear export protein CRM1, functions by maintaining the cellular distribution of tumor suppressors in MMCs.<sup>102,103</sup> Although single-agent activity was not observed in MM, phase 1/2 clinical trials in combination with dexamethasone, liposomal doxorubicin, pomalidomide/dexamethasone, or PIs/dexamethasone are ongoing, with promising interim results (NCT02336815, NCT02186834, NCT02343042, or NCT02199665, respectively).<sup>104</sup> Multiple studies have shown that PIs trigger apoptotic signaling but also induce AKT.<sup>105</sup> AKT inhibitors GSK2141795 and GSK2110183 are therefore being clinically evaluated in combination with bortezomib and other PIs. Lastly, a hallmark of MM is cyclin D dysregulation; and multiple preclinical studies have evaluated CDK inhibitors in MM.<sup>106,107</sup> Based on promising preclinical studies, the CDK inhibitors dinaciclib (SCH 727965), and SNS-032 are now being evaluated in phase 1/2 trials in RRMM (NCT01096342, NCT00446342, and NCT01711528).<sup>108-110</sup>

Among novel targeted therapies, BET bromodomain and STK4 inhibitors hold particular promise in MM and other hematologic malignancies.

### BET bromodomains

*Myc* is an oncogene in solid tumors and hematologic malignancies including MM, and BET bromodomains have recently been shown to regulate *Myc* transcription in MM (Figure 1D).<sup>111,112</sup> Importantly, inhibition of BET bromodomain 4 via small-molecule JQ1 down-regulates *Myc* transcription and its downstream targets and is associated with decreased MMC growth in vitro and in vivo in murine models. Phase 1 clinical trials of BET bromodomain inhibitors GSK525762 (NCT01943851) and CPI-0610 (NCT02157636) are ongoing in RRMM. These studies will, for the first time, evaluate the therapeutic efficacy of targeting *Myc* and also inform combination approaches, such as with IMiDs.

### YAP1/STK4

The Hippo coactivator Yes-associated protein 1 (YAP1) is essential for p53-independent, ABL1-induced apoptosis secondary to DNA damage.<sup>113</sup> We have recently shown that YAP1 mRNA and protein levels are low in a subset of lymphoid and myeloid malignancies, including MM, which portends poor survival. In the setting of constitutive ongoing DNA damage, restoration of YAP1 levels and function in MMCs results in apoptosis via induction of p73 and downstream target genes. Importantly, STK4 regulates YAP1 phosphorylation and its degradation in MM; conversely, knockdown of STK4 results in upregulation of YAP1, associated with MM cytotoxicity both in vitro and in vivo in mouse xenograft models. Based on this synthetic lethality, our ongoing studies are developing clinical-grade STK4 inhibitors to upregulate YAP1 and induce p73-mediated apoptosis in MM and other hematologic malignancies characterized by low YAP1 expression.<sup>114</sup> Importantly, STK4 inhibitors may restore YAP1 and p73 signaling even in high-risk, 17p-deleted MM lacking functional p53.

## The role of genomic profiling in identifying novel therapeutic targets

MM is characterized by complex genomic alterations, and no single predominant driver mutation has been identified.<sup>115</sup> The majority of mutations detected in MM are already present at the stage of monoclonal gammopathy of undetermined significance and/or SMM, suggesting that genetic mutations per se are not sufficient for oncogenesis and clonal evolution.<sup>116</sup> Whole-exon and -genome sequencing has been instrumental not only in identifying the genetic landscape of MM but also in delineating the mechanisms underlying progression and relapse. To date, genes identified to be mutated in MM are those implicated in protein homeostasis, nuclear factor  $\kappa$ B signaling, and histone methylation, consistent with MM pathogenesis.<sup>117</sup> Mutations have also been observed in genes not previously implicated in oncogenesis, such as FAM46C and SP140, which may therefore represent potential novel therapeutic targets in MM.<sup>117</sup> Of note, B-RAF mutations have been described in 4% of MM, and vemurafenib has achieved responses in this setting.<sup>118</sup> Our recent RNA sequencing study in patient-derived MMCs showed that only 27% of mutated alleles are expressed at the mRNA level and, therefore, have biological and clinical relevance.<sup>119</sup> Importantly, clonal heterogeneity and clonal evolution is a hallmark in MM pathogenesis and progression.<sup>117,120</sup>



This genomic heterogeneity and complexity in MM highlights the need to use combination therapies as early as possible to prevent genomic evolution and progression, as well as the need to define genomic signatures in patients at a particular time in their disease course to inform appropriate combination targeted therapies. In ongoing and future studies, it will be critical to identify those pathways to be targeted at a given point in time in order to inform combination targeted, epigenetic, and immune therapeutic approaches that will avoid genomic evolution underlying disease relapse.

## Conclusions and future directions

Novel agents targeting MMC in the context of the BM microenvironment, with or without stem cell transplantation, have prolonged patient survival three- to fourfold. We believe that translational research focus in 3 areas will assure further progress. First, genomic, epigenomic, and proteomic profiling of MMCs will identify aberrant signaling pathways in the tumor cell and host tumor milieu to enhance our understanding of disease pathogenesis and to identify novel molecular targets.<sup>121</sup> Second, given the genomic complexity of MM, immune therapies including mAbs, vaccines, immune checkpoint blockade, and CAR-T cells, likely in combination, will be integrated into the treatment paradigm to enhance autologous, anti-MM memory immunity. Lastly, utilization of effective, well-tolerated, and rational combination targeted and immune therapies early in the disease course, in SMM, or even in monoclonal gammopathy of

undetermined significance, will delay and may ultimately avoid the development of MM.<sup>122-124</sup>

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## Authorship

Contribution: G.B., P.G.R., and K.C.A. wrote the paper.

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