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Novel agents in multiple myeloma

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Abstract

The therapeutic landscape of multiple myeloma (MM) has dramatically changed in the last 15 years with the advent of Imids and proteasome inhibitors. However, majority of MM patients relapse and new therapies are needed. Various agents with diverse mechanisms of action and distinct targets, including cellular therapies, monoclonal antibodies, and small molecules are currently under investigation. In this review, we report novel drugs recently approved or under advanced investigation that will likely be incorporated in the near future as new standard for MM treatment, focusing on their mechanisms of action, cellular targets and stage of development.

The advent of Imids and proteasome inhibitors opened a new era in the therapy of multiple myeloma (MM) contributing to significantly prolongation of survival. In the last five years, the Food and Drug Administration approved six new drugs, pomalidomide (an analogue of lenalidomide), carfilzomib, ixazomib (two new proteasome inhibitors (PI)), panobinostat (a pan histone deacetylase) and two monoclonal antibodies, daratumumab (targeting CD38) and elotuzumab (targeting the signaling lymphocytic activation molecule F7 (SLAMF7)) (table 1). One of the new and most exciting challenges is now to identify the most efficient combinations of these new agents in induction and maintenance regimen, and to define the best therapeutic strategies according to risk stratification and patient characteristics[1]. Nevertheless, a subgroup of high-risk patients remain characterized by poor survival despite these most recent available treatment combinations and most patients continue to experience relapses, underlying the need for new active treatments to cure the disease[2].

The study of MM genomics along with the discovery of new critical signaling pathways directing MM cell survival has allowed development of new and efficient therapeutic agents. Intracellular targets such as protein degradation, apoptosis pathway, transcriptomic regulation are essential mechanisms of MM cell survival and represent new therapeutic avenues[3]. In addition, the rise of immunotherapy with the development of monoclonal antibodies directly targeting tumor cells such as daratumumab or isatuximab (anti-CD38 mAb) or elotuzumab (targeting SLAMF7)[4,5], monoclonal antibodies targeting immune checkpoints (such as pembrolizumab and nivolumab targeting PD1) and cellular therapies with Chimeric antigen receptors T cells (CAR T cells) are now under critical evaluation in

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myeloma[6]. In this review, we focus on the newest agents most recently approved or in advanced development in myeloma, excluding cellular immunotherapies and protein catabolism targeted therapies that are detailed elsewhere in this issue. For a matter of clarity, we present these new agents based on the their mechanisms of action or therapeutic target (table 2 and table 3).

1- Antibodies targeting MM cells

Anti-myeloma monoclonal antibodies are humanized or chimeric antibodies targeting malignant plasma cells that can correspond to monoclonal antibodies, drug-conjugated monoclonal antibodies or bi-specific antibodies.

A- Monoclonal antibodies targeting CS1

Elotuzumab is a humanized immunoglobulin G1 immunostimulatory monoclonal antibody targeted against signaling lymphocytic activation molecule F7 (SLAMF7, also called CS1 (cell-surface glycoprotein CD2 subset 1). SLAMF7 is a glycoprotein expressed on myeloma and natural killer cells[7,8]. SLAMF7 belongs to the SLAM family on chromosome 1q23 and is highly expressed in MM cells independently of cytogenetic abnormalities. The binding of elotuzumab to SLAMF7 activates NK cells by coupling with its adapter protein EAT-2 whereas it leads to antibody-dependent cell cytotoxicity (ADCC) in MM cells as EAT-2 is not expressed in MM cells[9,10]. Elotuzumab has modest impact as single agent in RRMM as shown in a phase 1 study in 35 relapse and refractory MM where 26.5% of the patients had stable disease but no overall response was observed[11]. However, considering the impact of Imids on the immune system, activating NK cells and inhibiting T cells regulators, several studies have combined elotuzumab with IMids and showed significant synergistic activity in combination. In two phase 1 studies in RRMM combining elotuzumab either with bortezomib/dexamethasone or with lenalidomide/dexamethasone, the ORR were 48 and 82% respectively[12,13]. In the phase 3 clinical trial ELOQUENT 2[14], elotuzumab was evaluated in addition to lenalidomide (Len) and dexamethasone (Dex) in relapse or refractory MM (RRMM). The overall response rate in the elotuzumab group was 79%, versus 66% in the control group ($P<0.001$) and the Median progression-free survival in the elotuzumab group was 19.4 months, versus 14.9 months in the control group ($P<0.001$). In another multicenter, randomized, open-label, phase 2 trial (ELOQUENT 3)[15], MM patients refractory to lenalidomide and to a proteasome inhibitor, were treated with elotuzumab plus pomalidomide and dexamethasone or pomalidomide dexamethasone alone. The overall response rate was 53% in the elotuzumab group as compared with 26% in the control group (odds ratio, 3.25; 95% CI, 1.49 to 7.11). The median progression-free survival was 10.3 months in the elotuzumab group and 4.7 months in the control group. The risk of progression or death was significantly lower among those who received elotuzumab. Importantly the combination of elotuzumab with lenalidomide or pomalidomide and dexamethasone was not associated with an increased toxicity.

Conversely, combining elotuzumab with bortezomib did not show significant benefit in a phase 2 clinical trial although overall survival and PFS trended to be increased[16]. Elotuzumab was approved in combination with lenalidomide in RRMM in the US in

11/2015 and in Europe in 05/2016 and in combination with pomalidomide in 11/2018. An ongoing phase 3 clinical trial (ELOQUENT 1, NCT01335399) is evaluating elotuzumab combined with lenalidomde/dexamethasone versus lenalidomide/dexamethasone alone in newly diagnosed elderly or unfit patient and a similar combination is also evaluated in high risk smoldering MM patients (NCT02279394).

B- Monoclonal antibodies targeting CD38

CD38 is a 45-kD, transmembrane glycoprotein that links with cell-surface receptors in lipid rafts, regulates cytoplasmic Ca^{2+} flux, and mediates signal transduction in lymphoid and myeloid cells[17]. CD38 is highly expressed on myeloma cells while its expression is low on normal lymphoid and myeloid cells and in some tissues of nonhematopoietic origin[18].

Daratumumab is a human IgG1κ monoclonal antibody that binds to a unique CD38 epitope[19]. Preclinical studies showed that activity of daratumumab is mediated by multiple mechanisms including complement-mediated and antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, apoptosis, and inhibition of the enzymatic activity of CD38[20]. In two phase 1/2 clinical trials, Daratumumab was tested as a single agent in RRMM[21]. In one study, The overall response rate was 36% in the cohort that received 16 mg per kilogram and 65% (95% CI, 28 to 86) of the patients who had a response did not have progression at 12 months[21]. In the second study, the overall responses were noted in 29% (95% CI 20.8–38.9), median duration of response was 7.4 months (95% CI 5.5-not estimable) and progression-free survival was 3.7 months (95% CI 2.8–4.6). The 12-month overall survival was 64.8% (95% CI 51.2–75.5) (SIRIUS trial)[22].

Subsequently, daratumumab was used in combination with either bortezomib/ Dexamethasone[23] or Lenalidomide/Dexamethasone[24] in two phase 3 clinical trials[23,24]. In the phase 3 clinical trial[23] comparing velcade/dexamethasone to velcade/dexamethasone/ daratumumab in 498 R/R MM patients (Castor trial) the 12-month rate of progression-free survival was 60.7% in the daratumumab group versus 26.9% in the control group. The rate of overall response was higher in the daratumumab[25] group than in the control group as well (82.9% vs. 63.2%, P<0.001), as were the rates of complete response or better (19.2% vs. 9.0%, P=0.001). After a median follow-up period of 7.4 months, the median progression-free survival was not reached in the daratumumab group and was 7.2 months in the control group (hazard ratio for progression or death with daratumumab vs. control, 0.39; 95% confidence interval, 0.28 to 0.53; P<0.001). In the phase 3 clinical trial comparing Len/Dex to Dara/Len/Dex (Pollux trial) in 569 R/R MM patients, the progression-free survival at 12 months was 83.2% (95% CI, 78.3 to 87.2) in the daratumumab group, as compared with 60.1% (95% CI, 54.0 to 65.7) in the control group. A significantly higher rate of overall response was observed in the daratumumab group than in the control group (92.9% vs. 76.4%, P<0.001), as was a higher rate of complete response or better (43.1% vs. 19.2%, P<0.001). In the daratumumab group, 22.4% of the patients had results below the threshold (1 tumor cell per 10^5 white cells) for minimal residual disease (MRD), as compared with 4.6% of those in the control group (P<0.001); results below the threshold for MRD were associated with improved outcomes.

As upfront therapy, Daratumumab has been evaluated in patients ineligible for autotransplant in a phase 3 clinical trial comparing bortezomib, melphalan, and prednisone (MPV) either alone (control group) or with daratumumab (ALCYONE clinical trial)[26]. At a median follow-up of 16.5 months, the 18-month progression-free survival rate was 71.6% in the daratumumab group and 50.2% in the control group (hazard ratio for disease progression or death, 0.50; 95% CI, 0.38 to 0.65; P<0.001). The overall response rate was 90.9% in the daratumumab group, as compared with 73.9% in the control group (P<0.001), and the rate of complete response or better (including stringent complete response) was 42.6%, versus 24.4% (P<0.001). In the daratumumab group, 22.3% of the patients were negative for minimal residual disease (at a threshold of 1 tumor cell per 10^5 cells), as compared with 6.2% of those in the control group (P<0.001). Daratumumab is now approved by the FDA since 2016.

Isatuximab (SAR650984) is another chimeric IgG1 mAb made by variable domain resurfacing, targeting a different amino acid sequence epitope of CD38 than daratumumab. In addition, isatuximab has a direct toxic effect on MM cells as well[27,28]. Initial data suggest that isatuximab has clinical activity as a single agent, with an ORR of 32% obtained in patients with RRMM[29]. Isatuximab, in combination with lenalidomide/dexamethasone has been evaluated in a phase 1b clinical trial in 57 R/R MM patients. The overall response rate[30] was 56% (29/52) and 52% in evaluable lenalidomide-refractory patients[31]. Isauximab is currently evaluated in RRMM as a single agent or with dexamethaosne (NCT01084252) and in combination with RVD in newly diagnosed patients (NCT02513186). Efficacy of Isatuximab inpatients relapsing after daratumumab will be interesting as both target slightly different epitopes on CD38 molecule.

A third anti-CD38 monoclonal antibody (MOR202)[32] is also in early clinical trials and bi-specific antibodies targeting CD38 and CD3 (AMG 424)[33], and a monoclonal antibody conjugated with α-emitter astatine-211 (^{211}At) an α-particle emitting isotopes[34,35], are also being evaluated in early phase clinical trial and pre-clinical models.

C- Monoclonal antibodies targeting BCMA

B-cell maturation antigen (BCMA), a member of the tumor necrosis factor receptor superfamily (TNFRSF17), is selectively induced during plasma cell differentiation and nearly absent on naive and memory B cells and CD34 positive hematopoietic stem cells. BCMA is highly expressed in MM cells. B-cell activating factor (BAFF) and A proliferation-inducing ligand (APRIL)[36] are 2 known ligands of BCMA that induce survival of long lived plasma cells. Significantly, soluble BCMA (sBCMA) levels are increased in MM patients in comparison to healthy individuals and correlate with disease status and prognosis. These data have highlighted BCMA as a very promising target in MM. Several monoclonal antibodies and cellular therapies targeting BCMA are under investigation including monoclonal antibodies, antibody-drug conjugate and bi-specific antibodies[37].

GSK2857916 is humanized and afucosylated antagonistic anti-BCMA antibody-drug conjugate via a noncleavable linker which specifically blocks cell growth via G2/M arrest and induces caspase 3-dependent apoptosis[38]. In an international, multicentre, open-label, first-in-human phase 1/2 study, 73 patients: 38 patients with RRMM in the dose-escalation

part 1 and 35 patients in the dose-expansion part 2 were treated. There were no dose-limiting toxicities and no maximum tolerated dose was identified in part 1. In part 2, 21 (60%; 95% CI 42·1–76·1) of 35 patients achieved an overall response suggesting a promising role of this conjugated monoclonal antibody. Of note, corneal events were common (53% of 38 patients in part 1 and 63% of 35 in part 2) but moderate in majority. The most common grade 3 or 4 events were thrombocytopenia (13 [34%] of 38 patients in part 1 and 12 [34%] of 35 in part 2) and anemia (6 [16%] in part 1 and 5 [14%] in part 2). There were 12 treatment-related serious adverse events and no treatment-related deaths. Other antibody-conjugated targeting BCMA are under investigation such as HDP-1, an antibody- amanitin conjugate or MeDi2228 a fully human antibody - specifically conjugated to a pyrrolobenzodiazepine dimer *via* a protease-cleavable linker[39,40].

Bispecific monoclonal antibodies targeting BCMA are also being actively developed. BI 836909, a bispecific single-chain variable fragment (scFv) that simultaneously bind to CD3 and BCMA was the first reported. Pre-clinical evaluation was promising in mouse and monkeys and further investigations are on going although the short half life of the molecule might require frequent infusions[41]. Several other bi-specific antibodies are under development and include TNB383B, TNB-384B, Ab-957, EM801 and BCMA-TCB2, that are also IgG-based human bi-specific antibodies with two binding sites for BCMA and CD3 with significant toxicity on MM cells in pre-clinical models[25,42,43]. PF-3135 is a humanized immunoglobulin G (IgG2a) CD3 and BCMA bispecific monoclonal antibody that is now evaluated in an ongoing phase 1 clinical trial (NCT03269136)[44]. AFM26 is a bispecific antibody, which targets BCMA and CD16A on NK cells with significant efficacy in pre-clinical models. Its impact on NK cells may suggest a potential for a synergistic activity with Imids[45]. Finally, tri-specific antibody-like molecules targeting BCMA are also under evaluation. An anti-CD16A/BCMA/CD200 antibody binding to CD16A on NK cells and to BCMA and CD200 on MM cells with potentially significant efficiency and increase selectivity of MM cells is under evaluation[46].

D. Monoclonal antibodies targeting April

A Proliferation-inducing ligand[36] is one of the 2 known ligands of BCMA and its binding to BCMA enhances plasma cell proliferation and survival. BION-1301 is a humanized anti-APRIL antibody blocking the binding of APRIL to BCMA and TACI that has significant impact in vitro and in co-culture models and currently evaluated in an early phase clinical trial in RRMM (NCT03340883).

E. Monoclonal antibodies targeting CD138

Indatuximab ravtansine (BT062) is a monoclonal antibody-drug conjugate under development targeting CD138 (syndecan1) which is universally highly expressed on MM cells. The monoclonal antibody is coupled to the maytansinoid DM4 toxin. In a phase 1/2 clinical trial evaluating BT062 in combination with lenalidomide/dexamethasone or pomalidomide/dexamthasone in RRMM, promising preliminary results were observed with an ORR of 54% and 79% respectively in each arm[47,48].

F. Monoclonal antibodies targeting immune checkpoints

The advent of immune checkpoint inhibitors is one of the most important progress in the last few years in oncology. The development of monoclonal antibodies targeting the immune checkpoints has considerably changed the treatment and prognosis of several cancer including melanoma, lung cancer and relapsed and refractory Hodgkin disease among others. In multiple myeloma, Programmed death 1 (PD-1) receptor is highly expressed suggesting that treatment targeting it or its ligand (PD-L1 or PD-L2) would be an effective strategy[49]. Several monoclonal antibodies targeting PD1 (pembrolizumab, Nivolumab) or PDL1 (durvolumab, atezolizumab) are approved for various other malignancies[50]. Based on promising phase 2 data with the combination of pembrolizumab with Pom/Dex and Len/Dex in RRMM, three phase 3 clinical trials- KEYNOTE-183 and KEYNOTE- 185 and checkmate 602- respectively evaluated pomalidomide/dexamathasone with or without pembrolizumab in RRMM, lenalidomide/Dexamethasone with and without pembrolizumab in newly diagnosed MM patients non eligible for auto-transplant and nivolumab plus pomalidomide–dexamethasone versus pomalidomide–dexamethasone alone or pomalidomamide/dexamethasone/elotuzumab/nivolumab in patients with RRMM. All studies were stopped prematurely because of an increased mortality in patients receiving pembrolizumab with a hazard ratio for death of 1.61 in KEYNOTE-183 and 2.06 in KEYNOTE-185, or nivolumab in checkmate 602 (hazard ratio for death was 1.19 (95% confidence interval, 0.64 to 2.20)). Furthermore the addition of pembrolizumab or nivolumab did not increase the ORR. Importantly, no specific cause of death was observed in all 3 trials and the pathogenesis behind the toxicity of the combination remains largely unknown as well as the absence of obvious efficacy of the monoclonal antibodies. These results have raised serious doubts regarding their utility in MM at least in combination with the immunomodulatory agents[51]. However, other immune checkpoints such as LAG3, TIM3 or TIGIT are under pre-clinical investigation[52–55].

Various other cell surface molecules have been targeted using antibodies which have undergone promising preclinical evaluation (Table 2).

2. DNA damaging agents

Alkylating agents, remain a corner stone of MM treatment with high dose melphalan as the conditioning regimen of choice for auto-transplant. New alkylating agents have been developed in order to improve efficacy and decrease toxicity of DNA-damaging agents.

a. Melflufen

Melphalan flufenamide ethyl ester (melflufen) is a peptidase-potentiated alkylating agent which appears to be more efficient than melphalan[56]. Especially, in vitro evaluation showed that melflufen is active in melphalan resistant cell line by generating rapid and irreversible DNA damage. Three clinical trials are ongoing to confirm its efficacy in MM. The phase 2 clinical trial 012M1 evaluating Melflufen in RRMM with at least 2 prior lines of therapy including bortezomib and lenalidomide, showed promising results with an ORR of 31% in advanced RRMM patients[57]. The phase 2 clinical trial HORIZON evaluating melflufen in RRMM with at least 2 prior lines of treatment including Imids, PI, pomalidomide and

daratumumab showed an ORR of 27%. A clinical phase 3 trial comparing melflufen versus pomalidomide in RRMM and a phase 1–2 trial combining melflufen with bortezomib and daratumumab in RRMM are ongoing and will likely confirm the role of this new alkylating agent in MM[58,59].

b. Bendamustine

Bendamustine is an alkylating agent with a purine analog ring that has been developed several decades ago although its cautious evaluation in MM is more recent[60]. A phase III clinical trial compared bendamustine + prednisone with melphalan + prednisone in newly diagnosed patients ineligible for autotranplant showed a benefit especially in terms of TTP (14 *vs.* 10 months)[61]. Several phase 2 clinical studies combining Bendamustine with PI or Imids have been reported with relatively good results making bendamustine as an available additional therapeutic option.[62–65]

c. EDO-S101

Preclinical data suggested a synergism between alkylating agents and HDACi although their combination in patients was associated with important toxicity[66–68]. EDO-S101 is a first in class fusion molecule derived from bendamustine that has been linked to a class 1 and 2 HDACi. Now under pre-clinical evaluation[69].

3. Inhibitors of BCL2 family proteins

Important efforts in research have been made to understand the mechanisms driving cancer cells survival. In the last two decades significant discoveries have shed light on the mechanisms regulating apoptosis in cancer cells. The BCL2 family proteins have been identified as critical regulators of apoptosis in cancer and healthy tissues. This family includes Bcl-2, Bcl-XL or Mcl-1, that are multi-domain anti-apoptotic proteins. Several groups have identified a tissue specific anti-apoptotic dependency and small molecules have been developed to target the BCL2 family proteins[70]. Interestingly, bcl2-dependency can be assessed functionally with a method using BH3 profiling, a flow-cytometry based method or simply by evaluating the levels of expression of BCL2, bcl-xl and MCL 1[71,72].

A. Venetoclax

Venetoclax (ABT-199) has been approved for several hematologic malignancies in the past few years including chronic lymphoid leukemia and mantle cell lymphoma. In MM, Venetoclax has been shown to be active in RRMM as a single agent in a phase 1 clinical trial[73]

Importantly, the presence of t(11 ;14) in MM confers a higher BCL2 dependency and prolonged, deep responses have been observed in the subgroup of t(11 ;14) MM which comprise ~20% of MM patients. In this trial, The ORR in patients with t(11;14) translocation was 40%, including 14% CR or better[30]. In the non t(11;14) group, two patients (6%) achieved at least a partial response. The phase 2 M13–367 study (NCT01794520) is currently evaluating the efficacy of venetoclax (800 mg daily) in combination with dexamethasone in relapsed myeloma patients with t(11;14) translocation.

Preliminary results revealed an ORR of 65%, including 35% VGPR in advanced relapsed MM patients (median of three prior therapies).

Venetoclax in combination with other agents has also shown efficacy in non-t(11 ;14) MM. Especially, bortezomib and other PIs have been shown to indirectly inhibit MCL-1 and potentially synergistic activity with venetoclax. Thus, in a phase 2 clinical trial evaluating Venetoclax/bortezomib/Dexamethasone in 66 RRMM patients, the overall response rate[30] was 67% (44/66). ORR of 97% and ≥VGPR 73% were seen in patients not refractory to bortezomib who had 1 to 3 prior therapies. Patients with high *BCL2* expression had a higher ORR (94%)[74].

B. MCL1 inhibitors

With success of targeting BCL2, other anti-apoptotic molecules involved in MM cell survival are being evaluated as potential targets. MCL1 inhibitors are the second most advanced drugs in development. Currently, a phase 2 clinical trial is ongoing to evaluate safety and efficacy of MCL1-inhibitor in MM using MIK665 (NCT02992483) and AMG 176 (NCT02675452).

4. Epigenetic inhibitors

-Histone Deacetylase (HDAC)

Epigenetic mechanisms play a critical role in deregulating MM cells transcriptome and enhancing tumor progression[75–77]. HDACs include four classes of proteins according to their structure and function: class I (HDAC 1, 2, 3, and 8), class IIa (HDACs 4, 5, 7, and 9), class IIb (HDACs 6 and 10), class III (sirtuins), and class IV (HDAC11). Pan-HDACs inhibitors have been the first molecules tested and developed in MM. While a modest impact have been shown in monotherapy, the role of HDAC in disrupting aggresomal protein degradation led to evaluation of the efficiency of HDAC and PIs. Thus, panobinistat (a pan HDAC inhibitor) combined with bortezomib has been approved by the FDA as a third line of treatment in patients previously treated with Imids and PIs following a phase 3 clinical trial confirming efficacy in the setting of RRMM with an improvement of 4 months in EFS[78]. A challenge resulting from pan HDAC inhibition is the lack of specificity and the side effects observed that often lead to treatment discontinuation. For this reason, selective HDACs inhibitors are now under investigation. Particularly, HDAC6 inhibitor (rocilinostat) is now investigated in clinical trials and a phase 1b study showed that RRMM patients treated with rocilinostat plus bortezomib/dexamethasone had a 37% ORR in RRMM[79]. Another phase 1b trial showed a promising ORR of 55% when ricolinostat was combined with lenalidome/dexamethasone in RRMM with limited toxicity[80].

-EZH2 inhibitors

Various epigenetic modifiers are altered in MM including overexpression of enhancer of zeste homologue 2 (EZH2) or MMSET overexpression and UTX/KDM6A mutations[81,82]. EZH2 is a histone -methyltransferase, component of polycomb repressive complex 2 (PRC2), which triggers H3K27me3 to repress gene transcriptome; MMSET is a histone methyl transferase which regulates gene expression through H3K36 methylation; and UTX

regulates H3K27 acetylation. MMSET is overexpressed in t(4 ;14) which represents ~15% of MM and is associated with high risk disease. UTX/KDM6A mutation are observed in up to 5% of MM patients. UTX loss and MMSET overexpression are associated with increased transcriptomic control by EZH2[83]. Recent advances include development of small molecule inhibitors of EZH2 which have shown significant efficacy against MM cells in vitro[84–86]. Tazemetostat, an oral EZH1/2 inhibitor is under pre-clinical evaluation in hematological malignancies. Alternatively, important efforts have been made to develop MMSET inhibitors to generate targeted therapy in this subgroup of patients but the improvements in bioavailability and specificity of the drugs are still in preclinical development.

6. MAPK pathway inhibitors

-Trametinib

Unlike other malignancies characterized by recurrent genomic driver such as MYD88 in Waldenström disease or BRAF V600E mutation in melanoma or hairy cell leukemia, MM is featured by a highly heterogeneous genetic background that includes various subtypes without clearly defined drivers. Only few recurrent mutations have been identified (NRAS, KRAS, TP53, DIS3, and FAM46C) with NFKB and MAPK pathways being the most recurrently affected pathways, in 43 % and 17 % of MM patients respectively[87]. For this reason, the MAPK pathway is an attractive target in MM. Vemurafenib as single agent or in combination with bortezomib has been reported as active in V600EBRAF mutated MM patients[88,89] but this mutation is only present in approximately 2 to 5% of MM patients and is not systematically screened[87]. MEK inhibition using trametinib or in combination with dabrafenib could represent interesting therapeutic option. A first retrospective study reported potential benefit of trametinib as a single agent or in combination with other MM approved treatment[90]. However, patients were heavily treated and presented with very advanced disease and toxicity was a concern (24/58 patients discontinued therapy because of toxicities)[90]. However, this study did not select patients based on presence of perturbation in MAPK pathway, and thus its real role in possibly susceptible patient population will be determined by ongoing studies utilizing Trametinib and Dabrafenib in targeted patient population. Alone or in combination, these agents may become an important and efficient therapeutic strategy in MM.

-Afuresertib

Afuresertib is an oral AKT inhibitor. That has been evaluated in two phase 1 clinical trials in RRMM as a single agent and in combination with bortezomib and dexamethasone. As a single agent, Afuresertib showed limited activity but when combined with bortezomib and dexamethasone the ORR was up to 61%[91,92]. In another phase 1 study, Afuresertib has been combined to trametinib and evaluated in MM and solids tumors but the toxicity was high and the study discontinued[93].

7. Inhibitors of nuclear cytoplasmic transport receptor: XPO1 inhibitor

The ubiquitous transport receptor chromosome maintenance protein 1 (CRM1, also known as XPO1) is a nuclear–cytoplasmic transport receptor that acts as a carrier molecule

enhancing transportation into (importins) and out of (exportins) the nucleus. XPO1 is a member of the karyopherin family, which includes 19 members. XPO1 mediates the nuclear export of RNAs, and a large number of proteins carrying a canonical hydrophobic leucine-rich amino-acid sequence, some transcription factors involved in NFκB signaling and HDACs[94]. XPO1 expression is high in MM cells and correlate with survival in MM patients suggesting a critical role in MM biology.

Selinexor (KPT-330) is a first-in-class, orally bioavailable, selective inhibitor of XPO1-mediated nuclear export. A phase I study, evaluated selinexor alone or in combination with low-dose dexamethasone and showed broad activity and promising response in RRMM. Two phase 2 clinical trials recently published evaluated selinexor and dexamethasone, and selinexor in combination with bortezomib and dexamethasone in heavily pretreated RRMM patients. In the first study evaluating selinexor/dexamthasone, the ORR was 21% in all patients and 35% in high risk patients while the ORR was 63% for PI non refractory and 43% for PI-refractory patients in the study evaluating the combination of bortezomib/selinexor/dexamethasone. Both studies showed good response and selinexor is a promising target in MM with a limited increased toxicity[95,96].

8. Imids

Approved immunomodulatory drugs (IMiDs) in MM include thalidomide, lenalidomide, and pomalidomide. These molecules share an antimyeloma activity that relates to its interaction with the intracellular complex Cereblon/E3 ubiquitin ligase/Cul4A/DDb1. This binding enhances the degradation of two key transcription factors Ikaros (IKZF1) and Aiolos (IKZF3) through the proteasome and lead to intrupt MM cell proliferation and growth. In addition, IMids enhance cells activation of various immune cells including natural killer (NK), CD4 and CD8 T cells while inhibiting regulatory T cells[97,98]. Therefore, IMids have synergistic activity with other immunotherapies such has monoclonal antibodies or checkpoint inhibitors. Two new Imids CC220 (or Iberdomide) and CC-92480, harboring greater affinity for the Cereblon/Cul4a/E3ligase complex and degradation of its substrate, are now under investigation in various hematologic malignancies including MM[99].

In addition, the understanding of the mechanism of action of the IMids has allowed for development of a new class of drug that are currently at in pre-clinical stage. These class of drugs called degraders use the properties of IMids to bind to the Cereblon/E3Ligase/Cul4a complex to degrade specific targets[100].

9. kinesin spindle protein

Filanesib (ARRY-520) is a kinesin spindle protein inhibitor, with clinical activity as monotherapy in heavily pretreated MM patients. Kinesin spindle protein (EG5/KIF11) is a critical molecule in mitosis during cell division by contributing to the spindle apparatus and centrosome formation.[101]

In a phase 1 study, Arry-520 was tested in heavily pre-treated RRMM and was associated with an ORR of 16% with a tolerable safety[102]. Several ongoing phase 2 clinical trials are evaluating ARRY-520 in combination with pomalidomide/dexamethasone (NCT02384083),

bortezomib/dexamethasone (NCT01248923) or carfilzomib/Dexamethasone (NCT01372540) in RRMM and plasma cell leukemia.

The identification of new therapeutic targets in MM along with the rise of immunotherapy and small molecules inhibitors provide significant change in MM therapeutic landscape. Several new molecules have recently been approved and several other therapies referenced in this review will likely be soon validated too. Altogether, with the advent of cellular therapies discussed in a separate article in this issue will deeply modify the course of MM and eventually allow for a curative outcome in this disease. The detection of minimal residual disease by either next generation flow cytometry or next generation sequencing will likely be used as a new surrogate marker to monitor the disease and guide therapy while incorporating all these new efficient agents.

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Table 1:

FDA approved agents in multiple myeloma in 2018.

Drug	Class	Target
Melphalan	Alkylating agent	DNA
BiCNU	Alkylating agent	DNA
Cyclophosphamide	Alkylating agent	DNA
Doxorubicin	Anthracyclin	DNA
Thalidomide	IMid	Cereblon/E3 ubiquitin ligase complex
Lenalidomide	IMid	Cereblon/E3 ubiquitin ligase complex
Bendamustine	Alkylating agent Purine analog	DNA
Bortezomib	Reversible proteasome Inhibitor	Proteasome 20s unit
Ixazomib	Reversible proteasome Inhibitor	proteasome 20s unit
Carfilzomib	Irreversible Proteasome Inhibitor	proteasome 20s subunit inhibition
Daratumumab	Moncolnal antibody	CD38
Pomalidomide	IMid	Cereblon/E3 ubiquitin ligase complex
Elotuzumab	Monoclonal antibody	CS1
Panobinostat	HDCA inhibitor	Pan-HDAC

Table 2:

Novel Immunotherapeutic agents in multiple myeloma

Agent	Class	Target	ClinicalTrials.gov Identifier	Clinical Phase	Single/Combination
Anti-CD38 CAR-T	Cellular	CAR-T CD 38	NCT03464916	Phase 1	Single
bb21217	Cellular	CAR-T BCMA	NCT03274219	Phase 1	Single
KITE-585	Cellular	CAR-T BCMA	NCT03318861	Phase 1	Single
Kymriah	Cellular	CAR-T CD19	NCT02529813	Phase 1	Single
NAM-NK Cells	Cellular	NK Cells	NCT03019666	Phase 1	Single
P-BCMA-101	Cellular	CAR-T BCMA	NCT03288493	Phase 1	Single
PNK-007	cellular	Natural Killer Cell	NCT02955550	Phase 1	Single
CYAD-01	Cellular	CAR-T-NKG2D	NCT02203825	Phase 1	Single
AUTO2	Cellular	CAR-T BCMA	NCT03287804	Phase1–2	Single
JCARH125	Cellular	CAR-T BCMA	NCT03430011	Phase1–2	Single
LCAR-B38M	Cellular	CAR-T BCMA	NCT03090659	Phase1–2	Single
bb2121	Cellular	CAR-T BCMA	NCT03361748, NCT03601078, NCT02658929	Phase 2	Single
AMG 424	Mab-bi	CD3-CD38	NCT03445663	Phase 1	Single
CJM112	Mab	IL-17	NCT03111992	Phase 1	Single and combination
DKN-01	Mab	Dickkopf-1 (DKK-1)	NCT01457417	Phase 1	Single
JNJ-64007957	Mab-bi	CD3-BCMA	NCT03145181	Phase 1	Single
JNJ-64407564	Mab-bi	CD3-GPRC5D	NCT03399799	Phase 1	Single
Lirilumab	Mab	KIR	NCT02252263	Phase 1	Combination with Elotuzumab
MEDI2228	Mab	Antibody-drug Conjugate anti BCMA	NCT03489525	Phase 1	Single
PF-06863135	Mab-bi	CD3-BCMA	NCT03269136	Phase 1	Single
SEA-BCMA	Mab	BCMA	NCT03582033	Phase 1	Single
SGN-CD48A	Mab	Antibody-drug Conjugate anti CD48	NCT03379584	Phase 1	Single
STRO-001	Mab	Antibody-drug Conjugate anti CD74	NCT03424603	Phase 1	Single
AMG 701	Mab-bi	CD-3 BCMA	NCT03287908	Phase 1	Single
CC-93269	Mab-bi	CD-3 BCMA	NCT03486067	Phase 1	Single
BION-1301	Mab	APRIL	NCT03340883	Phase1–2	Single
BT-062	Mab	Antibody-drug Conjugate anti CD 138	NCT01001442, NCT01638936	Phase1–2	Single and combination with Len or Pom and Dex
MOR202	Mab	CD38	NCT01421186	Phase1–2	Combination with Dex and Len or Pom
TAK-079	Mab	CD38	NCT03439280	Phase 1–2	Single
TAK-573	Mab	CD38	NCT03215030	Phase1–2	Single
BHQ880	Mab	Dickkopf-1 (DKK-1)	NCT01302886, NCT01337752	Phase 2	Single
GSK2857916	Mab	Antibody-drug Conjugate anti BCMA	NCT03525678	Phase 2	Single
ABBV-838	Mab	Antibody-drug Conjugate anti anti CS1	NCT02462525	Phase 1	Combination with Pom and Dex

Agent	Class	Target	ClinicalTrials.gov Identifier	Clinical Phase	Single/Combination
ImMucin	Peptide	Mucin 1	NCT01232712	Phase1–2	Single
PVX-410	Peptide	Vaccine	NCT02886065	Phase 1	Combination with Citarinostat and lenalidomide

Novel Immunotherapeutic agents in multiple myeloma and stage of ongoing clinical trials (Mab= monoclonal antibody, Mab-bi=monoclonal antibody bispecific, Dex=dexamethasone, Len= lenalidomide, Pom=pomalidomide)

Table 3:

Novel agents in multiple myeloma

Agent	Class	Target	ClinicalTrials.gov Identifier	Clinical Phase	Single/Combination
ALT-801	Protein	p53	NCT01670994	Phase1–2	Single
TAS4464	Small Molecule	NEDD8	NCT02978235	Phase1–2	Single
Vemurafenib*	Small molecule	V600E BRAF mutated	NCT02693535	Phase 2	In combination with Cobimetinib**
Dabrafenib and/or Trametinib	Samll molecule	BRAF and MAPK	NCT03091257	Phase 1	Single agent or combined
AMG 176	Small Molecule	MCL-1	NCT02675452	Phase 1	Single
CB-5083	Small Molecule	Cdc48p/p97	NCT02223598	Phase 1	
CC-122	Small Molecule	E3 ubiquitin ligase	NCT01421524	Phase 1	Combination with Dex
CPI-0610	Small Molecule	Bromodomains	NCT02157636	Phase 1	Single
CX-4945	Small Molecule	Protein kinase CK2/ Casein Kinase II	NCT00891280, NCT01199718	Phase 1	Single
Jakafi	Small Molecule	JAK/STAT	NCT03110822	Phase 1	Combination with Len and methyprednisolone
LGH447	Small Molecule	PIM Kinase Family	NCT02160951	Phase 1	Single
Venetoclax	Small Molecule	BCL-2	NCT01794520	Phase 2	Combination with Dex
MIK665	Small Molecule	MCL-1	NCT02992483	Phase 1	Single
TG02	Small Molecule	multi-kinase inhibitor	NCT01204164	Phase 1	Combination with Carfilzomib and Dex
Selinexor	Small Molecule	Exportin-1/CRM1/XPO1	NCT02389543	Phase1–2	Combination with Len and Dex
Iberdomide (CC-220)	Small Molecule	Cereblon E3 ubiquitin ligase complex	NCT02773030	Phase1–2	Single or Combination with Dex, with Dara/Dex or Bortezomib/Dex
CC-92480	Small molecule	Cereblon E3 ubiquitin ligase complex	NCT03374085	Phase 1	Combination with Dex
ONC201	Small Molecule	Dopamine 2 (D2) Receptor	NCT02863991	Phase1–2	Single
Oprozomib	Small Molecule	Proteasome	NCT01832727	Phase1–2	Combination with Dex
PT-112	Small Molecule	Apoptosis	NCT03288480	Phase1–2	Single
Ricolinostat	Small Molecule	Histone Deacetylase	NCT01997840	Phase1–2	Combination with Pom/Dex
EDO-S101	Small Molecule	Histone Deacetylase DNA	NCT02576496	Phase	Single
LCL161	Small Molecule	Apoptosis proteins)	NCT01955434	Phase 2	Single or in combination with cyclophosphamide
CLR 131	Small Molecule	Radio-pharmaceutical	NCT02952508	Phase 2	Single
Filanesib	Small molecule	kinesin spindle protein	NCT01372540	Phase 1	Combination with carfilzomib
Afuresertib	Small molecule	AKT	NCT02235740	Phase 1	Combination with carfilzomib
Pelareorep	Viral	Oncolytic Virus	NCT00450814	Phase1–2	Single or in combination with cyclophosphamide
Melflufen	Melphalanderivative	DNA	NCT02963493	Phase 2	Combination with Dex

Novel agents in multiple myeloma and stage of ongoing clinical trials (Mab= monoclonal antibody, Mab-bi=monoclonal antibody bispecific, Dex=dexamethasone, Len= lenalidomide, Pom=pomalidomide, * this trial is also evaluating 14 other targeted therapies and Vemurafenib is combined with cobimetinib (MEK1 inhibitor))