Sadaf *et al. J Transl Genet Genom* 2022;6:63-83
DOI: 10.20517/jtgg.2021.36

Journal of Translational Genetics and Genomics

Review

Open Access

Check for updates

Multiple myeloma etiology and treatment

Humaira Sadaf[1], Hanna Hong[2], Mohsin Maqbool[2], Kylin Emhoff[2], Jianhong Lin[2], Shan Yan[3], Faiz Anwer[4], Jianjun Zhao[2]

[1]Department of Pathology and Laboratory Medicine, University of Texas McGovern Medical School, Houston, TX 77030, USA.
[2]Department of Cancer Biology, Lerner Research Institute, Cleveland Clinic, Cleveland, OH 44195, USA.
[3]Department of Biological Sciences, College of Liberal Arts & Sciences, University of North Carolina at Charlotte, Charlotte, NC 28223, USA.
[4]Department of Hematology and Medical Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH 44195, USA.

Correspondence to: Jianjun Zhao, Department of Cancer Biology, Lerner Research Institute, Cleveland Clinic, 9500 Euclid Avenue, NB40, Cleveland, OH 44195, USA. E-mail: zhaoj4@ccf.org

How to cite this article: Sadaf H, Hong H, Maqbool M, Emhoff K, Lin J, Yan S, Anwer F, Zhao J. Multiple myeloma etiology and treatment. *J Transl Genet Genom* 2022;6:63-83. https://dx.doi.org/10.20517/jtgg.2021.36

Received: 22 July 2021 **First Decision:** 26 Oct 2021 **Revised:** 19 Nov 2021 **Accepted:** 21 Dec 2021 **Published:** 20 Jan 2022

Academic Editor: Susan L. Slager **Copy Editor:** Yue-Yue Zhang **Production Editor:** Yue-Yue Zhang

Abstract

Genomic aberrations comprise hallmarks of multiple myeloma (MM), a plasma cell malignancy with an overall poor prognosis. MM is heterogeneous and has different molecularly-defined subtypes according to varying clinical and pathological features. Hyperdiploidy or non-hyperdiploidy has usually been identified as early initiating genetic events that can be followed by secondary aberrations, including copy number changes, secondary translocations, and different epigenetic modifications, which cause immortalization of plasma cell and disease progression. Even though recent advances in drug discovery have offered new perspectives of treatment, MM remains incurable. However, understanding the molecular complexity of MM would allow patients to get precision treatment. Our review focuses on current evidence in myeloma biology with special attention to genomic and molecular variations.

Keywords: Multiple myeloma, cancer genetics, targeted therapy, clinical trial

INTRODUCTION

Multiple myeloma (MM) is an incurable neoplasm of terminally differentiated B lymphocytes called plasma cells, which occurs in bone marrow and secretes immunoglobulin[1]. MM mainly affects elderly people, and the median diagnosed age is 69[2]. It has a poor prognosis, and the 5-year overall survival rate is 48.5%[1].

Genomic aberrations are central to the development and progression of multiple myeloma[3]. Genomic instability affects all levels of the genome and leads to two types of aberrations: large-scale and small-scale[3]. Large-scale aberrations include insertions, deletions, translocations, and inversions[4]. These aberrations can be revealed in tumor cells during the metaphase of the mitotic cycle using traditional Giemsa banding and spectral karyotyping[5]. Similarly, fluorescence *in situ* hybridization and other molecular cytogenetic approaches can identify large-scale aberrations in interphase cells[6]. Small-scale aberrations include small insertions and deletions (indels), loss of heterozygosity, copy number changes, and base substitution mutations[3]. Next-generation sequencing (NGS) is a collection of methods that can identify small-scale aberrations and includes whole-genome sequencing and protein-encoding exome sequencing (WES)[7,8]. Recently, transcriptome-wide sequencing has allowed for the identification of subtypes stratified by cells of origin and genomic/epigenetic alterations[9]. To this end, analysis of a 70-gene prognostic signature developed by the University of Arkansas for Medical Sciences has been used and validated to stratify risk for relapse and survival[10]. Furthermore, transcriptome sequencing-based stratification can predict response to MM therapy, as shown with MCL1-M co-expression and bortezomib response[11].

In the cytogenetic approach, MM initiation and progression involve primary and secondary events. Primary events responsible for plasma cell immortalization are further categorized into two subtypes: hyperdiploid (HRD) and non-hyperdiploid (non-HRD). HRD subtype is correlated with trisomies of the odd-numbered chromosomes (3, 5, 7, 9, 11, 15, 19, and 21). Non-HRD subtype involves balanced chromosomal translocations, with more than 90% of non-HRD cases affecting the transcriptionally active IgH locus on 14q32. The primary translocations t(4;14), t(6;14), t(11;14), t(14;16), and t(14;20) cause over-expression of oncogenes *MMSET/FGFR3*, *CCND3*, *CCND1*, *MAF*, and *MAFB*[12,13]. These primary translocations can be found in about 50% monoclonal gammopathy of undetermined significance (MGUS) patients as an early event, which takes place in the lymphoid germinal center during physiological class-switch recombination and somatic hypermutation[14]. Either directly or indirectly, HRD and non-HRD events can cause dysregulation of the G1/S cell cycle transition point through the over-expression of cyclin D genes, which is a key to an early molecular abnormality in myeloma[15]. The secondary events involved in myeloma progression occur later in the disease and include secondary translocations: t(8;14) linked with MYC overexpression, loss of heterozygosity, copy number variations (CNV), acquired mutations, and epigenetic modifications[1,14].

One of the pivotal aspects of MM is the recognizable clinical phase linked to each step of MM development. MGUS and smoldering multiple myeloma (SMM) are both early premalignant phases. MGUS is asymptomatic and is characterized by a < 10% plasma cell count in the bone marrow and a progression rate of 1% per year to MM. SMM follows MGUS; it is also an asymptomatic phase with > 10% intramedullary clonal plasma cells and 10% per year progression risk to MM. Thirdly, overt MM presents clinical features of hypercalcemia, renal dysfunction, anemia, and bone disease (the acronym CRAB). Lastly, plasma cell leukemia (PCL) is characterized by extramedullary plasma cell clones and rapid progression to death. Hence, the disease continuity between MGUS, SMM, and MM involves genomic hierarchy, including germline events that increase predisposition to MM, followed by early initiating events, and later gaining of genomic aberrations that ultimately trigger disease progression and treatment resistance[15].

GENETIC PREDISPOSITION

The inherited susceptibility to MM is well established, with an estimated heritability of about 15% and 17% for MGUS and MM respectively[16]. In 2010, a Swedish study comprising 13,896 MM patients revealed first-degree relatives of MM patients having a higher relative risk (RR) to develop MM (RR = 2.1), MGUS (RR = 2.1), acute lymphoblastic leukemia (RR = 2.1) and, to a lesser extent, solid tumors (RR = 1.1)[17]. There is a

4.25-fold risk of MM in first-degree relatives (95%CI: 1.81-8.41) that was observed in the 1961-2003 Swedish national cancer registry data[18]. Similarly, among the first-degree relatives observed in Minnesota and Mayo Clinic cohorts exhibited the increased risk of MGUS (RR = 3.3; 95%CI: 2.1-4.8) and MM (RR = 2.0; 95%CI: 1.4-2.8)[19]. While the familial clustering of MM indicates a genetic predisposition to the disease, only recently (2012) has GWAS identified single-nucleotide polymorphisms associated with MM risk[20]. In addition to identifying multiple risk loci, GWAS has provided innovative insights into genetic-related risk[20]. Inherited variations at loci 2p23.3, 3p22.1, and 7p15.3 are associated with a genetic predisposition to MGUS and involves gene pairs 2p: *DNMT3A* and *DTNB*, 3p: *ULK4* and *TRAK1*, and 7p: *DNAH11* and *CDCA7L*[21,22]. Chubb *et al.*[23] verified that the seven common variant loci 2p23.3, 3p22.1, 3q26.2, 6p21.33, 7p15.3, 17p11.2, and 22q13.1 may account for 13% of the familial risk of MM. Further studies have confirmed more candidate loci summarized in Table 1. Additionally, rare variants such as *LSD1/KDM1A*, *KIF18A*, *USP45*, *ARDID1A*, *CDKN2A*, and *DIS3* may be contributed to missing heritability[16]. The reliable identification of these susceptible risk variants would be an important advancement in the early detection of MM. Furthermore, it could postulate potential personalized treatments or gene knockdown to limit progression to MM in the future.

The African American (AA) population has a higher prevalence of MGUS and MM than Caucasian Americans (CA) of European ancestry[30,31]. A study by Costa *et al.*[32] reported a 2.24-fold higher incidence of MM in AA men compared to CA men. Also, MM occurs in the AA population at an early age of 65.8 compared to age 69.8 in the CA population[33]. When considering polygenic risk scores (PRS), people of African ancestry in the top 10% PRS had a 1.82-fold (95%CI: 1.56-2.11) increased risk for MM compared to those with an average risk[34]. Although the confounding factors of healthcare inequalities, lifestyle, and environmental factors are significant, racial genetics is crucial in the etiology of MM in the AA population[20].

A study involving GWAS analysis revealed a stronger association between the 7p15.3 (rs4487645) locus and MM in AA[35]. The expression quantitative trait locus analysis on the biological function of the 7p15.3 (rs4487645) risk locus showed that the C risk allele is linked to elevated CDCA7L (cell division cycle-associated 7 like)[36]. The elevated CDCA7L attributes to the emergence of an IRF4 binding site on the 7p15.3 enhancer[37], hence, connecting the germline risk of MM to a genetic pathway IRF4-MYC.

Similarly, an NGS study about acquired somatic mutations in MMmyeloma has underlined new insights into racial differences between AA and CA patients. It demonstrated higher mutation frequency in genes *ABI3BP*, *ANKRD26*, *AUTS2*, *BCL7A*, *BRWD3*, *DDX17*, *GRM7*, *IRF4*, *MYH13*, *PARP4*, *PLD1*, *PTCHD3*, *RPL10*, *RYR1*, *SPEF2*, *STXBP4*, and *TP53* among AA than in CA myeloma patients[3]. Besides, myeloma MM-associated translocations t(11;14), t(14;16), and t(14;20) also play a critical role in racial AA *vs.* CA disparity[38].

TRANSLOCATIONS IN MYELOMA

Translocation (4;14) (p16.3;q32.3)

The translocaton t(4;14) is seen in 15% of MM cases and has a poor prognosis[39,40]. This translocation results in the over-expression of two genes: *FGFR3* (70% of cases) and *MMSET* (all cases)[41,42]. FGFR3 up-regulation results in the ectopic expression of the FGFR3 tyrosine kinase receptor types[43]. MMSET is a methyltransferase protein. Its up-regulation leads to enhanced methylation of histone H3K36, which modulates the expression of several genes. MMSET also regulates the methylation of histone H4K20, subsequently affecting the recruitment of tumor protein p53binding protein 1 (TP53BP1) at the site of DNA damage[44]. Both MMSET and FGFR3 over-expression up-regulate CCND2 and in some instances CCND1

Table 1. Susceptible loci for multiple myeloma

Study	Locus	Candidate gene
Broderick *et al.*[21], 2012	2p23.3	*DNMT3A*
Martino *et al.*[24], 2012	3p22	*ULK4*
	7p15.3	*CDCA7L*
Koura *et al.*[22], 2013	2p23.3	*DNMT3A*
	3p22.1	*ULK4*
	7p15.3	*CDCA7L*
	8q24	*MYC*
Chubb *et al.*[23], 2013	3q26.2	*TERC*
	6p21.3	*PSORS1C2*
	17p11.2	*TNFRSF13B*
	22q13.1	*APOBEC*
Weinhold *et al.*[25], 2014	2p23.3	*DNMT3A*
	3p22.1	*ULK4*
	3q26.2	*TERC*
	6p21.3	*PSORS1C2*
	7p15.3	*CDCA7L*
	17p11.2	*TNFRSF13B*
	22q13.1	*APOBEC*
Ziv *et al.*[26], 2015	16p13	*FOPNL*
Mitchell *et al.*[27], 2016	5q15	*ELL2*
	6p22.3	*JARID2*
	6q21.3	*ATG5*
	7q36.1	*SMARCD3*
	8q24.1	*CCAT1*
	9p21.3	*MTAP*
	16q23.1	*RFWD3*
	20q13.1	*PREX1*
Went *et al.*[28], 2018	2q31.1	*SP3*
	5q23.2	*CEP120*
	7q22.3	*CCDC71L*
	7q31.33	*POT1*
	16p11.2	*PRR14*
	19p13.11	*KLF2*
	22q13.1	*CBX7*
Duran-Lozanzo *et al.*[29], 2021	13q13.3	*SOHLH2*

via unknown mechanisms[12]. Notwithstanding t(4;14) being associated with a poor prognosis of MM, treatment of MM with bortezomib, a proteasome inhibitor (PI), results in an increased survival rate in these patients[45].

Translocation (6;14) (p21;q32)

The translocation t(6;14) is rare and is present in only 2% of MM patients[1]. It has a neutral prognosis. This translocation causes the juxtaposition of *CCND3* to the *IGH* enhancers, thus directly up-regulating *CCND3* expression[46].

Translocation (11;14) (q13;32)

The translocation t(11;14) is the most frequent translocation present in MM (15%-20% patients)[1]. It has a neutral prognosis, although t(11;14) patients show significant heterogeneity and may present as PCL[14]. This translocation up-regulates a cyclin D gene in the *CCND1* form. Gene studies demonstrated that the over-expression of *CCND1* and *CCND3* results in the deregulation of common downstream transcriptional events[47]. The central role of cyclin D gene deregulation in MM provided insight into research on cyclin D inhibitors *in vitro*. Human trials on cyclin D inhibition therapy for MM are also under consideration[48].

Translocation t(14;16) (q32.3;q23)

The translocation t(14;16) shows up in 5%-10% MM patients[1]. This translocation is associated with a poor prognosis; however, a large retrospective analysis of 1003 patients with t(14;16) revoked its prognostic significance[49]. The t(14;16) gives rise to over-expression of the *MAF* gene splice variant *c-MAF*, which is a transcription factor that up-regulates a couple of genes, including *CCND2*, by directly binding to its promoter[50]. *MAF* up-regulates the expression of *APOBEC3A* and *APOBEC3B*, two DNA-editing enzymes, in MM tumors carrying t(14;16). This leads to a mutational pattern termed as APOBEC signature with a high mutation rate[51].

Translocation t(14;20) (q32;q12)

The translocation t(14;20) is the rarest of 5 major translocations detected in only 1% MM patients, and has a poor prognosis. However, paradoxically, long-term stable disease is found in the MGUS and SMM stages[52]. It results in over-expression of the *MAF* gene paralog - *MAFB*[53]. Mutant *MAFB* is seen in 25% of patients with MM harboring t(14;20)[54]. Microarray studies have shown that *MAFB* over-expression results in *CCND2* deregulation like *c-MAF*[47]. Tumors with t(14;20) have the APOBEC mutational signature, which is induced by the up-regulated *APOBEC4*[51].

Secondary translocation affecting MYC

Secondary translocations are independent of class-switch recombination and occur later in the disease[14]. The c-*MYC* proto-oncogenes at 8q24 is the key target of secondary translocations. c-*MYC* over-expression is associated with poor prognosis and has a robust correlation to high levels of serum β_2 microglobulin[55]. The most common secondary translocation in MM is t(8;14), involving the *IGH* at 14q32.3[56]. The other partner loci in the remaining 40% *MYC* translocations include *IGL* at 22q11.2, *IGK* at 2p11.2, *FAM46C* at 1p12, *FOXO3* at 6q21, and *BMP6* at 6p24.3[51]. Importantly, all these translocations are unbalanced and associated with kataegis, which is a pattern of localized hypermutation linked with the deregulation of APOBEC activity near the translocation breakpoints. As APOBEC works on single-stranded DNA exposed around the translocation locate, kataegis occurs next to the point of chromosomal rearrangements[1].

COPY NUMBER VARIATIONS

CNVs involve either gain or loss of DNA. It comprises focal deletions/amplification, chromosomal arm loss/gain, and hyperdiploidy. CNVs contribute to genomic instability either via over-expression of proto-oncogenes or loss of tumor suppression genes. Therefore, CNVs act as important driver events in MM development and progression[1,3,57].

Hyperdiploidy

HRD is defined by a chromosome count greater than the diploid number of chromosomes (> 46). In MM, HRD involves trisomies of the odd-numbered chromosomes (3, 5, 7, 9, 11, 15, 19, and 21) and is noticed in approximately 50% of MM cases[51,58,59]. The underlying mechanism for HRD is unknown, but one hypothesis suggests that single disastrous mitosis causes the gain of all chromosomes rather than their serial gathering over time[60]. However, the contribution of HRD to myelomagenesis is unknown. In addition to the dysfunction of cyclin D genes, GEP studies have validated the involvement of many protein synthesis genes in hyperdiploid tumors. These include MYC, NF-κB, and MAPK signaling pathways[61]. From a prognostic perspective, HRD is associated with more favorable survival outcomes than hypodiploidy[62]. Furthermore, patients harboring trisomy 3 and trisomy 5 have better overall survival in comparison to trisomy 21[63]. In contrast, HRD MM with co-existent cytogenetic lesions like del(17p) t(4;14) and gain of 1q has a poor prognosis compared to HRD MM alone[64].

Gain of 1q

The gain of 1q arm is present in 30 to 40% of MM cases and is associated with a poor prognosis[14]. The amplification process involves 1q12 pericentromeric region instability due to hypomethylation and jumping translocation of the whole 1q arm[65]. Gene studies have shown a minimally amplified region between 1q21.1 and 1q23.3 carrying candidate oncogenes including *CKS1B*, *ANP32E*, *BCL9*, *PDZK1*, *ADAR1*, *PSMD4*, *ILF2*, *IL6R*, and *MCL1*[1,66]. The protein phosphatase 2A inhibitor *ANP32E* involved in chromatin remodeling and transcriptional regulation is independently associated with short survival[67]. The identified specific inhibitors of the candidate genes and pathways may help in the treatment of patients with 1q gain[14].

Loss of 1p

Loss of 1p is present in 30% of MM cases and may involve whole arm deletion or interstitial deletion. 1p loss correlates to poor prognosis[68]. 1p12 and 1p32.3 are two important regions involved in myelomagenesis[1]. Both these regions experience hemizygous or homozygous deletions[14]. Tumor suppressor gene *FAM46C* is located on 1p12, and its expression has been verified as positively correlated with ribosomal proteins, eukaryotic initiation, and elongation factors involved in protein translation[7]. Similarly, *FAF1* and *CDKN2C* are located on 1p32.3[1]. The protein encoded by *FAF1* is involved in apoptosis initiation via the Fas pathway, while *CDKN2C* is a cyclin-dependent kinase 4 (CDK4) inhibitor which negatively regulates the cell cycle[1]. 1p32.3 deletion correlates to a poor prognosis in MM patients undertaking an autologous stem cell transplantation (ASCT) and a neutral prognosis in those receiving non-intensive treatment[68].

Loss of chromosome 13/13q

Loss of chromosome 13 is present in 45%-50% of MM cases, and primarily in non-HRD tumors. 85% of cases involve whole 13q arm deletion whereas 15% encompass interstitial deletions[14]. The minimal deleted region located between 13q14.11 and 13q14.3 also contains some genes related to MM progression, including *RB1*, *RCBTB2*, *RNASEH2B*, *EBPL*, *mir15a*, and *mir161*. The under-expression of *RB1*, a tumor suppressor gene, results in negative cell cycle regulation[57]. In 90% of cases, del(13/13q) occurs concurrently with t(4;14) as determined by conventional cytogenetic studies and is linked with poor prognosis[69]. In the absence of concurrent lesion, del(13/13q) lacks prognostic significance. Hence, the correlation between del(13/13q) and poor prognosis can only be seen in some patients with other high-risk genetic lesions[70].

17p deletion

The chromosome 17 deletion is a late disease event. It is hemizygous and involves the whole p arm[14]. The most common gene deregulated in 17p deletion is the tumor suppressor gene *TP53*[71]. GEP has shown that monoallelic 17p deletions in MM samples exhibit remarkably lower *TP53* compared to non-deleted samples[57]. *TP53* influences DNA repair, cell cycle arrest, and apoptosis in response to DNA damage as a transcriptional regulator[14]. In MM, 17p deletion is related to more extramedullary involvement, an aggressive disease phenotype, and a shortened life span. It is hypothesized that PCL is the main consequence of *TP53* dysfunction[72,73].

Miscellaneous chromosomal gains & losses

Focal CNVs have extracted the list of potential driver genes affected by these changes. Gain of 8q24.21 can be discovered in 14% MM patients and disturbs *MYC* genes[1]. A gain of 11q13.2 is found in 15% of patients and involves the oncogene *CCND1*. *CCND1* is also affected by chromosomal translocations and somatic mutations[1]. 11q deletion is detected in 7% MM cases and downregulates tumor suppressor genes *BIRC2* and *BIRC3*[57]. Deletion of 14q occurs in 38% of cases and involves *TRAF3* (tumor suppressor gene)[1]. 16q deletion is another common event (in 35% myeloma cases) and reduces the expression of the tumor suppressor genes *CYLD* and *WWOX* (implicated in apoptosis)[57]. Del(8p) and del(12p) are independent

adverse prognostic markers[14]. Del 8p downregulates the *TRAIL* gene. *TRAIL* gene is linked with TNF-induced apoptosis. Its downregulation facilitates the immune escape of malignant clones from cytotoxic T lymphocytes and natural killer cells[74].

DEREGULATED CELLULAR PATHWAYS

Several signaling pathways are dys-regulated in MM and contribute towards pathogenesis by influencing proliferation, apoptosis, survival, migration, and drug resistance[75].

NF-κB pathway

NF-κB is a group of transcription factors that play important roles in cell proliferation, differentiation, and survival, as well as in inflammation and immunity[76]. The NF-κB pathway is active in 50% of MM cases and involves both plasma cells and bone marrow stromal cells (BMSCs)[77]. Activation of NF-κB within MM cells involves either activation of oncogenes or inactivation of tumor suppressor genes in the pathway[78]. Genes encoding components of the NFκB pathway include *TRAF3*, *CYLD*, *LTB*, *IKBKB*, *CARD11*, *BIRC2*, *BIRC3*, and *TRAF3IP1*[54]. The NF-κB pathway does not influence the survival in MM[14]. The pathway involves the proteasome protein complex, thereby suggesting the role of proteasome inhibitors in MM treatment[78].

Cell proliferation pathways

The cell proliferation pathways in MM include the MAPK pathway, the JAK-STAT pathway, and the phosphatidylinositol-3 kinase (PI3K) pathway.

The MAPK pathway

The MAPK pathway is a chain of proteins that communicate signals from cell surface receptors to the DNA in the cell nucleus[79]. The pathway is activated from inflammatory cytokines TNF-a, IL-6, and IGF-1 and, in return, triggers the downstream kinase cascades RAS, RAF, MEK, and MAPK, thus regulating gene expression. Two dominant oncogenes involved in this pathway include *NRAS* and *KRAS*[80]. Their mutations are frequently subclonal and are involved in disease progression. *RAS* mutations indicate a poor prognosis, aggressive phenotype, and shortened survival[51]. The involvement of *RAS* mutations across various cancers has given insight into the research on therapeutic inhibitors within this area[14]. Likewise, activation of mutation in the BRAF-MAPK signaling pathway, which encodes serine/threonine-protein kinase suggests the potential use of BRAF inhibitors in MM patients with BRAF mutations[81].

The JAK-STAT pathway

The JAK-STAT pathway is activated in both MM cells and BMSCs in approximately 50% of cases[82]. Cytokine IL-6 signaling induces JAK-STAT activation and myelomagenesis[14]. The over-activation of STAT3, a STAT family transcription factor, causes over-expression of Bcl-x an anti-apoptotic protein, and therefore triggers chemoresistance[83]. The *in vitro* inhibition of STAT3 with atiprimod, curcumin, and the JAK2 kinase inhibitor AG490 have already shown fair results for inhibition of IL-6-induced MM survival[84]. In addition, STAT3 inhibition has shown sensitization of the U266 cell line to apoptosis from conventional chemotherapy agents[85]. Hence, these results highlight the prospective conjoined role of STAT3 inhibitors and conventional chemotherapy in myeloma treatment[14].

The PI3K pathway

PI3K-Akt is a signal transduction pathway that supports cell growth and survival in response to extracellular signals[86]. The PI3K (phosphatidylinositol 3-kinase) gets activated with IL-6 and IGF-1 action on tyrosine kinase receptors, leading to phosphorylation of the serine-threonine-specific kinase AKT (serine/threonine kinase). AKT, in return, activates its downstream genes, including mTOR, GSK-3B, and FKHR, therefore

regulating cell proliferation and apoptosis resistance[14]. The phosphorylated AKT is a marker indicative of pathway activity, which is observed in approximately 50% of MM cases[87]. Therapeutic targeting of PI3K is an area of interest in MM research[14].

Cell cycle deregulation

The deregulation of the G1/S cell cycle transition point via cyclin D gene overexpression is central to an early molecular abnormality in MM[14]. Additionally, the defect of negative cell cycle regulatory genes is another major event that destabilizes cell cycle regulation. CDKN2C (Cyclin-Dependent Kinase Inhibitor 2C) downregulation either by 1p deletion or DNA methylation deregulates the G1/S transition[68]. Similarly, CDK inhibitors p15, p16, and p18 are important in the regulation of progression through the cell cycle. Studies have shown that hypermethylation and homozygous deletions of p15, p16, and p18 genes lead to uncontrolled growth and MM progression[88]. Treatment with the demethylating agent 5-deoxycytidine restores p16 protein expression and induces G1 growth arrest in MM cell lines[75]. p21, another potent cyclin-dependent kinase inhibitor, binds to and inhibits the activity of CDK2, CDK1, and CDK4/6 complexes. It protects the MM cells from apoptosis by the induction of cell cycle arrest and subsequent DNA repair, hence inducing resistance to apoptosis by chemotherapy and radiotherapy[89]. Furthermore, *RB1* (tumor suppressor gene) inactivation also affects the G1/S transition and may occur because of monosomy 13, homozygous deletion, or mutational inactivation[57].

Defective DNA repair

The DNA repair score is a predictive factor for progression-free and overall survival of MM patients. The score's strength is based upon the influence of aberrant DNA repair in MM[90]. The understanding of DNA repair mechanisms in MM is important for developing therapeutic approaches based on the concept of synthetic lethality. It states that a combination of deficiencies in two genes (e.g., gene X and a DNA repair gene) causes cell death, whereas a deficiency in only one of the genes (gene X) does not[3]. For example, poly ADP-ribose polymerase (PARP) inhibitors are used to treat solid tumors deficient in *BRCA1* and *BRCA2* function, which are important for maintaining the error-free homologous recombination (HR) pathway of DNA repair. PARP is a family of proteins involved in several cellular processes (e.g., DNA repair, genomic stability, and programmed cell death). *PARP1* expression is linked with shortened survival and high-risk disease in MM patients[91]. PARP inhibitors have given promising results in cancers with defective HR-mediated DNA repair mechanisms, as MM backbone drugs proteasome inhibitors (e.g., bortezomib) affect the apoptotic sensitivity of MM cells[91]. Therefore, bortezomib-induced impairment of homologous recombination in MM cells can pharmacologically sensitize them to PARP inhibition, resulting in synthetic lethality[91]. We recently found that a noncoding RNA MALAT1 is critical for PARP1 binding to LIG3 to mitigate an alternative end-joining DNA repair pathway and may serve as a novel therapeutic target for MM[92,93].

Abnormal RNA editing

Post-transcriptional RNA processing is important for the maintenance of genomic stability in MM[94]. MM patients may harbor mutations in genes controlling RNA processing and protein translation. *DIS3* gene on 13q22.1 encodes an exonuclease involved in regulating the abundance of RNA species. In MM patients, loss of DIS3 function is linked to monoallelic mutation or deletion. Exosomes play a vital role in regulating the mRNA pool. Therefore, loss of DIS3 activity may contribute to oncogenesis of MM due to protein translation deregulation. Similarly, the role of *FAM46C* in translational control and recurrent mutation in myelomagenesis is of biological relevance[95]. RNA processing includes splicing pattern modification of transcripts involved in DNA repair[96]. This alternative splicing of DNA repair depends upon the proper activity of RNA-binding proteins (RBPs)[97]. Genetically aggressive myeloma patients who have 1q21 amplification usually have 1q21-induced over-expression of the RBP-ILF2 (interleukin enhancer-binding

factor 2). As ILF2 is a key regulator in HR repair in MM, high ILF2 expression promotes resistance to genotoxic reagents by modulating the translocation of YB1 (Y-box binding protein 1). Therefore, blocking the ILF2 signaling pathway may improve the effect of DNA-damaging agents in MM therapy[98].

Deregulated plasma cell differentiation

IRF4 (interferon regulatory factor 4), also known as MUM1, is involved in the regulation of interferon transcription and B cell proliferation and differentiation[14]. An *in vitro* RNA-interference study discovered that IRF4 is necessary for the survival of MM cell lines[99]. IRF4 is also important therapeutically, as the backbone MM drug lenalidomide indirectly downregulates IRF4 by downregulating cereblon, the primary target of the CRBN-IKFZ1/3-IRF4-MYC pathway[100,101]. IRF4 acts as a transcription factor for BLIMP1, another transcription factor pivotal in plasma cell differentiation. A study by Chapman *et al.*[7] identified 2 out of 38 patients with MM harboring an identical mutation (K123R) in the DNA-binding domain of *IRF4*. The same study group also harbored loss of function mutations in *BLIMP1* usually identified in diffuse large B-cell lymphoma[7,102]. However, the role of differentiation pathway dysfunction in myelomagenesis needs further investigation as MM is a malignancy of terminally differentiated plasma cells.

Bone disease in myeloma

Bone disease in MM is associated with shorter overall survival and presents as focal/diffuse pain, pathological fractures, cord compression, and hypercalcemia. It is common in patients with hyperdiploidy, t(4;14), and *MAF* translocations[103]. A recent GEP study has identified approx. 50 genes linked with bone disease, with *DKK1* and *FRZB* being the most prominent. DKK1 and FRZB are Wnt pathway inhibitors and induce osteoblast differentiation inhibition and increase bone resorption via RANKL/OPG ratio imbalance[104,105]. The antibody against DKK1 is an important therapeutic area to approach bone disease in MM patients. Anti-DKK1 antibody has resulted in improved bone disease outcomes and myeloma cell growth inhibition in pre-clinical models[106].

EPIGENETIC MODIFICATIONS

First, genomic instability is the hallmark of MM, and dysfunctional DNA damage response is one of the many driving contributing factors[3]. *SIRT6* (NAD-dependent deacetylase) is highly expressed in MM cells and is linked with poor prognosis. Its expression is an adaptive response to maintain genomic stability. SIRT6 interacts with the promoter area of transcription factor *ELK1* and *ERK* signaling-related genes. SIRT6 also downregulates the MAPK pathway gene expression and signaling. Moreover, the inactivation of ERK2 signaling increases DNA repair via checkpoint kinase 1 and confers resistance to DNA damage[107]. RecQ helicase, a DNA unwinding enzyme, is involved in maintaining chromosome stability. MM cells have a higher expression of RECQ1, which is associated with poor prognosis. RECQ1 over-expression helps MM cells escape from cytotoxicity of melphalan and bortezomib. On the contrary, knockdown of RECQ1 suppresses cell growth and stimulates apoptosis in MM cells; RECQ1 depletion promotes double-strand breaks on DNA in MM cells and sensitizes them to PARP inhibitors. RECQ1 downregulation can also be induced by DNMT inhibitor treatment through dysregulation of miR-203 in MM. Hence, PARP inhibitors combined with DNMT inhibitors constitute an important therapeutic approach for MM patients[3,108].

The *HOXA9* gene encodes a DNA-binding transcription factor involved in cell differentiation, morphogenesis, and gene expression regulation. It is regulated by histone methyltransferases, and knockdown of it in MM cell lines incurs a competitive disadvantage as compared to those with intact *HOXA9* gene expression. This indicates the role of *HOXA9* expression in myelomagenesis and the utilization of epigenetic changes for devising new therapeutic targets in MM[7].

Secondly, studies have revealed that miRNAs may act as both tumor suppressors and oncogenes in various cancers. Substantial work has been done to investigate the role of miRNAs in MM. Studies indicate that miRNAs can negatively regulate genes and pathways relevant to myelomagenesis via transcriptional control through promoter methylation[14]. For example, miR-137 maintains genomic instability in an aurora kinase A (AURKA)-dependent manner, while miR-22 regulates DNA ligase III in MM[109,110]. In short, miRNA deregulation is a key contributor to malignancy, and further research will unravel potential treatment targets.

Third, DNA methylation regulates gene expression and contributes to MM progression from MGUS to PCL. DNA methylation is found at higher frequencies in promoter regions, repeat sequences, and transposable elements of genes. MM has a recognized pattern of global DNA hypomethylation and gene-specific hypermethylation affecting cell adhesion, proliferation, the stromal-clone relationship, cell cycle progression, and transcription, predominantly in t(4;14) tumors, resulting in *MMSET* gene over-expression[111].

CLONAL HETEROGENEITY

Intraclonal heterogeneity is a common feature of MM and occurs in the milieu of selection events in the tumor microenvironment[1]. The clonal evolution in MM follows the Darwinian model, which involves the random acquisition of genetic changes that offer a survival advantage[14]. WES sequencing analysis shows that clonal heterogeneity begins from a premalignant stage and follows either linear or branching evolution patterns. Linear evolution involves the emergence of a new subclone or predominance of a pre-existing subclone, resulting in the stepwise acquisition of driver mutations. Branching evolution involves the emergence of one or more subclones via divergent mutational pathways, while other subclones decline in frequency or disappear[2]. Another factor is clonal stability, where similar clonal and subclonal heterogeneity is found before and after treatment, which would equally repopulate the tumor. The study of intraclonal heterogeneity is important to improve the understanding of disease pathogenesis, as the genetic aberrations in the predominant clonal population at the time of sampling may not apply to all subclonal populations. Thus, such heterogeneity may explain relapse and drug resistance to anticancer treatments[14].

BONE MARROW MICROENVIRONMENT

A complex interaction exists between malignant plasma cells and non-malignant stromal cells in the bone marrow microenvironment. This interaction involves adhesion molecules and autocrine/paracrine cytokine signaling. The cytokines secreted by the stromal cells include IL-6, VEGF, IL-1b, IL-10, TNF-a, TGF-b, MMP-1, osteoprotegerin (OPG)/RANKL MIP-1a, FGFs, and IGFs[112]. IL-6 is the most significant with a role in B cell differentiation; however, in MM, it induces proliferation and apoptosis inhibition. The IL-6 receptor has two subunits: IL-6Ra and gp130 (a transmembrane signal transducer). IL-6 combines with IL-Ra, which then mediates signals via gp130. IL-Ra subunit has an agonist action. In contrast, gp130 may competitively inhibit the growth-promoting effects of IL-6/IL-6R complex at higher concentrations[113]. IL-6-IL-6R interaction activates 3 downstream pathways: STAT1/STAT3 pathway, STAT3/STAT3 pathway, and Ras/MAPK pathway[114].

Similarly, VEGF, FGFs, and HGFs play a role in angiogenesis and IL-1b, RANKL, and HGFs in osteoclast activation. TNF-a, IGFs, IL-1b, and VEGF have a direct effect on MM cells[75]. Some factors secreted by bone marrow are known to influence the efficacy of chemo and radiation therapy and have a role in disease progression. For example, MM cell interaction with fibronectin in the extracellular matrix up-regulates p27, which induces drug resistance[115]. Likewise, the binding of MM cells to hyaluronic acid synergizes IL-6 signaling and reduction in adhesion molecules CD56; very late antigen 4 facilitates the transition to the

extramedullary phase[75].

MULTIPLE MYELOMA TREATMENT

ASCT is standard care for MM. However, the foremost decision in MM patient management is ASCT eligibility. Patients less than 65 years of age with no severe comorbidities are usually eligible for ASCT. Furthermore, no definitive clinical data is available to support that ASCT is better in the early stage of disease than in later/relapsed cases[116]. All transplant-eligible MM patients must receive primary induction therapy. The induction therapy combination regimens are given in Table 2.

Lenalidomide is a derivative of thalidomide, which is also an immunomodulatory drug (IMiD) but has more powerful anti-tumor and anti-inflammatory effects. It induces MM cell growth arrest, binding inhibition to BM-ECM and stromal cells, and downregulation of IL-6 and NF-κB[117]. While lenalidomide has a partial response rate of 24%-29% in treatment-refractory MM patients, combinatory lenalidomide and dexamethasone has peaked partial remission to an additional 29% in the lenalidomide-responsive patient group[118].

Over time, more powerful triplet combinations of lenalidomide/dexamethasone with a monoclonal antibody (elotuzumab - anti-CD319, daratumumab - anti-CD38) or a PI (bortezomib, carfilzomib, ixazomib) have evolved with significant improvement in the progression-free survival (PFS) and overall survival (OS)[119,120]. Combination treatment strategies apply the concept of using therapies with distinct mechanisms of action[121]. The triple combination therapy trials of proteasome inhibitor and monoclonal antibodies are summarized in Tables 3 and 4.

Once remission is achieved, stem cells are harvested via apheresis. Maintenance therapy after transplantation includes (1) oral lenalidomide - 10 mg/day for the first 3 months; (2) oral Ixazomib - 3 mg on day 1, 8, and 15 in 28-day cycles in cycles 1 through 4 and increased to 4 mg from cycle 5 if tolerated; and (3) intravenous bortezomib - 1.3 mg/m^2 on days 1, 4, 8 and 11 every 3 months.

Despite these treatment advancements, a considerable number of MM patients have shown resistance to PI, IMiDs, and monoclonal antibodies. A retrospective study has revealed that refractoriness results in only 5.6 months median OS in MM patients[110]. Hence, there is an urgent need to devise more effective therapeutic interventions for this patient population[121,122].

Conventional chemotherapy

Conventional chemotherapy can serve as salvage therapy in relapsed/refractory MM (RRMM) patients non-responsive to the triple-drug combination therapies. Due to intense toxicity, these cytoreduction agents are used for short periods of time and serve best as a bridge to more effective therapies[121]. A study of dexamethasone without thalidomide administration with an infusion of cisplatin, doxorubicin, cyclophosphamide, and etoposide [D(T)PACE] resulted in an overall response rate (ORR) of 49%, median PFS of 5.5 months, and OS of 14 months[123]. Among patients that proceeded to ASCT, median PFS was 13.4 months, and OS was 20.5 months. Another study compared the outcome of three chemotherapy regimens (1) dexamethasone, cyclophosphamide, etoposide, and cisplatin; (2) bortezomib, thalidomide, dexamethasone, cisplatin, doxorubicin, cyclophosphamide, and etoposide (VTD-PACE); and (3) cyclophosphamide, vincristine, doxorubicin, and dexamethasone (CVAD) in RRMM. The three salvage regimens demonstrated similar overall RR (55%), PFS (4.5 months), and OS (8.5 months)[124].

Table 2. Induction therapy for transplant-eligible patients

1. Lenalidomide/Dexamethasone
2. Bortezomib/Thalidomide/Dexamethasone
3. Bortezomib/Lenalidomide (Revlimid)/Dexamethasone (VRd, RVd)
4. Bortezomib/Doxorubicin/Dexamethasone
5. Bortezomib/Cyclophosphamide/Dexamethasone (CyBorD, VCD)
6. Daratumumab/Bortezomib/Thalidomide/Dexamethasone (dara-VTD)

Table 3. Triple combination monoclonal antibody with lenalidomide and dexamethasone trials

Trial title	Trial ID	Phase	Treatment
AMN006	NCT03695744	II	Daratumumab + Bortezomib + Dexamethasone
CANDOR	NCT03158688	III	Daratumumab + Carfilzomib + Dexamethasone
Phase III trial comparing Poma, Dexa with/without Dara in RRMM with 1 prior therapy but not Lenalidomide & PI	NCT03180736	III	Daratumumab + Pomalidomide + Dexamethasone
VELCADE	NCT02541383	III	Daratumumab + Bortezomib + Thalidomide + Dexamethasone
CASTOR	NCT02136134	III	Daratumumab + Bortezomib + Dexamethasone
POLLUX	NCT02076009	III	Daratumumab + Dexamethasone + Lenalidomide
ALCYONE	NCT02195479	III	Daratumumab + Melphalan + Bortezomib + Prednisolone/Dexamethasone
Phase II single-arm study of Elotuzumab with Lenalidomide + Dexamethasone in newly diagnosed or RRMM	NCT02159365	II	Elotuzumab + Lenalidomide + Dexamethasone
Phase II study of elotuzumab in combination with Poma, Bort, & Dexa in RRMM	NCT02718833	II	Elotuzumab + Pomalidomide + Bortezomib + Dexamethasone
Single arm open-label anti-SLAMF7 mAB therapy after ASCT	NCT03168100	II	Elotuzumab + Bortezomib + Lenalidomide + Dexamethasone
ELOQUENT 3	NCT02654132	II	Elotuzumab + Pomalidomide + Dexamethasone
HRMM	NCT01668719	I/II	Bortezomib + Lenalidomide + Dexamethasone +/- Elotuzumab
ELOQUENT 2	NCT01239797	III	Lenalidomide + Dexamethasone +/- Elotuzumab

RRMM: Relapsed refractory multiple myeloma; PI: proteasome inhibitor, Poma: pomalidomide; Dexa: dexamethasone; Bor: bortezomib; mAB: monoclonal antibody.

Table 4. Proteasome inhibitor combination therapy trials

Trial title	Phase	Treatment
IFM2005-01	III	Bortezomib + Dexamethasone *vs.* Vincristine + Doxorubicin + Dexamethasone
DSSM-XI	II	Bortezomib + Cyclophosphamide + Dexamethasone
GIMEMA	III	Bortezomib + Thalidomide + Dexamethasone *vs.* Thalidomide + Dexamethasone
GEM05-MEN0S65	III	Bortezomib + Thalidomide + Dexamethasone *vs.* Thalidomide + Dexamethasone *vs.* Chemotherapy + Bortezomib
IFM2013-04	III	Bortezomib + Thalidomide + Dexamethasone *vs.* Bortezomib + Cyclophosphamide + Dexamethasone
HOVON-65/GMMG-HD4	III	Doxorubicin + Bortezomib + Dexamethasone *vs.* Vincristine + Doxorubicin + Dexamethasone
IFM2009	III	Bortezomib + Lenalidomide + Dexamethasone +/- ASCT
CASSIOPEIA	III	Daratumumab + Bortezomib + Thalidomide + Dexamethasone *vs.* Bortezomib + Thalidomide + Dexamethasone
ENDEAVOR	III	Carfilzomib + Dexamethasone *vs.* Bortezomib + Dexamethasone
A.R.R.O.W	III	Weekly *vs.* Biweekly Carfilzomib + Dexamethasone
ASPIRE	III	Carfilzomib + Lenalidomide + Dexamethasone *vs.* Lenalidomide + Dexamethasone
DKd	1b	Daratumumab + Carfilzomib + Dexamethasone
TOURMALINE-MM1	III	Ixazomib + Lenalidomide + Dexamethasone *vs.* Bortezomib + Dexamethasone

Bendamustine is a bifunctional alkylating agent. A retrospective study of bendamustine monotherapy and corticosteroid combination has resulted in 3% "very good" partial response, 33% partial response, 26% stable disease, and 20% progressive disease, along with a median PFS of 7 months and OS of 17 months in RRMM[125]. The combination regimens of bendamustine with thalidomide, lenalidomide plus dexamethasone, and bortezomib plus dexamethasone have also demonstrated good tolerability and improved efficacy in early trials of RRMM[126,127].

Histone deacetylase inhibitors (HDACi) target the effects of epigenetic modification and have demonstrated positive outcomes in RRMM patients, especially when used in combination with PIs. In the phase III PANORAMA-1 trial, RRMM patients received panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone. The results demonstrated a clinically significant improvement with a median PFS of 11.99 months *vs.* 8.08 months[128]. Similarly, the PANORAMA-2 trial tested panobinostat combination therapy in bortezomib-refractory patients with a subsequent 34.5% ORR and 6 months median response duration[129]. Another HDACi vorinostat was tested in the VANTAGE 095 trial involving heavily pretreated RRMM refractory to bortezomib and immunomodulators. A combination of vorinostat and bortezomib resulted in an ORR of 17%, median response duration of 6.3 months, PFS of 3.1 months, and OS of 11.2 months[130]. Furthermore, the phase III VANTAGE 088 trial compared the outcome of vorinostat plus bortezomib with the bortezomib group alone. The study's results included a PFS of 7.63 months *vs* 6.83 months and an ORR of 56.2% *vs* 40.6%[131].

Salvage ASCT

Salvage ASCT is an important therapeutic choice for RRMM. Several retrospective studies have demonstrated post-reinduction salvage ASCT success in MM patients who relapsed after first ASCT or RVD-alone treatment[132]. Although most patients with RRMM were not candidates for salvage ASCT due to age and comorbidities, those who underwent salvage ASCT exhibited a PFS of 7 to 22 months. The foremost factor predicting improved PFS and OS after salvage ASCT is the duration of remission after initial ASCT[121].

Selinexor

Selinexor is an oral, slowly reversible, first-in-class, potent selective inhibitor of nuclear export compound that specifically blocks exportin 1 (XPO1). The Food and Drug Administration has approved selinexor for RRMM patients who have had 4 previous therapies and disease refractoriness to 2 PIs, 2 IMiD agents, and anti-CD38 mAb[133]. The Selinexor trials are summarized in Table 5.

Immunotherapies for multiple myeloma

Advances in cellular immunotherapy - CAR (chimeric antigen receptor) T-cell therapy, B cell maturation antigen (BCMA)-targeted therapies, and bispecific T cell engager (BiTE) and tri-specific T cell engager (TiTE) - have good prospects in MM therapy[121]. In CAR T-cell therapy, T cells are modified to express CARs genetically through introducing fusion proteins that have an antigen recognition region and a co-stimulation domain. CAR T-cells targeting BCMA, CD138, CS1 glycoprotein antigen (SLAMF7), and light chains are in active development for RRMM treatment[134]. BCMA is a type of surface receptor, which belongs to the tumor necrosis factor superfamily. It is expressed in advanced B cell differentiation stages, and predominantly in plasma cells. Several BCMA-targeted therapeutics, including antibody-drug conjugates (e.g., belantamab mafodotin GSK2857916), CAR-T cells, BiTEs, and TiTE have also resulted in incredible clinical response in RRMM[135]. Tables 6 and 7 summarize immunotherapy clinical trials for MM.

Table 5. Selinexor combination trials

Trial title	Phase	Drug combination	Dose	Results
STORM Trial NCT02336815	II	Selinexor + Dexamethasone	Selinexor - 80 mg oral day 1 & 3 of each week Dexa - 20 mg prior to each dose	Partial response 26% Clinical benefit rate (CBR) 39% Median response duration 4.4 months Median PFS 3.7 months Median OS 8.6 months Pt with molecular response had medial OS of 15.6 months
BOSTON Trial NCT03110562	III	Selinexor + Dexamethasone + Bortezomib (SVd)	Selinexor - 100 mg once weekly Dexa - 40 mg weekly Bortezomib - 1.3 mg/m^2	PFS 13.93 months in SVd arm *vs.* 9.46 months in Vd arm

Further, 10 combination therapies of Selinexor in 11 treatment arms are under investigation in the STOMP Trial (NCT02343042).

Table 6. BCMA and non-BCMA CAR - T cell clinical trials in MM

Clinical trial	Phase	No. of Pt.	Dose	Outcome
Anti-BCMA CAR-T cell (NCT02215967)	I	12	0.3, 1.0, 3.0, 9.0 × 10^6 CAR cells/kg	PR 3, SD 8, sCR 1
bb2121 Anti-BCMA CAR-T cell (NCT02658929)	I	33	50, 150, 450, or 800 × 10^6 CART cells	ORR 85%, sCR 12, CR 3, VGPR 9, PR 4, SD 4, PD 1
bb21217 Anti-BCMA CAR-T cell (NCT03274219)	I	8	150 × 10^6 CAR T cells	sCR 1, VGPR 3, PR 2, -ve MRD 3
LCAR-B38M Anti-BCMA CAR-T cell (ChiCTR-ONH-17012285)	I	17	0.21-1.52 × 10^6 CAR T cells/kg	ORR 88.2%, sCR 13, VGPR 2, NR 1
LCAR-B38M Anti-BCMA CAR-T cell (NCT03090659) LEGEND-2 Trial	I/II	57	0.07-2.1 × 10^6 CAR T cells/kg	ORR: 88%, CR 39; VGPR 3, PR 8, -ve MRD 36
JCARH125 Anti-BCMA CAR-T cell (NCT03430011) EVOLVE Trial	I/II	19	50-150 × 10^6 CAR T cells/kg	sCR 2, CR 1, VGPR 2, PR 2, MR1
CT053 Anti-BCMA CAR-T cell (NCT03915184)	-	16	0.5-1.8 × 10^8 CAR T cells	ORR 100%, CR 2, PR 4, VGPR 6
MCARH171 Anti-BCMA CAR-T cell (NCT03070327)	I	11	72, 137, 475, 818 × 10^6 CAR T cells	ORR 64%, VGPR 2
CT103A Anti-BCMA CAR-T (ChiCTR1800018137)	I	9	1, 3, 6 × 10^6 CAR T cells/kg	ORR 100%, CR 4; VGPR1, PR 4
CD3ζ & 4-1BB Anti-BCMA CAR-T cell (NCT02546167)	I	25	1-50 × 10^7 CAR T cells	sCR 1, CR 1, VGPR 5, PR 5
P-BCMA-101 CAR-T cell (NCT03288493)	I	12	48-430 × 10^6 CAR+ T cells	sCR 1, nCR 1, VGPR 1, PR 2
CD4+: CD8+ BCMA CAR-T cell (NCT03338972)	I	7	5-15 × 10^7 CAR T cells	ORR 100%
Anti-CD19 non-BCMA CAR-T cell (NCT02135406)	I	10	1.1-6.0 × 10^8 CAR T cells	VGPR 6, PR 2; PD 2
Anti-CD138 non-BCMA CAR-T cell (NCT01886976)	I/II	5	0.44-1.51 × 10^7 CAR+ T cells/kg	SD 4, PD 1
κ light chain non-BCMA CAR-T cell (NCT00881920)	I	16 (7MM)	0.2-2.0 × 10^8 CAR+ T cells/m^2	4 SD of 7 MM

ORR: Overall response rate; VGPR: very good partial response; CR: complete response; PR: partial response; sCR: stringent complete response; MRD: minimal residual disease.

Targeted therapy for multiple myeloma

Clonal heterogeneity and clonal competition in the MM cancer cells have signified the role of targeted therapy (precision medicine) in patient management. Therefore, the identification of driver mutations is central to designing personalized targeted therapy. In addition, novel vaccines and immune-checkpoint

Table 7. BCMA targeted ADC and bispecific T-cell therapy clinical trials

Clinical trial	Phase	No. of Patients	Dose	Outcome
Belantamab mafodotin (GSK2857916) **DREAMM-1** (NCT02064387)	I	35	3.4 mg/kg every 3 weeks	ORR 60%, sCR 2 (6%), CR 3 (9%), VGPR 14 (40%), mPFS 12 months, mDOR 14.3 months
DREAMM-2 (NCT03525678)	II	196	2.5 or 3.4 mg/kg every 3 weeks	**2.5 mg/kg cohort** ORR 30 (31%), sCR/CR 3 (3%), VGPR 15 (15%), PD 56 (58%), mPFS 2.9 months **3.4 mg/kg cohort** ORR 34 (34%), sCR/CR 3 (3%), VGPR 17 (17%), PD 55 (56%), mPFS 4.9 months
BCMA/CD3 (AMG 420) (NCT02514239)	I	42	0.2-800 μg/day, 4 weeks infusion + 2 weeks off, for up to 5 cycles. Average 2.5 ± 2.6 cycles	ORR 31%, sCR 14%, CR 7%, VGPR 4.8%, PR 4.8%
BCMA(bivalent)/CD3 (monovalent) (CC-93269) (NCT03486067)	I	19	0.15-10 mg/day for a 28-day cycle (D1, 8, 15, and 22 for Cycles 1-3; D1 and 15 for Cycles 4-6; and on D1 for Cycle 7). Median 4 cycles Median DOT 14.6 weeks	12 patients w/dose of ≥ 6 mg; ORR 10 (83.3%); sCR/CR 4 (33.3%), VGPR 7 (58.3%)
BCMA/CD3, IgG2a backbone (PF-06863135) (NCT03269136)	I	17	Once weekly non-continuous infusion in 6 dose-escalation groups	Minimal response 1 (6%), SD 6 (35%), PD 9 (53%)
BCMA/CD3 (REGN5458) (NCT03761108)	I	7	6 mg/kg, 16 weekly doses + maintenance 12 doses per 2 weeks	ORR 4 (53.3%)

PD: Progressive disease; SD: stable disease; mDOR: median duration of response; mPFS: median progression-free survival; ORR: overall response rate; VGPR: very good partial response; CR: complete response; PR: partial response; sCR: stringent complete response; MRD: minimal residual disease.

Table 8. Targeted therapy in multiple myeloma

Mutations	Targeted therapy	Mutations	Targeted therapy
1. KRAS mutation	Selumetinib[136]	5. BRAF mutation	Vemurafenib[130]
2. NRAS mutation	Cobimetinib[137]	6. BCL-2 mutation (t 11:14)	BCL-2 Inhibitors[138] - Venetoclax - Navitoclax
3. MYC Translocations	BET inhibitors[139]	7. FGFR3 mutation (t 4:14)	BGJ398[140] AZD4547[141]
4. MEK mutation	MEK inhibitor[142] - Trametinib - Cobimetinib	8. del 1p (CDKN2C), t 11:14 (CCND1) t 6:14 (CCND3)	Palbociclib[143]
9. Immune Checkpoint Inhibitors- Nivolumab, Atezolizumab[144]			

inhibitors address another area of therapy development based on mutational landscapes. This would enable powerful therapeutic combinations for high-risk MM patients previously treated with a non-personalized approach. Table 8 includes examples of therapies targeting specific mutations in MM.

CONCLUSION

Genetic studies in MM patients have revealed mutational landscapes and a clearer understanding of disease pathophysiology and molecular heterogeneity. Hence, instead of a single treatment approach, a series of genetically-targeted treatment combinations based on the genetic subtypes would be effective. However, further studies using single-cell RNA sequencing technology are required on MM patient samples to extend our knowledge of clonal evolution and to precisely identify resistance mechanisms for novel therapeutic target identification. With current drug development, including antibody-drug, MM patients will eventually develop drug resistance. Obviously, there are patients either intrinsic-resistant or acquired-resistant to multiple drug treatments. There are very active drug development and clinical trials ongoing to develop bispecific antibody-drug conjugation to overcome multiple drug resistance, including single antibody-drug

treatment.

DECLARATIONS

Authors' contributions

Review paper writing and editing: Sadaf H, Hong H, Maqbool M, Emhoff K, Lin J, Yan S, Anwer F, Zhao J

Availability of data and materials

Not applicable.

Financial support and sponsorship

This work was financially supported by grants from: NCI R00 CA172292, 1R01CA251141 (to Zhao J) and start-up funds (to Zhao J) and two Core Utilization Pilot Grants (to Zhao J) from the Clinical and Translational Science Collaborative of Cleveland, V Foundation Scholar Award, American Society of Hematology (ASH) bridge grant (to Zhao J), National Institutes of Health training grant T32 CA094186, Training in Computational Genomic Epidemiology of Cancer (CoGEC) career development program (to Lin J).

Conflicts of interest

Jianjun Zhao has a consulting role for Curio Science. Faiz Anwer has a consulting or advisory role for Seattle Genetics, Incyte Corporation Speakers' Bureau, Company: Incyte Corporation; receives travel and accommodations expenses from Seattle Genetics, Incyte; receives honoraria from Incyte, Company: Seattle Genetics; and received research funding from Seattle Genetics, Company: Celgene, Acetylon Pharmaceuticals, Millennium, Astellas Pharma and AbbVie. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

REFERENCES

1. Manier S, Salem KZ, Park J, Landau DA, Getz G, Ghobrial IM. Genomic complexity of multiple myeloma and its clinical implications. *Nat Rev Clin Oncol* 2017;14:100-13. DOI PubMed
2. Talley PJ, Chantry AD, Buckle CH. Genetics in myeloma: genetic technologies and their application to screening approaches in myeloma. *Br Med Bull* 2015;113:15-30. DOI PubMed
3. Janz S, Zhan F, Sun F, et al. Germline risk contribution to genomic instability in multiple myeloma. *Front Genet* 2019;10:424. DOI PubMed PMC
4. Liyanage M, Coleman A, du Manoir S, et al. Multicolour spectral karyotyping of mouse chromosomes. *Nat Genet* 1996;14:312-5. DOI PubMed
5. Grade M, Difilippantonio MJ, Camps J. Patterns of Chromosomal Aberrations in Solid Tumors. *Recent Results Cancer Res* 2015;200:115-42. DOI PubMed PMC
6. Bahr GF. The fibrous structure of human chromosomes in relation to rearrangements and aberrations; a theoretical consideration. *Fed Proc* 1975;34:2209-17. PubMed
7. Chapman MA, Lawrence MS, Keats JJ, et al. Initial genome sequencing and analysis of multiple myeloma. *Nature* 2011;471:467-72. DOI PubMed PMC
8. Raffan E, Semple RK. Next generation sequencing--implications for clinical practice. *Br Med Bull* 2011;99:53-71. DOI
9. Went M, Kinnersley B, Sud A, et al. Transcriptome-wide association study of multiple myeloma identifies candidate susceptibility genes. *Hum Genomics* 2019;13:37. DOI PubMed PMC

10. van Laar R, Flinchum R, Brown N, et al. Translating a gene expression signature for multiple myeloma prognosis into a robust high-throughput assay for clinical use. *BMC Med Genomics* 2014;7:25. DOI PubMed PMC
11. Samo AA, Li J, Zhou M, et al. MCL1 gene co-expression module stratifies multiple myeloma and predicts response to proteasome inhibitor-based therapy. *Genes Chromosomes Cancer* 2018;57:420-9. DOI PubMed
12. Kuehl WM, Bergsagel PL. Early genetic events provide the basis for a clinical classification of multiple myeloma. *Hematology Am Soc Hematol Educ Program* 2005;346-52. DOI PubMed
13. Bergsagel PL, Kuehl WM. Molecular pathogenesis and a consequent classification of multiple myeloma. *J Clin Oncol* 2005;23:6333-8. DOI PubMed
14. Prideaux SM, Conway O'Brien E, Chevassut TJ. The genetic architecture of multiple myeloma. *Adv Hematol* 2014;2014:864058. DOI PubMed PMC
15. Bergsagel PL, Kuehl WM, Zhan F, Sawyer J, Barlogie B, Shaughnessy J Jr. Cyclin D dysregulation: an early and unifying pathogenic event in multiple myeloma. *Blood* 2005;106:296-303. DOI PubMed PMC
16. Clay-Gilmour AI, Hildebrandt MAT, Brown EE, et al. Coinherited genetics of multiple myeloma and its precursor, monoclonal gammopathy of undetermined significance. *Blood Adv* 2020;4:2789-97. DOI PubMed PMC
17. Kristinsson SY, Björkholm M, Goldin LR, et al. Patterns of hematologic malignancies and solid tumors among 37,838 first-degree relatives of 13,896 patients with multiple myeloma in Sweden. *Int J Cancer* 2009;125:2147-50. DOI PubMed PMC
18. Altieri A, Chen B, Bermejo JL, Castro F, Hemminki K. Familial risks and temporal incidence trends of multiple myeloma. *Eur J Cancer* 2006;42:1661-70. DOI PubMed
19. Vachon CM, Kyle RA, Therneau TM, et al. Increased risk of monoclonal gammopathy in first-degree relatives of patients with multiple myeloma or monoclonal gammopathy of undetermined significance. *Blood* 2009;114:785-90. DOI PubMed PMC
20. Morgan GJ, Johnson DC, Weinhold N, et al. Inherited genetic susceptibility to multiple myeloma. *Leukemia* 2014;28:518-24. DOI PubMed
21. Broderick P, Chubb D, Johnson DC, et al. Common variation at 3p22.1 and 7p15.3 influences multiple myeloma risk. *Nat Genet* 2011;44:58-61. DOI PubMed PMC
22. Koura DT, Langston AA. Inherited predisposition to multiple myeloma. *Ther Adv Hematol* 2013;4:291-7. DOI PubMed PMC
23. Chubb D, Weinhold N, Broderick P, et al. Common variation at 3q26.2, 6p21.33, 17p11.2 and 22q13.1 influences multiple myeloma risk. *Nat Genet* 2013;45:1221-5. DOI PubMed PMC
24. Martino A, Campa D, Jamroziak K, et al. Impact of polymorphic variation at 7p15.3, 3p22.1 and 2p23.3 loci on risk of multiple myeloma. *Br J Haematol* 2012;158:805-9. DOI PubMed
25. Weinhold N, Johnson DC, Rawstron AC, et al. Inherited genetic susceptibility to monoclonal gammopathy of unknown significance. *Blood* 2014;123:2513-7; quiz 2593. DOI PubMed
26. Ziv E, Dean E, Hu D, et al. Genome-wide association study identifies variants at 16p13 associated with survival in multiple myeloma patients. *Nat Commun* 2015;6:7539. DOI PubMed PMC
27. Mitchell JS, Li N, Weinhold N, et al. Genome-wide association study identifies multiple susceptibility loci for multiple myeloma. *Nat Commun* 2016;7:12050. DOI PubMed PMC
28. Went M, Sud A, Försti A, et al; PRACTICAL consortium. Identification of multiple risk loci and regulatory mechanisms influencing susceptibility to multiple myeloma. *Nat Commun* 2018;9:3707. DOI PubMed PMC
29. Duran-Lozano L, Thorleifsson G, Lopez de Lapuente Portilla A, et al. Germline variants at SOHLH2 influence multiple myeloma risk. *Blood Cancer J* 2021;11:76. DOI PubMed PMC
30. Landgren O, Weiss BM. Patterns of monoclonal gammopathy of undetermined significance and multiple myeloma in various ethnic/racial groups: support for genetic factors in pathogenesis. *Leukemia* 2009;23:1691-7. DOI PubMed
31. Greenberg AJ, Vachon CM, Rajkumar SV. Disparities in the prevalence, pathogenesis and progression of monoclonal gammopathy of undetermined significance and multiple myeloma between blacks and whites. *Leukemia* 2012;26:609-14. DOI PubMed PMC
32. Costa LJ, Brill IK, Omel J, Godby K, Kumar SK, Brown EE. Recent trends in multiple myeloma incidence and survival by age, race, and ethnicity in the United States. *Blood Adv* 2017;1:282-7. DOI PubMed PMC
33. Waxman AJ, Mink PJ, Devesa SS, et al. Racial disparities in incidence and outcome in multiple myeloma: a population-based study. *Blood* 2010;116:5501-6. DOI PubMed PMC
34. Du Z, Weinhold N, Song GC, et al. A meta-analysis of genome-wide association studies of multiple myeloma among men and women of African ancestry. *Blood Adv* 2020;4:181-90. DOI PubMed PMC
35. Cozen W, Gebregziabher M, Conti DV, et al. Interleukin-6-related genotypes, body mass index, and risk of multiple myeloma and plasmacytoma. *Cancer Epidemiol Biomarkers Prev* 2006;15:2285-91. DOI PubMed
36. Weinhold N, Meissner T, Johnson DC, et al. The 7p15.3 (rs4487645) association for multiple myeloma shows strong allele-specific regulation of the MYC-interacting gene CDCA7L in malignant plasma cells. *Haematologica* 2015;100:e110-3. DOI PubMed PMC
37. Li N, Johnson DC, Weinhold N, et al. Multiple myeloma risk variant at 7p15.3 creates an IRF4-binding site and interferes with CDCA7L expression. *Nat Commun* 2016;7:13656. DOI PubMed PMC
38. Baughn LB, Pearce K, Larson D, et al. Differences in genomic abnormalities among African individuals with monoclonal gammopathies using calculated ancestry. *Blood Cancer J* 2018;8:96. DOI PubMed PMC
39. Keats JJ, Reiman T, Maxwell CA, et al. In multiple myeloma, t(4;14)(p16;q32) is an adverse prognostic factor irrespective of FGFR3 expression. *Blood* 2003;101:1520-9. DOI PubMed
40. Chang H, Sloan S, Li D, et al. The t(4;14) is associated with poor prognosis in myeloma patients undergoing autologous stem cell transplant. *Br J Haematol* 2004;125:64-8. DOI PubMed

41. Santra M, Zhan F, Tian E, Barlogie B, Shaughnessy J Jr. A subset of multiple myeloma harboring the t(4;14)(p16;q32) translocation lacks FGFR3 expression but maintains an IGH/MMSET fusion transcript. *Blood* 2003;101:2374-6. DOI PubMed
42. Keats JJ, Maxwell CA, Taylor BJ, et al. Overexpression of transcripts originating from the MMSET locus characterizes all t(4;14)(p16;q32)-positive multiple myeloma patients. *Blood* 2005;105:4060-9. DOI PubMed PMC
43. Cappellen D, De Oliveira C, Ricol D, et al. Frequent activating mutations of FGFR3 in human bladder and cervix carcinomas. *Nat Genet* 1999;23:18-20. DOI PubMed
44. Pei H, Zhang L, Luo K, et al. MMSET regulates histone H4K20 methylation and 53BP1 accumulation at DNA damage sites. *Nature* 2011;470:124-8. DOI PubMed PMC
45. Avet-Loiseau H, Leleu X, Roussel M, et al. Bortezomib plus dexamethasone induction improves outcome of patients with t(4;14) myeloma but not outcome of patients with del(17p). *J Clin Oncol* 2010;28:4630-4. DOI PubMed
46. Shaughnessy J Jr, Gabrea A, Qi Y, et al. Cyclin D3 at 6p21 is dysregulated by recurrent chromosomal translocations to immunoglobulin loci in multiple myeloma. *Blood* 2001;98:217-23. DOI PubMed
47. Zhan F, Huang Y, Colla S, et al. The molecular classification of multiple myeloma. *Blood* 2006;108:2020-8. DOI PubMed PMC
48. Mao X, Cao B, Wood TE, et al. A small-molecule inhibitor of D-cyclin transactivation displays preclinical efficacy in myeloma and leukemia via phosphoinositide 3-kinase pathway. *Blood* 2011;117:1986-97. DOI PubMed
49. Avet-Loiseau H, Malard F, Campion L, et al; Intergroupe Francophone du Myélome. Translocation t(14;16) and multiple myeloma: is it really an independent prognostic factor? *Blood* 2011;117:2009-11. DOI PubMed
50. Hurt EM, Wiestner A, Rosenwald A, et al. Overexpression of c-maf is a frequent oncogenic event in multiple myeloma that promotes proliferation and pathological interactions with bone marrow stroma. *Cancer Cell* 2004;5:191-9. DOI PubMed
51. Walker BA, Wardell CP, Murison A, et al. APOBEC family mutational signatures are associated with poor prognosis translocations in multiple myeloma. *Nat Commun* 2015;6:6997. DOI PubMed PMC
52. Ross FM, Chiecchio L, Dagrada G, et al; UK Myeloma Forum. The t(14;20) is a poor prognostic factor in myeloma but is associated with long-term stable disease in monoclonal gammopathies of undetermined significance. *Haematologica* 2010;95:1221-5. DOI PubMed PMC
53. Solvason N, Wu WW, Kabra N, Wu X, Lees E, Howard MC. Induction of cell cycle regulatory proteins in anti-immunoglobulin-stimulated mature B lymphocytes. *J Exp Med* 1996;184:407-17. DOI PubMed PMC
54. Walker BA, Boyle EM, Wardell CP, et al. Mutational spectrum, copy number changes, and outcome: results of a sequencing study of patients with newly diagnosed myeloma. *J Clin Oncol* 2015;33:3911-20. DOI PubMed PMC
55. Avet-Loiseau H, Gerson F, Magrangeas F, Minvielle S, Harousseau JL, Bataille R; Intergroupe Francophone du Myélome. Rearrangements of the c-myc oncogene are present in 15% of primary human multiple myeloma tumors. *Blood* 2001;98:3082-6. DOI PubMed
56. Dib A, Gabrea A, Glebov OK, Bergsagel PL, Kuehl WM. Characterization of MYC translocations in multiple myeloma cell lines. *J Natl Cancer Inst Monogr* 2008;(39):25-31. DOI PubMed PMC
57. Walker BA, Leone PE, Chiecchio L, et al. A compendium of myeloma-associated chromosomal copy number abnormalities and their prognostic value. *Blood* 2010;116:e56-65. DOI PubMed
58. Debes-Marun CS, Dewald GW, Bryant S, et al. Chromosome abnormalities clustering and its implications for pathogenesis and prognosis in myeloma. *Leukemia* 2003;17:427-36. DOI PubMed
59. Chng WJ, Van Wier SA, Ahmann GJ, et al. A validated FISH trisomy index demonstrates the hyperdiploid and nonhyperdiploid dichotomy in MGUS. *Blood* 2005;106:2156-61. DOI PubMed PMC
60. Onodera N, Mccabe N, Rubin C. Formation of a hyperdiploid karyotype in childhood acute lymphoblastic leukemia [see comments]. *Blood* 1992;80:203-8. PubMed
61. Chng WJ, Kumar S, Vanwier S, et al. Molecular dissection of hyperdiploid multiple myeloma by gene expression profiling. *Cancer Res* 2007;67:2982-9. DOI PubMed
62. Smadja NV, Bastard C, Brigaudeau C, Leroux D, Fruchart C; Groupe Français de Cytogénétique Hématologique. Hypodiploidy is a major prognostic factor in multiple myeloma. *Blood* 2001;98:2229-38. DOI PubMed
63. Chretien ML, Corre J, Lauwers-Cances V, et al. Understanding the role of hyperdiploidy in myeloma prognosis: which trisomies really matter? *Blood* 2015;126:2713-9. DOI PubMed PMC
64. Pawlyn C, Melchor L, Murison A, et al. Coexistent hyperdiploidy does not abrogate poor prognosis in myeloma with adverse cytogenetics and may precede IGH translocations. *Blood* 2015;125:831-40. DOI
65. Sawyer JR, Tian E, Heuck CJ, et al. Jumping translocations of 1q12 in multiple myeloma: a novel mechanism for deletion of 17p in cytogenetically defined high-risk disease. *Blood* 2014;123:2504-12. DOI PubMed PMC
66. Schmidt TM, Barwick BG, Joseph N, et al. Gain of Chromosome 1q is associated with early progression in multiple myeloma patients treated with lenalidomide, bortezomib, and dexamethasone. *Blood Cancer J* 2019;9:94. DOI PubMed PMC
67. Li C, Wendlandt EB, Darbro B, et al. Genetic Analysis of multiple myeloma identifies cytogenetic alterations implicated in disease complexity and progression. *Cancers (Basel)* 2021;13:517. DOI PubMed PMC
68. Boyd KD, Ross FM, Walker BA, et al; NCRI Haematology Oncology Studies Group. Mapping of chromosome 1p deletions in myeloma identifies FAM46C at 1p12 and CDKN2C at 1p32.3 as being genes in regions associated with adverse survival. *Clin Cancer Res* 2011;17:7776-84. DOI PubMed PMC
69. Fonseca R, Bergsagel PL, Drach J, et al; International Myeloma Working Group. International Myeloma Working Group molecular classification of multiple myeloma: spotlight review. *Leukemia* 2009;23:2210-21. DOI PubMed PMC
70. Tricot G, Barlogie B, Jagannath S, et al. Poor prognosis in multiple myeloma is associated only with partial or complete deletions of

chromosome 13 or abnormalities involving 11q and not with other karyotype abnormalities. *Blood* 1995;86:4250-6. PubMed

71. Lodé L, Eveillard M, Trichet V, et al. Mutations in TP53 are exclusively associated with del(17p) in multiple myeloma. *Haematologica* 2010;95:1973-6. DOI PubMed PMC
72. Drach J, Ackermann J, Fritz E, et al. Presence of a p53 gene deletion in patients with multiple myeloma predicts for short survival after conventional-dose chemotherapy. *Blood* 1998;92:802-9. PubMed
73. Avet-Loiseau H, Attal M, Moreau P, et al. Genetic abnormalities and survival in multiple myeloma: the experience of the Intergroupe Francophone du Myélome. *Blood* 2007;109:3489-95. DOI PubMed
74. Gmidène A, Saad A, Avet-Loiseau H. 8p21.3 deletion suggesting a probable role of TRAIL-R1 and TRAIL-R2 as candidate tumor suppressor genes in the pathogenesis of multiple myeloma. *Med Oncol* 2013;30:489. DOI PubMed
75. Pratt G. Molecular aspects of multiple myeloma. *Mol Pathol* 2002;55:273-83. DOI PubMed PMC
76. Oeckinghaus A, Ghosh S. The NF-kappaB family of transcription factors and its regulation. *Cold Spring Harb Perspect Biol* 2009;1:a000034. DOI PubMed PMC
77. Annunziata CM, Davis RE, Demchenko Y, et al. Frequent engagement of the classical and alternative NF-kappaB pathways by diverse genetic abnormalities in multiple myeloma. *Cancer Cell* 2007;12:115-30. DOI PubMed PMC
78. Keats JJ, Fonseca R, Chesi M, et al. Promiscuous mutations activate the noncanonical NF-kappaB pathway in multiple myeloma. *Cancer Cell* 2007;12:131-44. DOI PubMed PMC
79. Zhang W, Liu HT. MAPK signal pathways in the regulation of cell proliferation in mammalian cells. *Cell Res* 2002;12:9-18. DOI PubMed
80. Chng WJ, Gonzalez-Paz N, Price-Troska T, et al. Clinical and biological significance of RAS mutations in multiple myeloma. *Leukemia* 2008;22:2280-4. DOI PubMed PMC
81. Patrawala S, Puzanov I. Vemurafenib (RG67204, PLX4032): a potent, selective BRAF kinase inhibitor. *Future Oncol* 2012;8:509-23. DOI PubMed
82. Bharti AC, Shishodia S, Reuben JM, et al. Nuclear factor-kappaB and STAT3 are constitutively active in CD138+ cells derived from multiple myeloma patients, and suppression of these transcription factors leads to apoptosis. *Blood* 2004;103:3175-84. DOI PubMed
83. Kawano M, Hirano T, Matsuda T, et al. Autocrine generation and requirement of BSF-2/IL-6 for human multiple myelomas. *Nature* 1988;332:83-5. DOI PubMed
84. De Vos J, Jourdan M, Tarte K, Jasmin C, Klein B. JAK2 tyrosine kinase inhibitor tyrphostin AG490 downregulates the mitogen-activated protein kinase (MAPK) and signal transducer and activator of transcription (STAT) pathways and induces apoptosis in myeloma cells. *Br J Haematol* 2000;109:823-8. DOI PubMed
85. Alas S, Bonavida B. Inhibition of constitutive STAT3 activity sensitizes resistant non-Hodgkin's lymphoma and multiple myeloma to chemotherapeutic drug-mediated apoptosis. *Clin Cancer Res* 2003;9:316-26. PubMed
86. Osaki M, Oshimura M, Ito H. PI3K-Akt pathway: its functions and alterations in human cancer. *Apoptosis* 2004;9:667-76. DOI PubMed
87. Aronson LI, Davenport EL, Giuntoli SG, et al. Autophagy is a key myeloma survival pathway that can be manipulated therapeutically to enhance apoptosis. *Blood* 2010;116:4083. DOI
88. Tasaka T, Berenson J, Vescio R, et al. Analysis of the p16INK4A, p15INK4B and p18INK4C genes in multiple myeloma. *Br J Haematol* 1997;96:98-102. DOI PubMed
89. Uchida T, Kinoshita T, Ohno T, Ohashi H, Nagai H, Saito H. Hypermethylation of p16INK4A gene promoter during the progression of plasma cell dyscrasia. *Leukemia* 2001;15:157-65. DOI PubMed
90. Kassambara A, Gourzones-Dmitriev C, Sahota S, et al. A DNA repair pathway score predicts survival in human multiple myeloma: the potential for therapeutic strategy. *Oncotarget* 2014;5:2487-98. DOI PubMed PMC
91. Neri P, Ren L, Gratton K, et al. Bortezomib-induced "BRCAness" sensitizes multiple myeloma cells to PARP inhibitors. *Blood* 2011;118:6368-79. DOI PubMed PMC
92. Hu Y, Lin J, Fang H, et al. Targeting the MALAT1/PARP1/LIG3 complex induces DNA damage and apoptosis in multiple myeloma. *Leukemia* 2018;32:2250-62. DOI PubMed PMC
93. Perrot A, Lauwers-Cances V, Corre J, et al. Minimal residual disease negativity using deep sequencing is a major prognostic factor in multiple myeloma. *Blood* 2018;132:2456-64. DOI PubMed PMC
94. Marchesini M, Fiorini E, Colla S. RNA processing: a new player of genomic instability in multiple myeloma. *Oncoscience* 2017;4:73-4. DOI PubMed PMC
95. Fucci C, Resnati M, Riva E, et al. The interaction of the tumor suppressor FAM46C with p62 and FNDC3 proteins integrates protein and secretory homeostasis. *Cell Rep* 2020;32:108162. DOI PubMed
96. Colla S, Ong DS, Ogoti Y, et al. Telomere dysfunction drives aberrant hematopoietic differentiation and myelodysplastic syndrome. *Cancer Cell* 2015;27:644-57. DOI PubMed PMC
97. Pereira B, Billaud M, Almeida R. RNA-binding proteins in cancer: old players and new actors. *Trends Cancer* 2017;3:506-28. DOI PubMed
98. Marchesini M, Ogoti Y, Fiorini E, et al. ILF2 is a regulator of RNA splicing and DNA damage response in 1q21-amplified multiple myeloma. *Cancer Cell* 2017;32:88-100.e6. DOI PubMed PMC
99. Shaffer AL, Emre NC, Lamy L, et al. IRF4 addiction in multiple myeloma. *Nature* 2008;454:226-31. DOI PubMed PMC
100. Greenberg AJ, Walters DK, Kumar SK, Rajkumar SV, Jelinek DF. Responsiveness of cytogenetically discrete human myeloma cell lines to lenalidomide: lack of correlation with cereblon and interferon regulatory factor 4 expression levels. *Eur J Haematol* 2013;91:504-13. DOI PubMed PMC

101. Schuster SR, Kortuem KM, Zhu YX, et al. The clinical significance of cereblon expression in multiple myeloma. *Leuk Res* 2014;38:23-8. DOI PubMed PMC
102. Mandelbaum J, Bhagat G, Tang H, et al. BLIMP1 is a tumor suppressor gene frequently disrupted in activated B cell-like diffuse large B cell lymphoma. *Cancer Cell* 2010;18:568-79. DOI PubMed PMC
103. Esteve FR, Roodman GD. Pathophysiology of myeloma bone disease. *Best Pract Res Clin Haematol* 2007;20:613-24. DOI PubMed
104. Tian E, Zhan F, Walker R, et al. The role of the Wnt-signaling antagonist DKK1 in the development of osteolytic lesions in multiple myeloma. *N Engl J Med* 2003;349:2483-94. DOI PubMed
105. Qiang YW, Chen Y, Stephens O, et al. Myeloma-derived Dickkopf-1 disrupts Wnt-regulated osteoprotegerin and RANKL production by osteoblasts: a potential mechanism underlying osteolytic bone lesions in multiple myeloma. *Blood* 2008;112:196-207. DOI PubMed PMC
106. Fulciniti M, Tassone P, Hideshima T, et al. Anti-DKK1 mAb (BHQ880) as a potential therapeutic agent for multiple myeloma. *Blood* 2009;114:371-9. DOI PubMed PMC
107. Cea M, Cagnetta A, Adamia S, et al. Evidence for a role of the histone deacetylase SIRT6 in DNA damage response of multiple myeloma cells. *Blood* 2016;127:1138-50. DOI PubMed PMC
108. Song Y, Li S, Ray A, et al. Blockade of deubiquitylating enzyme Rpn11 triggers apoptosis in multiple myeloma cells and overcomes bortezomib resistance. *Oncogene* 2017;36:5631-8. DOI PubMed PMC
109. Qin Y, Zhang S, Deng S, et al. Epigenetic silencing of miR-137 induces drug resistance and chromosomal instability by targeting AURKA in multiple myeloma. *Leukemia* 2017;31:1123-35. DOI PubMed
110. Caracciolo D, Di Martino MT, Amodio N, et al. miR-22 suppresses DNA ligase III addiction in multiple myeloma. *Leukemia* 2019;33:487-98. DOI PubMed PMC
111. Walker BA, Wardell CP, Chiecchio L, et al. Aberrant global methylation patterns affect the molecular pathogenesis and prognosis of multiple myeloma. *Blood* 2011;117:553-62. DOI PubMed
112. Tricot G. New insights into role of microenvironment in multiple myeloma. *Lancet* 2000;355:248-50. DOI PubMed
113. Klein B, Zhang X, Lu Z, Bataille R. Interleukin-6 in human multiple myeloma. *Blood* 1995;85:863-72. PubMed
114. Zhan F, Hardin J, Kordsmeier B, et al. Global gene expression profiling of multiple myeloma, monoclonal gammopathy of undetermined significance, and normal bone marrow plasma cells. *Blood* 2002;99:1745-57. DOI PubMed
115. Hazlehurst LA, Damiano JS, Buyuksal I, Pledger WJ, Dalton WS. Adhesion to fibronectin via beta1 integrins regulates p27kip1 levels and contributes to cell adhesion mediated drug resistance (CAM-DR). *Oncogene* 2000;19:4319-27. DOI PubMed
116. Mohty M, Harousseau JL. Treatment of autologous stem cell transplant-eligible multiple myeloma patients: ten questions and answers. *Haematologica* 2014;99:408-16. DOI PubMed PMC
117. Hideshima T, Raje N, Richardson PG, Anderson KC. A review of lenalidomide in combination with dexamethasone for the treatment of multiple myeloma. *Ther Clin Risk Manag* 2008;4:129-36. DOI PubMed PMC
118. Weber DM, Chen C, Niesvizky R, et al; Multiple Myeloma (009) Study Investigators. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. *N Engl J Med* 2007;357:2133-42. DOI PubMed
119. Abramson HN. Monoclonal antibodies for the treatment of multiple myeloma: an update. *Int J Mol Sci* 2018;19:3924. DOI PubMed PMC
120. Ito S. Proteasome inhibitors for the treatment of multiple myeloma. *Cancers (Basel)* 2020;12:265. DOI PubMed PMC
121. Mikhael J. Treatment options for triple-class refractory multiple myeloma. *Clin Lymphoma Myeloma Leuk* 2020;20:1-7. DOI PubMed
122. Gandhi UH, Cornell RF, Lakshman A, et al. Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy. *Leukemia* 2019;33:2266-75. DOI PubMed PMC
123. Gerrie AS, Mikhael JR, Cheng L, et al. D(T)PACE as salvage therapy for aggressive or refractory multiple myeloma. *Br J Haematol* 2013;161:802-10. DOI PubMed
124. Griffin PT, Ho VQ, Fulp W, et al. A comparison of salvage infusional chemotherapy regimens for recurrent/refractory multiple myeloma. *Cancer* 2015;121:3622-30. DOI PubMed
125. Michael M, Bruns I, Bölke E, et al. Bendamustine in patients with relapsed or refractory multiple myeloma. *Eur J Med Res* 2010;15:13-9. DOI PubMed PMC
126. Lau IJ, Smith D, Aitchison R, et al. Bendamustine in combination with thalidomide and dexamethasone is a viable salvage option in myeloma relapsed and/or refractory to bortezomib and lenalidomide. *Ann Hematol* 2015;94:643-9. DOI PubMed
127. Ludwig H, Kasparu H, Leitgeb C, et al. Bendamustine-bortezomib-dexamethasone is an active and well-tolerated regimen in patients with relapsed or refractory multiple myeloma. *Blood* 2014;123:985-91. DOI PubMed PMC
128. San-miguel JF, Hungria VTM, Yoon S, et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. *Lancet Oncol* 2014;15:1195-206. DOI PubMed
129. Richardson PG, Schlossman RL, Alsina M, et al. PANORAMA 2: panobinostat in combination with bortezomib and dexamethasone in patients with relapsed and bortezomib-refractory myeloma. *Blood* 2013;122:2331-7. DOI PubMed
130. Siegel DS, Dimopoulos M, Jagannath S, et al. VANTAGE 095: an international, multicenter, open-label study of vorinostat (MK-0683) in combination with bortezomib in patients with relapsed and refractory multiple myeloma. *Clin Lymphoma Myeloma Leuk* 2016;16:329-34.e1. DOI PubMed
131. Dimopoulos M, Siegel DS, Lonial S, et al. Vorinostat or placebo in combination with bortezomib in patients with multiple myeloma (VANTAGE 088): a multicentre, randomised, double-blind study. *Lancet Oncol* 2013;14:1129-40. DOI PubMed

132. Attal M, Lauwers-Cances V, Hulin C, et al; IFM 2009 Study. Lenalidomide, bortezomib, and dexamethasone with transplantation for myeloma. *N Engl J Med* 2017;376:1311-20. DOI PubMed PMC
133. Richter J, Madduri D, Richard S, Chari A. Selinexor in relapsed/refractory multiple myeloma. *Ther Adv Hematol* 2020;11:2040620720930629. DOI PubMed PMC
134. Lin Q, Zhao J, Song Y, Liu D. Recent updates on CAR T clinical trials for multiple myeloma. *Mol Cancer* 2019;18:154. DOI PubMed PMC
135. Yu B, Jiang T, Liu D. BCMA-targeted immunotherapy for multiple myeloma. *J Hematol Oncol* 2020;13:125. DOI PubMed PMC
136. Jänne PA, Shaw AT, Pereira JR, et al. Selumetinib plus docetaxel for KRAS-mutant advanced non-small-cell lung cancer: a randomised, multicentre, placebo-controlled, phase 2 study. *Lancet Oncol* 2013;14:38-47. DOI PubMed
137. Abdel-Wahab O, Klimek VM, Gaskell AA, et al. Efficacy of intermittent combined RAF and MEK inhibition in a patient with concurrent BRAF- and NRAS-mutant malignancies. *Cancer Discov* 2014;4:538-45. DOI PubMed PMC
138. Punnoose EA, Leverson JD, Peale F, et al. Expression profile of BCL-2, BCL-XL, and MCL-1 predicts pharmacological response to the BCL-2 selective antagonist venetoclax in multiple myeloma models. *Mol Cancer Ther* 2016;15:1132-44. DOI PubMed
139. Filippakopoulos P, Qi J, Picaud S, et al. Selective inhibition of BET bromodomains. *Nature* 2010;468:1067-73. DOI PubMed PMC
140. Guagnano V, Kauffmann A, Wöhrle S, et al. FGFR genetic alterations predict for sensitivity to NVP-BGJ398, a selective pan-FGFR inhibitor. *Cancer Discov* 2012;2:1118-33. DOI PubMed
141. Gavine PR, Mooney L, Kilgour E, et al. AZD4547: an orally bioavailable, potent, and selective inhibitor of the fibroblast growth factor receptor tyrosine kinase family. *Cancer Res* 2012;72:2045-56. DOI PubMed
142. Pawlyn C, Davies FE. Toward personalized treatment in multiple myeloma based on molecular characteristics. *Blood* 2019;133:660-75. DOI PubMed PMC
143. Baughn LB, Di Liberto M, Wu K, et al. A novel orally active small molecule potently induces G1 arrest in primary myeloma cells and prevents tumor growth by specific inhibition of cyclin-dependent kinase 4/6. *Cancer Res* 2006;66:7661-7. DOI PubMed
144. Jelinek T, Paiva B, Hajek R. Update on PD-1/PD-L1 inhibitors in multiple myeloma. *Front Immunol* 2018;9:2431. DOI PubMed PMC