

# Novel Therapeutic Targets in Multiple Myeloma

Francesca Cottini, MD, and Kenneth Anderson, MD

Dr Cottini is a research fellow in Dr Anderson's laboratory and Dr Anderson is the Director of the Jerome Lipper Multiple Myeloma Center at the Dana-Farber Cancer Institute and the Kraft Family Professor of Medicine at Harvard Medical School in Boston, Massachusetts.

Address for correspondence:  
Kenneth Anderson, MD  
Dana-Farber Cancer Institute  
Mayer 557  
450 Brookline Ave  
Boston, MA 02215-5450

**Abstract:** Multiple myeloma (MM) is a disorder of clonal plasma cells that accumulate in the bone marrow and secrete a monoclonal protein detectable in the blood and/or urine. In the last decade, the outcome of patients with MM has markedly improved owing to the introduction of agents such as proteasome inhibitors (bortezomib) and immunomodulatory drugs (thalidomide, lenalidomide) as induction, consolidation, and maintenance strategies. Nonetheless, drug resistance leading to relapse commonly occurs, and novel therapies are urgently needed. In this review, we will describe the most promising new approaches to treat MM, including those based on targeting protein homeostasis, enhancing anti-MM immunity, targeting MM with monoclonal antibodies and immunotoxins, modulating bone metabolism, targeting histone modifications, targeting genomic instability and cell cycle alterations, and the use of genomic profiling to provide personalized therapies. These advances will continue to transform MM into a chronic illness, and have curative potential.

## Introduction

Multiple myeloma (MM) is characterized by the clonal proliferation of bone marrow plasma cells that leads to the presence of monoclonal protein in the blood and/or urine, bone destruction, anemia, hypercalcemia, and renal function abnormalities. Until recently, the median survival of MM patients was 2 to 5 years. The introduction of novel agents, however, including proteasome inhibitors (PIs; bortezomib [Velcade, Millennium Pharmaceuticals]) and immunomodulatory drugs (IMiDs; thalidomide, lenalidomide [Revlimid, Celgene]) has dramatically improved patient outcomes, providing the platform for several combination treatment options.

Despite this remarkable progress, MM commonly acquires drug resistance, leading to relapse of disease. A new generation of PIs (carfilzomib [Kyprolis, Onyx] and the experimental ixazomib, marizomib, and oprozomib)<sup>1</sup> and IMiDs (pomalidomide [Pomalyst, Celgene]) is already demonstrating efficacy in relapsed/refractory MM (RRMM). Multiple other novel strategies include:

### Keywords

Antitumor immunity, genomic profiling, monoclonal antibodies, multiple myeloma, novel targets, protein homeostasis

(1) agents that interfere with protein catabolism (deubiquitinating enzyme [DUB] inhibitors, histone deacetylase 6 [HDAC6]-specific inhibitors);

(2) epigenetic therapies (HDAC inhibitors, bromodomain inhibitors);

(3) immune-based therapies (vaccines, programmed death ligand 1/programmed death 1 [PD-L1/PD-1] inhibitors, toll-like receptor (TLR) agonists, cellular therapies);

(4) monoclonal antibodies and immunotoxins (daratumumab, elotuzumab, SAR650984, and BT062); and

(5) other agents targeting signaling pathways, such as those targeting kinesin spindle protein (KSP), Akt, CRM1, c-MYC, and nuclear factor  $\kappa$ B (NF $\kappa$ B).

Moreover, recent studies with array comparative genomic hybridization, gene expression profiling, and whole-genome sequencing have advanced our knowledge of MM heterogeneity and pathogenesis, as well as identified innovative therapeutic targets. These studies showed that marked genetic heterogeneity, with features such as nonhyperdiploid karyotypes, t(4:14), del(17p), and chromosome 1 aberrancies, was associated with an inferior outcome. Moreover, distinct patient subgroups have been identified that highlight the possible use of selective targeted therapies. These include fibroblast growth factor receptor 3 (FGFR3) inhibitors in t(4:14) MM, BRAF inhibitors in MM with specific *BRAF* mutations, anti-CD20 monoclonal antibody therapy in CD20+ MM, and synthetic lethality approaches in MM patients with defective DNA repair or DNA damage responses. In this review, novel targets and promising targeted therapies will be discussed.

### Interfering With Protein Catabolism

MM cells are exquisitely sensitive to protein overload and lethal endoplasmic reticulum (ER) stress, given their high rate and amount of immunoglobulin secretion. Several strategies can be applied to target this Achilles heel of MM, including blockade of proteasome activity, inhibition of the protein deubiquitinating and chaperoning processes, and modulation of the unfolded protein response (Figure 1).

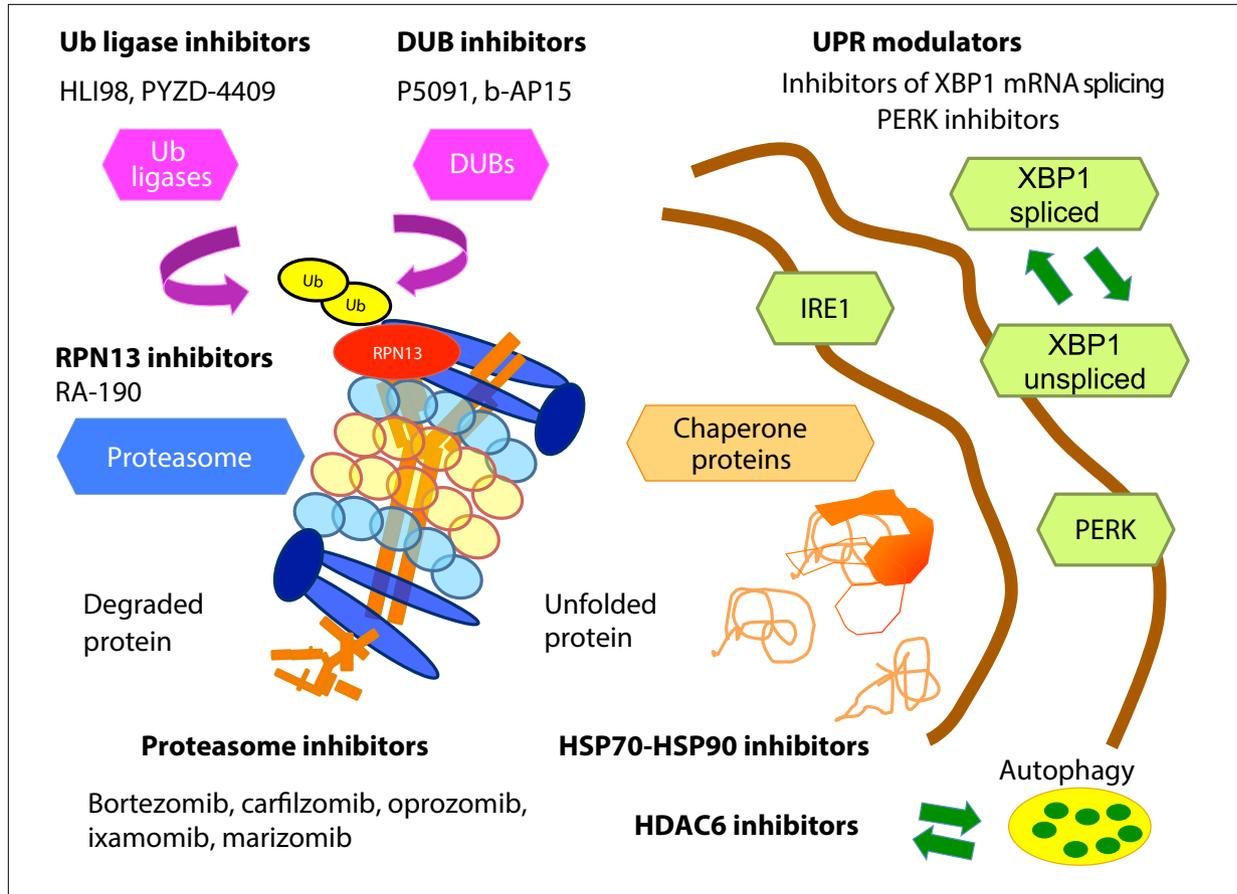
Inhibition of proteasome subunits is now a well-validated therapeutic strategy in MM. Importantly, anti-MM activity was observed in both in vitro and in vivo preclinical studies. This finding was rapidly translated to clinical trials that led to approval by the US Food and Drug Administration of bortezomib for RRMM, and subsequently for newly diagnosed MM.

Although bortezomib represents a major advance, some patients with MM do not respond to it, and acquisition of resistance leading to relapse is common among responders. Second-generation PIs have already demonstrated remarkable activity in both bortezomib-resistant

and newly diagnosed MM. Carfilzomib is a highly selective PI that irreversibly binds to the chymotrypsin-like catalytic activities of the 20S proteasome unit and to LMP7 subunits. Carfilzomib is more potent than bortezomib, achieving a 24% response rate as a single agent in bortezomib-refractory MM; moreover, a 78% overall response rate (ORR) and a tolerable safety profile were observed when carfilzomib was combined with lenalidomide and low-dose dexamethasone in relapsed MM after at least 1 prior therapy.<sup>2-4</sup> The phase 3 ASPIRE (Carfilzomib, Lenalidomide, and Dexamethasone Versus Lenalidomide and Dexamethasone for the Treatment of Patients with Relapsed Multiple Myeloma) clinical trial compared carfilzomib/lenalidomide plus low-dose dexamethasone vs lenalidomide/dexamethasone alone in RRMM, demonstrating 87.1% vs 66.7% ORR and improved progression-free survival.<sup>5</sup> The phase 3 ENDEAVOR (Phase 3 Study With Carfilzomib and Dexamethasone Versus Velcade and Dexamethasone for Relapsed Multiple Myeloma Patients) study is comparing carfilzomib/dexamethasone vs bortezomib/dexamethasone, and results are expected soon. Finally, carfilzomib in combination with pomalidomide and low-dose dexamethasone achieves a 70% ORR, even in RRMM.

Three other novel PIs have already demonstrated promising activity. Ixazomib (MLN9708) is an oral reversible PI that achieved a 20% ORR and a 30% rate of stable disease in RRMM.<sup>6,7</sup> Remarkably, ixazomib in combination with lenalidomide to treat newly diagnosed MM and as maintenance therapy showed a 92% ORR, a 58% rate of very good partial response or better, and a 27% rate of complete response. A total of 42% of the increased extent of response occurred with maintenance.<sup>8</sup> Ixazomib is currently under evaluation in clinical trials as up-front therapy in newly diagnosed patients in combination with lenalidomide and dexamethasone (NCT01936532) or cyclophosphamide (NCT02046070); as maintenance after autologous stem cell transplant (ASCT; NCT02181413); and as salvage therapy in RRMM together with lenalidomide/dexamethasone or pomalidomide/dexamethasone (NCT02119468) or panobinostat (Farydak, Novartis; NCT02057640).

Marizomib (NPI-0052) is an irreversible PI that more broadly inhibits the chymotrypsin-like, trypsin-like, and caspase-like protease activities within the proteasome. Hence, in preclinical studies marizomib has a unique efficacy and safety profile, with no cross-resistance with other PIs.<sup>9</sup> A phase 1/2 clinical trial of marizomib with or without dexamethasone has shown encouraging responses even in bortezomib- and lenalidomide-resistant MM (NCT00461045), and marizomib in combination with pomalidomide and dexamethasone is under evaluation in RRMM (NCT02103335).



**Figure 1.** Strategies to target protein homeostasis in multiple myeloma (MM). MM cells rely on tight control of protein homeostasis in order to prevent terminal unfolded protein response and apoptosis. Inhibition of proteasomes by targeting the 20S catalytic subunits or proteins involved in the degradation process, such as RPN13, is a successful strategy in MM. Moreover, modulation of enzymes responsible for ubiquitin ligation or removal can affect tumor growth as well. A fine-tuning of the unfolded protein response is also crucial to promote correct protein folding and prevent endoplasmic reticulum stress and apoptosis. Inhibitors of chaperone proteins, such as HSP70 and HSP90, or modulators of PERK and XBP1 splicing, can shift the balance towards terminal protein stress. Finally, HDAC6 inhibitors can prevent prosurvival autophagy and induce apoptosis in MM.

DUB, deubiquitinating enzyme; ER, endoplasmic reticulum; HDAC6, histone deacetylase 6; HSP, heat shock protein; PERK, protein kinase R-like ER kinase; Ub, ubiquitin; UPR, unfolded protein response; XBP1, X-box binding protein 1.

Finally, oprozomib is an oral chymotryptic PI that is active *in vitro* and *in vivo* in preclinical models.<sup>10</sup> It is in early clinical evaluation as monotherapy (NCT01416428) or in combination with lenalidomide or cyclophosphamide in newly diagnosed MM (NCT01881789) or with pomalidomide in RRMM (NCT01999335).

Novel strategies targeting protein homeostasis are also under evaluation to overcome PI resistance. In the ubiquitin proteasome cascade, proteins must be first tagged with ubiquitins<sup>11</sup>; conversely, DUBs can reverse this process and are often dysregulated in cancer, thereby abrogating degradation of oncoproteins. Furthermore, in MM DUB inhibition blocks the unfolded protein response, leads to lethal ER stress, and can overcome PI resistance. For example, the DUB ubiquitin-specific protease 7 (USP7)

controls important biological signaling pathways by regulating the stability of proteins such as FOXO4, PTEN, and murine double minute 2 (MDM2). USP7 is markedly elevated in MM cells, and the small molecule USP7 inhibitor P5091 induces MM cytotoxicity in preclinical models of MM, including bortezomib-resistant MM.<sup>12</sup> The DUBs USP14 and ubiquitin carboxyl-terminal hydrolase L5 (UCHL5) are also highly expressed in MM cells. The agent b-AP15, which selectively blocks the deubiquitinating activity of these 2 DUBs, shows preclinical anti-MM activity—even in bortezomib-resistant MM—and is entering clinical trials.<sup>13</sup>

Other strategies to target protein catabolism include E1, E2, and E3 ubiquitin ligases, which promote protein degradation with different profiles of selectivity. For

example, MDM2 is an E3 ligase that specifically controls p53 levels; and nutlin-3a is a potent nonpeptide MDM2 antagonist that blocks the interaction of p53 with MDM2, thereby stabilizing p53 and p21. In preclinical studies, nutlin-3a induces additive cytotoxicity with bortezomib.<sup>14</sup> Analogues of nutlin-3a, including DS-3032b, R7112, RITA, and HLI98, are under evaluation in both preclinical models and in clinical trials. Knockdown or inhibition of E1 ligase by PYZD-4409 reduces the abundance of ubiquitinated proteins and induces terminal ER stress in preclinical models of MM as well.<sup>15</sup> Proteins marked with ubiquitin chains are recognized by 2 proteasome subunits, RPN10 and RPN13.<sup>16</sup> RA190, a specific inhibitor of RPN13, blocks this interaction and has shown promising activity in preclinical models.<sup>17</sup> An alternative strategy is to target the unfolded protein response, a key survival pathway activated in MM in response to ER stress. In fact, inhibition of X-box binding protein 1 (XBP1) mRNA splicing by MKC-3946<sup>18</sup> or STF-083010,<sup>19</sup> and of protein kinase R-like ER kinase (PERK) by GSK2656157,<sup>20</sup> have shown anti-MM activity in preclinical models, either alone or in combination with PIs. Heat shock proteins (HSPs) play a chaperoning role in protein folding and degradation of misfolded proteins, and HSP70-HSP90 inhibitors are in preclinical and clinical evaluation in MM.<sup>21</sup> Finally, HDAC6, a class IIb cytoplasmic HDAC with tubulin as its substrate, plays a major role in shuttling misfolded proteins for degradation via the alternative aggresome pathway. Combined proteasome inhibition using bortezomib with HDAC6 inhibition via a specific HDAC6 inhibitor (ACY-1215) causes massive accumulation of misfolded proteins, triggers apoptosis, and can overcome PI resistance.<sup>22</sup> Ongoing phase 1/2 clinical trials are testing ACY-1215 alone or in combination with bortezomib, lenalidomide, and pomalidomide (NCT01323751 and NCT01583283).

### Modulating Immune Response in the MM Microenvironment

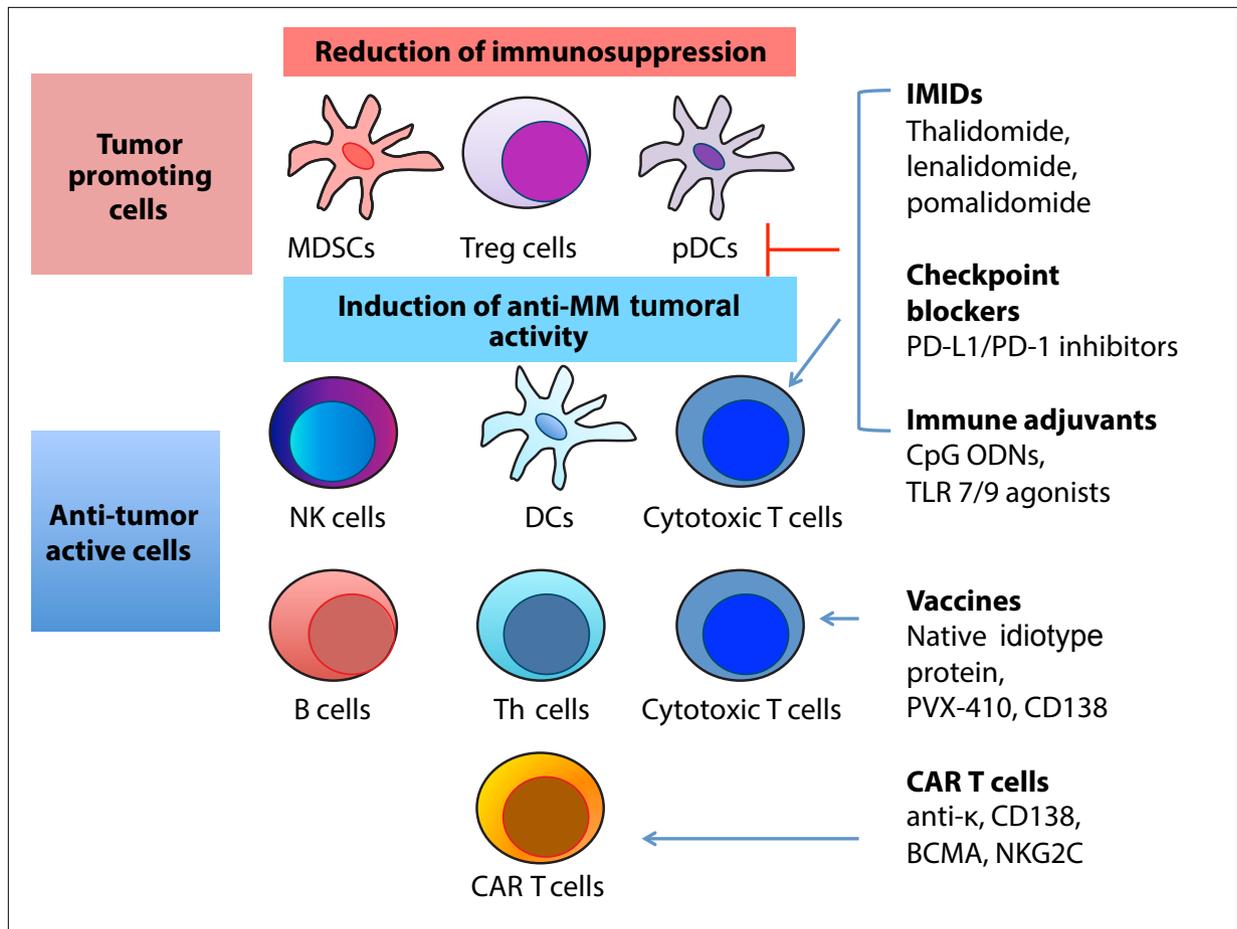
Patients with MM have a broad immune dysfunction that affects B lymphocytes, T lymphocytes, natural killer (NK) cells, and dendritic cells (DCs). These abnormalities result in an increased risk of infections, but also prevent effective immune antitumor activity.<sup>23</sup> Indeed, MM cells or bone marrow stromal cells (BMSCs) produce several cytokines, such as transforming growth factor  $\beta$  (TGF- $\beta$ ), interleukin 10 (IL-10), and IL-6. These cytokines block T-cell anti-MM responses,<sup>24</sup> stimulate T regulatory (Treg) cell proliferation, and reduce antigen-presenting capabilities of DCs.

Several classes of agents have been evaluated to overcome the antitumor immunosuppressive environment in MM (Figure 2).

IMiDs (thalidomide, lenalidomide, and pomalidomide) have direct activity against MM, but also enhance host anti-MM immunity by multiple mechanisms. By targeting cereblon, they downregulate Ikaros (IKZF1) and Aiolos (IKZF3) proteins. This in turn mediates, at least in part, their direct antitumor and host immune effects. IMiDs induce proliferation and activation of T and NK cells by triggering positive costimulatory molecule CD28 signaling in T cells, as well as promoting production of IL-2 and interferon- $\gamma$ . In addition, IMiDs downregulate Treg cells in MM. IMiDs also enhance DC antigen-presenting capabilities by inhibiting IL-6, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and IL-10 release. As a result of these direct and host effects, thalidomide- and lenalidomide-based regimens are the standard of care for newly diagnosed patients. Furthermore, lenalidomide is used as maintenance therapy until progression because several clinical trials in both transplant-eligible and transplant-ineligible patients have shown that it can prolong progression-free and overall survival.<sup>25-28</sup>

Pomalidomide/dexamethasone has been recently approved to treat RRMM, and is active even in lenalidomide- and bortezomib-refractory disease.<sup>29</sup> An ongoing trial is evaluating bortezomib/dexamethasone vs pomalidomide/bortezomib/dexamethasone (NCT01734928) in relapsed MM. Hence IMiDs, together with PIs, represent a cornerstone of treatment of both newly diagnosed and relapsed MM.

Novel therapies are also targeting the immunosuppressive microenvironment in MM. PD-L1 is a transmembrane protein expressed on MM cells as well as accessory plasmacytoid dendritic cells (pDCs) and myeloid-derived suppressor cells, which promote MM cell growth.<sup>30</sup> It interacts with PD-1, a member of the CD28 family of receptors, thereby blocking IL-2 production and proliferation/activation of CD8+ cytotoxic T cells (CTLs). Moreover, upregulation of PD-L1 on MM cells is triggered by their interaction with BMSCs.<sup>31,32</sup> Additionally, co-culture of MM cells with CD4+ T cells generates Tregs with high PD-1 levels, confirming the role of the PD-L1/PD-1 axis in the activation of Tregs in MM. Interestingly, PD-1 expression on T cells normalizes after ASCT,<sup>33</sup> suggesting that the PD-1/PD-L1 axis is transiently activated in MM and can be normalized with treatment. Lenalidomide decreases the expression of PD-1 on T cells<sup>34</sup> and of PD-L1 on MM cells.<sup>35</sup> Indeed, the growth of MM cells is inhibited in syngeneic PD-1-deficient mice or after treatment with an anti-PD-L1 specific antibody,<sup>36</sup> either of which reactivates T cell-NK cell function. Remarkably, several antibodies targeting PD-1 or PD-L1 have been studied in phase 1 and 2 clinical trials in patients with advanced solid or hematologic cancers as single agents, showing safe profile responses and durable responses.<sup>37,38</sup>



**Figure 2.** Strategies to modulate immune response in multiple myeloma (MM). MM cells are embedded in a dense tumor microenvironment that tends to suppress antitumor responses. Several strategies are under investigation for relieving the immunosuppressive phenotype of myeloid-derived suppressor cells, T regulatory cells, and plasmacytoid dendritic cells and promoting anti-MM responses by natural killer (NK) cells, dendritic cells (DCs), cytotoxic and helper T cells, and B cells. Specifically, IMiDs, checkpoint inhibitors, and immune adjuvants can both reduce the function of tumor-promoting cells and increase the antitumor activity of cells. Moreover, vaccines can induce specific anti-MM activity, promoting humoral responses (B cells), or tumor recognition (DC and T cells). Finally, chimeric antigen receptor T cells engineered from patient T cells can represent a novel strategy to specifically target malignant plasma cells.

BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; DC, dendritic cell; IMiD, immunomodulatory drug; MDSC, myeloid-derived suppressor cell; NK, natural killer; ODN, oligodeoxynucleotide; PD-1, programmed death 1; PD-L1, programmed death ligand 1; pDC, plasmacytoid dendritic cell; Th, T helper; TLR, toll-like receptor; Treg, T regulatory.

Recently, anti-PD-1 antibody therapy has been approved as therapy for relapsed melanoma, suggesting its clinical utility more broadly. In preclinical studies in MM, PD-L1 antibodies can abrogate the myeloid-derived suppressor cell (MDSC) and pDC immunosuppressive interaction with NK and T cells, thereby restoring effector cell anti-MM immunity, and lenalidomide further augments that response.<sup>30</sup> Early clinical trials are ongoing to test anti-PD-1 or anti-PD-L1 antibodies in MM, either as a single agent (NCT01375842) or in combination with lenalidomide (NCT02077959), anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA4) antibodies

(NCT01592370), or cancer vaccines (NCT01067287). Finally, anti-CTLA4 is another inhibitory molecule for T cells. Dual blockade of CTLA4 and PD-1/PD-L1 causes reversal of tumor-induced dysfunction of CD8+ tumor-infiltrating lymphocytes,<sup>39</sup> but clinical toxicities including pneumonitis and colitis have been reported in early clinical trials.<sup>40</sup>

Vaccine strategies have been evaluated in MM to overcome immunosuppressive effects and promote autologous anti-MM immunity. For example, the variable segment of the monoclonal immunoglobulin (idiotype) is antigen specific for each MM. Preclinical models using idiotype

vaccines have shown promising results, with death of the tumor cells and disease regression in a murine plasmacytoma MOPC-315 model. Native idiotype protein can be easily isolated from patient serum and then injected intradermally together with IL-12, with or without granulocyte-macrophage colony-stimulating factor, or pulsed on dendritic cells. These approaches have been evaluated in patients in remission after ASCT<sup>41</sup>; however, phase 1 and 2 clinical trials have not shown benefit<sup>42</sup> owing to the immunosuppressive MM microenvironment and/or the weak surface expression of idiotype proteins on MM cells.

Another vaccine strategy is based on stimulating immunity against MM antigens such as XBP1, CD138, signaling lymphocyte activating molecule family member 7 (SLAMF7), mucin 1 (MUC-1), or HSP90, individually or in combination. For example, a combined XBP1, CS1, and CD138 peptide vaccination strategy (PVX-410) is currently under evaluation, alone and with lenalidomide, to boost natural autologous antitumor immunity in smoldering MM and prevent progression to active MM.

An alternative tumor vaccine is produced by fusing patient-derived MM cells with autologous dendritic cells (MM-DC fusions). Vaccination with MM-DC fusions stimulated both helper and cytotoxic T-cell responses in preclinical models, and achieved stable disease along with humoral and cellular responses in a phase 1 study in RRMM.<sup>43</sup> Vaccination with MM-DC fusions after ASCT has induced anti-MM immunity with expansion of myeloma-specific CD4 and CD8+ T cells, associated with conversion of patients from partial response to complete response/near complete response in the late posttransplant period. An ongoing clinical trial is evaluating this vaccination strategy after ASCT in combination with PD-1 blockade; moreover, a randomized trial is scheduled to start this year to evaluate the efficacy of lenalidomide with or without MM-DC vaccination as maintenance after ASCT.

As noted above, another immune approach is to target pDCs, which are expanded in MM and promote tumor cell growth, survival, and drug resistance, as well as fail to induce effector cell responses.<sup>44</sup> Targeting these cells by CpG oligodeoxynucleotides<sup>44</sup> or with a novel TLR9 agonist<sup>45</sup> named C792 leads to their maturation and both abrogates their ability to stimulate MM cell growth and restores their stimulatory capacity for host immunity. IL-3 receptor immunotoxins, TLR7 agonists, and anti-PD-L1 antibodies target and promote maturation of pDCs, and also block pDC interaction with MM cells, showing promise in preclinical studies.

Finally, a novel exciting immunotherapeutic approach is based on the modification of autologous T cells with chimeric antigen receptors (CARs), to promote potent anti-MM immunity. CARs are synthetic transmembrane

proteins with an extracellular domain that recognizes a cell-surface antigen specific for the target tumor. They are composed of variable regions from the heavy and light chains of an immunoglobulin configured as a single polypeptide chain, and 1 or more intracellular signaling domains, such as the  $\zeta$  chain of the CD3 complex that initiates T cell-activating cascades upon antigen binding.<sup>46</sup> Anti-MM CARs are currently under evaluation in RRMM. The ideal CAR target should be a cell-surface molecule that is exclusive to the tumor cell in order to avoid off-target effects. In MM, clinical trials of CAR-modified T cells directed against the  $\kappa$  immunoglobulin light chain (NCT00881920), CD138, B-cell maturation antigen (NCT02215967), and NKG2D are ongoing. The anti- $\kappa$  CAR strategy causes depletion of  $\kappa$  light chain-restricted cells, sparing the repertoire of normal B cells expressing the uninvolved light chain. Although this approach is effective in preclinical studies,<sup>47</sup> only a minority of MM cells express surface immunoglobulins.<sup>48</sup> Anti-CD19 attached to T-cell receptor  $\zeta$  and 4-1BB signaling has been evaluated in an in vitro system and in a phase 1/2 clinical trial (NCT01886976; NCT02135406). Another strategy using 4-1BB-based second-generation CARs directed against CD138 is under evaluation; however, the plasticity in CD138 expression and the presence of CD138-low/negative subsets with enhanced clonogenicity within the MM clone<sup>49</sup> might limit this approach in patients. Finally, a phase 1 trial for MM and acute myeloid leukemia/myelodysplastic syndrome with CAR T cells expressing a chimeric NKG2D, an activating receptor to trigger NK-cell mediated lysis, will start soon at Dana-Farber Cancer Institute (NCT02203825).

## Monoclonal Antibodies and Immunotoxins

Monoclonal antibodies (mAbs) induce cytotoxicity by several mechanisms. mAbs can directly trigger apoptosis or induce growth arrest by blocking the agonist signals; they can cause antibody-dependent cellular cytotoxicity (ADCC), phagocytosis by macrophages, or cytolysis by NK cells due to the interaction between the Fc region of the mAb bound to the tumor cell and the Fc receptors present on neutrophils, macrophages or NK cells; or they can induce recruitment and activation of the complement proteolytic cascade, forming a membrane attack complex that kills the target cell by disrupting its cell membrane (complement-dependent cytotoxicity).

Several new mAbs are under evaluation in MM, with promising responses. Daratumumab and SAR650984 are 2 novel mAbs directed against CD38, a transmembrane glycoprotein expressed by the majority of MM cells. Daratumumab induces a potent ADCC against CD38-expressing MM cell lines and patient cells, maintains its activity in

the presence of BMSCs, and is active in vivo in xenograft MM models.<sup>50</sup> In the first phase 1 trial in RRMM, daratumumab showed a 42% response rate. In combination with lenalidomide/dexamethasone to augment ADCC, a remarkable extent and frequency of durable responses were observed in RRMM. Trials are ongoing with bortezomib/dexamethasone or lenalidomide/dexamethasone in patients with RRMM, as well as in smoldering MM (NCT02316106). SAR650984 is another CD38-directed mAb that, with lenalidomide/dexamethasone, has achieved a 63% partial response in RRMM.

Another promising target for mAb therapy is SLAMF7, a novel member of the SLAM-related receptor family that is highly expressed in MM cells, but weakly detectable on NK cells and absent in other tissues. SLAMF7 promotes MM growth and adhesion with different mechanisms, in part mediated via c-MAF activation.

Elotuzumab is a humanized anti-SLAMF7 mAb capable of inducing significant ADCC against MM cells even in the presence of BMSCs, overcoming resistance to bortezomib, and triggering synergic cytotoxicity with lenalidomide in preclinical MM models. Moreover, elotuzumab promotes SLAMF7-SLAMF7 interactions between NK cells and SLAMF7-positive target cells to enhance cytotoxicity and activate NK cells against MM. In a phase 1 study in RRMM, elotuzumab was well tolerated and induced stable disease. In a phase 1/2 trial, the combination elotuzumab/lenalidomide/dexamethasone achieved responses in 80% to 90% of RRMM patients lasting up to 33 months.<sup>51</sup> Phase 3 trials of elotuzumab/lenalidomide/dexamethasone vs lenalidomide/dexamethasone are ongoing in both RRMM and newly diagnosed MM (elotuzumab 1 substudy); elotuzumab is also being tested as monotherapy in smoldering MM (NCT01441973).

Other mAbs include dacetuzumab (SGN-40) and lucatumumab (HCD122), which recognize CD40-expressing MM cells, have antitumor activity in xenograft mouse models, and block IL-6-mediated MM growth.<sup>52,53</sup> Synergistic effects were observed in vitro with lenalidomide.<sup>54</sup> A phase 1 clinical trial in RRMM showed an acceptable safety profile and some preliminary evidence of clinical activity as monotherapy,<sup>55,56</sup> and phase 1b clinical trials of dacetuzumab combined with lenalidomide/dexamethasone or bortezomib have been completed.

HM1.24, also known as tetherin or CD317, is a type 2 transmembrane protein that is overexpressed on malignant plasma cells and behaves as a human leukocyte antigen-A2 (HLA-A2)-restricted T-cell epitope.<sup>57</sup> Antibodies recognizing this antigen (XmAb5592)<sup>58</sup> or immunotoxins generated by fusion of the HM1.24 antibody with a truncated variant of *Pseudomonas aeruginosa* exotoxin A have antitumor activity by ADCC or by induction of phagocytosis and

activation of NK cells both in vitro and in vivo. In addition, they demonstrate synergy with lenalidomide.<sup>59</sup>

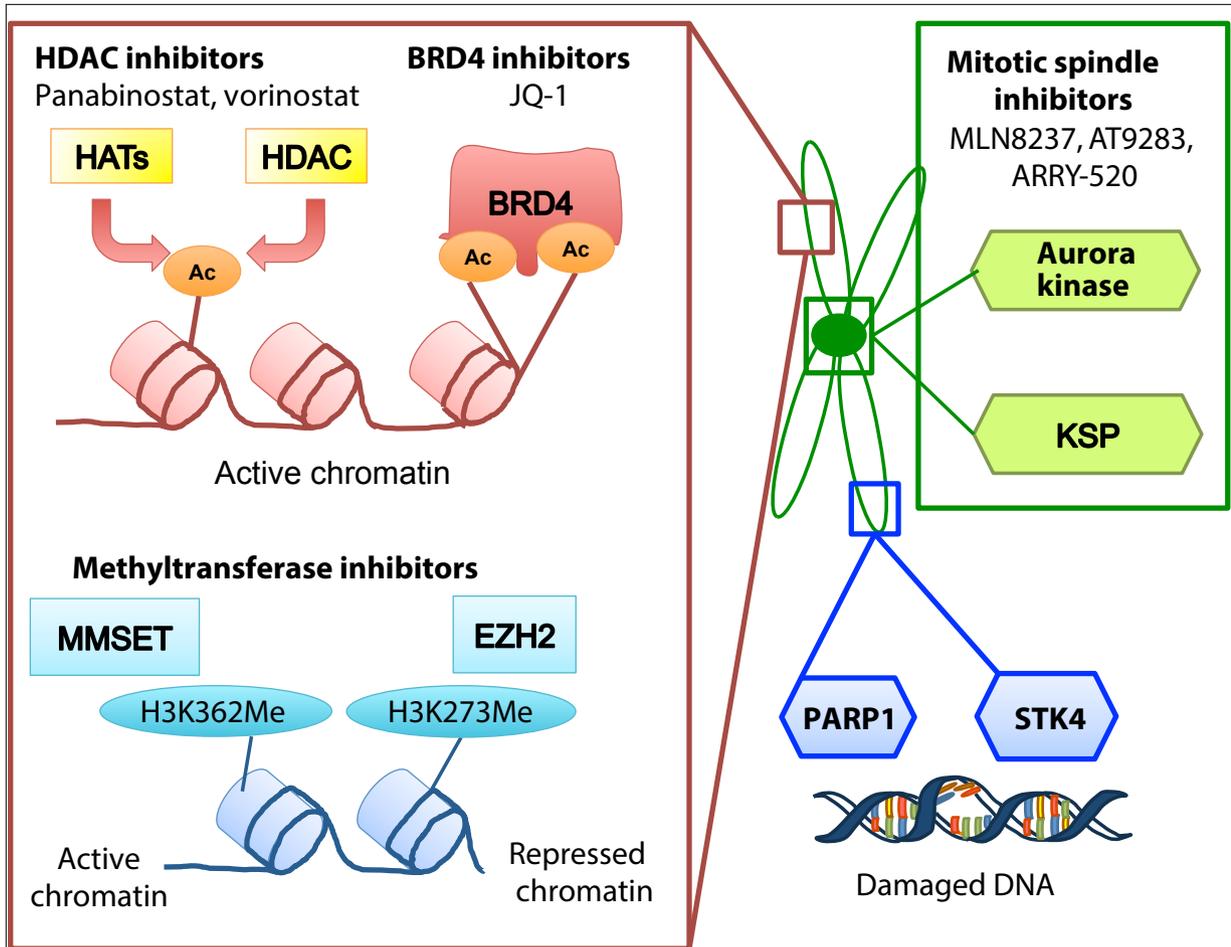
Sixty percent of MM patients express CD74, a transmembrane major histocompatibility complex (MHC) class II chaperone. Milatuzumab is a humanized anti-CD74 mAb<sup>60</sup> that demonstrates activity in MM xenograft models and in vitro, alone and in combination with bortezomib, doxorubicin, and dexamethasone.<sup>61</sup> A phase 1 trial of milatuzumab in heavily pretreated RRMM showed disease stabilization in 5 of 19 patients that continued for up to 17 months.<sup>62</sup>

Other mAbs against B-cell activating factor of the TNF family<sup>63</sup> are under evaluation in preclinical studies or early clinical trials. These include B-cell activating factor (BAFF) cognate receptors (transmembrane activator and calcium modulator<sup>64</sup> and B-cell maturation antigen<sup>65</sup>); TNF-related apoptosis-inducing ligand<sup>66</sup>; and killer cell immunoglobulin-like receptor.<sup>67</sup>

Malignant plasma cells normally lack or only weakly express CD20; however, a subgroup of patients with CD20+ MM can benefit from rituximab (Rituxan, Genentech/Biogen Idec), a mAb that recognizes the CD20 antigen.<sup>28</sup> IL-6 is a major growth factor in MM cells; multiple mAbs targeting IL-6 (tocilizumab, elsilimomab, and siltuximab) have shown promising results in preclinical studies.<sup>68</sup> For example, a phase 2 trial in RRMM of siltuximab in combination with either dexamethasone alone or bortezomib/dexamethasone achieved a 23% ORR.<sup>69,70</sup> However, in a randomized phase 3 study comparing siltuximab plus bortezomib/melphalan/prednisolone (VMP) vs VMP alone in patients with newly diagnosed MM ineligible for ASCT, only modest activity and no improvement in progression-free survival was observed.<sup>71</sup> Siltuximab is also under evaluation in smoldering MM (NCT01484275), given the high dependency on tumor microenvironment during early-stage disease.

Antibodies against CD56 (BB-10901 [huN901/DM1]) and CD138 (BT062) antigens expressed on the surface of plasma cells<sup>31</sup> have been conjugated with a maytansinoid (DM1 or DM4) toxin, a potent antimicrotubular cytotoxic agent, to increase their selective anti-MM activity,<sup>72</sup> and are under evaluation in clinical trials. BB-10901 reduces adhesion of CD56+ MM cell lines and patient MM cells to BMSCs and shows growth inhibitory effects in preclinical studies.<sup>73</sup> A small phase 1 clinical trial showed good tolerability and few durable minimal responses; BB-10901 is now under evaluation in combination with lenalidomide/dexamethasone in RRMM (NCT00991562).

CD138 is a hallmark marker of MM cells, expressed at higher levels in malignant compared with normal plasma cells. B-B4-DM1 and BT062 have potent CD138-dependent cytotoxicity that is maintained in the



**Figure 3.** Targeting histone modification and cell cycle in multiple myeloma (MM). MM cells have alterations in the control of transcription of oncogenes and tumor suppressors, which can be targeted by modulating BRD4 or blocking histone deacetylases or methyltransferases. Moreover, MM cells have genomic instability and ongoing DNA damage that can be modulated by different strategies.

Ac, acetylated; BRD4, bromodomain-containing protein 4; HAT, histone acetyltransferase; HDAC, histone deacetylase; KSP, kinesin spindle protein; MMSET, multiple myeloma SET domain; PARP, poly(adenosine diphosphate-ribose) polymerase; STK4, serine/threonine kinase 4.

presence of IL-6, insulin-like growth factor 1 (IGF-1), or adhesion of MM cells to BMSCs.<sup>74,75</sup> BT062 has a good safety profile in humans, and an ongoing phase 1/2 clinical trial in RRMM of BT062 with lenalidomide/dexamethasone in RRMM has shown a 75% to 90% ORR.

### Modulation of Bone Metabolism

An imbalance between osteoblast and osteoclast activity is a hallmark of MM, with suppression of bone formation and uncoupled activation of osteoclasts leading to bone lesions and bone pain.

Bisphosphonates such as pamidronate and zoledronic acid inhibit osteoclast activity and have shown efficacy in reducing bone pain, preventing bone-related complications, and controlling hypercalcemia.<sup>76</sup> Novel agents include mAbs directed against Dickkopf-1 (DKK1), activin

A, and nuclear factor  $\kappa$ B ligand (RANKL) to prevent MM-induced bone catabolism and/or promote bone formation. BHK880 targets DKK1, a soluble molecule secreted by MM cells that inhibits Wnt signaling and contributes to osteolytic bone disease by blocking the differentiation of osteoblasts.<sup>77</sup> Anti-DKK1 mAb induces a bone anabolic effect and a reduction in MM tumor burden in a severe combined immunodeficiency rabbit (SCID-rab) xenograft MM model.<sup>78</sup> A phase 1b trial of BHK880 in combination with zoledronic acid in RRMM showed a trend toward increased bone mineral density over time and was well tolerated.<sup>79</sup> BHK880 has also been evaluated in smoldering MM to prevent development of bone disease.

ACE-011 (sotatercept) recognizes activin A, a TGF- $\beta$  superfamily member upregulated in MM patients with bone involvement, which promotes osteoclastogenesis and inhibits osteoblast formation and function.<sup>80</sup> ACE-011

treatment in bone-lytic MM models causes an increase in bone mineral density, with improvement in bone architecture and mechanical stress.<sup>81,82</sup> ACE-011 was first evaluated in postmenopausal women who were randomly assigned to receive either a single dose of ACE-011 or placebo. Women in the ACE-011 group showed an increase in markers of bone formation and a reduction in markers of bone catabolism.<sup>83</sup> Interestingly, ACE-011 also has robust effects on erythropoiesis. Given its dual action on 2 main features of MM (bone lesions and anemia), ACE-011 may be beneficial in a broad group of patients. A recent phase 2 trial of ACE-011 combined with melphalan, prednisolone, and thalidomide (MPT) showed both bone anabolic effects and an increase in hemoglobin levels.<sup>84</sup> This agent is now under evaluation in RRMM in combination with lenalidomide/dexamethasone (NCT01562405) and also in transfusion dependent-anemia.

Finally, MM cells produce RANKL, a cytokine that binds to RANK receptors and stimulates osteoclast differentiation, formation, and survival.<sup>85</sup> Denosumab is a fully human mAb against RANKL under clinical investigation for the treatment of cancer-induced bone disease and other bone loss disorders.<sup>86</sup> In 1 study (NCT20050244), denosumab was more effective than zoledronic acid in preventing skeletal-related events in patients with bone metastases from advanced cancer, but unexpectedly showed a detrimental effect on overall survival in a subgroup analysis of MM patients.<sup>87</sup> A phase 3 trial evaluating denosumab vs zoledronic acid in MM is ongoing (NCT01345019).

## Targeting Histone Modifications

Histone proteins package DNA into structural units named nucleosomes, and undergo posttranslational modifications such as methylation and acetylation on lysine residues to regulate chromatin condensation and DNA accessibility (Figure 3, left panel). Histone acetylation is mediated by specific histone acetyltransferases, leading to open chromatin and active gene expression. Conversely, removal of acetyl groups by HDACs reduces transcription.<sup>88</sup> Eighteen HDACs exist divided into 4 classes: class I (HDACs 1, 2, 3, and 8), class IIa (HDACs 4, 5, 7, and 9), class IIb (HDACs 6 and 10), class III (SIRT family), and class IV (HDAC11).

Interestingly, apart from regulating transcription via histone modifications, HDACs also modulate the acetylation status of other substrate proteins, including NF- $\kappa$ B, p53, and signal transducer and activator of transcription (STAT) proteins.<sup>89,90</sup> HDAC proteins are upregulated in MM and can be targeted by HDAC inhibitors such as panobinostat and vorinostat, which have been tested recently in *in vitro* models and also in clinical trials.<sup>91-93</sup>

Panobinostat and vorinostat have activity against class I and class II HDACs. Despite modest efficacy as single-agent therapy, panobinostat in combination with melphalan, thalidomide, and prednisone in RRMM patients achieved partial responses in 38.5% of patients.<sup>94</sup> Together with bortezomib in a phase 2 study (PANORAMA 2; Efficacy of Panobinostat in Patients With Relapsed and Bortezomib-Refractory Multiple Myeloma)<sup>95</sup> and in a phase 3 study (PANORAMA 1) in patients with RRMM, panobinostat induced an increase in the median progression-free survival and complete responses.<sup>96</sup> Based on the results of these trials, panobinostat was recently approved as a treatment for RRMM.

Vorinostat is also a class I and II HDAC inhibitor. In a phase 1 study in which vorinostat was combined with lenalidomide, bortezomib, and dexamethasone in heavily treated MM patients, 52% of the patients responded, with 28% complete responses. A phase 3 trial of vorinostat/bortezomib vs bortezomib showed increased responses and a modest increase in progression-free survival in the combination treatment cohort.<sup>97</sup> However, in both the panobinostat and vorinostat phase 3 trials, side effects—including thrombocytopenia, diarrhea, and fatigue—limited therapy tolerability and duration. As noted earlier, the HDAC6 selective HDAC inhibitor ACY-1215 appears to be well tolerated and is under clinical evaluation in combination with both bortezomib and lenalidomide.

Histone proteins are also subjected to methylations; based on the number and type of methylated residues, transcription can either be promoted or inhibited. Multiple myeloma SET domain (MMSET) is a histone methyltransferase paired with FGFR3 in 15% of MM with t(4;14). Upregulation of MMSET causes a global alteration of histone methylation patterns, with accumulation of H3K36me2 marks causing transcriptional activation of oncogenic loci such as NF- $\kappa$ B, and a global reduction of H3K27me3 marks.<sup>98</sup> MMSET inhibitors are under development, representing a novel approach in t(4;14) MM.

Mutations in histone methyltransferases (*MLL*, *MLL2*, *MLL3*, *WHSC1*, and *WHSC1L1*), which increase *HOX9* expression; and in histone demethylase *UTX*, which is also deleted in up to 30% of MM patients, have recently been reported.<sup>99</sup> The histone-lysine N-methyltransferase *EZH2* is also upregulated in MM by IL-6 stimulation or c-MYC activation, or as a consequence of miR-26a downregulation, causing increased levels of the H3K27me3 silencing signature. Histone methylation-modifying drugs, including *EZH2* inhibitors, are therefore under development and might benefit a broad group of patients. Finally, a novel promising approach involves targeting the so-called super-enhancers that are “readers” of epigenetic marks.

Bromodomain-containing protein 4 (BRD4) is a member of the bromodomain and extraterminal (BET) subfamily of human bromodomain proteins, which associates with acetylated chromatin and facilitates transcriptional activation. BRD4 binds at exceptionally high levels to a small set of large enhancer regions called super enhancers, genomic areas associated with *MYC* and other key genes in MM biology. Preclinical studies showed that MM cells treated with the BRD4 inhibitor JQ1 have preferential loss of transcription at super enhancer-associated genes, including the *MYC* oncogene and other plasma cell-specific genes (*IGLL5*, *IRF4*, *PRDM1/BLIMP-1*, and *XBPI1*), but not of other BRD4 target genes.<sup>100,101</sup> This elegant epigenetic approach is one of the first attempts to target the genes specific for MM survival, exploiting the concept of oncogene addiction of cancer cells with minimal effects on other enhancers.

### Targeting Genomic Instability and Cell Cycle Alterations

A series of novel kinase inhibitors that target different aspects of genome integrity are under investigation in MM (Figure 3, right panel). Aurora kinase A and B are expressed at varying levels in primary MM cells, and patients whose MM has high Aurora kinase A expression have a higher tumor cell proliferation rate and inferior event-free and overall survival.<sup>102</sup> Several Aurora kinase inhibitors, including VX-680,<sup>102</sup> VE-465,<sup>103</sup> MLN8237 (alisertib),<sup>104</sup> and AT9283,<sup>105</sup> show anti-MM effects in preclinical models. To date, MLN8237 and AT9283 as monotherapy have been evaluated in phase 1 clinical trials,<sup>106</sup> and an ongoing study is combining MLN8237 with bortezomib (NCT01034553).

KSP is a microtubule motor protein essential for the formation of bipolar spindles during mitosis. Although transient inhibition of KSP leads to reversible mitotic arrest, prolonged exposure to a KSP inhibitor, such as ARRY-520 (filanesib), induces apoptosis in MM cells.<sup>107</sup> ARRY-520 is now undergoing evaluation in RRMM, alone (NCT00821249) or in combination with bortezomib (NCT01248923) or carfilzomib (NCT01989325 and NCT01372540). Interestingly, ARRY-520 binds  $\alpha$ -1 acid glycoprotein (AAG), an acute-phase reactant protein elevated in the blood of MM patients. Indeed, AAG levels can affect the free fraction of ARRY-520, and may therefore represent a biomarker to predict response.

Another promising therapeutic target is nuclear export protein CRM1/XPO1, which is highly expressed in several cancers as well as in MM. Inhibitors targeting CRM1 (KPT-185, KPT-330) induce cytotoxicity against MM cells, block c-MYC, Mcl-1, and NF- $\kappa$ B activity, and sensitize resistant cells to bortezomib.<sup>108</sup> In SCID mice

with diffuse bone lesions, these drugs showed strong anti-MM activity, and also inhibited osteoclastogenesis and bone resorption.<sup>109</sup> As monotherapy with dexamethasone, KPT-330 demonstrated a 67% ORR; studies combining KPT-330 with carfilzomib (NCT02199665) and liposomal doxorubicin (Doxil, Janssen) (NCT02186834) are ongoing and are showing promising results in RRMM.

Finally, another interesting approach is related to the concept of synthetic lethality, in which simultaneous perturbation of 2 genes results in cellular death. Specifically, we recently discovered that MM cells have high levels of constitutive DNA double strand breaks and DNA damage. To survive, MM cells inactivate YAP1 by homozygous deletion or downregulation through serine/threonine kinase 4 (STK4). STK4 silencing reactivates YAP1, thereby restoring p73-mediated apoptosis of MM cells with ongoing constitutive DNA damage.<sup>110</sup> Novel STK4 inhibitors are currently under development. Additionally, bortezomib can induce a “BRCAness” phenotype that interferes with DNA repair pathways. The use of PARP1/2 inhibitors with bortezomib can indeed trigger a contextual synthetic lethality in *in vitro* and *in vivo* models of MM<sup>111</sup> (Figure 3, right panel).

### Personalized Target Therapy in MM

The introduction of routine cytogenetics and fluorescence *in situ* hybridization studies, together with the frequent use of comparative genomic hybridization and whole-genome sequencing analysis for research purposes, has unveiled a plethora of genetic aberrations that can potentially be targeted in MM.

Cyclin D proteins are involved in G1/S phase cycle transition and dysregulated in the majority of MM patients, by both increased mRNA expression and chromosomal translocations.<sup>112</sup> Flavopiridol (alvocidib) is an inhibitor of several cyclin-dependent kinases (CDKs 1, 2, 4, 6, and 7) that has demonstrated cytotoxicity against MM cell lines.<sup>113</sup> Interestingly, flavopiridol also targets c-MET, a receptor for hepatocyte growth factor that mediates proliferation, migration, adhesion, and survival of MM cells. Unfortunately, flavopiridol used as monotherapy showed only marginal responses in RRMM, with attendant diarrhea, cytopenias, and transaminase elevation.<sup>114,115</sup> When flavopiridol was combined at lower doses with bortezomib, a 12% complete response and a 31% partial response were observed in a phase 1 study in patients with MM, indolent lymphomas, and mantle cell lymphomas.

Seliciclib (CYC202, R-roscovitine) is a novel CDK inhibitor with activity against CDK2/cyclin E, CDK7/cyclin H, and CDK9/cyclin D. Seliciclib reduces tumor growth in xenografts in nude mice,<sup>116</sup> and is currently in phase 2 clinical trials (NCT00112723). NS-032 (formerly

BMS-387032) is another potent, selective inhibitor of CDKs 2, 7, and 9 that is currently in phase 1 clinical trial for chronic lymphocytic leukemia and MM.<sup>117</sup>

Dinaciclib is another CDK inhibitor that is under evaluation as a single agent (NCT01096342) and in combination with bortezomib/dexamethasone (NCT01711528) in RRMM. Two of 29 patients treated with dinaciclib as monotherapy achieved very good partial responses, with others achieving disease stabilization. AT7519 and RGB-286638 are multitargeted cyclin-dependent kinase inhibitors with promising activity in preclinical settings.<sup>118,119</sup>

Importantly, a subset of MM carries an activating mutation (V600E) in the BRAF kinase, especially those with extramedullary disease and a short overall survival.<sup>120</sup> Anecdotal reports show responses in patients with BRAF-mutated MM treated with vemurafenib (Zelboraf, Genentech/Daiichi Sankyo), a specific kinase inhibitor.<sup>120,121</sup> A subset (15%-20%) of MM patients have a t(4;14) translocation that couples MMSET with FGFR3; this translocation is a poor prognostic marker.<sup>122</sup> Both small-molecule inhibitors and mAbs against FGFR3 are under clinical development. Multikinase inhibitors, such as PD173074, PKC412, and dovitinib, demonstrated anti-MM activity in FGFR3-expressing cell lines and also in xenograft models, even in the presence of *RAS* mutations.<sup>123-125</sup> Dovitinib is being evaluated in an ongoing phase 2 study in RRMM (NCT01058434). Finally, mAbs (PRO-011, R3Mab) against FGFR3 are also under evaluation.<sup>126</sup>

## Conclusion

The novel therapies introduced in the last 10 years have markedly expanded our therapeutic approach in patients with MM, extending the survival at least 3-fold. Novel targeted therapies, alone and in combination, will further improve patient outcome. In particular, novel immunotherapies with vaccines, checkpoint inhibitors, CAR T-cell therapies, mAbs, and IMiDs, alone and especially in combination, can enhance host anti-MM immunity, even in high-risk MM. These and other novel strategies are necessary to treat patients with unfavorable prognostic factors, such as chromosome 17p deletions and/or *TP53* mutations, and to target specific tumoral abnormalities in subsets of patients with MM. Ongoing basic and translational research will define disease heterogeneity, identify novel biomarkers, validate new targeted therapies, and ultimately allow for effective personalized medicine in MM.

## Disclosures

Dr Anderson is on the advisory boards of Celgene, Millennium, Gilead, Sanofi-Aventis, and Bristol Myers Squibb, and he is a scientific founder of Acetylon and Oncopep. Dr Cottini has declared no financial conflicts of interest.

## References

1. Lawasut P, Chauhan D, Laubach J, et al. New proteasome inhibitors in myeloma. *Curr Hematol Malign Rep*. 2012;7(4):258-266.
2. Jakubowiak AJ, Siegel DS, Martin T, et al. Treatment outcomes in patients with relapsed and refractory multiple myeloma and high-risk cytogenetics receiving single-agent carfilzomib in the PX-171-003-A1 study. *Leukemia*. 2013;27(12):2351-2356.
3. Siegel DS, Martin T, Wang M, et al. A phase 2 study of single-agent carfilzomib (PX-171-003-A1) in patients with relapsed and refractory multiple myeloma. *Blood*. 2012;120(14):2817-2825.
4. Andreu-Vieyra C, Berenson JR. Carfilzomib in multiple myeloma. *Expert Opin Biol Ther*. 2014;14(11):1685-1699.
5. Stewart AK, Rajkumar SV, Dimopoulos MA, et al; ASPIRE Investigators. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. *N Engl J Med*. 2015;372(2):142-152.
6. Kumar SK, Bensinger WI, Zimmerman TM, et al. Phase 1 study of weekly dosing with the investigational oral proteasome inhibitor ixazomib in relapsed/refractory multiple myeloma. *Blood*. 2014;124(7):1047-1055.
7. Richardson PG, Baz R, Wang M, et al. Phase 1 study of twice-weekly ixazomib, an oral proteasome inhibitor, in relapsed/refractory multiple myeloma patients. *Blood*. 2014;124(7):1038-1046.
8. Kumar SK, Berdeja JG, Niesvizky R, et al. Safety and tolerability of ixazomib, an oral proteasome inhibitor, in combination with lenalidomide and dexamethasone in patients with previously untreated multiple myeloma: an open-label phase 1/2 study. *Lancet Oncol*. 2014;15(13):1503-1512.
9. Potts BC, Albitar MX, Anderson KC, et al. Marizomib, a proteasome inhibitor for all seasons: preclinical profile and a framework for clinical trials. *Curr Cancer Drug Targets*. 2011;11(3):254-284.
10. Chauhan D, Singh AV, Aujay M, et al. A novel orally active proteasome inhibitor ONX 0912 triggers in vitro and in vivo cytotoxicity in multiple myeloma. *Blood*. 2010;116(23):4906-4915.
11. Lim KH, Baek KH. Deubiquitinating enzymes as therapeutic targets in cancer. *Curr Pharm Des*. 2013;19(22):4039-4052.
12. Chauhan D, Tian Z, Nicholson B, et al. A small molecule inhibitor of ubiquitin-specific protease-7 induces apoptosis in multiple myeloma cells and overcomes bortezomib resistance. *Cancer Cell*. 2012;22(3):345-358.
13. Tian Z, D'Arcy P, Wang X, et al. A novel small molecule inhibitor of deubiquitylating enzyme USP14 and UCHL5 induces apoptosis in multiple myeloma and overcomes bortezomib resistance. *Blood*. 2014;123(5):706-716.
14. Ooi MG, Hayden PJ, Kotoula V, et al. Interactions of the Hdm2/p53 and proteasome pathways may enhance the antitumor activity of bortezomib. *Clin Cancer Res*. 2009;15(23):7153-7160.
15. Xu GW, Ali M, Wood TE, et al. The ubiquitin-activating enzyme E1 as a therapeutic target for the treatment of leukemia and multiple myeloma. *Blood*. 2010;115(11):2251-2259.
16. Deveraux Q, Ustrell V, Pickart C, Rechsteiner M. A 26 S protease subunit that binds ubiquitin conjugates. *J Biol Chem*. 1994;269(10):7059-7061.
17. Anchoori RK, Karanam B, Peng S, et al. A bis-benzylidene piperidone targeting proteasome ubiquitin receptor RPN13/ADRM1 as a therapy for cancer. *Cancer Cell*. 2013;24(6):791-805.
18. Mimura N, Fulciniti M, Gorgun G, et al. Blockade of XBP1 splicing by inhibition of IRE1 $\alpha$  is a promising therapeutic option in multiple myeloma. *Blood*. 2012;119(24):5772-5781.
19. Papanreou I, Denko NC, Olson M, et al. Identification of an Ire1 $\alpha$  endonuclease specific inhibitor with cytotoxic activity against human multiple myeloma. *Blood*. 2011;117(4):1311-1314.
20. Atkins C, Liu Q, Minthorn E, et al. Characterization of a novel PERK kinase inhibitor with antitumor and antiangiogenic activity. *Cancer Res*. 2013;73(6):1993-2002.
21. Zhang L, Fok JH, Davies FE. Heat shock proteins in multiple myeloma. *Oncotarget*. 2014;5(5):1132-1148.
22. Santo L, Hideshima T, Kung AL, et al. Preclinical activity, pharmacodynamic, and pharmacokinetic properties of a selective HDAC6 inhibitor, ACY-1215, in combination with bortezomib in multiple myeloma. *Blood*. 2012;119(11):2579-2589.
23. Pratt G, Goodyear O, Moss P. Immunodeficiency and immunotherapy in multiple myeloma. *Br J Haematol*. 2007;138(5):563-579.
24. Cook G, Campbell JD. Immune regulation in multiple myeloma: the host-tumour conflict. *Blood Rev*. 1999;13(3):151-162.
25. Attal M, Lauwers-Cances V, Marit G, et al; IFM Investigators. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. *N Engl J Med*. 2012;366(19):1782-1791.

26. McCarthy PL, Owzar K, Hofmeister CC, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. *N Engl J Med*. 2012;366(19):1770-1781.
27. Palumbo A, Cavallo F, Gay F, et al. Autologous transplantation and maintenance therapy in multiple myeloma. *N Engl J Med*. 2014;371(10):895-905.
28. Benboubker L, Dimopoulos MA, Dispenzieri A, et al; FIRST Trial Team. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. *N Engl J Med*. 2014;371(10):906-917.
29. Usmani SZ, Zhang Q, Stratton K, et al. Phase II study of pomalidomide in high-risk relapsed and refractory multiple myeloma. *Leukemia*. 2014;28(12):2413-2415.
30. Ray A, Das DS, Song Y, et al. Targeting PD1-PDL1 immune checkpoint in plasmacytoid dendritic cell interactions with T cells, natural killer cells and multiple myeloma cells [published online January 30, 2015]. *Leukemia*. doi:10.1038/leu.2015.11.
31. Liu J, Hamrouni A, Wolowicz D, et al. Plasma cells from multiple myeloma patients express B7-H1 (PD-L1) and increase expression after stimulation with IFN-gamma and TLR ligands via a MyD88-, TRAF6-, and MEK-dependent pathway. *Blood*. 2007;110(1):296-304.
32. Atanackovic D, Luetkens T, Kröger N. Coinhibitory molecule PD-1 as a potential target for the immunotherapy of multiple myeloma. *Leukemia*. 2014;28(5):993-1000.
33. Rosenblatt J, Glotzbecker B, Mills H, et al. PD-1 blockade by CT-011, anti-PD-1 antibody, enhances ex vivo T-cell responses to autologous dendritic cell/myeloma fusion vaccine. *J Immunother*. 2011;34(5):409-418.
34. Luptakova K, Rosenblatt J, Glotzbecker B, et al. Lenalidomide enhances anti-myeloma cellular immunity. *Cancer Immunol Immunother*. 2013;62(1):39-49.
35. Benson DM Jr, Bakan CE, Mishra A, et al. The PD-1/PD-L1 axis modulates the natural killer cell versus multiple myeloma effect: a therapeutic target for CT-011, a novel monoclonal anti-PD-1 antibody. *Blood*. 2010;116(13):2286-2294.
36. Iwai Y, Ishida M, Tanaka Y, Okazaki T, Honjo T, Minato N. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. *Proc Natl Acad Sci USA*. 2002;99(19):12293-12297.
37. Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Engl J Med*. 2012;366(26):2455-2465.
38. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med*. 2012;366(26):2443-2454.
39. Duraiswamy J, Kaluzs KM, Freeman GJ, Coukos G. Dual blockade of PD-1 and CTLA-4 combined with tumor vaccine effectively restores T-cell rejection function in tumors. *Cancer Res*. 2013;73(12):3591-3603.
40. Wolchok JD, Kluger H, Callahan MK, et al. Nivolumab plus ipilimumab in advanced melanoma. *N Engl J Med*. 2013;369(2):122-133.
41. Rasmussen T, Hansson L, Osterborg A, Johnsen HE, Mellstedt H. Idiotype vaccination in multiple myeloma induced a reduction of circulating clonal tumor B cells. *Blood*. 2003;101(11):4607-4610.
42. Titzler S, Christensen O, Manzke O, et al. Vaccination of multiple myeloma patients with idiotype-pulsed dendritic cells: immunological and clinical aspects. *Br J Haematol*. 2000;108(4):805-816.
43. Rosenblatt J, Vasir B, Uhl L, et al. Vaccination with dendritic cell/tumor fusion cells results in cellular and humoral antitumor immune responses in patients with multiple myeloma. *Blood*. 2011;117(2):393-402.
44. Chauhan D, Singh AV, Brahmandam M, et al. Functional interaction of plasmacytoid dendritic cells with multiple myeloma cells: a therapeutic target. *Cancer Cell*. 2009;16(4):309-323.
45. Ray A, Tian Z, Das DS, et al. A novel TLR-9 agonist C792 inhibits plasmacytoid dendritic cell-induced myeloma cell growth and enhance cytotoxicity of bortezomib. *Leukemia*. 2014;28(8):1716-1724.
46. Maus MV, Grupp SA, Porter DL, June CH. Antibody-modified T cells: CARs take the front seat for hematologic malignancies. *Blood*. 2014;123(17):2625-2635.
47. Vera J, Savoldo B, Vigouroux S, et al. T lymphocytes redirected against the kappa light chain of human immunoglobulin efficiently kill mature B lymphocyte-derived malignant cells. *Blood*. 2006;108(12):3890-3897.
48. Ocqueteau M, Orfão A, García R, San Miguel JF. Detection of monoclonality in bone marrow plasma cells by flow cytometry: limitations for minimal residual disease detection. *Br J Haematol*. 1996;93(1):251-252.
49. Chaidos A, Barnes CP, Cowan G, et al. Clinical drug resistance linked to interconvertible phenotypic and functional states of tumor-propagating cells in multiple myeloma. *Blood*. 2013;121(2):318-328.
50. de Weers M, Tai YT, van der Veer MS, et al. Daratumumab, a novel therapeutic human CD38 monoclonal antibody, induces killing of multiple myeloma and other hematological tumors. *J Immunol*. 2011;186(3):1840-1848.
51. Lonial S, Vij R, Harousseau JL, et al. Elotuzumab in combination with lenalidomide and low-dose dexamethasone in relapsed or refractory multiple myeloma. *J Clin Oncol*. 2012;30(16):1953-1959.
52. Hayashi T, Treon SP, Hideshima T, et al. Recombinant humanized anti-CD40 monoclonal antibody triggers autologous antibody-dependent cell-mediated cytotoxicity against multiple myeloma cells. *Br J Haematol*. 2003;121(4):592-596.
53. Tai YT, Li X, Tong X, et al. Human anti-CD40 antagonist antibody triggers significant antitumor activity against human multiple myeloma. *Cancer Res*. 2005;65(13):5898-5906.
54. Tai YT, Li XF, Catley L, et al. Immunomodulatory drug lenalidomide (CC-5013, IMiD3) augments anti-CD40 SGN-40-induced cytotoxicity in human multiple myeloma: clinical implications. *Cancer Res*. 2005;65(24):11712-11720.
55. Hussein M, Berenson JR, Niesvizky R, et al. A phase I multidose study of dacetuzumab (SGN-40; humanized anti-CD40 monoclonal antibody) in patients with multiple myeloma. *Haematologica*. 2010;95(5):845-848.
56. Bensinger W, Maziarsz RT, Jagannath S, et al. A phase 1 study of lucatumumab, a fully human anti-CD40 antagonist monoclonal antibody administered intravenously to patients with relapsed or refractory multiple myeloma. *Br J Haematol*. 2012;159(1):58-66.
57. Hundemer M, Schmidt S, Condomines M, et al. Identification of a new HLA-A2-restricted T-cell epitope within HM1.24 as immunotherapy target for multiple myeloma. *Exp Hematol*. 2006;34(4):486-496.
58. Tai YT, Horton HM, Kong SY, et al. Potent in vitro and in vivo activity of an Fc-engineered humanized anti-HM1.24 antibody against multiple myeloma via augmented effector function. *Blood*. 2012;119(9):2074-2082.
59. Harada T, Ozaki S, Oda A, et al. Combination with a defucosylated anti-HM1.24 monoclonal antibody plus lenalidomide induces marked ADCC against myeloma cells and their progenitors. *PLoS One*. 2013;8(12):e83905.
60. Mark T, Martin P, Leonard JP, Niesvizky R. Milatuzumab: a promising new agent for the treatment of lymphoid malignancies. *Expert Opin Investig Drugs*. 2009;18(1):99-104.
61. Stein R, Smith MR, Chen S, Zalath M, Goldenberg DM. Combining milatuzumab with bortezomib, doxorubicin, or dexamethasone improves responses in multiple myeloma cell lines. *Clin Cancer Res*. 2009;15(8):2808-2817.
62. Kaufman JL, Niesvizky R, Stadmauer EA, et al. Phase I, multicentre, dose-escalation trial of monotherapy with milatuzumab (humanized anti-CD74 monoclonal antibody) in relapsed or refractory multiple myeloma. *Br J Haematol*. 2013;163(4):478-486.
63. Neri P, Kumar S, Fulciniti MT, et al. Neutralizing B-cell activating factor antibody improves survival and inhibits osteoclastogenesis in a severe combined immunodeficient human multiple myeloma model. *Clin Cancer Res*. 2007;13(19):5903-5909.
64. Yaccoby S, Pennisi A, Li X, et al. Atacicept (TACI-Ig) inhibits growth of TACI(high) primary myeloma cells in SCID-hu mice and in coculture with osteoclasts. *Leukemia*. 2008;22(2):406-413.
65. Tai YT, Mayes PA, Acharya C, et al. Novel anti-B-cell maturation antigen antibody-drug conjugate (GSK2857916) selectively induces killing of multiple myeloma. *Blood*. 2014;123(20):3128-3138.
66. Menoret E, Gomez-Bougie P, Geffroy-Luseau A, et al. Mcl-1L cleavage is involved in TRAIL-R1- and TRAIL-R2-mediated apoptosis induced by HGS-ETR1 and HGS-ETR2 human mAbs in myeloma cells. *Blood*. 2006;108(4):1346-1352.
67. Benson DM Jr, Bakan CE, Zhang S, et al. IPH2101, a novel anti-inhibitory KIR antibody, and lenalidomide combine to enhance the natural killer cell versus multiple myeloma effect. *Blood*. 2011;118(24):6387-6391.
68. Fulciniti M, Hideshima T, Vermot-Desroches C, et al. A high-affinity fully human anti-IL-6 mAb, 1339, for the treatment of multiple myeloma. *Clin Cancer Res*. 2009;15(23):7144-7152.
69. Kurzrock R, Voorhees PM, Casper C, et al. A phase I, open-label study of siltuximab, an anti-IL-6 monoclonal antibody, in patients with B-cell non-Hodgkin lymphoma, multiple myeloma, or Castleman disease. *Clin Cancer Res*. 2013;19(13):3659-3670.
70. Voorhees PM, Manges RF, Sonneveld P, et al. A phase 2 multicentre study of siltuximab, an anti-interleukin-6 monoclonal antibody, in patients with relapsed or refractory multiple myeloma. *Br J Haematol*. 2013;161(3):357-366.
71. San-Miguel J, Bladé J, Shpilberg O, et al. Phase 2 randomized study of bortezomib-melphalan-prednisone with or without siltuximab (anti-IL-6) in multiple myeloma. *Blood*. 2014;123(26):4136-4142.
72. Lutz RJ, Whiteman KR. Antibody-maytansinoid conjugates for the treatment of myeloma. *MAbs*. 2009;1(6):548-551.
73. Tassone P, Gozzini A, Goldmacher V, et al. In vitro and in vivo activity of the maytansinoid immunoconjugate huN901-N2'-deacetyl-N2'-3-mercapto-1-oxopropyl)-maytansine against CD56+ multiple myeloma cells. *Cancer Res*. 2004;64(13):4629-4636.
74. Ikeda H, Hideshima T, Fulciniti M, et al. The monoclonal antibody nBT062 conjugated to cytotoxic maytansinoids has selective cytotoxicity against CD138-positive multiple myeloma cells in vitro and in vivo. *Clin Cancer Res*. 2009;15(12):4028-4037.

75. Tassone P, Goldmacher VS, Neri P, et al. Cytotoxic activity of the maytansinoid immunoconjugate B-B4-DM1 against CD138+ multiple myeloma cells. *Blood*. 2004;104(12):3688-3696.
76. Raje N, Roodman GD. Advances in the biology and treatment of bone disease in multiple myeloma. *Clin Cancer Res*. 2011;17(6):1278-1286.
77. Heath DJ, Chantry AD, Buckle CH, et al. Inhibiting Dickkopf-1 (Dkk1) removes suppression of bone formation and prevents the development of osteolytic bone disease in multiple myeloma. *J Bone Miner Res*. 2009;24(3):425-436.
78. Fulciniti M, Tassone P, Hideshima T, et al. Anti-DKK1 mAb (BHQ880) as a potential therapeutic agent for multiple myeloma. *Blood*. 2009;114(2):371-379.
79. Iyer SP, Beck JT, Stewart AK, et al. A Phase IB multicentre dose-determination study of BHQ880 in combination with anti-myeloma therapy and zoledronic acid in patients with relapsed or refractory multiple myeloma and prior skeletal-related events. *Br J Haematol*. 2014;167(3):366-375.
80. Terpos E, Kastritis E, Christoulas D, et al. Circulating activin-A is elevated in patients with advanced multiple myeloma and correlates with extensive bone involvement and inferior survival; no alterations post-lenalidomide and dexamethasone therapy. *Ann Oncol*. 2012;23(10):2681-2686.
81. Vallet S, Mukherjee S, Vaghela N, et al. Activin A promotes multiple myeloma-induced osteolysis and is a promising target for myeloma bone disease. *Proc Natl Acad Sci USA*. 2010;107(11):5124-5129.
82. Scullen T, Santo L, Vallet S, et al. Lenalidomide in combination with an activin A-neutralizing antibody: preclinical rationale for a novel anti-myeloma strategy. *Leukemia*. 2013;27(8):1715-1721.
83. Ruckle J, Jacobs M, Kramer W, et al. Single-dose, randomized, double-blind, placebo-controlled study of ACE-011 (ActRIIA-IgG1) in postmenopausal women. *J Bone Miner Res*. 2009;24(4):744-752.
84. Abdulkadyrov KM, Salogub GN, Khuazheva NK, et al. Sotatercept in patients with osteolytic lesions of multiple myeloma. *Br J Haematol*. 2014;165(6):814-823.
85. Li J, Sarosi I, Yan XQ, et al. RANK is the intrinsic hematopoietic cell surface receptor that controls osteoclastogenesis and regulation of bone mass and calcium metabolism. *Proc Natl Acad Sci USA*. 2000;97(4):1566-1571.
86. Body JJ, Facon T, Coleman RE, et al. A study of the biological receptor activator of nuclear factor-kappaB ligand inhibitor, denosumab, in patients with multiple myeloma or bone metastases from breast cancer. *Clin Cancer Res*. 2006;12(4):1221-1228.
87. Lipton A, Fizazi K, Satoeck AT, et al. Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: a combined analysis of 3 pivotal, randomised, phase 3 trials. *Eur J Cancer*. 2012;48(16):3082-3092.
88. Grunstein M. Histone acetylation in chromatin structure and transcription. *Nature*. 1997;389(6649):349-352.
89. Spange S, Wagner T, Heinzl T, Krämer OH. Acetylation of non-histone proteins modulates cellular signalling at multiple levels. *Int J Biochem Cell Biol*. 2009;41(1):185-198.
90. Minami J, Suzuki R, Mazitschek R, et al. Histone deacetylase 3 as a novel therapeutic target in multiple myeloma. *Leukemia*. 2014;28(3):680-689.
91. Dimopoulos K, Gimsing P, Grønbaek K. The role of epigenetics in the biology of multiple myeloma. *Blood Cancer J*. 2014;4(5):e207.
92. Minucci S, Pelicci PG. Histone deacetylase inhibitors and the promise of epigenetic (and more) treatments for cancer. *Nat Rev Cancer*. 2006;6(1):38-51.
93. Hideshima T, Anderson KC. Histone deacetylase inhibitors in the treatment for multiple myeloma. *Int J Hematol*. 2013;97(3):324-332.
94. Offidani M, Polloni C, Cavallo F, et al. Phase II study of melphalan, thalidomide and prednisone combined with oral panobinostat in patients with relapsed/refractory multiple myeloma. *Leuk Lymphoma*. 2012;53(9):1722-1727.
95. Richardson PG, Schlossman RL, Alsina M, et al. PANORAMA 2: panobinostat in combination with bortezomib and dexamethasone in patients with relapsed and bortezomib-refractory myeloma. *Blood*. 2013;122(14):2331-2337.
96. San-Miguel JF, Hungria VT, Yoon SS, et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. *Lancet Oncol*. 2014;15(11):1195-1206.
97. Dimopoulos M, Siegel DS, Lonial S, et al. Vorinostat or placebo in combination with bortezomib in patients with multiple myeloma (VANTAGE 088): a multicentre, randomised, double-blind study. *Lancet Oncol*. 2013;14(11):1129-1140.
98. Martinez-Garcia E, Popovic R, Min DJ, et al. The MMSSET histone methyltransferase switches global histone methylation and alters gene expression in t(4;14) multiple myeloma cells. *Blood*. 2011;117(1):211-220.
99. Chapman MA, Lawrence MS, Keats JJ, et al. Initial genome sequencing and analysis of multiple myeloma. *Nature*. 2011;471(7339):467-472.
100. Delmore JE, Issa GC, Lemieux ME, et al. BET bromodomain inhibition as a therapeutic strategy to target c-Myc. *Cell*. 2011;146(6):904-917.
101. Lovén J, Hoke HA, Lin CY, et al. Selective inhibition of tumor oncogenes by disruption of super-enhancers. *Cell*. 2013;153(2):320-334.
102. Hose D, Rème T, Meissner T, et al. Inhibition of aurora kinases for tailored risk-adapted treatment of multiple myeloma. *Blood*. 2009;113(18):4331-4340.
103. Negri JM, McMillin DW, Delmore J, et al. In vitro anti-myeloma activity of the Aurora kinase inhibitor VE-465. *Br J Haematol*. 2009;147(5):672-676.
104. Görgün G, Calabrese E, Hideshima T, et al. A novel Aurora-A kinase inhibitor MLN8237 induces cytotoxicity and cell-cycle arrest in multiple myeloma. *Blood*. 2010;115(25):5202-5213.
105. Santo L, Hideshima T, Cirstea D, et al. Antimyeloma activity of a multitargeted kinase inhibitor, AT9283, via potent Aurora kinase and STAT3 inhibition either alone or in combination with lenalidomide. *Clin Cancer Res*. 2011;17(10):3259-3271.
106. Kelly KR, Shea TC, Goy A, et al. Phase I study of MLN8237—investigational Aurora A kinase inhibitor—in relapsed/refractory multiple myeloma, non-Hodgkin lymphoma and chronic lymphocytic leukemia. *Invest New Drugs*. 2014;32(3):489-499.
107. Tunquist BJ, Woessner RD, Walker DH. Mcl-1 stability determines mitotic cell fate of human multiple myeloma tumor cells treated with the kinesin spindle protein inhibitor ARRY-520. *Mol Cancer Ther*. 2010;9(7):2046-2056.
108. Turner JG, Dawson J, Emmons MF, et al. CRM1 inhibition sensitizes drug resistant human myeloma cells to topoisomerase II and proteasome inhibitors both in vitro and ex vivo. *J Cancer*. 2013;4(8):614-625.
109. Tai YT, Landesman Y, Acharya C, et al. CRM1 inhibition induces tumor cell cytotoxicity and impairs osteoclastogenesis in multiple myeloma: molecular mechanisms and therapeutic implications. *Leukemia*. 2014;28(1):155-165.
110. Cottini F, Hideshima T, Xu C, et al. Rescue of Hippo coactivator YAP1 triggers DNA damage-induced apoptosis in hematological cancers. *Nat Med*. 2014;20(6):599-606.
111. Neri P, Ren L, Gratton K, et al. Bortezomib-induced "BRCAness" sensitizes multiple myeloma cells to PARP inhibitors. *Blood*. 2011;118(24):6368-6379.
112. Bergsagel PL, Kuehl WM, Zhan F, Sawyer J, Barlogie B, Shaughnessy J Jr. Cyclin D dysregulation: an early and unifying pathogenic event in multiple myeloma. *Blood*. 2005;106(1):296-303.
113. Semenov I, Akyuz C, Roginskaya V, Chauhan D, Corey SJ. Growth inhibition and apoptosis of myeloma cells by the CDK inhibitor flavopiridol. *Leuk Res*. 2002;26(3):271-280.
114. Dispenzieri A, Gertz MA, Lacy MQ, et al. Flavopiridol in patients with relapsed or refractory multiple myeloma: a phase 2 trial with clinical and pharmacodynamic end-points. *Haematologica*. 2006;91(3):390-393.
115. Hofmeister CC, Poi M, Bowers MA, et al. A phase I trial of flavopiridol in relapsed multiple myeloma. *Cancer Chemother Pharmacol*. 2014;73(2):249-257.
116. Raje N, Kumar S, Hideshima T, et al. Seliciclib (CYC202 or R-roscovitine), a small-molecule cyclin-dependent kinase inhibitor, mediates activity via down-regulation of Mcl-1 in multiple myeloma. *Blood*. 2005;106(3):1042-1047.
117. Conroy A, Stockett DE, Walker D, et al. SNS-032 is a potent and selective CDK 2, 7 and 9 inhibitor that drives target modulation in patient samples. *Cancer Chemother Pharmacol*. 2009;64(4):723-732.
118. Cirstea D, Hideshima T, Santo L, et al. Small-molecule multi-targeted kinase inhibitor RGB-286638 triggers P53-dependent and -independent anti-multiple myeloma activity through inhibition of transcriptional CDKs. *Leukemia*. 2013;27(12):2366-2375.
119. Santo L, Vallet S, Hideshima T, et al. AT7519, A novel small molecule multi-cyclin-dependent kinase inhibitor, induces apoptosis in multiple myeloma via GSK-3beta activation and RNA polymerase II inhibition. *Oncogene*. 2010;29(16):2325-2336.
120. Andrusis M, Lehnert N, Capper D, et al. Targeting the BRAF V600E mutation in multiple myeloma. *Cancer Discov*. 2013;3(8):862-869.
121. Sharman JR, Chmielecki J, Morosini D, et al. Vemurafenib response in 2 patients with posttransplant refractory BRAF V600E-mutated multiple myeloma. *Clin Lymphoma Myeloma Leuk*. 2014;14(5):e161-e163.
122. Gertz MA, Lacy MQ, Dispenzieri A, et al. Clinical implications of t(11;14)(q13;q32), t(4;14)(p16.3;q32), and -17p13 in myeloma patients treated with high-dose therapy. *Blood*. 2005;106(8):2837-2840.
123. Trudel S, Ely S, Farooqi Y, et al. Inhibition of fibroblast growth factor receptor 3 induces differentiation and apoptosis in t(4;14) myeloma. *Blood*. 2004;103(9):3521-3528.
124. Trudel S, Li ZH, Wei E, et al. CHIR-258, a novel, multitargeted tyrosine kinase inhibitor for the potential treatment of t(4;14) multiple myeloma. *Blood*. 2005;105(7):2941-2948.
125. Xin X, Abrams TJ, Hollenbach PW, et al. CHIR-258 is efficacious in a newly developed fibroblast growth factor receptor 3-expressing orthotopic multiple myeloma model in mice. *Clin Cancer Res*. 2006;12(16):4908-4915.
126. Trudel S, Stewart AK, Rom E, et al. The inhibitory anti-FGFR3 antibody, PRO-001, is cytotoxic to t(4;14) multiple myeloma cells. *Blood*. 2006;107(10):4039-4046.