




Understanding and addressing resistance to IMiDs immunomodulatory compounds in multiple myeloma

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Keywords

CELMoDs; combination therapies; epigenetic agents; immunomodulatory drugs (IMiDs); multiple myeloma; therapy resistance

Immunomodulatory drugs (IMiDs), including lenalidomide and pomalidomide in combination with proteasome inhibitors, dexamethasone and anti-CD38 monoclonal antibodies, play a central role in the treatment of multiple myeloma (MM) across newly diagnosed and relapsed stages. These treatment regimens have significantly improved patient outcomes worldwide, establishing IMiDs as one of the backbones of MM therapy. A new

Abbreviations

ADC, antibody–drug conjugate; ADO, adenosine; APOBEC, apolipoprotein B mRNA editing enzyme catalytic polypeptide-like; ATG, autophagy-related protein; BIRC5, baculoviral inhibitor of apoptosis repeat-containing 5; BM, bone marrow; BMSC, bone marrow stromal cell; BpD, belantamab mafodotin-pomalidomide-dexamethasone; BRD4, bromodomain-containing protein 4; Bregs, regulatory B cells; CAM-DR, cell adhesion-mediated drug resistance; CAR T, chimeric antigen receptor T cell; CCL5, C-C motif chemokine ligand 5; CCR7, C-C chemokine receptor type 7; CDK6, cyclin-dependent kinase 6; CELMoD, cereblon E3 ligase modulating drug; CoMMpass, Multiple Myeloma Research Foundation study database; COP9, constitutive photomorphogenesis 9 signalosome; CRBN, cereblon; CRL4CRBN, CUL4-RBX1-DDB1-CRBN E3 ubiquitin ligase complex; CUL4, Cullin-4; DC, dendritic cell; DEX/d, dexamethasone; DNAM-1, DNAX accessory molecule-1; DRd, daratumumab-lenalidomide-dexamethasone; DUOX2, dual oxidase 2; DVRd, daratumumab-bortezomib-lenalidomide-dexamethasone; ECM, extracellular matrix; ETV4, E-twenty-six variant transcription factor 4; EZH2, enhancer of zeste homologue 2; FAM72, family with sequence similarity 72; FcRH5, Fc receptor-like 5; FGF, fibroblast growth factor; FXP3, Forkhead Box P3; GM-CSF, granulocyte–macrophage colony-stimulating factor; GPRC5D, G protein-coupled receptor class C group 5 member D; H3K27Ac, histone H3 lysine 27 acetylation; H3K27me3, histone H3 lysine 27 trimethylation; H3K36me2, histone H3 lysine 36 dimethylation; HIF1 α , hypoxia-inducible factor 1-alpha; HLA, human leukocyte antigen; ICAM-1, intercellular adhesion molecule 1; ICOS, inducible T-cell costimulator; ID, immune depleted; IDH1, isocitrate dehydrogenase 1; IE, immune excluded; IFN- γ , interferon-gamma; IGF1, insulin growth factor 1; IKZF, Ikaros family zinc finger proteins; IL, interleukin; IMiD, immunomodulatory drug; IP, immune permissive; IR, immune resistant; IRF4, interferon regulatory factor 4; IS, immune suppressed; Isa, isatuximab; Isa-KRd, isatuximab-carfilzomib-dexamethasone; JAK/STAT, Janus kinase/signal transducer and activator of transcription; K, carfilzomib; KLRG1, killer cell lectin-like receptor G1; LAG-3, lymphocyte activation gene-3; LC3, microtubule-associated proteins 1A/1B light chain 3; Len/R, lenalidomide; LOH, loss of heterozygosity; MCP-1/2, monocyte chemoattractant protein-1/2; MDSC, myeloid-derived suppressor cell; MEK/ERK, Mitogen-Activated Protein Kinase Kinase/Extracellular Signal-Regulated Kinase; Mezi, mezigdomide; MGUS, monoclonal gammopathy of undetermined significance; MICA, MHC class I polypeptide-related sequence A; MIP-1 α , macrophage inflammatory protein-1 alpha; MM, multiple myeloma; MMP, matrix metalloproteinase; MRD, minimal residual disease; mRNA, messenger ribonucleic acid; MRP, multidrug resistance protein; NDMM, in newly diagnosed multiple myeloma; NEDD8, neural precursor cell-expressed developmentally downregulated protein 8; NK, natural killer cell; NKT, natural killer T cell; NOS2, nitric oxide synthase 2; NSD2/MMSET, nuclear receptor binding SET domain protein 2; OS, overall survival; PBX1, PD-1 cell, programmed death-1 cell, pre-B-cell leukaemia transcription factor 1; PFS, progression-free survival; P-Gp, P-glycoprotein; Pom/P, pomalidomide; PTGS2, prostaglandin-endoperoxide synthase 2; PvD, pomalidomide-bortezomib-dexamethasone; RBX1, RING-box protein 1; RRMM, relapsed/refractory multiple myeloma; RUNX, Runt-related transcription factor; RVd, lenalidomide-bortezomib-dexamethasone; SASP, senescence-associated secretory phenotype; Sel/S, selinexor; shRNA, short hairpin ribonucleic acid; SMAD3, mothers against decapentaplegic homologue 3; STAT3, signal transducer and activator of transcription 3; TCE, T-cell engager; Tcm, central memory T cell; TCR, T-cell receptor; TGF- β , transforming growth factor beta; TH17, T helper 17 cells; TIGIT, T-cell immunoreceptor with Ig and ITIM domains; TIM-3, T-cell immunoglobulin and mucin domain-containing protein 3; TME, tumour microenvironment; Tregs, regulatory T cells; UBE2, ubiquitin-conjugating enzyme E2; VVd, bortezomib (alone or in combination with dexamethasone); VCAM-1, vascular cell adhesion molecule 1; VEGF, vascular endothelial growth factor; VGPR, very good partial response; WGS, whole genome sequencing; XPO1, exportin-1.

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(Received 9 September 2025, revised 21 February 2026, accepted 14 May 2026)

doi:10.1111/febs.70599

generation of more potent compounds called cereblon E3 ligase modulators (CELMoDs) is now being developed to potentially replace the older IMiDs. In addition, novel immunotherapeutic approaches led by chimeric antigen receptor (CAR T), T-cell engagers and antibody–drug conjugates are also increasingly used in relapsed and refractory myeloma patient care. However, despite these advances, resistance to IMiD-based therapies inevitably develops and represents a major clinical challenge. Understanding the biological basis of resistance to IMiD-based therapy is crucial to plan and maximise treatment options for patients when they relapse on IMiD containing regimens. Emerging evidence underscores the role of genetic and epigenetic alterations, changes in downstream signalling, and dysregulation of the bone marrow immune microenvironment in driving therapeutic resistance. In this review, we explore current literature on the molecular and immune mechanisms related to the onset of therapeutic resistance. We then suggest ways to overcome resistance and exemplify options for the future, focusing on immunotherapy combinations with IMiDs or CELMoDs and novel agents.

Introduction

Immunomodulatory drug (IMiD) lenalidomide plays a pivotal role in newly diagnosed multiple myeloma (NDMM) as part of combinational triplet and quadruplet therapeutic regimens. Lenalidomide is also approved for use as monotherapy in the maintenance setting following autologous stem cell transplantation. Pomalidomide, a next-generation IMiD, is similarly a cornerstone of triplet therapies in relapsed and refractory multiple myeloma (RRMM). Despite their widespread use and clinical effectiveness, most patients eventually relapse and develop resistance to IMiDs and IMiD-based regimens. The underlying mechanisms driving clinical resistance to IMiDs remain incompletely understood, but growing evidence highlights the role of genetic and immune factors as key contributors. A next generation of more potent IMiD compounds such as Iberdomide and Mezigdomide (also known as CELMoDs) that can partially overcome resistance to older IMiDs is being developed.

All clinical IMiDs and CELMoD compounds act via a common target Cereblon (CRBN), through engagement with the CUL4-RBX1-DDB1-CRBN (CRL4^{CRBN}) E3 ubiquitin ligase complex, comprising the scaffold Cullin-4 (CUL4), the RING-finger protein RING-box1 (RBX1), the adapter protein damage-specific DNA binding protein 1 (DDB1), and the substrate receptor CRBN. The active/inactive state of the CRL4^{CRBN} E3 ligase is tightly regulated by the process of neddylation/deneddylation mediated by the COP9 signalosome (Fig. 1). Binding of IMiDs to the tri-tryptophan pocket of CRBN functions like a

molecular glue to recruit critical neo-substrates, most notably the transcription factors Ikaros and Aiolos, targeting them for proteasomal degradation. This rapid degradation cascade results in the suppression of downstream targets such as c-Myc and IRF4, ultimately leading to antiproliferative effects and apoptosis [1–3]. In the immune cells, the molecular mechanism leads to immunomodulatory effects on various immune subsets promoting T-cell expansion and NK cell activation through increased production of IL-2 and IFN- γ , while also suppressing the activity of immunosuppressive regulatory T cells (Tregs). Additionally, they enhance antigen presentation by dendritic cells, improving the immune system's ability to recognise and target myeloma cells [4]. Within the bone marrow, IMiDs disrupt the protective interactions between myeloma cells and stromal cells by downregulating adhesion molecules like VCAM-1 and ICAM-1. They also impair tumour-supportive signals by reducing the activity of angiogenic factors such as VEGF and FGF, further weakening the tumour microenvironment [4].

A number of recent reviews describe the landscape of IMiD resistance and how to address them [3–5]. A previous review authored by one of us described the mechanistic features of IMiDs (lenalidomide and pomalidomide) and CELMoDs (iberdomide and mezigdomide) and suggested ways to differentiate the latter from each other and the IMiDs [6]. Since then, both iberdomide and mezigdomide have advanced in the clinic and studies are underway to demonstrate the

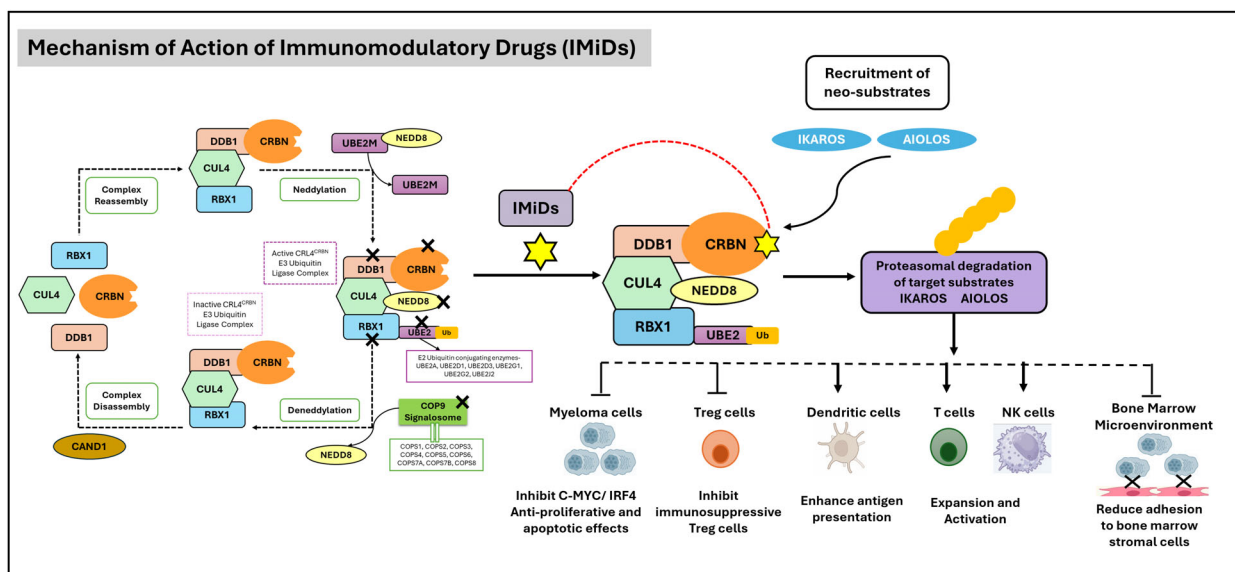


Fig. 1. Mechanism of Action of Immunomodulatory Drugs (IMiDs) and mutations related to resistance. The IMiDs function by binding to the cereblon (CRBN), a substrate receptor of the CRL4^{CRBN} E3 ubiquitin ligase complex, comprising CUL4, RBX1, DDB1 and CRBN. The activity of this complex is tightly regulated by the process of neddylation–deneddylation mediated by COP9 signalosome. IMiD binding to the CRBN leads to recruitment and proteasomal degradation of neo-substrates such as IKAROS and AIOLOS leading to downregulation of their downstream targets such as C-MYC and IRF4, and thereby exerting antiproliferative effects on MM cells. The immunomodulatory effects of IMiDs include inhibition of the immunosuppressive Tregs, enhanced antigen presentation by dendritic cells, expansion and activation of T and NK cells. IMiDs also reduce adhesion of MM to stromal cells. Aberrations (crossed) affecting CRBN, the other components of the CRL4^{CRBN} E3 ubiquitin ligase complex and the COP9 signalosome have all been linked to IMiD resistance. COP9, Constitutive Photomorphogenesis 9 signalosome; CRBN, Cereblon; CUL4, Cullin-4; DDB1, Damage-specific DNA binding protein 1; IRF4, Interferon regulatory factor 4; RBX1, the RING-finger protein RING-box1; MM, Multiple Myeloma; NEDD8, Neural precursor cell-expressed developmentally downregulated protein 8; NK cells, Natural Killer cells; Tregs, regulatory T cells; UBE2, Ubiquitin-conjugating enzyme E2.

efficacy of these drugs in NDMM as well as in RRMM. At the intervening time, a number of new therapeutic agents have been approved in myeloma care, including anti-BCMA CAR T, T-cell engagers (TCE), antibody–drug conjugate (ADC), anti-GPRC5D and anti-FcRH5 TCE, and XPO1 small molecule inhibitor. Many of these agents are competing for their use in RRMM and potentially in NDMM treatment paradigms. Under this evolving landscape of myeloma care, it is critical to understand the key issues related to IMiD resistance and how to address them therapeutically. And more specifically, what role CEL-MoD based regimens could play in overcoming IMiD resistance. In this review, we look at the clinical and preclinical evidence around the diversity of contributors, focusing on genetic, epigenetic, immune, and patient-derived factors and potential mechanisms underlying resistance to this class of drugs. We address the unmet medical need in the context of new and evolving therapeutic landscape and indicate ways to overcome IMiD resistance, especially focusing on the combination of approved drugs with emerging agents in the clinic.

Cell intrinsic genetic factors

The genetic landscape of IMiD resistance can be broadly categorised into cereblon-dependent and cereblon-independent resistance mechanisms.

CRBN dependent genetic determinants

On drug exposure, the expression level of *CRBN* mRNA and protein levels generally decrease over time in malignant plasma cells, and patients acquiring lenalidomide resistance show a markedly reduced expression of CRBN [7,8].

As such, the four cysteine residues in the IMiD binding domain of the CRBN are highly conserved among vertebrates showing their functional importance. The mutations in these cysteine residues can critically impact the zinc finger domain formation resulting in protein misfolding and aggregation [9,10]. Interestingly, there was a significant increase in exon 10 spliced variant of *CRBN* in pomalidomide RRMM patients compared to NDMM patients [11]. The exon-10 splice variant of CRBN lacks the critical

tri-tryptophan binding pocket encoded by exons 10–11, hence impairing the IMiD interaction with the ligase complex. Functional validation in myeloma cell lines confirmed that exon 10 exclusion alone was sufficient to abrogate lenalidomide-induced cytotoxicity, highlighting its direct role in mediating resistance [12]. A recent study has also pointed out the dual deletion of exon 8 and 10 in NDMM and IMiD-refractory patients, although the exact role of this variant in IMiD resistance is yet to be deciphered [13].

In a study of 50 RRMM patients who were pre-treated with IMiDs, there was a 12% and 10% increased prevalence of mutations in *CRBN* and *CRBN* pathway genes, respectively, when compared to NDMM [14]. A more recent study using whole genome sequencing (WGS) data from 455 patients and RNAseq data from 655 patients, IMiD-refractory patients exhibit a significantly higher incidence of *CRBN*-related genetic aberrations including mutations in the *CRBN* gene, gene copy loss of *CRBN* and the presence of exon 10-spliced variant of *CRBN*, when compared to NDMM [11]. Additionally, the cumulative proportion of *CRBN* alterations increased from lenalidomide-resistant patients (20%) to pomalidomide-resistant patients (30%). Importantly, the genetic aberrations of *CRBN* significantly correlated with a reduced overall survival and progression-free survival (PFS) [11]. In the Iberdomide phase 1 study, Amatangelo *et al.* reported that among 81 late line RRMM patients, *CRBN* exon 10 splicing was detected in 15%, loss of heterozygosity (LOH) at the *CRBN* locus in 14%, and *CRBN* mutations in 6%, highlighting the prevalence of *CRBN* alterations in RRMM. Collectively, *CRBN* disruption is one of the most prominent genetic contributors to clinical resistance in RRMM upon acquiring IMiD resistance [15].

CRBN independent genetic determinants

Initial analysis of some pomalidomide-resistant cell lines had no loss in *CRBN* expression [1], indicating a *CRBN*-independent pathway for IMiD resistance. Emerging evidence from genomics analysis also suggests that resistance to IMiDs can also occur through *CRBN*-independent mechanisms in patients.

COP9 Signalosome plays an important role in the neddylation/denedylation of CRL4^{CRBN} E3 ubiquitin ligase complex. The conjugation of NEDD8 stimulates the CRL4^{CRBN} complex into an active state whereas the COP9 signalosome mediated removal of NEDD8 switches the complex back into an inactive state [16]. A specific chromosomal region, 2q37, harbouring COP9 signalosome components *COPS7B* and *COPS8*,

was found to exhibit increasing copy loss frequency across disease stages, from 5.5% in newly diagnosed patients to 10.0% in those refractory to lenalidomide and rising to 16.4% in patient's refractory to both lenalidomide and pomalidomide [17]. In an independent cohort of 50 patients with serial samples collected during treatment, 2q37 deletion emerged in 16% of cases exposed to IMiDs, while it was absent in patients without IMiD treatment [17]. In the Iberdomide phase I study, WGS and RNAseq data from 81 patients revealed that 17% had loss of *COPS7B* and 16% had loss of *COPS8*, further underscoring the therapeutic significance of the 2q37 chromosomal region, where both genes are located [15].

As such, the intrinsic fitness of the myeloma clone can significantly contribute to drug resistance. Analysis of the myeloma genomes of 386 RRMM patients resistant to the IMiDs also revealed the enrichment of mutations in *DUOX2*, *EZH2*, *TP53* and gain in 1q, del17p and double hit events that are associated with high risk, suggesting the contribution of other genomic or epigenomic factors could drive resistance to the IMiDs [18].

Indeed, pathway analysis in resistant myeloma cell lines revealed enrichment of the JAK/STAT signalling pathway, with *IL6* and *STAT3* among the most up-regulated genes. Increased expression of *STAT3* and its downstream targets *PIM2* and *BIRC5* was confirmed in XG1 lenalidomide-resistant cells. Moreover, *IL6* exposure induced lenalidomide resistance in wild-type XG1 cells, supporting the role of *IL6*-driven *STAT3* activation in mediating resistance [19].

Elevated c-MYC protein levels have been observed at lenalidomide-refractory stages, compared to diagnosis, implying a potential role of c-MYC in driving resistance [7]. Among other preclinical evidence, truncated *IRF4* is resistant to lenalidomide-induced down-regulation [19].

Furthermore, in an *in vivo* model of acquired resistance, Ocio *et al.* found that resistance to lenalidomide–dexamethasone and pomalidomide–dexamethasone was associated with activation of the MEK/ERK pathway [20]. Also, overexpression of *CDK6* in multiple myeloma (MM) cell lines resulted in markedly reduced IMiD sensitivity. Inhibiting *CDK6* demonstrates strong synergy with IMiDs both *in vitro* and *in vivo* [21]. Notably, this resistance mechanism is kinase-dependent, as expression of a catalytically inactive *CDK6* mutant (K43M) failed to protect cells from lenalidomide-induced cytotoxicity [21]. Zhou *et al.* identified *RUNX1* and *RUNX3* as transcription factors that bind to Ikaros and Aiolos, protecting them from *CRBN*-mediated degradation and thereby reducing IMiD efficacy [22].

Finally, gene expression profiling and pathway analysis on lenalidomide-resistant cell lines developed through chronic exposure to IMiDs showed dysregulation of Wnt/ β -catenin pathway [23]. Activation of the Wnt/ β -catenin pathway either through recombinant Wnt-3a or β -catenin overexpression diminished the antiproliferative effects of lenalidomide. In contrast, silencing β -catenin using shRNAs re-established drug sensitivity in plasma cells [23]. Lenalidomide-resistant myeloma models exhibited elevated expression of CD44, a Wnt/ β -catenin target, correlating with increased adhesion to bone marrow stroma and hyaluronan-coated surfaces, showing how adhesion pathways drive tumour microenvironment (TME)-mediated IMiD resistance [24].

These observations taken together confirm drug mechanism-based, CRBN-dependent and CRBN-independent genetic drivers of resistance in myeloma in cell lines and IMiD-resistant patients.

Immunological mechanisms driving IMiD resistance

Immunological mechanisms causing IMiD resistance include patient-related factors—where the systemic characteristics (inflammatory, metabolic and immunological) of the patients at diagnosis can modulate response to IMiDs, and treatment-related factors—where the changes in the immune system after exposure to IMiDs drive the resistance (Fig. 2).

Patient-related factors: Baseline immune characteristics

State of immunodeficiency at diagnosis

The alterations of the immune profile in patients with MM, which may begin early in myelomagenesis, have allowed the description of immunophenotypes in patients with the disease, based mainly on the distribution of dendritic cells (DCs) and T cells and its correlation with patients' outcomes and responses to treatment. This classifies the patients into 5 subgroups: immune depleted (ID), immune permissive (IP), immune excluded (IE), immune suppressed (IS) and immune resistant (IR) [25]. Dysregulation of the immune system due to an imbalance in the regulatory and cytotoxic equilibrium is one of the predominant biological mechanisms in MM, contributing to the chronic course of the disease and its frequent relapses [26,27]. In NDMM patients, baseline immunological characteristics that have been demonstrated to contribute to this myelomagenesis include an increase in CD4⁺ and CD8⁺ T cells [28–30], and in the T helper T_H17 cells, which is a subset of CD4⁺

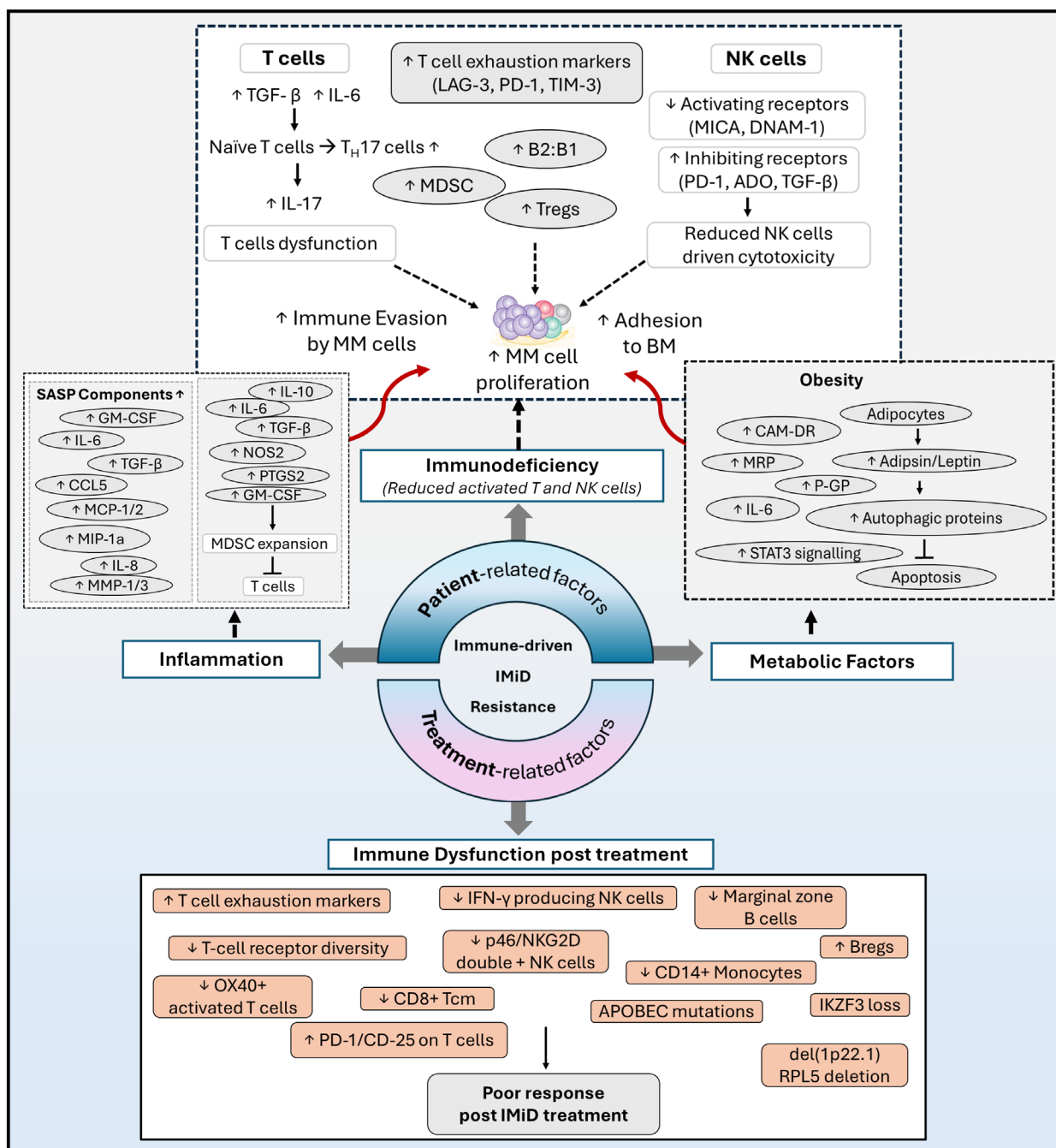
T cells that have an immunosuppressive phenotype. This is driven by increased levels of cytokines such as TGF- β and IL-6 in the bone marrow microenvironment which induces the differentiation of naïve T cells to T_H17 cells. These T_H17 cells induce production of IL-17 which further promotes MM cell proliferation, colony formation and adhesion to bone marrow stromal cells (BMSCs) (Fig. 2). Supporting all these, both T_H17 cell population as well as IL-17 levels were elevated in the peripheral blood and bone marrow of NDMM patients [31]. Similarly, there is an enrichment of NK cells in NDMM patients compared to healthy individuals [28,30,32].

At first relapse, there is an increase in the proportion of plasmacytoid DCs, T_H17 cells and myeloid-derived suppressor cells (MDSC), along with dysfunction of NK cells, and an elevated ratio of B2 to B1 cells [27]. Particularly, CD11b⁺CD14⁻HLA⁻DR^{-/low}CD33⁺CD15⁺ MDSCs are significantly increased in both the peripheral blood and the bone marrow of patients compared with healthy donors, which stimulate MM growth while suppressing T-cell-mediated immune responses [33].

However, as the disease progresses, the cytotoxic function of NK cells declines due to reduced expression of activating receptors such as MICA, DNAM-1, increased PD-1 expression and the influence of immunosuppressive cytokines like ADO and TGF- β . These changes contribute to immune evasion by myeloma cells [28]. These last changes adopt a predictive value as lenalidomide-refractory patients show a significant reduction in the proportion of activated NK cells and effector T cells [34]. Other changes predictive of response with IMiD include immune cell levels, as described in the analysis of baseline immune characteristics of a subset of RRMM patients (len/pom or triple-class refractory) from the phase 1/2 iberdomide study; median absolute counts of several immune cell types including the B cells, total T cells and CD4⁺ T cells were below the lower limit of normal [15]. Also, despite an 'activated immunophenotype', a low proportion of T cells were observed to be in a proliferative state, suggesting immune dysfunction. These findings were accompanied by an increase in T cells (Tregs) and T-cell exhaustion markers, specifically Lag-3 (CD223), PD-1 (CD279) and Tim-3 (CD366) [15]. Therefore, the baseline immune characteristics including dysfunctional NK cells and immunosuppressive T-cell profiles could manifest as resistance or reduce the impact of IMiD-based therapy in MM.

Role of inflammation

An intact immune microenvironment is essential for controlling myeloma. Given that most MM patients



are older adults, both inflammaging (age-related proinflammatory changes in the bone marrow microenvironment) and immune cell senescence play important roles in tumour development and growth mechanisms [35,36].

In the TME of MM patients, several *senescence-associated secretory phenotype* (SASP) components have been found to be elevated, particularly IL-6, IL-

8, TGF- β , CCL5, MIP-1a, MMP-1/3, MCP-1/2, among others [37]. These SASPs, produced in an auto-crine manner by MM cells, have a direct trophic effect on neoplastic cells, promoting their proliferation.

Additionally, elevated IL-6, GM-CSF and factors such as PTGS2, TGF β , NOS2 and IL-10 from mesenchymal cells promote MDSC expansion, which suppresses T-cell function by producing reactive oxygen

Fig. 2. Immune-mediated IMiD resistance. Schematic overview of patient-related and treatment-related factors contributing to immune dysfunction and IMiD resistance. Patient-related contributors include inflammation, metabolic syndrome/obesity and the state of immunodeficiency at diagnosis which leads to immune evasion strategies by MM cells leading to reduced T and NK cell activity. Treatment-related factors include immune dysfunction post-treatment characterised by T-cell exhaustion, impaired NK cell cytotoxicity, altered monocyte and B-cell subsets, and genetic alterations such as IKZF3 loss, APOBEC mutations and del(1p22.1) affecting RPL5. Collectively, these factors drive poor responses to IMiD therapy and highlight opportunities for novel immune-restorative strategies. ADO, adenosine; APOBEC, apolipoprotein B mRNA editing enzyme catalytic polypeptide-like; BM, bone marrow; Bregs, B regulatory cells; CAM-DR, cell adhesion-mediated drug resistance; CCR7, C-C chemokine receptor type 7; CCL5, C-C motif chemokine ligand 5; del(1p22.1), deletion of chromosome 1p22.1; DNAM1, DNAX accessory molecule-1; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN- γ , interferon-gamma; IKZF3, IKAROS family zinc finger protein 3; IL, interleukin; IMiD, immunomodulatory drug; LAG-3, lymphocyte activation gene-3; MCP-1/2, monocyte chemoattractant protein-1/2; MDSC, myeloid-derived suppressor cell; MICA, MHC class I polypeptide-related sequence A; MIP-1 α , macrophage inflammatory protein-1 alpha; MMP, matrix metalloproteinase; MRP, multidrug resistance protein; NK, natural killer; NKG2D, Natural Killer group 2, member D; NKT, natural killer T cell; NOS2, nitric oxide synthase 2; PD-1, programmed cell death protein 1; P-GP, P-glycoprotein; PTGS2, Prostaglandin-endoperoxide synthase 2; SASP, senescence-associated secretory phenotype; STAT3, signal transducer and activator of transcription 3; TGF- β , transforming growth factor beta; T_H cells, T helper cells; TIGIT, T-cell immunoreceptor with Ig and ITIM domains; TIM-3, T-cell immunoglobulin and mucin domain-containing protein 3; Treg, regulatory T cell.

species, arginase and nitric oxide synthase [38–40]. These mechanisms of immunosenescence are relevant as IMiDs downregulate the MDSC-promoting chemokines such as CCL5, MIF, to control the disease [41]. However, some studies report increased MDSC-like CD14⁺CD15⁺ cells after treatment with lenalidomide, which suppress T-cell activity and may contribute to drug resistance [42].

Metabolic factors

Metabolic syndrome, particularly obesity, is associated with increased incidence and worse outcomes for MM patients. The risk is higher in individuals categorised as overweight or obese compared to those of normal weight, and obesity also increases the risk of progression from MGUS to MM [43,44]. In the same meta-analysis, relative risk estimates for mortality were also higher for obese patients compared to patients with normal body mass index. Similarly, Ochiai, *et al.* demonstrated that adipocytes from overweight and obese individuals increased cell adhesion-mediated drug resistance (CAM-DR), P-glycoprotein (P-gp) and multidrug resistance-associated protein (MRP) transporter expression in MM cells [45]. Furthermore, myeloma cell lines cocultured with adipocytes proliferated faster and displayed increased pSTAT-3/STAT-3 signalling in adipocyte-conditioned media [46]. Interestingly, adipocytes from obese patients had higher production of other inflammatory proteins, including IL-6 [46]. Among other mechanisms, the contact between tumour cells and adipocytes in bone marrow leads to the secretion of adipokines such as adiponectin and leptin (typically seen in obese MM patients), which further upregulate autophagic proteins such as ATG3, ATG5

and LC3-1/II via JAK/STAT signalling and inhibit caspase cleavage and apoptosis in MM cells [47].

Treatment-related factors: Pharmacodynamic changes after exposure to IMiDs

The disease evolution takes a multistep trajectory whereby the immune system exerts selective pressure on tumour cells through a process known as immunoeediting. The first stage, 'elimination' involves the innate and adaptive immune system-mediated killing of transformed cells that have initially escaped the apoptotic/senescence checkpoints. The second stage, 'equilibrium' involves the expansion of those resistant tumour subclones that have evaded the elimination stage through various genetic alterations. Even at this stage, the net tumour growth is controlled by the adaptive immunity. Eventually, in the final 'escape' stage, the selective pressure on tumour subclones leads to their outgrowth and establishment of a clinically apparent immunosuppressive tumour microenvironment [48,49].

Emerging evidence highlights that IMiD resistance is closely linked to impairment of immune effector functions during treatment. Although pomalidomide exerts pleiotropic effects on multiple immune cell populations, not all of these changes translate into clinical benefit. Immune profiling of peripheral blood samples collected at screening, cycle 1 day 8, cycle 3 day 8 post-treatments from the CC4047-MM-007 (OPTIMISM, NCT01734928) study involving 186 patients treated with pomalidomide in combination with bortezomib and dexamethasone (Pvd) demonstrated significant enhancements in NK, NKT and T-cell activation compared to those receiving only Vd. Specifically, increased double positive expression of NK cell

activation markers (p46/NKG2D), increased OX-40+ activated CD8⁺ T cells (OX-40⁺), decreased PD-1 and CD25 expression on CD4⁺ T cells, expansion of marginal zone B-cell subsets, and decrease in B regulatory cells were all associated with significantly better PFS among PVD treated patients [27].

Based on RRMM patients from a phase 2 trial (NCT01319422, n = 39) treated with pom (received prior len therapy), treatment induced increases in total T cells, particularly CD8⁺ T cells, correlated with objective therapeutic responses, whereas NK cell expansion did not. Moreover, clinical response was specifically associated with Pom-induced elevations in IFN γ - and TNF α -producing CD8⁺ T cells and poly-functional T-cell populations, highlighting the importance of robust cytotoxic T-cell activation. In contrast, treatment induced changes in T cells producing other cytokines (IL-13 and IL-17), cytolytic markers (granzyme, perforin), FOXP3^{hi} Tregs, or NK cell numbers did not significantly correlate with response [50].

Pierceall *et al.* analysed whether baseline immune cell profiles and their early changes during treatment were linked to outcomes in MM. In this study, immune cell phenotyping was performed both at baseline and at cycle 2 day 15 (C2D15) to evaluate associations with PFS (relapsed vs. nonrelapsed patients) and depth of response (\geq very good partial response [VGPR] vs. <VGPR). At the 18-month PFS, higher baseline counts of total CD4⁺ T cells and specific CD4⁺ subsets, such as naïve, central memory (T_{cm}) and activated ICOS⁺ cells, were significantly associated with longer PFS and better response rates (\geq VGPR). Elevated CD4⁺ counts after treatment start also correlated with improved outcomes. While CD8⁺ T-cell counts did not significantly relate to PFS, higher baseline and post-treatment CD8⁺ T_{cm} counts were significantly associated with deeper responses. NK cells showed a trend toward PFS benefit, but no associations were found for B cells, monocytes, Tregs or exhausted T cells [34].

As such, MM progression during treatment is shaped by a dynamic interaction between the tumour and the immune microenvironment. Analysis of the MM tumour microenvironment (TME) in patients enrolled in the MANHATTAN trial (NCT03290950; n = 49) with NDMM treated with carfilzomib–lenalidomide–dexamethasone–daratumumab combination revealed that those who failed to achieve minimal residual disease (MRD) negativity had significantly shorter PFS [51,52]. These patients had multiple immune dysregulations such as a decrease in CD14⁺ monocytes, increased markers of T-cell exhaustion, persistence of IFN γ -producing natural killer (NK)

cells, and diminished T-cell receptor (TCR) diversity. Notably, these immune alterations co-occurred with genomic abnormalities such as elevated APOBEC mutational signatures, deletions at 1p22.1 (RPL5), and loss of IKZF3 [52].

In heavily pretreated IMiD-refractory patients, immune dysfunction was evident, characterised by reduced T-cell activation and proliferation, diminished cytokine secretion and impaired NK cell activity. Subsequent treatment with Iberdomide resulted in immune restimulation noted by an increase in activated NK and T cells. However, consistent with the role of Ikaros and Aiolos in B-cell maturation, iberdomide treatment led to a decrease in B-cell population possibly driven by the degradation of these transcription factors [15]. Similarly, treatment with mezigdomide in heavily pretreated RRMM patients was associated with immune cells switching from exhausted to activated phenotype, across both adaptive and innate compartments [53,54]. NK and NKT cells significantly increased, while CD4⁺ and CD8⁺ T cells shifted toward an effector memory phenotype with increased HLA-DR and ICOS expression, indicating enhanced activation. Exhausted and senescent populations such as KLRG1⁺ and CD57⁺ subsets, as well as TIGIT-expressing CD8⁺, NK and NKT cells, were markedly reduced, with a dose-dependent decline in TIGIT⁺ populations. Although PD-1 expression alone was unchanged, dual PD-1/TIGIT-positive T cells decreased significantly. Importantly, patients who failed to respond to mezigdomide had higher baseline frequencies of PD-1⁺ and TIGIT⁺ CD8⁺ and NKT cells [53].

These deficits, likely arising from the combined effects of chronic IMiD exposure and tumour-driven immunosuppression, impair effector immune cell responsiveness to subsequent IMiD-mediated costimulation. Collectively, these findings highlight that both baseline immune status and therapy-induced immune perturbations critically influence IMiD resistance in multiple myeloma. A summary of immunological changes correlating with response is described in Table 1.

Epigenetic drivers of resistance

Epigenetic plasticity serves as an adaptive strategy through which MM cells evade IMiD treatment, with such mutations comprising almost a quarter of the genes mutated in NDMM, including mutations in *EP300*, *IDH1 and 2*, *KMT2B and 2C*, *KDM5C* and *6A* [55]. In a study involving 324 patients, approximately 15% of IMiD-resistant cases exhibited no discernible

Table 1. Immunological changes correlating with response to immunomodulatory drugs (IMiDs).

Changes correlating with response	References
<ul style="list-style-type: none"> Elevations in IFNγ- and TNFα-producing CD8⁺ T cells and polyfunctional T-cell populations 	[50]
<ul style="list-style-type: none"> Higher baseline counts of total CD4⁺ T cells and specific CD4⁺ subsets, such as naïve, central memory (Tcm), and activated ICOS⁺ cells 	[33]
<ul style="list-style-type: none"> Elevated CD4⁺ counts after treatment start 	
<ul style="list-style-type: none"> Higher baseline and post-treatment CD8⁺ Tcm counts 	
<ul style="list-style-type: none"> Increased double-positive expression of NK cell activation markers (p46/NKG2D) 	[27]
<ul style="list-style-type: none"> Increased OX-40+ activated CD8⁺ T cells (OX-40⁺) 	
<ul style="list-style-type: none"> Decreased PD-1 and CD25 expression on CD4⁺ T cells 	
<ul style="list-style-type: none"> Expansion of marginal zone B-cell subsets 	
<ul style="list-style-type: none"> Decrease in B regulatory cells 	
<ul style="list-style-type: none"> Higher baseline frequencies of PD-1⁺ and TIGIT⁺ CD8⁺ and NKT cells 	[53]
Changes that may correlate with lack of response	References
<ul style="list-style-type: none"> Production of IL-13 and IL-17, cytolytic markers (granzyme, perforin) 	[50]
<ul style="list-style-type: none"> FOXP3^{hi} Tregs 	
<ul style="list-style-type: none"> NK cells expansion alone 	
<ul style="list-style-type: none"> Levels of B cells, monocytes, Tregs, or exhausted T cells 	[33]
<ul style="list-style-type: none"> Decrease in CD14⁺ monocytes 	[52]
<ul style="list-style-type: none"> Increased markers of T-cell exhaustion 	
<ul style="list-style-type: none"> Persistence of IFNγ-producing natural killer (NK) cells 	
<ul style="list-style-type: none"> Diminished T-cell receptor (TCR) diversity 	

genetic mutational drivers, prompting a strong speculation whether transcriptional regulation driven by epigenetic changes in the chromatin organisation underwrites their resistant biology [18]. As this mechanism is both reversible and potentially targetable, it is crucial to understand the epigenetic basis of IMiD resistance to develop effective resensitisation strategies.

The epigenetic drivers of IMiD resistance are summarised in Fig. 3. Hypermethylation of the *CRBN* enhancer region resulting in the silencing of *CRBN* has been linked to IMiD resistance, with an increased differential hypermethylation in IMiD-refractory cases compared to healthy plasma cells [56]. A phase 1b study on 18 heavily pretreated RRMM patients (Len/Pom refractory), azacytidine which is a hypomethylating agent when combined with LEN and DEX showed an overall clinical benefit of 50% [57].

Hypomethylation of 1q12 has been shown to amplify the genomic regions juxtaposed to it leading to 1q21 copy number gains [58]. 1q gain was a key

genetic driver of lenalidomide and pomalidomide resistance in RRMM gene analysis [18]. Around 25% of MM-specific differentially methylated genes lie within the 1q21.1 locus, including *FAM72*, which promotes myeloma cell proliferation via FOXM1 activation following promoter demethylation [59]. Epigenetic activation of *PBX1*, another 1q gene, enhances FOXM1-driven transcriptional programmes linked to poor prognosis [60]. In the same study, *EZH2* mutation was identified as a novel driver of IMiD-resistant clones.

In preclinical resistant cell line model, transcriptomic profiling indicated that the resistant phenotype was largely driven by widespread gene downregulation through DNA methylation, with SMAD3 emerging as a consistently suppressed gene across resistant lines. Importantly, treatment with a combination of 5-azacytidine and an EZH2 inhibitor restored chromatin accessibility, reactivated SMAD3 expression and significantly resensitised resistant cells to both lenalidomide and pomalidomide [61].

Histone modifications, particularly those affecting histone H3, play a critical role in mediating epigenetic drug resistance. Methylation at lysine residues 4 and 36 (H3K4 and H3K36), as well as at lysine 27 and 9 (H3K27 and H3K9), have been prominently implicated in these mechanisms [62].

H3K27me₃, a key repressive histone mark catalysed by EZH2, has been previously implicated in CAM-DR-mediated IMiD resistance. Akt-mediated inactivating phosphorylation of EZH2, driven by the bone marrow microenvironment and IL-6 signalling, leads to reduced H3K27me₃, sustaining the expression of anti-apoptotic genes such as *IGF1*, *BCL2* and *HIF1 α* [63,64].

Analysis of large clinical trial datasets involving nearly 1500 myeloma patients has revealed that high EZH2 expression is independently linked to poor outcomes [65]. Targeting EZH2 with selective small molecule inhibitors in myeloma cell lines and patient samples led to cell cycle arrest and apoptosis, supporting its role as a promising therapeutic target, including in high-risk disease. Mechanistically, EZH2 inhibition upregulated CDK inhibitors such as *p21* and *p15*, genes normally repressed by H3K27me₃ [65].

IMiD resistance can also be mediated by pathways involving ETV4/p300/BRD4 axis. In resistant myeloma cells, MYC and IRF4 expression are sustained by the binding of transcription factors such as ETV4 and BATF, which recruit p300 and BRD4 [66–68]. High ETV4 expression correlated with shorter PFS and OS in CoMMpass patients receiving IMiDs and in POLLUX trial patients treated with lenalidomide and dexamethasone [4,66].

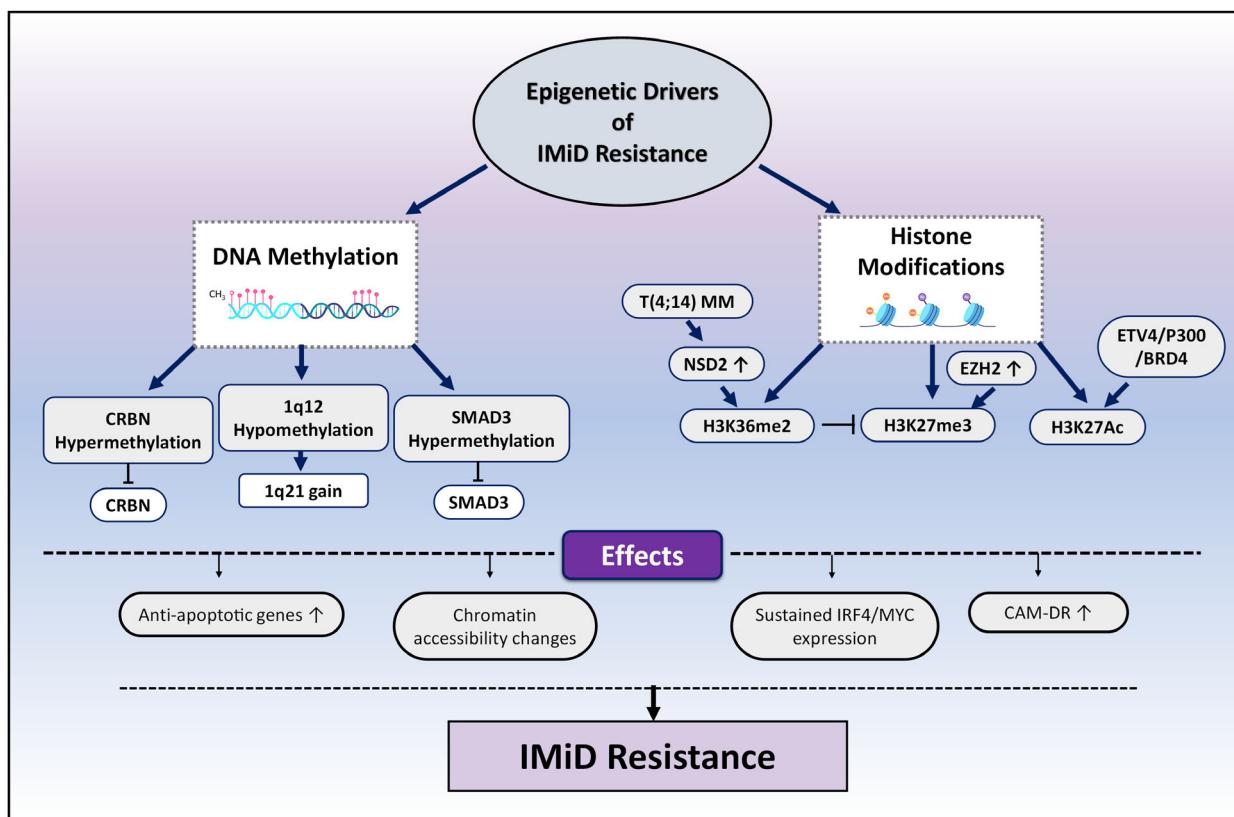


Fig. 3. Epigenetic drivers of drug resistance in MM. DNA methylation and histone modifications are the critical epigenetic changes driving IMiD resistance. Among the DNA methylation related changes, hypermethylation of CRBN results in silencing of CRBN gene expression resulting in IMiD target reduction driven resistance. Also, hypomethylation of 1q12 contributes to 1q21 gain leading to the overexpression of many critical genes such as FAM72 and PBX1 that promote MM cell proliferation and IMiD resistance. Similarly, SMAD3 hypermethylation has been observed in many of the IMiD-resistant cell models. Among the key histone modifications, H3K36me2 is driven by high NSD2 (histone methyltransferase) expression due to translocation (4;14), which is a frequent event in MM, leading to poor prognosis. Also, overexpression of EZH2 drives an increase in H3K27me3 levels, which leads to the silencing of many tumour suppressor genes. Notably, H3K36me2 has an antagonising relationship with H3K27me2. In addition, IMiD-resistant cells maintain P300/BRD4 super-enhancer occupancy on IKAROS/AIOLOS when cobound by ETV4, leading to sustained expression of IRF4/c-MYC. P300/BRD4 is a critical regulator of H3K27Ac, which drives active gene expression. Overall, these above-mentioned epigenetic changes along with others can drive chromatin accessibility changes, leading to upregulation of anti-apoptotic genes, downregulation of tumour suppressor genes, sustained expression of MM driver genes such as IRF4/c-MYC and upregulation of genes responsible for increased adhesion between MM cells and BMSC contributing to IMiD resistance. BRD4, Bromodomain 4; CAM-DR, Cell adhesion-mediated drug resistance; CRBN, cereblon; ETV4, E-twenty-six (ETS) variant transcription factor 4; EZH2, Enhancer of zeste homologue 2; FAM72, Family with sequence similarity 72; H3K27Ac, histone H3 lysine 27 acetylation; H3K27me3, histone H3 lysine 27 trimethylation; H3K36me2, histone H3 lysine 36 dimethylation; NSD2, Nuclear Receptor Binding SET Domain Protein 2; P300, Histone acetyltransferase p300; IMiD, immunomodulatory drug; IRF4, Interferon regulatory factor 4; PBX1, pre-B-cell leukaemia transcription factor 1; SMAD3, Mothers against decapentaplegic homologue 3; t(4;14), translocation (4;14).

In addition, emerging evidence has identified NCOR2, a chromatin remodelling factor, as a key contributor to multidrug resistance in MM, including resistance to IMiDs. NCOR2 was shown to form a repressive complex with the nucleosome remodelling and deacetylase (NuRD) complex, which binds directly to the CD180 promoter and suppresses its transcription, resulting in a reduction in MYC [69]. IMiD-resistant cell models showed a downregulation in

NCOR2 and CD180, with a subsequent upregulation in MYC [69].

Overcoming IMiD resistance in the clinic

As elaborated above, many cell intrinsic and extrinsic mechanisms drive clinical resistance to IMiD and IMiD-based combination therapy in myeloma patients. As a result, when patients are exposed to frontline

multiagent therapy and subsequently relapse, both the tumour and its resident tumour microenvironment are significantly altered. To address clinical resistance to IMiDs and IMiD-based combination regimens, we must appreciate the evolving therapeutic landscape. The current options to therapeutically overcome IMiD resistance and some potential clinical combinations that could be considered are summarised in Fig. 4A,B, respectively.

Myeloma care is rapidly changing worldwide with the expanding use of the triplet and adoption of quadruplet-based regimens in NDMM (Fig. 4B). Triplets such as daratumumab (D)-lenalidomide (R)-dexamethasone (d) [DRd] or lenalidomide (R)-bortezomib (V)-dexamethasone (d) [RVd] are established and routinely used followed by transplant and lenalidomide maintenance in transplant-eligible patients. Notably, RRMM patients treated with the triplet regimen of daratumumab, pomalidomide and low-dose dexamethasone showed a coordinated immune response whereby the depletion of NK and B cells by daratumumab treatment was counterbalanced by increased proliferation and activation of NK and CD8⁺ T cells along with a shift from naïve to effector memory T cells induced by pomalidomide treatment [34]. This combination showed similar and potent immunostimulatory effects in len-refractory and nonrefractory patient subgroups [34].

More recently, clinical studies of quadruplet-based regimens using DVRd (PERSEUS study), Isatuximab (Isa)-Carfilzomib (K)-Rd [Isa-KRd] (MIDAS study), and Isa-VRd (IMROZ study) have improved clinical outcomes with estimated median PFS between 100 and 200 months (median not reached) across these regimens from frontline therapy [70–73]. These studies also demonstrate MRD-guided and a time-limited maintenance approach with lenalidomide and anti-CD38 antibody as a possible new standard of care.

Developing effective therapeutic strategies against relapsed disease in these patients is critical to improving outcomes. Immunotherapies as a class are emerging as a core component of myeloma care in relapse and there are multiple options based on new target and therapeutic modalities to engage these targets (Fig. 4A). Both monotherapy and combinations of immunotherapeutic approaches against these targets are currently reporting improved clinical outcomes in comparison to historical standard of care. Immunotherapeutic target choice is a key area of research and BCMA, GPRC5D or FcRH5 are competitive in this space. Following target selection (e.g. BCMA), currently it is crucial to consider what modality of single agent therapy is to be selected between bispecific T-cell engagers or CAR T.

Understanding the benefit of properly sequencing the anti-BCMA therapies would be crucial, especially for CAR T-based therapies. Alternatively, combination therapies are also a current option for anti-BCMA-ADC. In the United Kingdom, belantamab mafodotin has received approval in combination with both pomalidomide-dex and bortezomib-dex. For the T-cell engagers, it is reasonable to pair them with immunomodulatory drugs over proteasome inhibitors due to established mechanistic synergy. Trials are underway combining T-cell engagers with IMiDs or CELMoDs such as the phase I trial (NCT06348108) evaluating the combination of talquetamab (Tal) with iberdomide and dex in RRMM patients, MonumentAL-6 phase III trial (NCT06208150) comparing Tal-pomalidomide combination with Tal-teclistamab, OPTIMMAL trial (NCT06461988) evaluating the combination of Tal-lenalidomide as maintenance therapy [74].

Data available to date do not clarify if CELMoD (Iberdomide and Mezigdomide) will be clinically effective to replace pomalidomide as part of new triplet combinations in early relapse. Mezigdomide and Iberdomide demonstrate significantly stronger binding to CRBN than earlier IMiDs, with an IC₅₀ of 0.03 μM and 0.06 μM, respectively, compared to 1.5 μM and 1.2 μM for lenalidomide and pomalidomide [5]. This > 20-fold higher affinity results in faster degradation of CRBN substrates, as shown by the more rapid protein reduction observed with 0.1 μM Iberdomide versus 1 μM pomalidomide. Both mezigdomide and iberdomide have demonstrated clinical activity in heavily pretreated RRMM, including patients with triple-class refractory disease who had previously received lenalidomide, pomalidomide, proteasome inhibitor or anti-CD38 therapies [54,75]. The enhanced activity may be attributed to both greater CRBN-binding strength and potentially more efficient recruitment and function of the E3 ubiquitin ligase complex.

In the CC-220-MM-001 trial, Iberdomide induced strong substrate protein degradation even in IMiD-refractory patients and those with low CRBN levels. Immunohistochemical analysis of 114 bone marrow biopsies showed that CRBN remained detectable in nearly all CD138⁺ cells even in patients refractory to one or both IMiDs. No significant differences in CRBN or Aiolos expression were observed based on IMiD-refractory status, triple-class resistance or prior lines of therapy, though a slight decrease in CRBN was noted in patients recently treated with pomalidomide. Responders with CRBN genetic alterations had similar progression-free survival (10.9 months) and duration of response (9.5 months) to those without such alterations [15].

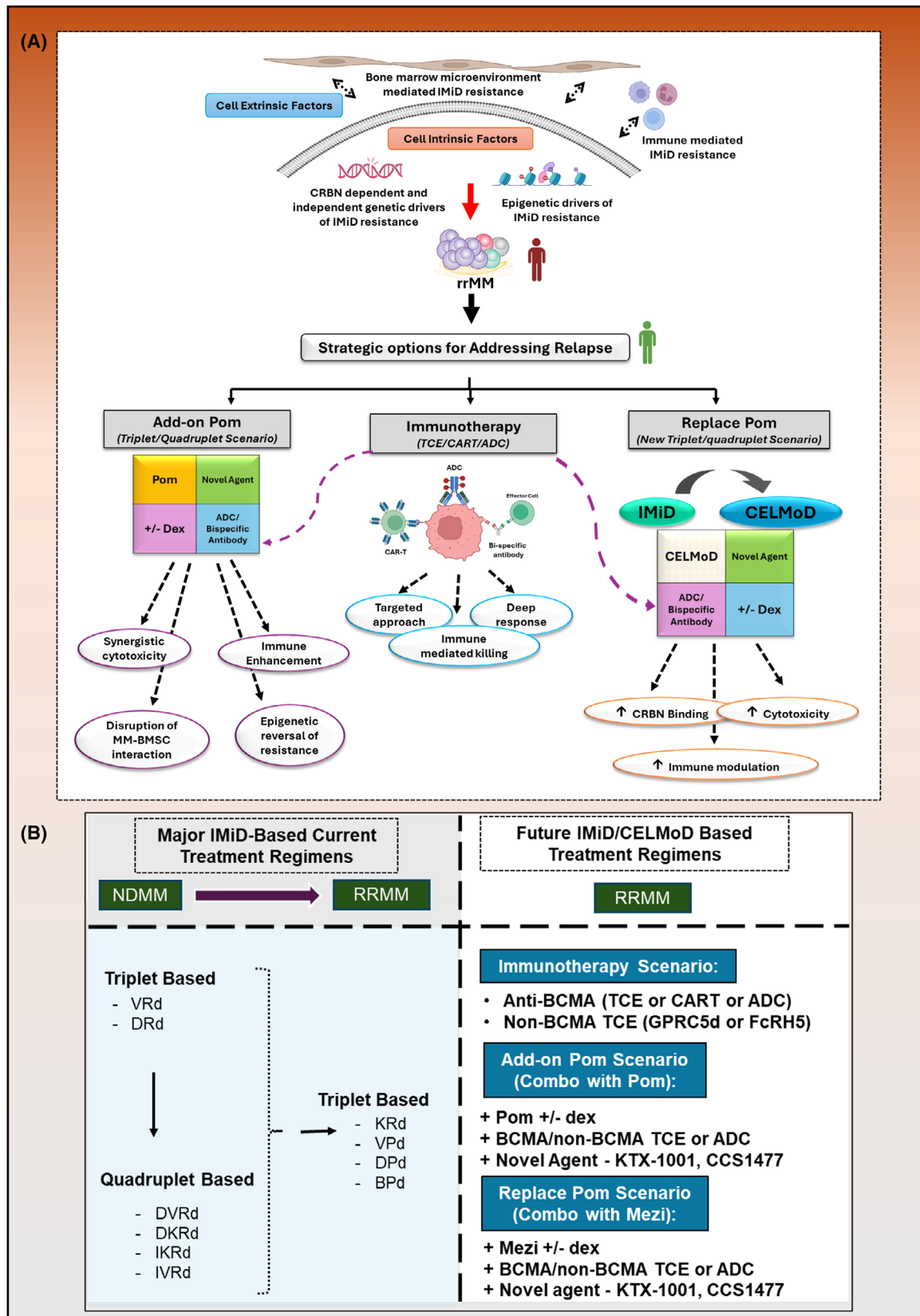


Fig. 4. Current and emerging strategies to overcome resistance to IMiD and IMiD-based regimens in relapsed myeloma. (A) Sources of resistance and therapeutic strategies in relapse. Various cell intrinsic genetic and epigenetic factors as well as cell extrinsic factors such as adhesion to bone marrow microenvironment and immune-mediated factors drive IMiD resistance in MM. The current therapeutic strategies for reversing resistance are (i) immunotherapy using bispecific antibody or CAR T or ADC (ii) combination triplet- Add-on to Pom or Quadriplet where a combination of (A) Pom, (B) a novel agent (e.g. epigenetic resensitiser) that can reverse/reprogramme resistance mechanisms, (c) Immunotherapy agents such as ADC (e.g. belantamab) or TCE that can synergise and enhance cell killing (D) with or without dexamethasone. Collectively, these strategies address RRMM through a multifaceted therapeutic approach. (iii) Replace-Pom (Triplet combination) where Pom can be replaced with a more potent drug such as a Mezigdomide in combination with approved agents as in (ii). (B) Potential combination approaches for approved agents in relapse with IMiDs and CELMoDs. Various combinations in triplet and quadriplet regimens will establish key 'winning' combinations based on safety and efficacy data. ADC, antibody–drug conjugate; BCMA, B-cell maturation antigen; BMSC, bone marrow stromal cell; BPd, belantamab mafodotin–pomalidomide–dexamethasone; CART-T, chimeric antigen receptor T cell; CBP, CREB-binding protein; CELMoD, cereblon E3 ligase modulator; CRBN, cereblon; Dex, dexamethasone; DPd, daratumumab–pomalidomide–dexamethasone; DRd, daratumumab–lenalidomide–dexamethasone; DVd, daratumumab–bortezomib–dexamethasone; DVRd, daratumumab–bortezomib–lenalidomide–dexamethasone; DKRd, daratumumab–carfilzomib–lenalidomide–dexamethasone; EP300, E1A-binding protein p300; FcRH5, Fc receptor-homologue 5; GPRC5D, G protein-coupled receptor class C group 5 member D; IMiD, immunomodulatory drug; IKRd, isatuximab–carfilzomib–lenalidomide–dexamethasone; IVRd, isatuximab–bortezomib–lenalidomide–dexamethasone; KRd, carfilzomib–lenalidomide–dexamethasone; MM, multiple myeloma; NDMM, newly diagnosed multiple myeloma; NK, natural killer; Pom, pomalidomide; RRMM, relapsed/refractory multiple myeloma; TCE, T-cell engager; TCR, T-cell receptor; VRd, bortezomib–lenalidomide–dexamethasone; VPd, bortezomib–pomalidomide–dexamethasone.

Mezigdomide, the most potent drug of the class, has shown superior clinical activity in Phase I trials and could be a preferred choice to combine with other agents [54]. Interestingly, Mezigdomide is being tested in combination with Carfilzomib/Bortezomib and dexamethasone in RRMM patients who had more than one line of therapy and are lenalidomide resistant (SUCCESSOR 1 and 2 trials) [76,77]. If approved, this combination will provide an option to replace pomalidomide in early relapse. Further therapeutic options on the improvement on the T-cell engagers or CAR Ts would be to add a CELMoD in combination with other novel agents. For belantamab mafodotin, adding novel combinations including CELMoDs would be logical, to improve upon currently licenced therapeutic combinations.

In parallel with advances in CELMoDs and immune-based combinations, increasing attention has focused on biomarker-driven strategies, particularly the exploitation of BCL-2 dependence in t(11;14) multiple myeloma using venetoclax. The t(11;14)(q13;q32) translocation, which occurs in approximately 15–20% of multiple myeloma (MM) cases, identifies a biologically distinct subgroup marked by elevated BCL-2 expression and increased reliance on BCL-2-dependent anti-apoptotic signalling [78]. Consistent with this biology, venetoclax has demonstrated preferential activity in t(11;14) relapsed/refractory MM (RRMM), including as monotherapy in a cohort of 30 patients (including those who were double refractory to lenalidomide and bortezomib) where an overall response rate (ORR) of 40% was observed, significantly exceeding responses in non-t(11;14) patients ($n = 36$) [79].

Enhanced efficacy has been reported with combination approaches: in the phase I study NCT03314181, venetoclax plus daratumumab and dexamethasone (VenDd) in t(11;14) RRMM and venetoclax plus bortezomib (VenDVd) in cytogenetically unselected RRMM achieved ORRs of 96% (all \geq VGPR) and 92% (79% \geq VGPR), respectively, further supporting the clinical activity of venetoclax-based combinations, particularly in t(11;14) disease [80]. These findings are reinforced by a large retrospective analysis of 232 MM patients treated at the Mayo Clinic between January 2015 and December 2023, in which t(11;14) patients ($n = 190$) achieved an ORR of 64% and a median PFS of 11.8 months; notably, inferior PFS was associated with the presence of additional high-risk cytogenetic abnormalities [81]. Importantly, the majority of patients in this real-world cohort were refractory to lenalidomide (75%) and pomalidomide (61%), underscoring the activity of venetoclax in heavily pretreated and IMiD-refractory populations [81]. Sonrotoclax (BGB-11417) is a next-generation, highly selective and more potent BCL-2 inhibitor than venetoclax. Preliminary data suggest encouraging activity, with the sonrotoclax plus carfilzomib and dexamethasone cohort (BGB-11417-105) achieving an 84% ORR and a 32% CR/sCR rate in heavily pretreated patients with t(11;14) relapsed/refractory multiple myeloma [82].

Given the role of cullin neddylation and COP9-mediated regulation of CRL4^{CRBN}, inhibition of the neddylation pathway has been explored as a potential therapeutic strategy in multiple myeloma. Preclinical studies have shown that the NEDD8-activating enzyme inhibitor pevonedistat (MLN4924) can

enhance NK cell-mediated cytotoxicity by increasing surface expression of the NKG2D ligands MICA and MICB on myeloma cells [83]. In this context, neddylation inhibition may cooperate with IMiDs via increased CRBN expression to further augment MICA upregulation. However, while these findings highlight an immunomodulatory role for neddylation targeting, early phase clinical trials on pevonedistat demonstrate modest clinical activity and its clinical significance in IMiD-resistant multiple myeloma has yet to be defined [84].

In addition, as an add-on approach, trials looking for mechanisms for resensitisation to IMiD have described the use of epigenetic drugs as a possible alternative. After culturing lenalidomide-resistant (–LR) and pomalidomide-resistant (-PR) human myeloma cell lines, Dimopoulos *et al* showed that after exposure of these cell lines to 5-azacytidine and EPZ-6438, chromatin accessibility changes and expression of SMAD3 were restored, and resensitisation of cells to both lenalidomide and pomalidomide was observed [61]. Also, EZH2 represents a compelling therapeutic target, and several studies are currently investigating its inhibition either as monotherapy or in combination with established agents such as bortezomib or lenalidomide [61].

Among the novel agents and mechanisms, two epigenetic compounds in the clinic are noteworthy. KTX-1001, a selective NSD2 inhibitor currently in clinical trials, represents a promising strategy to overcome IMiD resistance in NSD2^{high} and t(4;14)-positive relapsed and refractory MM [85]. t(4;14) chromosomal translocation is found in approximately 15–19% of MM cases. This translocation juxtaposes the *NSD2* gene encoding a histone methyltransferase specific for H3K36 near a potent super-enhancer region, resulting in its overexpression. Elevated NSD2 activity promotes transcriptional changes that enhance cell proliferation and adhesion, thereby contributing to a drug-resistant phenotype [86]. The t(4;14) translocation in MM has been associated with early relapse following immunomodulatory drug (IMiD) therapy, highlighting its role in promoting treatment resistance [4]. Functional studies have demonstrated that *NSD2* knockdown in MM cell lines significantly impairs their ability to adhere to the extracellular matrix (ECM) and leads to a marked reduction in clonogenicity and proliferation [87]. In preclinical resistant models, KTX1001 shows potent anti-adhesive effects resulting in increased sensitivity to anticancer agents [88]. These findings underscore the therapeutic potential of targeting NSD2-driven epigenetic alterations. Notably, mechanism driven combination of KTX1001 with belantamab and pomalidomide

in high NSD2 or t(4;14) lenalidomide-refractory patients could be a potential approach.

Additionally, and as previously discussed, the ETV4/p300/BRD4 axis mediated upregulation of MYC and IRF4 plays a crucial role in IMiD resistance and because of this, there is interest in exploring ways to block these complementary pathways. One promising approach is using epigenetic agents such as Inobrodib (CCS1477), which blocks p300 and its partner protein CBP. Inobrodib has shown strong effects against myeloma cells and works even better when combined with IMiDs like pomalidomide, offering a potential new strategy to overcome IMiD resistance [89,90]. SGC-CBP30, a CBP/EP300 bromodomain inhibitor which targets the IRF4/c-Myc axis resensitised MM cells to lenalidomide, effectively restoring drug response [19]. Notably, SGC-CBP30 also reactivated lenalidomide sensitivity in two additional resistant cell lines with low but detectable CRBN levels, indicating a therapeutic strategy where CRBN is present but functionally insufficient, demonstrating scientific rationale for developing p300 inhibitors in IMiD-resistant myeloma [19]. These novel agents can potentially open an alternative quadruplet approach replacing CD38 which is used front-line with new immunotherapeutic targets (BCMA, GPRC5D and FcRH5).

As such, the combination of (i) immunotherapeutic agents targeting surface membrane proteins (BCMA, GPRC5D and FcRH5) (ii) IMiD (pomalidomide) (iii) an IMiD resensitising novel agent with or without (iv) dexamethasone has robust strategic rationale for clinical testing. In this context, novel therapies such as the NSD2 inhibitor or CBP/EP300 inhibitor which have the potential to resensitise myeloma cells to immunomodulatory agents hold significant promise and potentially could be used as the IMiD resensitising agent in the quadruplet therapeutic strategy. However, the current evidence is limited to preclinical studies and early phase clinical trials, and further clinical evaluation is required to establish efficacy and safety. Overall, in early relapse, therapeutically augmenting pomalidomide by adding novel agents to reverse IMiD-resistant biology will open up a space for exploring cost effective, clinically competent treatment combinations. If successful, these novel agents could augment the licenced triplets in early relapse.

Author contributions

MF and DN are listed as cofirst authors and contributed equally to this manuscript. MF and DN conceived the review, conducted the literature search, synthesised the data and wrote the initial draft of the manuscript.

KR contributed to the writing of the clinical sections of the review and, together with AT, provided critical intellectual input and contributed to the interpretation of the literature. AT provided overall scientific supervision and critical guidance during the development, writing and revisions of the manuscript. All authors contributed to and approved the final version of the manuscript.

Acknowledgements

This work was supported by Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford. The authors thank colleagues and collaborators for helpful discussions and critical feedback during the preparation of this manuscript.

Conflict of interest

AT is funded by research grants from K36 Therapeutics, Cell Centric and Oxford Translational Myeloma Centre. The other authors declare no conflict of interest.

Peer review

The peer review history for this article is available at <https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/febs.70599>.

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