Promising Therapies in Multiple Myeloma

Giada Bianchi, Paul G. Richardson and Kenneth C. Anderson

LeBow Institute for Myeloma Therapeutics and Jerome Lipper Multiple Myeloma Center, Division of Hematologic Malignancy, Department of Medical Oncology, Dana Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

Corresponding Author: Kenneth C. Anderson, MD

Dana-Farber Cancer Institute

Mayer 557

450 Brookline Ave, Boston, MA, 02215, USA.

E-mail: Kenneth_Anderson@dfci.harvard.edu

Phone: 617 632 2140

Fax: 617 632 2144

Word Count

Abstract: 218

Text: 4973

References: 124

Tables: 1

Figures: 1
Abstract

Progress in medical research has enhanced our understanding of tumor biology, delineated genetic and molecular mechanisms of tumor growth and survival, as well as 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 inhibitors; immune therapies including IMiDs, monoclonal antibodies, immune checkpoint inhibitors, agents targeting accessory plasmacytoid dendritic cells, vaccines, and CAR T cells; drugs targeting tumor cell homing to and exploiting hypoxia in the bone marrow microenvironment; molecularly targeted therapies against kinesin spindle inhibitors, AKT, CRM, CDK, BET bromodomain 4, and 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 Multiple Myeloma Treatment?

Melphalan plus prednisone treatment for multiple myeloma (MM) was introduced in the 1960s and achieved median survival of 2 to 3 years. High dose intravenous 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 versus conventional chemotherapy showing a 5-year overall survival (OS) of 52% versus 12%, respectively, in the 1990s. Remarkably, over the last decade the introduction of novel agents targeting MM in the context of the bone marrow (BM) microenvironment has transformed the MM treatment paradigm and markedly improved patient outcome. Landmark studies of the immunomodulatory drugs (IMiDs) thalidomide and lenalidomide and the proteasome inhibitor (PI) bortezomib provided the basis for rapid FDA approval of these treatments for patients with MM. Incorporation of combination novel agents into the ASCT algorithm as induction, consolidation, and maintenance therapy has resulted in unprecedented overall response rates (ORR) and a three-fold increase in OS. In this perspective, we focus on the targeted therapies, which, in our view, hold the greatest potential to even further improve upon this progress (Table 1 outlines investigational agents in advanced clinical development).

Drugs Targeting the Ubiquitin-Proteasome System (UPS)

In preclinical studies, bortezomib, the first in class, boronic acid inhibitor of the chymotrypsin-like (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 9-mediated apoptosis, terminal unfolded protein response (UPR), proteotoxic stress, and heat shock protein response.\textsuperscript{8-10} In addition, it targets the BM microenvironment, evidenced by its anti-osteoclast, anti-angiogenesis, and pro-osteoblast activities.\textsuperscript{11,12} Preclinical studies moved rapidly to phase I, II, and III clinical trials which demonstrated durable responses to bortezomib and provided the basis for its FDA approval in all stages of MM management.\textsuperscript{5,13,14} Together with IMiDs and dexamethasone, bortezomib is now integrated as frontline therapy in the majority of MM patients, with ORR as high as 100\% with lenalidomide, bortezomib, and dexamethasone (RVd), demonstrating the powerful synergy of using both PIs and IMiDs in combination.\textsuperscript{7,15} The relative inconvenience of parenteral administration, peripheral neuropathy attendant to intravenous (versus subcutaneous) bortezomib administration, and the emergence of resistance has since stimulated the development of second generation PIs with improved pharmacodynamics, 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 upon 23.7\% ORR and median progression free survival (PFS) of 3.7 months.\textsuperscript{16} In bortezomib-naïve patients, carfilzomib combined with low dose dexamethasone achieved 52.2\% ORR in patients treated with the 27 mg/m\textsuperscript{2} dose, and median PFS was not reached at the
time trial was reported. When compared to the 41% ORR to single agent bortezomib in the APEX trial, this data suggests that carfilzomib may be more effective than bortezomib. Indeed, interim analysis of the phase III ENDEAVOR trial (NCT01568866) in relapsed MM showed that carfilzomib/dexamethasone achieved a PFS of 18.7 months versus 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/m²). The recently completed phase III randomized ASPIRE trial compared carfilzomib/lenalidomide/dexamethasone (KRd) to lenalidomide/dexamethasone (Rd) in relapsed or relapsed and refractory MM (RRMM) and showed 26.3 versus 17.6 months PFS, respectively (p<0.0001), 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 98% ORR with 62% near complete response (nCR) or better, and an estimated PFS at 2 years of 92% at a median follow up of 13 months. Importantly, this combination can achieve molecular complete responses without attendant neuropathy but again some caution is warranted, as both venous thrombosis and significant shortness of breath (possibly due to diastolic dysfunction) were noted in some patients in this study. Randomized trials are now underway comparing KRd with RVd 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. It triggers both caspase-8 and -9 mediated apoptosis, up-regulates p53 and p21, induces terminal UPR, and can overcome bortezomib resistance in preclinical studies. It also induces tumor-suppressor microRNA (miR) 33b, with associated down-regulation of the oncogene PIM-1. As a single agent, weekly, oral ixazomib achieved 18% ORR in RRMM, including bortezomib-resistant MM, and was also active when given twice weekly in more heavily pre-treated patients. It is well tolerated, with low rates of peripheral neuropathy and treatment discontinuation. Remarkably, in a phase I/II study, the combination of ixazomib/Rd achieved 90% ORR, with 59% very good partial response (VGPR) or better in newly diagnosed MM (NDMM). Moreover, maintenance therapy with ixazomib, given as one tablet weekly, was well tolerated and further improved response. Ixazomib/Rd is being compared to Rd in two phase III clinical trials in RRMM (NCT01564537) and NDMM (NCT01850524), TOURMALINE1 and 2. At the first interim analysis for patients enrolled in the TOURMALINE1 trial in RRMM, the primary endpoint of PFS extension with ixazomib/Rd versus 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 utilized 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 analogue, is cytotoxic in preclinical MM models, including against bortezomib-resistant patient MMCs, and triggers synergistic cytotoxicity with lenalidomide and histone deacetylase (HDAC) inhibitors. Similar to bortezomib and carfilzomib, it also has a bone anabolic effect in preclinical models. Oprozomib achieved 33-37% ORR in RRMM, including bortezomib- and carfilzomib-refractory MM (NCT01416428). However, 20% of patients experienced severe (grade 3 or higher) gastrointestinal side effects, including 2 patients with fatal outcome. Preliminary results from a phase Ib/II study of oprozomib/dexamethasone in RRMM showed 42% ORR, with improved tolerability (NCT01832727) and phase I/II studies of oprozomib/dexamethasone plus IMiDs or cyclophosphamide in RRMM are ongoing.

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

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 (DUBs), which remove
ubiquitin from target proteins prior to their degradation.\textsuperscript{33,34} The 19S ubiquitin receptor RPN13, as well as the DUBs ubiquitin specific peptidase 7 (USP7) and USP14/ubiquitin carboxyl-terminal hydrolase L5 (UCHL5), are up-regulated in MM cell lines (MMCLs) and patient MMCs; conversely, knockdown of these targets decreases MM viability.\textsuperscript{35-37} RA190, P5091, and B-AP15 are small molecule inhibitors of RPN13, USP7, and USP14/UCHL5, respectively. All are enzyme-specific inhibitors and cytotoxic \textit{in vitro} and \textit{in vivo} against MMCLs and patient MMCs, including bortezomib-resistant MMCs.\textsuperscript{37} Culture of MMCs with BM stromal cells (BMSCs) does not overcome the cytotoxic effect of these therapies, which trigger synergistic MM cytotoxicity when combined with IMiDs, bortezomib, and HDAC inhibitor (HDACi) vorinostat.\textsuperscript{35,38} Importantly, these agents block the UPS upstream of the proteasome, thereby causing accumulation of polyubiquitinated proteins without blocking the proteasome; they overcome PI resistance and trigger activation of both intrinsic and extrinsic apoptotic pathways in a p53-independent fashion. The first in man USP14/UCHL5 inhibitor B-AP15 clinical trial in RRMM is beginning soon, and will both 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, panel A).

\textbf{Histone Deacetylase Inhibitors}

HDACs are multifunction enzymes with distinct structure and target specificities which mediate epigenetic silencing of gene expression, thereby modulating key cellular processes including proliferation, migration, and survival (Figure 1, panel
D). HDACi therefore represent a promising targeted therapy in oncology. In MM, a particular rationale for use of HDACi is their role in disrupting aggresomal protein degradation. Combining bortezomib and HDACi to simultaneously block the proteasome and aggresome, respectively, triggers synergistic cytotoxicity and overcomes bortezomib resistance in preclinical studies. Based on this data, the phase III Vantage 088 trial in RRMM compared bortezomib alone or in combination with the class I and IIb HDACi vorinostat. Although combination therapy achieved 54% ORR versus 41% ORR for bortezomib alone (p < 0.0001), there was only a modest prolongation in PFS (7.6 versus 6.8 months, respectively, p = 0.01), primarily due to diarrhea, fatigue, and thrombocytopenia leading to increased discontinuation of treatment in the combination arm. In contrast, a phase I trial of vorinostat in combination with Rd in RRMM achieved 47% partial response (PR) and was better tolerated, but the therapeutic index remained narrow. A phase III clinical trial of bortezomib with or without the pan-HDACi panobinostat achieved a 4-month prolongation of PFS with combination versus bortezomib alone treatment (12 versus 8 months, p < 0.0001); moreover, 28% patients versus 16% patients achieved nCR or better (p = 0.00006). Based on 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 II trial in bortezomib resistant RRMM patients, including patients with high-risk cytogenetics, which further supports its clinical activity in this setting. As with vorinostat, however, the...
side-effect profile observed in the phase III study led to discontinuation of
treatment in 34% combination-versus 17% bortezomib-treated patients,
highlighting the need for more selective HDACi approaches with potential for an
improved therapeutic index.\textsuperscript{44}

In this context, HDAC6 plays a key role in aggresomal protein degradation, since
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.\textsuperscript{45} Ricolinostat (ACY-1215) is a specific,
orally bioavailable HDAC6 inhibitor which is cytotoxic against MMCs and
synergizes with bortezomib and Rd \textit{in vitro}.\textsuperscript{46} A phase Ib study of ricolinostat plus
bortezomib/dexamethasone in RRMM showed 45% ORR and 29% ORR in
bortezomib-refractory MM (NCT01323751).\textsuperscript{47} Importantly, preclinical studies
showed that ricolinostat with IMiDs down-regulates MYC and triggers synergistic
cytotoxicity.\textsuperscript{48} A phase Ib trial of ricolinostat plus Rd in RRMM achieved 64%
ORR, including 85% lenalidomide-sensitive and 50% lenalidomide-refractory MM
(NCT01583283).\textsuperscript{49} 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. Finally, preclinical studies are further evaluating other isoform-selective
HDACi targeting HDACs relevant for MM growth and proliferation. For example,
HDAC3-knock down triggers MM cytotoxicity and apoptosis, and HDAC3
selective inhibitor BG45 is active, alone or with bortezomib, in MM preclinical
models.\textsuperscript{50} Thus, isoform selective, oral HDACi may improve tolerability, allowing
for their future clinical evaluation in combination with targeted and immune therapies.

**Immune Therapies**

**Immunomodulatory Drugs**

The rationale for using thalidomide, the first in class IMiD, in MM was its anti-angiogeneic properties. 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. IMiDs are now incorporated into therapies for RRMM and NDMM due to a series of FDA approvals based on their remarkable clinical activity. 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. Importantly, both the FDA and the European Commission (EC) approved continuous Rd for treatment of newly diagnosed, transplant-ineligible MM patients based on the results of the FIRST trial, which compared continuous Rd versus Rd for 72 weeks versus melphalan/prednisone/thalidomide (MPT) for 72 weeks. Patients treated with continuous Rd achieved 25.5 months PFS, versus 20.7 and 21.2 months PFS for limited Rd and MPT, respectively ($p<0.001$); 4 year OS was 59% versus 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 BMSC; modulation of cytokine secretion; upregulation of T, natural killer (NK) and NK-T cells; and downregulation of regulatory T (T reg) cells. Most recently, the E3 ubiquitin ligase cereblon has been identified as the molecular target of lenalidomide. Binding of lenalidomide to cereblon causes proteasome-dependent degradation of Ikaros family zinc finger proteins 1 and 3 (IKZF1 and IKZF3), which in turn mediates both MM cytotoxic and immune effects of IMiDs. Ongoing research is focusing on identifying biomarkers predictive of lenalidomide sensitivity on the one hand and designing novel IMiDs based upon the IMiD binding site to cereblon, on the other. Moreover, efforts are attempting to delineate the mechanism of synergy underlying IMiD/PI combination therapy, since in vitro data indicates that an intact UPS is required for IMiD activity. PIs may only partially inhibit the proteasome at therapeutic concentrations, allowing degradation of certain substrates such as the Ikaros protein; or alternatively, the polyubiquitinated Ikaros proteins could act as dominant negative, impairing the physiologic function of their non-ubiquitinated counterpart. These efforts will allow for rational, next generation combination therapies. Importantly, predicated on their immunostimulatory effects, IMiDs enhance activities of immune therapies including monoclonal antibodies (MoAbs), checkpoint inhibitors, and vaccines, providing the framework for combination clinical trials. 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).

**Monoclonal Antibodies**

Elotuzumab is a fully humanized MoAb directed against the glycoprotein SLAM family member 7 (SLAMF-7), which is highly expressed on the cell surface of MMCLs and patient MMCs. Elotuzumab both triggers antibody dependent cellular cytotoxicity (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 augments ADCC, a phase II study of elotuzumab with Rd in patients with RRMM, including patients with high-risk disease, achieved 92% ORR and 32.5 months PFS. Phase III studies of this combination versus Rd in patients with NDMM (NCT01335399, ELOQUENT-1) and RRMM (NCT01239797, ELOQUENT-2) are ongoing.

The target of the MoAb 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; as well as immune-mediated via ADCC, complement-dependent cytotoxicity (CDC), and antibody-dependent cellular phagocytosis (ADCP) (Figure 1, panel B). Preliminary studies showed very promising single agent activity, with 31% ORR in heavily pre-treated RRMM, leading to designation of breakthrough status by FDA as well as a strong rationale for
combination approaches. Specifically, as with elotuzumab, the addition of Rd to daratumumab significantly increased depth of response to 75% PR or better in RRMM. Phase III trials of daratumumab with Rd or bortezomib/dexamethasone in RRMM are currently accruing (NCT02076009 and NCT02136134, respectively); and a phase III study of daratumumab/Rd in NDMM is planned (NCT02252172). Similar results have been observed with another CD38 MoAb, SAR650984, with responses even in carfilzomib- and pomalidomide-resistant MM.

Indatuximab ravtansine (BT062) is an antibody-drug conjugate (ADC) comprised of anti-CD138 MoAb targeting syndecan1 (CD138) coupled to the potent maytansinoid DM4 toxin. Upon internalization of the CD138-ADC complex and lysosome-mediated proteolysis, DM4 is released and inhibits tubulin polymerization, resulting in cell cycle arrest and apoptosis. In a phase I/II trial in combination with Rd, indatuximab ravtansine achieved 78% ORR, including responses in bortezomib- and lenalidomide-refractory MM (NCT01638936). J6M0-mcMMAF (GSK2857916) is a humanized, afucosylated MoAb directed against B-cell maturation antigen (BCMA) conjugated via a non-cleavable linker to the anti-mitotic agent monomethyl aurastatin-F. The latter is released intracellularly via a mechanism similar to DM4 for BT062, and induces cell cycle arrest and apoptosis. Since BCMA is the receptor for B-cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL), J6M0-mcMMAF also blocks BAFF- and APRIL-induced nuclear factor κB (NF-κB) activation. A phase I study of J6M0-mcMMAF in RRMM is now ongoing (NCT02064387).
Additional preclinical and clinical studies are evaluating MoAbs directed against antigens expressed on MMCs such as CD40, CD54 (also known as Intercellular Adhesion Molecule 1, ICAM1), CD56, and GM2 ganglioside; as well as the anti-VEGF-A MoAb 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.\(^74\) In MM, the importance of host anti-tumor immunity is evidenced by long-term molecular complete response (CR) observed post allogeneic HSCT due to ongoing graft versus MM effect.\(^75\) Most recently, MoAbs to block the inhibitory interaction of programmed cell death 1 (PD-1) on T or NK cells with its ligand programmed death ligand 1 (PD-L1) on tumor cells or tumor-promoting accessory cells, have achieved remarkable responses in both solid tumors and hematologic malignancies.\(^74,76\)

In MM, tumor cells, plasmacytoid dendritic cells (pDCs), and myeloid derived suppressor cells (MDSCs) all express PD-L1; while BM-resident cytotoxic T, NK, and NK-T cells express PD-1.\(^77,78\) Our preclinical *in vitro* and *ex vivo* studies showed that blockade of PD-1/PD-L1 inhibits accessory cell (pDC or MDSC)-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 II study of a humanized anti-PD1 MoAb pemprolizumab (MK-3475) with
lenalidomide post-ASCT (NCT02331368); and a phase I/II study of pemprolizumab plus pomalidomide/dexamethasone in RRMM (NCT02289222) are ongoing. The humanized anti-PD1 MoAb 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 IgG4 anti-PD1 antibody nivolumab (BMS936558), alone or in combination with the CTLA4 blocking antibody ipilimumab or the killer cell immunoglobulin-like receptor (KIR)-blocking antibody lirilumab, is being evaluated in a phase I clinical trial in relapsed or refractory hematologic malignancies, including MM (NCT01592370) (Figure 1, panel E). Future trials will combine checkpoint inhibitors, MoAbs, 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 anti-tumor immune response, particularly in the settings of early stage or minimal residual disease. For example, we are vaccinating patients with smoldering multiple myeloma (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 (XBP-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).\textsuperscript{79}

An alternative approach involves vaccination of patients with their own tumor cells fused to autologous DCs (MM-DC fusion vaccine) (Figure 1, panel 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.\textsuperscript{80} Excitingly, MM-DC vaccination post-ASCT achieved 78% VGPR and 47% CR or nCR, with responses improving from PR to CR/nCR after 100 days post-transplant in 24% patients, suggesting its utility to treat minimal residual disease.\textsuperscript{81} A phase II 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 post-transplant 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, anti-PD-1 antibodies, or both.

\textit{Plasmacytoid Dendritic Cells}

pDCs are increased in MM BM and promote tumor cell proliferation, survival, and drug resistance; moreover, they also fail to trigger host anti-tumor immune response.\textsuperscript{82} Either CpG oligodeoxynucleotides (ODN) A and C792 (a CpG ODN C acting as a Toll-like receptor 9 agonist) can mature MM pDCs, thereby restoring their immune-stimulatory ability, while abrogating their pro-MM activities.\textsuperscript{83} Clinical trials of TLR-7 agonist are planned to test the therapeutic
benefit of solely targeting immune accessory cells, since these agents have no
direct anti-MM activity. Importantly, since PD-L1 is expressed on pDCs,
checkpoint inhibitor therapy can also abrogate the functional sequelae of pDCs in
MM.  

**Modulation of Cellular anti-MM Immune Surveillance**

CD19-directed chimeric antigen receptor engineered T (CAR-T) cells have
achieved remarkable responses in relapsed refractory chronic lymphocytic
leukemia (CLL), non Hodgkin’s lymphoma (NHL), and acute lymphoblastic
leukemia (ALL).  

CAR-T cells directed against CD38 and SLAMF-7 are in
preclinical development in MM, while CAR-T cells against BCMA are already
being evaluated in a phase I clinical trial (NCT02215967) (Figure 1, panel C).  

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 two single chain variable
fragments connected by a linker.  

BiTEs redirect anticancer immunity by binding
to a T cell specific antigen, typically CD3, with one 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 43% CR in RR B cell-precursor ALL.  

CD3-CD38 BiTEs are in
preclinical development for MM.
**Novel Therapies Directly Targeting the BM Microenvironment**

MMCs establish a bi-directional pro-survival relationship with both cellular and non-cellular 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 (four corners of Figure 1).\(^8^9\) Therefore, directly targeting the BM microenvironment represents a novel strategy to indirectly abrogate MM growth and survival.

**CXCL12/CXCR4 Axis Inhibitors**

Chemokine (CXC motif) ligand 12 (CXCL12, also known as SDF-1\(\alpha\)) mediates trafficking and homing of MMCs to the BM microenvironment.\(^9^0\) Plerixafor, an inhibitor of the CXCL12 ligand CXCR4, is used for mobilization of normal BM hematopoietic stem cells for ASCT, and has also been tested as an anti-MM therapy, predicated on mobilizing MMCs from their protective BM milieu.\(^9^1,9^2\) Inhibition of CXCL12 using NOX-A12 (olaptesed-pegol), a high-affinity anti- SDF-1\(\alpha\) PEGylated mirror-image L-oligonucleotide, triggers MM cytotoxicity in preclinical studies.\(^9^3\) In a phase IIa trial in RRMM, combination NOX-A12/bortezomib/dexamethasone achieved 6.5 months PFS and 73% ORR, even in high risk- and/or bortezomib refractory- patients.\(^9^4\) The regimen was well tolerated, and this combination is now entering phase III trials.

**Exploiting Hypoxia against MM**

The BM microenvironment in MM is hypoxic, and hypoxia inducible factor 1\(\alpha\) (HIF-1\(\alpha\)) is upregulated in patient MMCs.\(^9^5\) Moreover, hypoxia is a driver of epithelial to mesenchymal transition (EMT) in MMCs, thereby promoting their
dissemination.  TH-302 is a DNA alkylation prodrug selectively activated under hypoxic conditions, which triggers MM cytotoxicity, alone and with bortezomib, in preclinical models. A phase I/II study of TH-302 with dexamethasone/bortezomib showed no dose limiting toxicity at the recommended phase 2 dose, with 29% and 50% ORR in the phase I and II cohorts, respectively. Thus exploiting MMC vulnerability due to hypoxia may allow for selective tumor cytotoxicity and a favorable therapeutic index.

**Promising Targeted Therapies**

Predicated on pre-clinical studies, a number of signaling molecules have been identified as potential molecular targets of MM therapy. Inhibitors of aurora kinase A and B, kinesin spindle (KSP), nuclear transport, v-akt murine thymoma viral oncogene homolog (AKT), and cyclin dependent kinases (CDKs) are among those in promising early phase clinical trials. The kinesin spindle inhibitor filanesib (ARRY-520) causes apoptosis in MM and is being evaluated in phase I and II trials in RRMM, alone (NCT02092922 and NCT00821249) or in combination with bortezomib/dexamethasone (NCT01248923) or carfilzomib/dexamethasone (NCT01372540 and NCT01989325). Since this agent is highly bound in serum to α1-acid glycoprotein (AAG), its activity is enhanced in patients with low AAG levels. Selinexor (KPT-330), an inhibitor of the nuclear export protein chromosome region maintenance 1 (CRM-1), functions by maintaining the cellular distribution of tumor suppressors in MMCs. Although single agent activity was not observed in MM, phase I/II clinical trials in
combination with dexamethasone, liposomal doxorubicin, pomalidomide/dexamethasone or PIs/dexamethasone are ongoing, with promising interim results (NCT02336815, NCT02186834, NCT02343042, NCT02199665, respectively).\textsuperscript{104} Multiple studies have shown that PIs trigger apoptotic signaling, but also induce AKT.\textsuperscript{105} AKT inhibitors GSK2141795 and GSK2110183 are therefore being clinically evaluated in combination with bortezomib and other PIs. Finally, a hallmark of MM is cyclin D dysregulation; and multiple preclinical studies have evaluated CDK inhibitors in MM.\textsuperscript{106,107} Based upon promising preclinical studies, the CDK inhibitors dinaciclib (SCH 727965), seliciclib (CYC202) and SNS-032 are now being evaluated in phase I/II trials in RRMM (NCT01096342, NCT00446342, NCT01711528).\textsuperscript{108-110} Among novel targeted therapies, BET bromodomain and STK4 inhibitors hold particular promise in MM and other hematologic malignancies.

\textbf{BET Bromodomains}

\textit{Myc} is an oncogene in solid tumors and hematologic malignancies including MM, and BET bromodomains have recently been shown to regulate \textit{Myc} transcription in MM (Figure 1, panel D).\textsuperscript{111,112} Importantly, inhibition of BET bromodomain 4 via small molecule JQ1 down-regulates \textit{Myc} transcription and its downstream targets, associated with decreased MMC growth \textit{in vitro} and \textit{in vivo} in murine models. Phase I 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 \textit{Myc} and also inform combination approaches, such as with IMiDs.
YAP1/STK4

The Hippo co-activator Yes-associated protein 1 (YAP1) is essential for P53-independent, ABL1-induced apoptosis secondary to DNA damage.\textsuperscript{113} 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, serine/threonine kinase 4 (STK4) regulates YAP1 phosphorylation and its degradation in MM; and conversely, knockdown of STK4 results in upregulation of YAP1, associated with MM cytotoxicity both \textit{in vitro} and \textit{in vivo} in mouse xenograft models. Based upon 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.\textsuperscript{114} 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.\textsuperscript{115} The majority of mutations detected in MM are already present at the stage of monoclonal gammopathy of undetermined significance (MGUS) and/or SMM, suggesting that genetic mutations \textit{per se} are not sufficient for oncogenesis and clonal evolution.\textsuperscript{116} 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, NF-κB signaling, and histone methylation, consistent with MM pathogenesis.\textsuperscript{117} Mutations have also been observed in genes not previously implicated in oncogenesis, such as FAM46C and SP140, which therefore may represent potential novel therapeutic targets in MM.\textsuperscript{117} Of note, B-RAF mutations have been described in 4% MM, and vemurafenib has achieved responses in this setting.\textsuperscript{118} Our recent RNA sequencing study in patient-derived MMCs showed that only 27% mutated alleles are expressed at the mRNA level and therefore have biological and clinical relevance.\textsuperscript{119} Importantly, clonal heterogeneity and clonal evolution is a hallmark in MM pathogenesis and progression.\textsuperscript{117,120} This genomic heterogeneity and complexity in MM highlights the need to use combination therapies as early as possible in order 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 which 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 four-fold. We believe that translational research focus in three 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 both enhance our understanding of disease pathogenesis and identify novel molecular targets.\textsuperscript{121} Second, given the genomic complexity of MM, immune therapies including MoAbs, 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. Finally, utilization of effective, well-tolerated, rational combination targeted and immune therapies early in the disease course, in SMM or even MGUS, will delay and may ultimately avoid the development of MM.\textsuperscript{122-124}
Acknowledgements

We gratefully acknowledge our colleagues in the MM research community. We also gratefully acknowledge the administrative assistance of Michelle Maglio in the preparation of this manuscript.

Authorship


Table 1. Promising Investigational Agents in Advanced Clinical Development in MM. The table summarizes the most salient properties of novel agents in advanced clinical development.

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Drug Name</th>
<th>Relevant PK/PD Properties</th>
<th>Mechanisms of Effectiveness</th>
<th>Most Advanced Phase of Development</th>
<th>Study Design</th>
</tr>
</thead>
</table>
| PI         | Ixazomib (MLN9708) | Orally bioavailable, reversible, boronate-based inhibitor of CT-L proteasome activity | • PolyUb protein accumulation  
• Caspase 8- and 9-mediated apoptosis  
• p53 and p21 up-regulation  
• Terminal UPR induction  
• miR33b up-regulation  
• PIM1 down-regulation | Phase III | • Ixazomib/Len/D ex vs Placebo/Len/D ex in RRMM  
• Ixazomib/Len/D ex vs Placebo/Len/D ex in transplant-ineligible, NDMM |
|            | Marizomib (NPI-0052) | Orally bioavailable, irreversible, β-lactone-γ-lactam inhibitor of CT-L, T-L and C-L proteasome activities | • PolyUb protein accumulation  
• Caspase 8- and 9-mediated apoptosis | Phase I | Marizomib/Pom/Dex in RRMM |
|            | Oprozomib (ONX 0912, PR-047) | Orally bioavailable, irreversible | • PolyUb protein accumulation  
• Caspase 8- and 9-mediated apoptosis | Phase Ib/II | • Oprozomib/Dex in RRMM  
• Oprozomib in RRMM |
<table>
<thead>
<tr>
<th>HDACi</th>
<th>MoAbs</th>
<th>Targets</th>
<th>Phase</th>
<th>Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vorinostat (SAHA)</td>
<td>Small molecule class I/II HDACi</td>
<td>p21 and p53 up-regulation, Rb dephosphorylation, BID cleavage, Calpain activation</td>
<td>Phase III</td>
<td>Vorinostat/Bort vs Bort alone in RRMM</td>
</tr>
<tr>
<td>Ricolinostat</td>
<td>Orally bioavailable, small molecule HDAC6 inhibitor</td>
<td>Caspase 8- and 9-mediated apoptosis, Terminal UPR induction, PolyUb protein accumulation, Aggresome disruption</td>
<td>Phase I/II</td>
<td>Ricolinostat/Le n/Dex in RR MM, Ricolinostat/Bort/Dex in RRMM, Ricolinostat/Pom/Dex in RRMM</td>
</tr>
<tr>
<td>Elotuzumab (ELO)</td>
<td>Anti-CS1 humanized MoAb</td>
<td>ADCC, Enhanced NK function</td>
<td>Phase III</td>
<td>Elo/Len/Dex vs Placebo/Len/Dex in NDMM</td>
</tr>
<tr>
<td>Daratumumab (DARA)</td>
<td>Anti-CD38 human MoAb</td>
<td>Crosslinking-mediated cytotoxicity, ADCC, CDC, ADCP</td>
<td>Phase III</td>
<td>Dara/Len/Dex vs Placebo/Len/Dex in RRMM, Dara/Bort/Dex vs Placebo/Bort/Dex in RRMM</td>
</tr>
<tr>
<td>SAR650984 (SARA)</td>
<td>Anti-CD38 humanized IgG1 MoAb</td>
<td>Homotypic aggregation-mediated cytotoxicity, ADCC, CDC</td>
<td>Phase I</td>
<td>SARA/Len/Dex in RRMM, SARA/Pom/Dex in RRMM</td>
</tr>
<tr>
<td>Indatuximab ravtansine (BT062)</td>
<td>Chimeric, anti-CD138-conjugated maytansinoid DM4</td>
<td>Maytansinoid DM4 released intracellularly upon CD138-MoAb internalization, Tubulin polymerization inhibition leading to cell cycle arrest and apoptosis</td>
<td>Phase I/II</td>
<td>Indatuximab ravtansine/Len/Dex in RRMM</td>
</tr>
<tr>
<td>Immune Therapies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td><strong>Table</strong> Bianchi et al. Promising Therapies in Myeloma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>J6M0-mcMMAF (GSK2857916)</td>
<td>Humanized and afucosylated anti-BCMA-conjugated monomethyl aurastatin-F</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Monomethyl aurastatin-F released intracellularly upon BCMA-MoAb internalization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Tubulin polymerization inhibition leading to cell cycle arrest and apoptosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Blockade of BAFF- and APRIL-induced NF-κB activation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase I</td>
<td>Dose escalation of J6M0-mcMMAF in RRMM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pemprolizumab (MK-3475)</td>
<td>Humanized, anti-PD-1 MoAb</td>
<td>Increased anti-MM T, NK and NK-T-mediated cytotoxicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pemprolizumab plus lenalidomide post-ASCT</td>
<td>Pemprolizumab plus Pom/Dex in RRMM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pidilizumab (CT-011)</td>
<td>Humanized, anti-PD-1 MoAb</td>
<td>Increased anti-MM T, NK and NK-T-mediated cytotoxicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pidilizumab plus Len in RRMM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nivolumab (BMS936558)</td>
<td>Human IgG4 anti-PD1 MoAb</td>
<td>Increased T, NK and NK-T antitumor cytotoxicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nivolumab plus/minus Ipilimumab or Lirilumab in R/RMM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PVX-410</td>
<td>XBP-1, CD138- and CS1-derived peptide vaccine targeting HLA2-restricted antigen presenting cells</td>
<td>Expansion and activation of MM-specific T cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PVX-410 alone or in combination with Len in SMM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MM/DC vaccine</td>
<td>Chemically fused autologous MM and DC targeting CD4+ and CD8+ T cells</td>
<td>Anti-MM humoral and cytotoxic response</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MM/DC vaccine alone or in combination with pidilizumab post ASCT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-BCMA CAR T cells</td>
<td>Anti-BCMA CAR T cells</td>
<td>Specific, anti-MM T cell response</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-BCMA CAR T cells in RRMM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table

Bianchi et al. Promising Therapies in Myeloma

<table>
<thead>
<tr>
<th>BM-targeting therapies</th>
<th>TH-302</th>
<th>Hypoxia-activated DNA alkylator prodrug</th>
<th>Genotoxic damage</th>
<th>Phase I/II</th>
<th>TH-302/Bort/Dex in RRMM</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOX-A12</td>
<td>CXCL12 PEGylated mirror-image L-oligonucleotide</td>
<td>CXCL12-CXCR4 signaling inhibition</td>
<td>Phase Ila</td>
<td>NOX-A12/Bor/Dex in RRMM</td>
<td></td>
</tr>
</tbody>
</table>

| Molecularly Targeted Therapies | Filanesib (ARRY-520) | Kinesin spindle inhibitor | • Mitotic Arrest  
• Apoptosis | Phase II | Filanesib alone or in combination with Carf/Dex in RRMM |
|--------------------------------|----------------------|--------------------------|----------------|-----------|------------------------|
| Selinexor (KPT-330)           | CRM-1 inhibitor      |                          | • Cell cycle arrest  
• Apoptosis  
• MYC inhibition  
• Mcl-1 inhibition  
• NF-kB inhibition | Phase I/II | • Selinexor/Dex  
• Selinexor/liposomal Dox/Dex  
• Selinexor/Pom/Dex  
• Selinexor/Bor/Dex  
• Selinexor/Carf/Dex in RRMM |
| GSK2141795 Afuresertib (GSK2110183) | Akt inhibitors      | • IL6-pro-MM effect inhibition  
• Cell cycle arrest  
• UPR induction  
• Apoptosis | Phase II | GSK2141795 plus trametinib in RRMM  
GSK2110183 in PI-refractory MM |
| Dinaciclib NS-032 Seliciclib | CDK inhibitors      | • Apoptosis  
• UPR induction  
• p53 accumulation  
• BH3 only protein upregulation  
• miR-19, miR-92a-1 and miR-21 down-regulation | Phase II | Dinaciclib in RRMM |
| GSK525762 CPI-0610           | BET bromodomain small molecule inhibitor | • Myc down-regulation  
• Cell cycle arrest  
• Cell senescence | Phase I | • GSK525762 in RR hematologic malignancies |
Table

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th>CPI-0610 in RRMM</th>
</tr>
</thead>
</table>

Abbreviations: PI: proteasome inhibitors; Len: lenalidomide; Dex: dexamethasone; Bort: bortezomib; HDACi: histone deacetylase inhibitors; Carf: carfilzomib; RR: relapsed and refractory; ND: newly diagnosed; MoAb: monoclonal antibodies; BM: bone marrow; UPR: unfolded protein response
Figure 1. Multimodality targeting of MM in the context of the bone marrow microenvironment. In the center is the MMC (in light pink), with nuclear clumped chromatin and endoplasmic reticulum (ER). The surrounding five sections each represent a different modality of anti-MM therapy, with investigational agents outlined in red. In section A is the ubiquitin-proteasome system (UPS), closely interacting with the aggresome pathway. Deubiquitinating enzymes (DUBs) USP7 and USP14/UCHL5 are symbolized by a scissor and the 19S ubiquitin receptor RPN13 as a receptor associated with the proteasome cap. Section B contains the monoclonal antibodies (MoAbs) daratumumab (DARA) and SAR650984 (SAR), targeting CD38 as well as elotuzumab (ELO), targeting SLAMF7, which mediate complement-dependent cytotoxicity (CDC), direct cytotoxicity from crosslinking, and antibody-dependent cell cytotoxicity (ADCC). The antibody-drug conjugates (ADCs) indatuximab raltansine (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. Panel C represents several strategies for modulation of cytotoxic immunity. In red is an anti-BCMA chimeric antigen receptor engineered (CAR) T cell; in orange is a MM-specific cytotoxic T cell activated via direct interaction with MM-dendritic cell (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 panel D.
are represented as spheres (histones) wrapped in a black thread (DNA). Open nucleosomes with acetylated (Ac) sites are green while closed chromatin structure is pink. The BET bromodomain 4 protein (BRD4) is represented as a red, trapezoid shape, binding to acetylated nucleosomes and inducing Myc transcription. Finally, section E contains a representation of immune checkpoint blockade, with cytotoxic T and NK-T cells represented in shades of green and blue, respectively. Programmed cell death 1 (PD-1) and its ligand programmed death ligand 1 (PD-L1) are represented as complementary transmembrane structures on effector cells and target cells (MMCs, myeloid-derived suppressor cells and plasmacytoid DCs), respectively. Cytotoxic T-lymphocyte-associated protein 4 (CTLA4) and killer cell immunoglobulin-like receptor (KIR) are also pictured on effector cells. TH-302 hypoxia activated alkylating agent, and NOX-A12 CXCL12 inhibitor are represented. Finally, in the four corners are key cellular and non-cellular elements of the BM niche that contribute to MM pathogenesis: excess of osteoclasts compared to osteoblasts (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 bone marrow stromal cells (BMSC) (lower left corner). Relevant cytokines in the BM milieu are represented as orange ovals.
References


References


24. Kumar SK, Berdeja JG, Niesvizky R, et al. Safety and tolerability of ixazomib, an oral proteasome inhibitor, in combination with lenalidomide and
References

Bianchi et al. Promising Therapies in Myeloma


References


49. Yee AJ, Voorhees PM, Bensinger W, et al. Ricolinostat (ACY-1215), a Selective HDAC6 Inhibitor, in Combination with Lenalidomide and Dexamethasone: Results of a Phase 1b Trial in Relapsed and Relapsed...
References

Bianchi et al. Promising Therapies in Myeloma


References


References


References


91. Azab AK, Runnels JM, Pitsillides C, et al. CXCR4 inhibitor AMD3100 disrupts the interaction of multiple myeloma cells with the bone marrow microenvironment and enhances their sensitivity to therapy. *Blood*. 2009;113(18):4341-4351.


94. Ludwig H, Weisel K, Petrucci MT, et al. Final Results from the Phase IIa Study of the Anti-CXCL12 Spiegelmer® Olaptesed Pegol (NOX-A12) in
References

Bianchi et al. Promising Therapies in Myeloma


References


Promising therapies in multiple myeloma

Giada Bianchi, Paul G. Richardson and Kenneth C. Anderson

Information about reproducing this article in parts or in its entirety may be found online at: http://www.bloodjournal.org/site/misc/rights.xhtml#repub_requests

Information about ordering reprints may be found online at: http://www.bloodjournal.org/site/misc/rights.xhtml#reprints

Information about subscriptions and ASH membership may be found online at: http://www.bloodjournal.org/site/subscriptions/index.xhtml

Advance online articles have been peer reviewed and accepted for publication but have not yet appeared in the paper journal (edited, typeset versions may be posted when available prior to final publication). Advance online articles are citable and establish publication priority; they are indexed by PubMed from initial publication. Citations to Advance online articles must include digital object identifier (DOIs) and date of initial publication.