



Review

Contemporary patient-tailored treatment strategies against high risk and relapsed or refractory multiple myeloma


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ABSTRACT

Recurrence of disease due to chemotherapy drug resistance remains a major obstacle to a more successful survival outcome of multiple myeloma (MM). Overcoming drug resistance and salvaging patients with relapsed and/or refractory (R/R) MM is an urgent and unmet medical need. Several new personalized treatment strategies have been developed against molecular targets to overcome this drug resistance. There are several targeted therapeutics with anti-MM activity in clinical pipeline, including inhibitors of anti-apoptotic proteins, monoclonal antibodies, antibody-drug conjugates, bispecific antibodies, fusion proteins, and various cell therapy platforms. For example, B-cell maturation antigen (BCMA)-specific CAR-T cell platforms showed promising activity in heavily pretreated R/R MM patients. Therefore, there is renewed hope for high-risk as well as R/R MM patients in the era of personalized medicine.

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1. Introduction

Multiple myeloma (MM) represents the second most common hematologic malignancy after non-Hodgkin lymphoma with ~30,000 new cases per year [1]. MM is a molecularly, biologically and clinically heterogeneous group of diseases with some high risk cytogenetic subsets having a very poor prognosis [2–4]. The survival of MM patients has significantly improved due in part to the application of autologous hematopoietic stem cell transplantation (ASCT) and the introduction of immunomodulatory drugs (IMiDs) lenalidomide and pomalidomide as well as the proteasome inhibitors (PI) bortezomib and carfilzomib as initial induction treatment and as maintenance therapy [5–7]. These improved outcomes have caused a paradigm shift in treatment of MM, from a palliative approach toward more active management, including the use of sequential therapies, with the goal of prolonging progression-free survival (PFS) and OS as well as further therapy at relapse. There are several other new promising drugs/biologics with anti-MM activity in clinical pipeline, including tyrosine kinase inhibitors, inhibitors of anti-apoptotic proteins, monoclonal antibodies (MoAb), antibody-drug conjugates (ADC), bispecific antibodies (bsAbs), fusion proteins, and various cell therapy platforms, including BCMA-directed CAR-T cells [8–19].

2. Role of autologous stem cell transplantation (ASCT) in high-risk and R/R MM

Autologous stem cell transplantation (ASCT) offers the best chance of achieving a minimal residual disease (MRD)-negative deep complete response (CR), which is associated with better survival outcomes of newly diagnosed patients with high-risk MM, as defined by staging, chromosomal abnormalities, disease biology, and gene expression [9] and can also be performed upon first relapse [5,20–25]. The role of ASCT may evolve as new strategies are developed including biotherapeutic agents such as bispecific T-cell engagers (BiTEs) and CAR-T cells, which are showing promising results as salvage treatment in patients with R/R MM [26]. Table S1 lists ongoing Phase 2 and Phase 3 clinical trials evaluating multi-modality treatment strategies for high-risk or R/R MM in the context of ASCT.

3. Therapeutic landscape of high risk and relapsed/refractory multiple myeloma in the era of personalized medicine

Intrinsic as well as acquired drug resistance of cancer cells to standard drugs is a major obstacle for a more successful survival outcome of MM patients being treated on contemporary clinical protocols [5–9,19,26,27]. Almost all patients with MM who survive initial treatment will eventually relapse and require further therapy. Treatment in R/R MM is often complicated by increased frailty and additional comorbidities, more aggressive disease refractory to commonly used modalities and unresolved toxicity from previous treatments. The main treatment options for R/R MM patients include ASCT, PIs (bortezomib, carfilzomib, ixazomib), IMiDs (e.g., lenalidomide, pomalidomide, MoAb (e.g. daratumumab [DARA], elotuzumab), alkylating chemotherapy drugs, anthracyclines, panobinostat, and corticosteroids, administered alone, or more commonly as part of two- or three-drug combinations [19,26–35]. The combination of daratumumab DARA, lenalidomide, and dexamethasone (Dex) has been proposed as the most effective regimen in the population of R/R MM patients. According to the clinicaltrials.gov data repository, interventional trials in R/R MM patients are playing an increasingly important role in the clinical

development path of oncology drugs that are being developed to overcome chemotherapy drug resistance in MM (Fig. S1).

3.1. Immunomodulatory drugs (IMiDs)

IMiDs are thalidomide analogues with pleiotropic anti-MM activities including immune modulation (enhanced T-cell mediated and NK mediated immunity), pro-apoptotic activity as well as anti-angiogenic, anti-inflammatory (e.g. blocking of the proinflammatory cytokines TNF and IL6) and anti-proliferative effects. Lenalidomide (Revlimid; Celgene) has remarkable activity in patients with newly diagnosed MM and R/R MM and it has contributed to significantly improved survival of MM patients. Pomalidomide (Pomalyst; Celgene) is a 2nd generation IMiD that showed excellent activity alone as well as when combined with low dose Dex in R/R MM patients and appears to have stronger immune modulatory effects compared to lenalidomide [36]. FDA also approved the use of Pom in combination with DARA (Darzalex) and Dex for the treatment of patients with MM who have received at least two prior therapies including lenalidomide (Revlimid) and a PI based on an overall response rate (ORR) of 59% with a median time to response of only one month and a median duration of response of 13.6 months [36].

3.2. Proteasome inhibitors (PIs)

PIs act through multiple mechanisms to suppress tumor survival pathways and to arrest tumor growth, tumor spread and angiogenesis. Two prospective, Phase 2 trials and two randomized Phase 3 trials have evaluated the efficacy of the PI bortezomib in the treatment of patients with R/R MM. ORRs for single agent bortezomib are approximately 30%. Bortezomib has also been evaluated in combination therapy with ORRs of approximately 65%. Carfilzomib is a second generation selective PI that has demonstrated excellent activity in patients with R/R MM [37]. Carfilzomib is FDA-approved for R/R MM patients who have received at least two prior therapies, including bortezomib and an IMiD. Carfilzomib is also approved for use in combination with lenalidomide and Dex (KRd) for the treatment of patients with relapsed MM who have received one to three prior lines of therapy. Ixazomib (Ninlaro) is the first oral PI that has demonstrated activity in patients with MM when given with Dex or in combination with lenalidomide and Dex (IRd) [31]. Ixazomib in combination with lenalidomide and Dex (IRd) is FDA-approved for the treatment of R/R MM patients who have received at least one prior therapy [31]. In a randomized Phase 2 study in newly diagnosed MM patients not eligible for ASCT, the combination of Ixazomib plus thalidomide and Dex for induction followed by maintenance therapy with Ixazomib was highly effective with a high ORR of 81% [31].

3.3. Biotherapy with monoclonal antibodies (MoAb), antibody-drug conjugates (ADCs), bispecific antibodies (bsAb), bispecific T-cell engagers (BiTE), Chimeric Antigen Receptor (CAR) T-cells (Fig. 1; Fig. S2)

The ideal antigen for effective biotherapy of MM would be protein receptors highly expressed on tumor cell membrane during all stages of MM development. In MM, BCMA, CS1, CD19, CD33, CD38, CD138, and CD56 among others are being evaluated as target antigens for biotherapy.

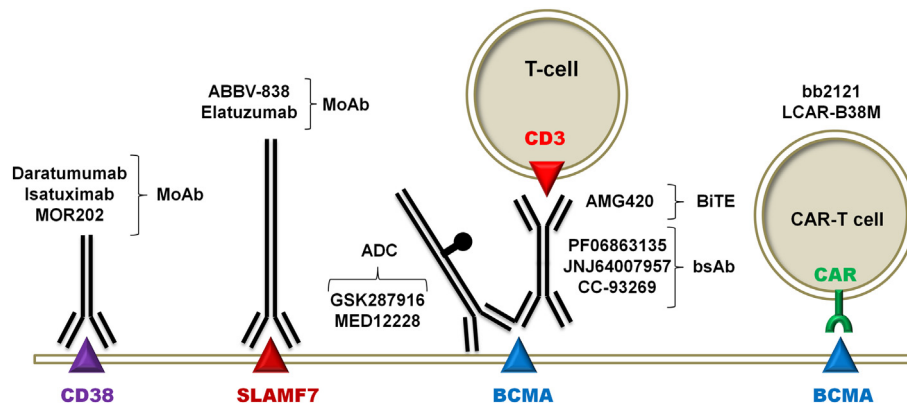


Fig. 1. Effective Biotherapy Targets on the Surface of Multiple Myeloma Cells. Abbreviations: MoAb: monoclonal antibody; BiTE: bispecific T-cell engager; ADC: antibody-drug conjugate; bsAb: bispecific antibody; CAR-T: chimeric antigen receptor carrying T-cell. There are 2 ADCs targeting BCMA in clinical development, namely GSK2857916 and MEDI2228. GSK2857916 is a humanized anti-BCMA MoAb conjugated to the cytotoxic agent monomethyl auristatin-F, via the non-cleavable linker maleimidocaproyl. GSK2857916 monotherapy has demonstrated a 60% ORR and a median PFS of 7.9 months in a group of hard to treat and heavily pretreated R/R MM [18]. It has recently received Breakthrough Therapy designation from FDA and also received PRIME designation from the European Medicines Agency (EMA). MEDI2228, a fully human MoAb that is conjugated to pyrrolobenzodiazepine dimer via a protease-cleavable linker is being evaluated in the Phase 1 study NCT03489525 for the treatment of MM. BiTEs are composed of two single-chain variable fragments (scFvs) connected by a flexible linker. One scFv fragment binds to a T cell-specific antigen (typically CD3), whereas the other scFv fragment binds to a tumor-specific antigen. This bispecificity allows BiTEs to juxtapose T-cells and tumor cells physically and promotes the formation of immunological synapses by the simultaneous binding of multiple BiTEs, leading to T-cell activation, cytokine production and cytotoxicity of the tumor cells. BI 836909 (AMG 420) is a BiTE targeting BCMA and CD3 ϵ . BsAbs are a class of engineered antibody and antibody-like proteins that, in contrast to 'regular' monospecific antibodies, combine two or more different specific antigen binding elements in a single construct. Since bsAbs do not typically occur in nature, they are constructed either chemically or biologically, using techniques such as cell fusion or recombinant DNA technologies. There are 3 clinical stage anti-CD3xBCMA bsAbs, namely Johnson and Johnson's JNJ64007957 (NCT03145181), Pfizer's PF-06863135 (NCT03269136), and Celgene's CC-93269/EM901 (NCT03486067) that have entered Phase 1 testing. See the text for a detailed discussion of the CAR-T cell platforms.

3.3.1. Targeting CD38 with MoAb

CD38-targeting MoAb such as DARA have single agent activity in heavily pretreated MM patients [38–40] (Fig. 1). DARA is a first-in-class human anti-CD38 MoAb. DARA mediates complement-dependent cytotoxicity (CDC), induces antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and tumor cell apoptosis [38–40]. In the randomized, open-label, multicenter Phase 3 ALCYONE trial (NCT02195479), DARA (Darzalex) in combination with bortezomib (Velcade), melphalan, and prednisone (DVMP) reduced the risk of disease progression or death by 50%,

compared to treatment with VMP alone, in patients with newly diagnosed MM who were not eligible for ASCT [39], and FDA approved DARA for this indication.

DARA received initial approval as monotherapy in patients with heavily pretreated R/R MM who were refractory to PIs and IMiDs. In 2 randomized Phase 3 trials of R/R MM patients, addition of DARA to standard of care regimens improved outcomes regardless of cytogenetic risk status (NCT02136134 and NCT02076009). DARA in combination with lenalidomide and Dex (DaraRD regimen) and DARA in combination with bortezomib and Dex (DaraVD regimen) [40] are approved by the

Table 1
Randomized Phase 3 Clinical Trials Evaluating Anti-CD38 Monoclonal Antibodies in High-Risk or R/R Multiple Myeloma.

Study NCT#	Reference URL	Study title	Phase of trial
NCT02541383	https://ClinicalTrials.gov/show/NCT02541383	Study of Daratumumab in Combination With Bortezomib (VELCADE), Thalidomide, and Dexamethasone (VTD) in the First Line Treatment of Transplant Eligible Subjects With Newly Diagnosed Multiple Myeloma	3
NCT02136134	https://ClinicalTrials.gov/show/NCT02136134	Phase 3 Study Comparing Daratumumab, Bortezomib and Dexamethasone (DVd) vs Bortezomib and Dexamethasone (Vd) in Subjects With Relapsed or Refractory Multiple Myeloma	3
NCT02076009	https://ClinicalTrials.gov/show/NCT02076009	Phase 3 Study Comparing Daratumumab, Lenalidomide, and Dexamethasone (DRd) vs Lenalidomide and Dexamethasone (Rd) in Subjects With Relapsed or Refractory Multiple Myeloma	3
NCT03234972	https://ClinicalTrials.gov/show/NCT03234972	A Randomized, Multicenter, Open-label, Phase 3 Study to Compare Daratumumab, Bortezomib, and Dexamethasone (DVd) vs Bortezomib and Dexamethasone (Vd) in Chinese Subjects With Relapsed or Refractory Multiple Myeloma	3
NCT03180736	https://ClinicalTrials.gov/show/NCT03180736	A Phase 3 Study Comparing Pomalidomide and Dexamethasone With or Without Daratumumab in Subjects With Relapsed or Refractory Multiple Myeloma Who Have Received at Least One Prior Line of Therapy With Both Lenalidomide and a Proteasome Inhibitor.	3
NCT03158688	https://ClinicalTrials.gov/show/NCT03158688	A Randomized, Open-label, Phase 3 Study Comparing Carfilzomib, Dexamethasone, and Daratumumab to Carfilzomib and Dexamethasone for the Treatment of Patients With Relapsed or Refractory Multiple Myeloma CANDOR Study of Carfilzomib and Daratumumab for Relapsed Myeloma	3
NCT03277105	https://ClinicalTrials.gov/show/NCT03277105	A Phase 3 Randomized, Multicenter Study of Subcutaneous vs. Intravenous Administration of Daratumumab in Subjects With Relapsed or Refractory Multiple Myeloma	3
NCT02195479	https://ClinicalTrials.gov/show/NCT02195479	A Phase 3, Randomized, Controlled, Open-label Study of VELCADE (Bortezomib) Melphalan-Prednisone (VMP) Compared to Daratumumab in Combination With VMP (D-VMP), in Subjects With Previously Untreated Multiple Myeloma Who Are Ineligible for High-dose Therapy	3
NCT03275285	https://ClinicalTrials.gov/show/NCT03275285	Randomized, Open Label, Multicenter Study Assessing The Clinical Benefit Of Isatuximab Combined With Carfilzomib (Kyprolis®) And Dexamethasone Versus Carfilzomib With Dexamethasone In Patients With Relapsed And/Or Refractory Multiple Myeloma Previously Treated With 1 to 3 Prior Lines	3
NCT02990338	https://ClinicalTrials.gov/show/NCT02990338	A Phase 3 Randomized, Open-label, Multicenter Study Comparing Isatuximab (SAR650984) in Combination With Pomalidomide and Low-Dose Dexamethasone Versus Pomalidomide and Low-Dose Dexamethasone in Patients With Refractory or Relapsed and Refractory Multiple Myeloma	3

US FDA for use in patients with MM who have received at least one prior therapy. In a prospective trial of DARA, Pom, and Dex in multiply relapsed MM (NCT01998971), the ORR was 60% and the median PFS was 8.8 months [36]. FDA has approved this regimen for patients with MM who have received at least two prior therapies including lenalidomide and a PI. In the ongoing Phase 2 and Phase 3 clinical studies, DARA is being evaluated in novel combinations with other treatment modalities, including PI's, IMiDs and Dex (Table 1). Notably, a recent observational study indicated that the immunomodulatory effects of DARA may contribute to a high objective response rate of previously IMiD-refractory or PI-refractory MM patients who are treated with DARA monotherapy to retreatment with IMiD/PI-based salvage regimens [29]. Likewise, other anti-CD38 MoAb, including Isatuximab (ISA) [41] and MOR202 [42], have shown promising activity in clinical trials of R/R MM patients.

3.3.2. Targeting SLAMF7 with MoAb

Elotuzumab (Empliciti) is a first-in-class humanized MoAb targeting SLAMF7 [18,43,44] (Fig. 1). The mechanisms of the antitumor effects of elotuzumab include disrupting MM cell adhesion to bone marrow stromal cells, enhancing NK cell cytotoxicity, and mediating ADCC but not CDC. Elotuzumab is FDA-approved for use in combination with lenalidomide and Dex for the treatment of patients with MM who have received one to three prior therapies. In an open-label, multicenter, Phase 3 trial (ELOQUENT-2, NCT01239797), 646 patients with MM relapsed after one to three prior lines of therapy were randomly assigned to receive standard dose oral lenalidomide plus Dex (Ld) with or without elotuzumab [44]. After a median follow-up of 24 months, Ld plus elotuzumab (ELd) resulted in higher ORR (79 versus 66%) and better PFS when compared with Ld alone. Elotuzumab in combination with Pom-Dex is being examined for relapsed MM in an ongoing Phase 2 randomized trial (NCT02654132). Elotuzumab is being studied in combination with lenalidomide as maintenance after high-dose therapy as well (NCT02420860) (Table 2).

3.3.3. Targeting B-cell maturation antigen (BCMA) with BsAbs, BiTEs, and Chimeric Antigen Receptor (CAR) T-cells (Fig. 1, Fig. S2)

BCMA is a transmembrane glycoprotein in the TNF receptor superfamily 17 (TNFRSF17) that has a very restricted expression pattern and is undetectable on normal human tissues except for PCs. Current BCMA-targeting biotherapeutic agents in clinical development include ADCs, BiTEs, bsAbs, and CAR-T cell therapy [17,45,46] (Fig. 1). There are several CAR-T platforms targeting BCMA in development [45–50] and several have demonstrated activity in MM. In the first-in-human study of CAR-T cells targeting BCMA, the overall response rate was 81% with 63% very good partial response or complete response for R/R MM patients who had a median of 9.5 prior lines of MM therapy [36]. In a Phase 1 study (CRB-401), b2121 (Bluebird Bio and Celgene), 2nd generation autologous T-cells transduced with a lentiviral vector, showed an ORR of 94% with a CR rate of 56% [50]. These CAR-T cells produced deep and durable responses with 50% of the evaluable patients having ongoing responses >1 year. Notably, the clinical responses have continued to improve even after a year [45,48]. A global pivotal Phase 2 KarMMA trial evaluating bb2121 is open for enrollment (NCT03361748) (Table 3). Likewise, investigators from Jiatong University in China reported at the 2017 ASCO meeting that their BCMA-“bispecific” CAR-T cells (LCAR-B38M, Nanjing Legend Biotech) binding to 2 key BCMA epitopes yielded a 100% ORR with 74% stringent CR rate in R/R MM patients [49].

3.4. Immune-checkpoint inhibitors

Immune-checkpoint inhibitors (ICI) targeting the PD-1/PD-L1 axis have recently emerged as promising agents against hematologic malignancies, including MM [51]. Early clinical trials of IMiDs combined with PD-1 pathway blocking MoAb have shown promising preliminary results. For example, the Phase 1 KEYNOTE-023 (NCT02036502) study of the anti-PD1 MoAb pembrolizumab plus lenalidomide and Dex in relapsed MM showed an ORR of 76%. Unfortunately, excessive and unpredictable toxicity has raised serious safety concerns about anti-PD1

Table 2
Phase 2 and Phase 3 Clinical Trials Evaluating Elotuzumab in High-Risk or R/R Multiple Myeloma.

Study NCT#	Reference URL	Study title	Phase of Trial
NCT02718833	https://ClinicalTrials.gov/show/NCT02718833	A Phase 2 Study of Elotuzumab in Combination With Pomalidomide, Bortezomib, and Dexamethasone in Relapsed and Refractory Multiple Myeloma	2
NCT03155100	https://ClinicalTrials.gov/show/NCT03155100	Phase 2 Study of Carfilzomib + Elotuzumab + Dexamethasone for Relapsed or Progressed Multiple Myeloma After 1–3 Prior Treatment Lines	2
NCT03030261	https://ClinicalTrials.gov/show/NCT03030261	A Phase 2 Study of Elotuzumab, Pomalidomide, & Dexamethasone (Elo-Pom-Dex) With Second Autologous Stem Cell Transplantation for Relapsed Multiple Myeloma	2
NCT02654132	https://ClinicalTrials.gov/show/NCT02654132	An Open Label, Randomized Phase 2 Trial of Pomalidomide/Dexamethasone With or Without Elotuzumab in Relapsed and Refractory Multiple Myeloma (ELOQUENT-3)	2
NCT02612779	https://ClinicalTrials.gov/show/NCT02612779	A Phase 2, Multiple Cohort Study of Elotuzumab in Combination With Pomalidomide and Low-Dose Dexamethasone (EPd), and in Combination With Nivolumab (EN), in Patients With Multiple Myeloma Relapsed or Refractory to Prior Treatment With Lenalidomide.	2
NCT03361306	https://ClinicalTrials.gov/show/NCT03361306	LCI-HEM-MYE-CRD-002: A Phase 2 Study of Carfilzomib- Revlimid-Dexamethasone-Elotuzumab in Relapsed/Refractory Multiple Myeloma	2
NCT02843074	https://ClinicalTrials.gov/show/NCT02843074	Phase 2 Study to Assess the Feasibility and Tolerance of the Combination of Elotuzumab, Lenalidomide and Dexamethasone (ErD) in the Induction, Consolidation and Maintenance Treatment of Transplant-Eligible Patients Newly Diagnosed With Multiple Myeloma	2
NCT03411031	https://ClinicalTrials.gov/show/NCT03411031	A Randomized Parallel Phase 2 Study of Elotuzumab Plus Lenalidomide (Elo/Rev) for the Treatment of Serologic Relapse/Progression While on Lenalidomide Maintenance for Multiple Myeloma	2
NCT01891643	https://ClinicalTrials.gov/show/NCT01891643	A Phase 3, Randomized, Open Label Trial of Lenalidomide/Dexamethasone With or Without Elotuzumab in Subjects With Previously Untreated Multiple Myeloma	3
NCT03104270	https://ClinicalTrials.gov/show/NCT03104270	A Phase 2 Trial of the Efficacy and Safety of Elotuzumab in Combination With Pomalidomide, Carfilzomib and Dexamethasone Among High Risk Relapsed/Refractory Multiple Myeloma Patients	2
NCT02420860	https://ClinicalTrials.gov/show/NCT02420860	Phase 2 Study of the Combination of Elotuzumab With Lenalidomide as Maintenance Therapy Post Autologous Stem Cell Transplant in Patients With Multiple Myeloma	2
NCT02495922	https://ClinicalTrials.gov/show/NCT02495922	A Randomized Phase 3 Trial on the Effect of Elotuzumab in VRD Induction/Consolidation and Lenalidomide Maintenance in Patients With Newly Diagnosed Myeloma	3
NCT02726581	https://ClinicalTrials.gov/show/NCT02726581	An Open-Label, Randomized Phase 3 Trial of Combinations of Nivolumab, Pomalidomide and Dexamethasone in Relapsed and Refractory Multiple Myeloma	3

Table 3
Interventional Clinical Trials Evaluating CAR-T Cell Platforms in Relapsed or Refractory Multiple Myeloma.

Study NCT#	Reference URL	Study title	Phase of trial	CAR-T platform
NCT03287804	https://ClinicalTrials.gov/show/NCT03287804	A Single-Arm, Open-Label, Multi-Center, Phase 1/2 Study Evaluating the Safety and Clinical Activity of AUTO2, a CAR-T Cell Treatment Targeting BCMA and TAC1 in Patients With Relapsed or Refractory Multiple Myeloma	1/2	CAR-T BCMA + TAC1
NCT03322735	https://ClinicalTrials.gov/show/NCT03322735	A Study of BCMA CAR-T Cells for Patients With Relapsed and Refractory Multiple Myeloma	1/2	CAR-T BCMA
NCT03661554	https://ClinicalTrials.gov/show/NCT03661554	BCMA Nano Antibody CAR-T Cells for Patients With Refractory and Relapsed Multiple Myeloma	1	CAR-T Nanobody/CAR-T BCMA
NCT03664661	https://ClinicalTrials.gov/show/NCT03664661	A Single-center, One Arm, Open-Label Clinical Study of BCMA Nanobody CAR-T Cells in Refractory/Relapsed Myeloma	1	CAR-T BCMA
NCT02546167	https://ClinicalTrials.gov/show/NCT02546167	Pilot Study of Redirected Autologous T Cells Engineered To Contain an Anti-BCMA scFv Coupled To TCR ζ And 4-1BB Signaling Domains in Patients With Relapsed and/or Refractory Multiple Myeloma	1	CAR-T BCMA
NCT03548207	https://ClinicalTrials.gov/show/NCT03548207	A Phase 1b-2, Open-Label Study of JNJ-68284528, A Chimeric Antigen Receptor T-Cell (CAR-T) Therapy Directed Against BCMA in Subjects With Relapsed or Refractory Multiple Myeloma	1/2	JNJ-68284528/CAR-T BCMA
NCT03448978	https://ClinicalTrials.gov/show/NCT03448978	Phase 1 Safety and Feasibility Study of Autologous CD8+ T-cells Transiently Expressing a Chimeric Antigen Receptor Directed to B-Cell Maturation Antigen in Patients With Multiple Myeloma	1	CAR-T BCMA
NCT03318861	https://ClinicalTrials.gov/show/NCT03318861	A Phase 1 Multicenter Study of KITE-585, an Autologous Anti-BCMA CAR-T Cell Therapy, in Subjects With Relapsed/Refractory Multiple Myeloma	1	KITE-585/CAR-T BCMA
NCT03274219	https://ClinicalTrials.gov/show/NCT03274219	A Phase 1 Study of bb21217, an Anti-BCMA CAR- T Cell Drug Product, in Relapsed and/or Refractory Multiple Myeloma	1	bb21217/CAR-T BCMA
NCT03361748	https://ClinicalTrials.gov/show/NCT03361748	A Phase 2, Multicenter Study to Determine the Efficacy and Safety of bb21217 in Subjects With Relapsed and Refractory Multiple Myeloma	2	bb21217/CAR-T BCMA
NCT03430011	https://ClinicalTrials.gov/show/NCT03430011	Protocol H125001: An Open-Label Phase 1/2 Study of JCARH125, BCMA-targeted Chimeric Antigen Receptor (CAR)-T Cells, in Subjects With Relapsed or Refractory Multiple Myeloma	1/2	JCARH125/CAR-T BCMA
NCT03288493	https://ClinicalTrials.gov/show/NCT03288493	Open-Label, Multicenter, Single Ascending Dose Study to Assess the Safety of P-BCMA-101 in Subjects With Relapsed and/or Refractory Multiple Myeloma (MM)	1	P-BCMA-101 CAR-T/CAR-T BCMA
NCT03196414	https://ClinicalTrials.gov/show/NCT03196414	Study of T Cells Targeting CD138/BCMA (CAR-T CD138/BCMA) for Chemotherapy Refractory and Relapsed Multiple Myeloma	1/2	CAR-T CD138/BCMA
NCT03464916	https://ClinicalTrials.gov/show/NCT03464916	A Phase 1, Open-Label, Dose-Escalation, Pharmacokinetic and Pharmacodynamic Study of the Safety and Efficacy of CAR2 Anti-CD38 A2 CAR-T Cells in Patients With Relapsed or Refractory Multiple Myeloma	1	CAR-T CD38

MoAb, as reflected by several advanced clinical trials in R/R MM as well as newly diagnosed high-risk MM having been suspended by the FDA (e.g. NCT02579863, NCT02576977, NCT02906332) [52]. Further investigation and randomized trials are needed to further evaluate the safety and effectiveness of the ICI targeting the PD-1/PD-L1 axis [52,53].

3.5. Targeted therapeutics and personalized medicine for MM (Fig. 2)

MM is characterized by a heterogeneous mutational landscape [2–4]. Some of the molecular mutations which are believed to be among the driver mutations of MM are druggable with available targeted therapeutics that can be matched to a specific targeted therapy for that aberration, thereby providing the foundation for a patient-tailored precision medicine program for MM [6,13]. Mutations involving CCND1 and CDKN2C are found in 18% of MM patients. Palbociclib (PD0332991) selectively inhibits CDK4/6, causing a G1 arrest in primary myeloma cells [54] (Fig. 2). Activated RAS initiates the RAS-RAF-MAPK signaling cascade by activating the protein kinase activity of the RAF kinase. RAF phosphorylates and activates the serine/tyrosine/threonine kinase MAP2K (also known as MAPKK or MEK - MEK1 and MEK2). MEK phosphorylates and activates the serine/threonine-selective MAPK. RAF kinase inhibitors as well as MEK kinase inhibitors disrupt the activation of MAPK and therefore serve as functional MAPK inhibitors (MAPKi) [13]. In the NCT02834364 (GMMG-BIRMA) Phase 2 study in R/R MM patients with the BRAF V600E/K mutation are being treated with the kinase inhibitors Encorafenib (LGX818; RAF kinase inhibitor) in combination with the MEK inhibitor Binimetinib (MEK162) (Fig. 2). Other RAF kinase inhibitors include dabrafenib, encorafenib, vemurafenib, XL281. Other MEK inhibitors include binimetinib (MEK162), trametinib (GSK1120212), and cobimetinib [13] (Fig. 2). In 2013/2014 FDA approved trametinib and dabrafenib combination for treatment of metastatic melanoma patients with BRAF mutations. It has been reported that MM cases with BRAF V600E mutations can

respond to vemurafenib [55]. However, NRAS mutations have been shown to confer resistance to vemurafenib in BRAF-mutated MM [56] and spatial genomic heterogeneity in MM has also been associated with delayed onset treatment failure in vemurafenib-treated BRAF-mutated MM patients [57]. Inhibition of BRAF using BRAF V600E inhibitors can result in paradoxical activation of the MAPK pathway, a phenomenon that is exaggerated in KRAS-mutated cancers. Inhibition of MAPKK/MEK has emerged as a viable strategy to treat patients with BRAF-mutated cancers and to overcome paradoxical activation in the setting of therapy with BRAF V600E-directed agents. Trametinib is an oral, allosteric inhibitor of MEK1/2 that has shown early clinical activity in tumors with activating BRAF mutations (Fig. 2). In the NCI-MATCH study (NCT02465060), R/R MM patients with BRAF V600E/R/K/D mutation receive in a Phase 2 setting dabrafenib and trametinib, whereas patients with BRAF fusion or BRAF non-V600 mutation receive trametinib and patients with NRAS mutation in codon 12, 13, or 61 receive binimetinib. Likewise, dabrafenib plus trametinib, dabrafenib alone, or trametinib alone are being evaluated in patients with R/R MM and BRAF/NRAS/KRAS mutations (NCT03091257). The t(4;14) translocation is associated with upregulation of the FGFR3. Patients with t(4;14) demonstrate an overall poor prognosis. There may be additional mutations by which FGFR3 is dysregulated in MM that are independent of t(4;14) translocation. There are several FGFR inhibitors (FGFRi), including non-selective inhibitors (e.g. Dovitinib, Lenvatinib, Nintedanib, Ponatinib, Lucitanib, Pazopanib) and selective inhibitors (e.g. AZD4547, BGJ398, ARQ-087, JNJ 42756493, BAY-1163877) (Fig. 2). Dovitinib (NCT01058434) has been evaluated in MM patients with FGFR3 gene alterations. NCT02952573 is an ongoing proof of concept study of the oral FGFRi JNJ 42756493/Erdaftinib comparing R/R MM patients with and without FGFR3 mutations. In the NCI-MATCH study (NCT02465060), R/R MM patients with FGFR pathway alterations are treated with the selective FGFR3i AZD4547. BTK also emerged as a promising new molecular target in R/R MM (Fig. 2). In primary

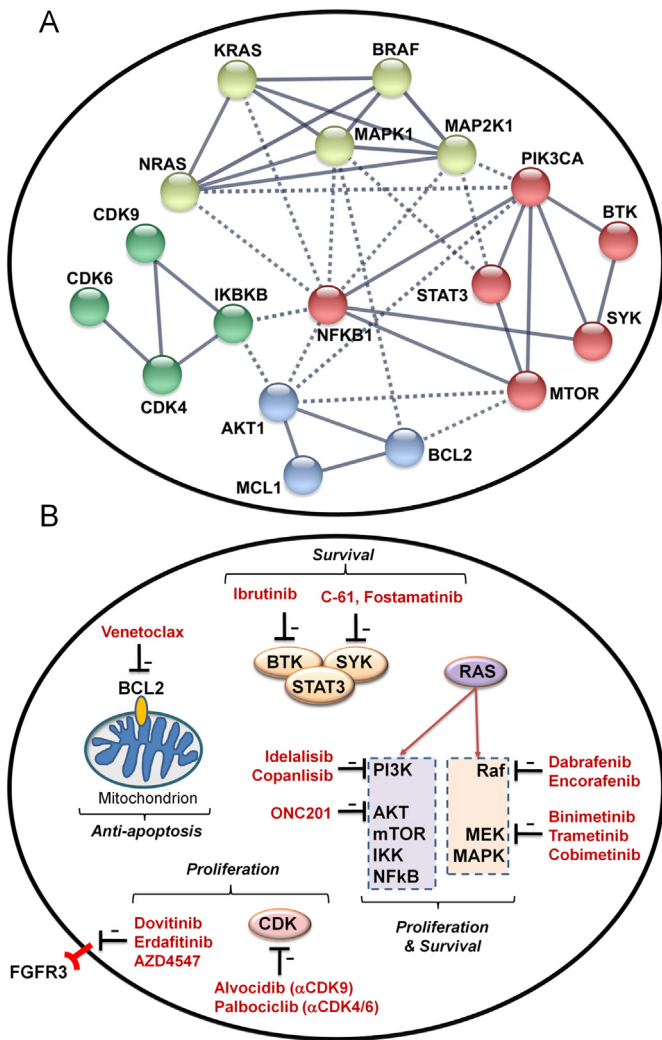


Fig. 2. Molecular Targets and Targeted Therapeutics in R/R MM and High-Risk MM. [A] Network of Molecular Targets. The publicly available STRING (Search Tool for the Retrieval of Interacting Genes/Proteins) database (<http://string-db.org>) provides a critical assessment and integration of protein–protein interactions, including direct (physical) as well as indirect (functional) associations. The depicted STRING network view of the protein–protein interaction network for molecular targets in MM cells was constructed using STRING10 algorithm and the STRING database. Nodes show the protein identifiers and lines depict known interactions between the proteins. The lines represent experimental associations between the proteins, as determined by the STRING data mining algorithm. Associations were filtered with confidence parameter >90% (highest confidence from the datamining algorithm) and depicted by the connecting lines. Clustering algorithm was performed on the association scores to group protein–protein interaction networks for the most closely networked interactions (“MCL clustering algorithm” provided by the software). The MCL inflation parameter was set to a value of 2.5 to distinguish 4 inter-connected cluster groupings. Solid lines represent connections within clusters and dotted lines depict connections between clusters. [B] Targeted Therapeutics and Their Targets. Depicted are the molecular targets according to their functional significance and available targeted medicines that inhibit their function.

myeloma-bearing SCID-rab mice, the rationally designed non-covalent Bruton’s tyrosine kinase (BTK) inhibitor LFM-A13 inhibited osteoclast activity, prevented myeloma-induced bone resorption and moderately suppressed myeloma growth [58]. Ibrutinib, a first-in-class, once-daily, oral covalent inhibitor of BTK, exhibited promising clinical activity in R/R MM patients who had received ≥ 2 prior lines of therapy, including an immunomodulatory agent [10]. Spleen tyrosine kinase (SYK) inhibitors also show potential as new therapeutic agents for R/R MM [11,15] (Fig. 2). While these TKI, especially the FGFRi and BTKi hold clinical promise based on preliminary clinical trial data, currently, there is insufficient information regarding the clinical potential of TKI as possible components of future personalized treatment strategies for R/R MM.

The BCL-2-specific BH3 mimetic Venetoclax (ABT-199) is a selective, orally bioavailable BCL-2 inhibitor that induces cell death in MM cells, particularly in those harboring t(11;14), which express high levels of BCL-2 relative to BCL-X_L and MCL-1 [14,59] (Fig. 2). Intrinsic resistance to Venetoclax treatment observed in MM patient samples has been attributed to a low BCL-2-to-MCL-1 gene expression ratio, suggesting a central role for MCL-1 [60]. Livingston et al. reported that the CDK9 inhibitor Alvocidib suppresses MCL-1 expression via CDK9-mediated regulation of RNA polymerase II and potentiates the activity of venetoclax against MM cells, reminiscent of the findings reported for AML cells [61]. Furthermore, Dexamethasone has been reported to enhance the sensitivity of MM cells to venetoclax [62]. FDA previously granted accelerated approval to Venetoclax (Venclexta, AbbVie/Roche) in 2016 for the treatment of patients with recurrent CLL who have 17p deletion. Kumar et al. reported that Venetoclax monotherapy exhibited an acceptable safety profile and evidence of single-agent activity in patients with heavily pre-treated R/R MM, predominantly in patients with t(11;14) abnormality (NCT01794520) [14]. Most responses (86%) were reported in patients with t(11;14). In this group, ORR was 40%, with 27% of patients achieving very good partial response or better. A Phase 3, multicenter, randomized, double blind, placebo-controlled study is active and will evaluate the efficacy and safety of Venetoclax plus bortezomib and Dex in subjects with R/R MM who are considered sensitive or naïve to PI and received 1 to 3 prior lines of therapy for MM (NCT02755597). Other combinations are being explored in separate clinical trials (e.g. NCT03399539, NCT0331418, NCT03539744). The pending clinical data from the ongoing clinical trials of venetoclax in R/R MM patients are anticipated to provide critical insights regarding the clinical potential of this promising agent and how to best integrate it into the standard of care for R/R MM patients.

4. Future directions and outstanding questions

4.1. Detection of MRD

Recently, a EuroFlow-based next generation flow (NGF) approach was reported for highly sensitive and standardized detection of MRD in MM, and the results of its validation vs. a conventional 8-color flow-MRD method and NGS [63]. Such standardized and validated NGF-MRD methods can be applied to virtually every MM patient for MRD monitoring in BM after therapy and provide the opportunity for adding MRD negativity to criteria for response to treatment assessments and including it (together with PFS and OS) as an efficacy endpoint [63–65]. Even in patients who achieve an early CR, the use of MRD detection methodologies would allow clinical researchers to assess the contribution of additional interventions and time to the quality (i.e. “depth”) of CR. The use of fused functional and anatomic imaging using positron emission tomography-computed tomography (¹⁸F-FDG PET/CT) [66–68] combined with MRD monitoring using highly sensitive new detection methods [63–65] provides a unique opportunity to better evaluate clinical activity of innovative treatment platforms and new combination regimens in R/R MM as well as newly diagnosed high-risk MM patients.

4.2. Optimizing risk mitigation to maximize patient safety and quality of life

Protocols of targeted therapeutics should consider incorporating specific monitoring and management guidelines for specific toxicities for risk mitigation based on the most recent and up to date integrated safety analysis of the particular drug that will be used [69–71]. The higher mortality rate for early toxicity in patients ≥ 80 years emphasizes the need for a careful frailty assessment and more effective risk-mitigation measures for elderly.

4.3. Proof-of-concept studies with specific cellular PD/PK endpoints

Secondary plasma cell leukemia (PCL) is observed in advanced MM with a frequency of 1–4% [72]. The circulating PCL cells in blood can be easily collected before, during and after treatment with the different single agent as well as combination modalities for (i) cellular PK analyses, (ii) evaluation of on-target and off-target effects at the cellular level using phosphoproteomics; (iii) evaluation of the kinetics of cytotoxic activity against MCL cells using multi-color flow cytometry in a quantitative apoptosis assay. Well-designed mechanism of action (MOA) studies that leverage PCL cells can provide clinically meaningful new insights that inform the design of future MM studies. In view of the oligoclonality of MM, it is likely to be helpful to characterize the dynamics of the mutational profile of persistent/outgrowing MM clones, elucidate the clonal diversity, persistence or disappearance of multi-mutated clones, acquisition of additional mutations. Rashid et al. National University of Singapore recently reported an artificial intelligence (AI) technology based experimental platform labeled as the Quadratic Phenotypic Optimization Platform (QPOP) to rapidly identify patient-tailored novel drug combinations for R/R MM [73]. Notably, Lagana et al. reported an integrated multiomics approach for personalized therapy of MM and its application in a pilot precision medicine clinical trial in R/R MM patients. Their data appeared to demonstrate the feasibility of NGS-guided personalized therapy [27].

4.4. Real-world data (RWD) and real-world evidence (RWE) to evaluate the relative effectiveness, safety and utility of new anti-MM treatment strategies

The 21st Century Cures Act (“Cures Act”) encourages the Food and Drug Administration to consider RWE of the safety and comparative effectiveness of drugs in its approval process [74]. Additional RWD will be essential to an improved understanding of the current clinical practice patterns, so that new agents can be effectively incorporated into existing treatment strategies for MM or used instead of less effective treatments to ensure that patients receive the best possible care. Randomized adaptive clinical trials aimed at comparing the efficacy of different treatment strategies with respect to their achieved rate of sustained deep responses with MRD negativity as well as their tolerability as well as randomized hybrid interventional x observational studies that collect real-world data regarding their real-world effectiveness/treatment burden ratio and relative tolerability are needed to reach a consensus regarding the “best” treatment strategies for high-risk and R/R MM.

5. Conclusion

The therapeutic landscape for MM is rapidly evolving in the era of personalized medicine. New treatment strategies have markedly improved the survival of MM patients and caused a paradigm shift in therapy in treatment of MM, from a palliative approach for an incurable hematologic malignancy to a more patient-tailored active management strategy of a potentially curable disease, including the use of sequential therapies, with the goal of prolonging PFS and OS as well as further salvage therapy at relapse. The observation that some of the innovative treatment platforms have resulted in durable MRD-negative deep CRs even in heavily pretreated R/R MM patients has renewed the hope for development of potentially curative therapies for MM as predicted by Barlogie et al. [75]. There is a growing list of promising targeted therapeutics with anti-MM activity in clinical pipeline, including TKI, inhibitors of anti-apoptotic proteins, MoAbs, ADC, bsAbs, fusion proteins, and various cell therapy platforms. Which of these treatment modalities will ultimately evolve into components of a new standard of care regimen for R/R or high-risk MM patients remains to be determined. Several challenges remain and require a multi-stake holder collaboration for successful integration of new technology platforms as well as clinical

management guidelines into the contemporary MM treatment programs.

Search strategy and selection criteria

Data for this Review were identified by searches of MEDLINE, Current Contents, PubMed, and references from relevant articles using the search terms “multiple myeloma”, “clinical trial”, and “therapy”. Abstracts and reports from meetings were included only when they related directly to previously published work. Only articles published in English between 2010 and 2018 were included. We also interrogated the clinicaltrials.gov data repository (<https://clinicaltrials.gov/>) to determine the number of interventional trials in R/R MM patients that were initiated from 1993 to 2018. Search terms to identify the trials were “Relapse OR Refractory”, “Interventional studies”, and “Multiple Myeloma”. The following search terms were used for the Tables 1–3: Recruiting, Active not recruiting, completed; Interventional Studies; Multiple Myeloma; CD38; Start date from 09/01/2013 to 09/01/2018. Additional terms were: CD38 (Table 1), Elotuzumab (Table 2), CAR-T (Table 3).

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Conflict-of-interest disclosure

The authors declare no competing financial interests or other conflict of interests.

Authorship contribution

All authors have made significant and substantive contributions to the study. All authors have participated in the review of relevant literature, drafting of the manuscript, review and revisions of the final draft. F.M.U. and SQ have equally contributed to this article.

Appendix A. Supplementary data

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