# Lenalidomide use in multiple myeloma (Review)

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**Abstract.** Lenalidomide is a second-generation new immunomodulatory medication used to treat multiple myeloma (MM). Its mechanism of action involves affecting the expression of vascular endothelial growth factor, interleukin-6, cytochrome *c*, caspase-8, as well as other factors including immunological modulation and the direct killing of cells, among others, rendering it a fundamental medication, useful for the treatment of MM. Combining lenalidomide with other medications such dexamethasone, bortezomib, ixazomib, carfilzomib and daratumumab can markedly alleviate MM. When autologous-hematopoietic stem cell transplantation (ASCT) cannot be utilized to treat newly diagnosed individuals with MM (NDMM), monotherapy maintenance following lenalidomide and dexamethasone may be employed. Following ASCT, single-agent maintenance with lenalidomide can be performed as an additional treatment. The combination of bortezomib and lenalidomide has been demonstrated to be associated with favorable response rates, tolerable toxicity, and therapeutic benefits although caution is warranted to prevent the onset of peripheral neuropathy with its use. A new-generation oral drug with an excellent safety profile, ixazomib, is more practical and therapeutically applicable in relapsed refractory MM. However, the frequent occurrence of cardiovascular events, hematocrit, and infections with it require flexible adjustment in its clinical application. Carfilzomib produces a rapid and profound response in patients with NDMM eligible for transplantation, but its cardiovascular side effects need to be closely monitored. The primary aim of the present review was to examine the pharmacological properties and pharmacokinetics of lenalidomide, as well as the efficacy and safety of lenalidomide-based treatments with reference to data from clinical trials and real-world studies.

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**Contents**



## 1. Introduction

Multiple myeloma (MM) has become the second-most common hematological malignancy, accounting for 10% of all hematological malignancies (1). MM can be identified by serum immunofixation electrophoresis and the features of MM are the buildup of clonal proliferative malignant plasma cells in the bone marrow as well as the release of monoclonal immunoglobulin (M protein). Anemia, hypercalcemia, osteolytic lesions and renal insufficiency are some of its clinical manifestations (which are commonly referred to as 'CRAB' symptoms, denoting hypercalcemia, renal failure, anemia, and bone destruction) (2). In the past two decades, a notable development has been made in the treatment of MM. MM treatment has been linked to extremely positive outcomes owing to the rapid uptake of autologous hematopoietic stem cell transplantation, the advent of immunomodulatory medications (IMids), and proteasome inhibitors (PIs), with small molecule antitumor medications, such as dexamethasone and other glucocorticoids (3,4). However, MM is considered a fatal illness (5). The most important concerns include improving patient prognoses, decreasing adverse drug reactions, extending the lives of patients, and enhancing their quality of life. Myeloma cells may die directly or indirectly with the use of an immunomodulator (6), and MM cells may be indirectly affected by changes to the bone marrow microenvironment. Thalidomide was the first novel medication to be authorized by the US Food and Drug Administration (FDA) for the management of MM in 1999. It has been reported to inhibit tumor necrosis factor production, MM cell growth, and anti-angiogenesis, albeit its therapeutic efficacy is significantly hampered by the neurological side effects of thalidomide, which include drowsiness and peripheral neuropathy (7). Lenalidomide and pomalidomide are two new IMiDs that were created and used as the result of preclinical studies and subsequent clinical trials. Both

could be utilized in MM therapy regimens. Lenalidomide was the first thalidomide analog to be marketed, and it was more potent than its parent drug despite only two differences at the molecular level: The addition of an amino group at position four of the phthaloyl ring and the removal of a carbonyl group from the phthaloyl ring (8). Lenalidomide was developed by Celgene Corporation (now part of Bristol Myers Squibb) in the U.S. and was approved by the FDA on December 17, 2005 for fast-track marketing for the treatment of anemia caused by myelodysplastic syndromes associated with deletions of chromosome 5q, and has since been approved for a variety of indications, including MM (9). Lenalidomide, which is a structural and functional analog of thalidomide, can enhance the immunomodulatory, anticancer, and tolerability properties of thalidomide (10). Lenalidomide has been a global bestseller for numerous years since its introduction to the market, but with the entry of generics into the market, there has been a significant decrease in the price of lenalidomide, rendering it available to a wider range of patients.

## 2. Pharmacological mechanism

Lenalidomide, a second-generation imine medication, is relatively less toxic and with a higher potency when compared with thalidomide (11). Lenalidomide has been demonstrated to exhibit an array of effects and mechanisms of action that can contribute to its antitumor properties (12) (Fig. 1).

*Non-immune regulation*. Vascular endothelial growth factor (VEGF) is inhibited by lenalidomide, which makes it challenging for tumor cells to form blood vessels. It blocks VEGF and can prevent the production of interleukin-6 (IL-6) (13). As per a previous study, IL-6 is a cytokine with a wide range of inflammatory and immune regulatory properties (14). In addition, IL-6 can promote the progression of MM. Lenalidomide has also been linked to the growth arrest of myeloma cells in the G1 phase (15,16), and this direct cytotoxicity is associated with a decrease in IL-6 production. However, the precise mechanism underlying this effect is unknown.

A well-known mitochondrial protein, cytochrome *c*, can maintain life by transporting electrons to the respiratory chain and allowing continued ATP production. Cell survival and apoptosis significantly depend on cytochrome *c* (17). By influencing the release of cytochrome *c*, lenalidomide can impact the apoptosis of MM cells (18). In addition, by altering caspase-8, lenalidomide can also affect the apoptosis of MM cells (19,20).

Lenalidomide can directly induce MM cell apoptosis and cell cycle arrest. Previous studies have demonstrated several downstream changes after lenalidomide treatment, which may be associated with the direct anti-myeloma activities of the drug, in addition to the previously mentioned mechanism. These changes include the upregulation of *P21* expression (21), nuclear factor-κB (NF-κB) deactivation (22), CCAAT/enhancer binding protein-β (C/EBP-β) downregulation (23), and caspase-8 inhibition or genetic depletion (20).

By suppressing the production of surface-adhesion molecules on both MM cells and bone marrow stromal cells (BMSCs), lenalidomide prevents contact between them (24). Lenalidomide can prevent MM-related bone damage by either directly preventing osteoporosis development or by indirectly decreasing the tumor load. The effect of lenalidomide on osteoclasts can slow the development of MM, as osteoclasts have been demonstrated to increase MM growth and medication resistance (25).

*Immune regulation*. In contrast to other anti-MM medications, lenalidomide possesses immunoregulatory effects. First, it can improve the co-stimulation of $CD4^+$ and $CD8^+$ T cells (26). When compared to the first-generation IMiD thalidomide, lenalidomide increases T-cell proliferation and the production of IL-2 and γ-interferon (27). Lenalidomide can also inhibit regulatory T cells, which are a subset of immunosuppressive T cells, that are important for self-tolerance and the reaction of the the immune system to tumor cells (28). With the natural killer (NK) cell-surface markers, lenalidomide increases the activity of NK and T lymphocytes (NKT) (29). In patients with MM who have received suitable treatment, NK cell proliferation is promoted, an important pharmacological effect of lenalidomide. It has also been demonstrated that the ability of human peripheral blood mononuclear cells (PBMC) to produce the pro-inflammatory cytokines tumor necrosis factor-α (TNF-α), IL-1, IL-6, and IL-12 is inhibited by the effect of lenalidomide (30). Lenalidomide reduces the immune checkpoint inhibitor programmed death-1 (PD-1) expression on both T and NK cells in patients with MM; it also reduces the expression of PD-1 and programmed death ligand-1 (PD-L1) on MM cells (31-33).

## 3. Pharmacokinetics

Oral lenalidomide is promptly and effectively absorbed (>90% of the dose) under fasting conditions as per the results of a control study conducted on healthy volunteers (34). Drug oral absorption effectiveness can be affected by food type. The maximum concentration ($C_{max}$) and the area under the concentration-time curve (AUC) both decreased by 20-50%, respectively, when combined with a high-fat diet. The increase in AUC and $C_{max}$ was dose-dependent, with minimal to moderate inter-individual variability in plasma exposure. After 24 h, ~80% (34,35) of the oral dose was eliminated in the urine. Lenalidomide has a very brief (3-4 h) half-life and it does not build up in plasma when administered repeatedly.

Renal function is the only significant factor affecting lenalidomide plasma exposure as per a study that assessed the dose range of patients with MM (36). These researchers also confirmed that plasma AUC and $C_{max}$ were proportional to the dose used in the treatment of patients with MM, without exhibiting any differences when compared with the healthy volunteers.

## 4. Clinical research and application

The application of lenalidomide for the treatment of MM was approved by the FDA in March 2006. Since then, clinical trials and real-world studies (37-61) on the single-drug (R) treatment of lenalidomide and the combination of lenalidomide and dexamethasone (RD) as well as various treatment schemes based on the combination of RD have been widely conducted. These studies aimed to confirm the therapeutic efficacy of

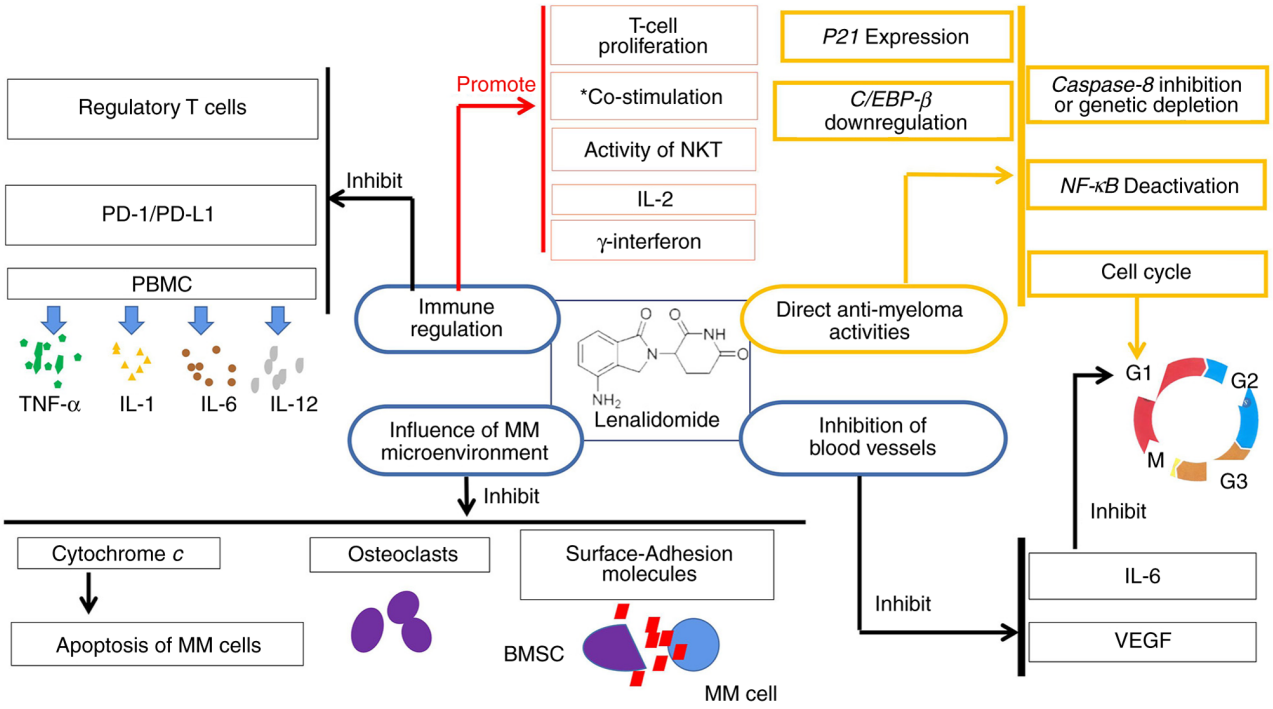


Figure 1. Pharmacological mechanism of lenalidomide. *Co-stimulation of $CD4^+$ and $CD8^+$ T cells. MM, multiple myeloma; VEGF, vascular endothelial growth factor; IL, interleukin; NKT, natural killer cells and T lymphocytes; C/EBP-β CCAAT/, enhancer binding protein-β; NF-κB, nuclear factor-κB; BMSC, bone marrow stromal cell; PBMC, human peripheral blood mononuclear cell; TNF-α, tumor necrosis factor-A; PD-1 programmed death-1; PD-L1, programmed death ligand-1.

lenalidomide in patients with newly diagnosed MM (NDMM) or relapsed refractory MM (RRMM) (Table I).

*Application of lenalidomide alone and with dexamethasone in MM*. The conventional course of treatment for young patients with NDMM is autologous-hematopoietic stem cell transplantation (ASCT) after effective induction therapy (62). Lenalidomide was authorized by the FDA in 2017 for use as a maintenance therapy for patients with MM following ASCT (63).

A clinical study (NCT02215980) (37) showed the effectiveness and viability of continuing 10 mg lenalidomide monotherapy (RD-R) daily in comparison with continuous RD after receiving dose/schedule-adjusted RD in elderly, moderately healthy individuals with NDMM who did not undergo ASCT. Additionally, the data revealed that low-dose lenalidomide may be used without dexamethasone after nine cycles of RD, and the outcomes were comparable with those of continuous RD.

According to a randomized controlled trial by Lund *et al* (38), a single medication, lenalidomide, may be useful for the prolonged treatment of RRMM once patients exhibit preliminary responsiveness to the induction of the RD regimen. In a subsequent phase 2 clinical trial (NCT01450215), patients with RRMM who responded to first-line RD in an observational study (NCT01430546) received up to 24 cycles of R or RD as extended treatment. The median reaction time in the observational study was 1.7 months, with a range of 0.6-9.6 months. In these two investigations, 11% of the patients experienced a complete response (CR) to all treatments received. Very good partial response (VGPR) and partial response (PR) were observed in 31 and 38% of the patients, respectively. In the subset of patients who were not enrolled in the second phase of the experiment, the equivalent remission rates were 3, 18, and 39%, respectively. RD did not develop within the median time to progress (TTP) during a median follow-up of 36 months for the surviving patients; RD-R was 24.9 months (95% CI, 12.5-not calculable; P<0.001).

*Application of lenalidomide combined with bortezomib and dexamethasone in MM*. The first PI to receive FDA approval was bortezomib (V) (64). It can connect to the amino acid residues of the 26S proteasome and block the ubiquitin-proteasome system pathway, thereby preventing the breakdown of protein products involved in fighting tumors (65). Bortezomib is indispensable in the management of MM. In a phase 3 study and real world research data (39,66), the combination of bortezomib and RD (VRD) was established to be associated with an excellent response rate, manageable toxicity, and therapeutic advantages.

A phase 3 study (S0777) (39) revealed that when VRD was used instead of RD alone, progression-free survival (PFS) and overall survival (OS) were significantly improved in newly diagnosed patients without immediate ASCT. Additionally, a study by Medhekar *et al* (66) which analyzed patient characteristics and treatment outcomes, revealed a median PFS of 26.5 months that was shorter than the pivotal median PFS of 43 months achieved in the SWOG S0777 study (39). According to a meta-analysis (41), PFS was continually increased with lenalidomide treatment compared with conventional therapy alone.

Table I. Use of lenalidomide in clinical trials and real-world studies in MM.

| Lenalidomide-based treatment scheme | Patients | Key trials or studies | Efficacy | Notable adverse effects | (Refs.) |
|---|---|---|---|---|---|
| RD-R | NDMM | Clinical study (NCT02215980) | EFS, 10.4 months<br>Median PFS, 20.2 months<br>OS rate in 3 years, 74% | Neutropenia, 21%<br>Infection, 10%<br>Dermatosis, 7% | (37) |
| RD | | | EFS, 6.9 months<br>Median PFS, 18.3 months<br>OS rate in 3 years, 63% | Neutropenia, 18%<br>Infection, 12%<br>Dermatosis, 3% | |
| Not responded to first-line RD | RRMM | Randomized controlled trial by Lund *et al*[a] (NCT01430546) (NCT01450215) | CR, 3%<br>VGPR, 18%<br>PR, 39% | Data not available | (38) |
| RD-R vs. RD | | | CR, 11%<br>VGPR, 31%<br>PR, 38%<br>TTP (24.9 months vs. not reached) | Neutropenia and thrombocytopenia were more frequent in RD-R | |
| VRD | NDMM | Phase 3 study (S0777) | Median PFS, 43 months<br>Median OS, 75 months<br>CR, 16%<br>≥PR, 82% | ≥ Grade 3 AEs, 82% | (39) |
| RD | NDMM | | Median PFS, 30 months<br>Median OS, 64 months<br>CR, 8%<br>≥PR, 72% | ≥ Grade 3 AEs, 75% | |
| VRD | NDMM | Real world study by Medhekar *et al* | Median PFS, 26.5 months | Data not available | (66) |
| Lenalidomide-based treatment | NDMM | Meta-analysis | PFS was increased compared with conventional therapy alone | Gastrointestinal problems (RR 2.36)<br>Thromboembolic events (RR 2.55)<br>Second primary cancers (RR 2.61) | (41) |
| VRD + ASCT | NDMM | Joseph *et al* and McCaughan *et al* | Median PFS, 63 months<br>Median OS, 123.4 months | Data not available | (42,43) |
| CD38 monoclonal antibody, isatuximab and VRD | NDMM | Part 1 of a phase 3 trial (NCT03617731) | MRD negativity, 50% | Neutropenia, 23%<br>Infections, 12% | (44) |
| Dara-VRD<br>VRD | NDMM | Griffin trial by Voorhees *et al* (NCT02874742)[b] | sCR, 62.6%<br>MRD negativity, 51.0%<br>sCR, 45.4%<br>MRD negativity, 20.4% | Grade 3/4 hematologic AEs and infections were more common with Dara-VRD, but infection rates were similar | (45) |
| VRD | NDMM | Attal *et al* (NCT01191060) | Median PFS, 36 months<br>CR, 48% | Neutropenia, 92%<br>Gastrointestinal disorders, 28%<br>Infections, 20% | (46) |
| VRD + ASCT + VRD | | | Median PFS, 50 months<br>CR, 59% | Neutropenia, 47%<br>Gastrointestinal disorders, 7%<br>Infections, 9% | |

Table I. Continued.

| Lenalidomide-based treatment scheme | Patients | Key trials or studies | Efficacy | Notable adverse effects | (Refs.) |
|---|---|---|---|---|---|
| VRD + ASCT | | | ORR, 100%<br>CR + sCR, 73.3%<br>VGPR, 95.6%<br>PFS rate in 2 years, 84.5%<br>OS rate in 2 years, 100% | | (46) |
| VRD | RRMM | Phase 2 study | ORR, 86%<br>VGPR, 66%<br>Median PFS, 35.1 months | Peripheral neuropathy, 62%<br>≥ Grade 3 AEs, 1.9% | (47) |
| VRD | RRMM | Phase 2 study (JCOG0904) | PFS rate in 1 year, 45.5%<br>OS rate in 3 years, 70.0% | Thrombocytopenia, 54.5%<br>Sensory peripheral neuropathy, 22.7% | (48) |
| Weekly IRD | NDMM | Integrated analysis of four phase I/II studies[c] | Median PFS, 25.8 months<br>OS rate in 3 years, 96% | Data not available | (49) |
| IRD | NDMM | Kumar *et al* | ORR, 80%<br>CR, 32%<br>VGPR, 63%<br>Median PFS, 29.4 months | ≥ Grade 3 AEs, 68% | (50) |
| IRD + ASCT | NDMM | Clinical trial (NCT01850524) | ORR, 100%<br>CR, 44%<br>VGPR, 76%<br>Median PFS, 29.4 months | ≥ Grade 3 AEs, 86% | (51) |
| IRD | | | CR, 26%<br>VGPR, 63%<br>Median PFS, 35.3 months | ≥3 Grade TEAEs 88%<br>Severe TEAEs, 66%<br>Mortality, 8% | |
| Ixazomib and lenalidomide | NDMM[d] | Patel *et al* | Median PFS, 73 months<br>CR/sCR, 43% | ≥3 Grade hematologic AEs<br>Neutropenia, 46.88%<br>Leukopenia, 20.31%<br>Thrombocytopenia, 15.63% | (52) |
| Ixazomib and lenalidomide | | | Median PFS, 73 months<br>CR/sCR, 43% | ≥3 Grade nonhematologic AEs<br>Lung infections, 26.6%<br>Diarrhe, a 12.5%<br>Rash (maculopapular), 12.5% | |
| IRD | RRMM | Phase 3 clinical trial (NCT01564537) | Median OS, 53.6 months | ≥3 Grade AEs, 80.1%<br>Serious AEs, 56.8% | (53) |
| IRD | RRMM | Multicenter real-world study[e] | Median PFS, 11.9 months (IgG type 19.3 months)<br>Median OS, not attained | Data not available | (54) |
| Dara-KRD | NDMM | Open phase 1b research | ORR, 95%<br>CR, 67%<br>PR, 86% | Diarrhea:<br>• Any grades AEs, 68%<br>• ≥3 Grade AEs, 18%<br>Lymphopenia:<br>• Any grades AEs, 64%<br>• ≥3 Grade AEs, 59%<br>Cough:<br>• Any grades AEs, 59%<br>• ≥3 Grade AEs, 5% | (55) |

Table I. Continued.

| Lenalidomide-based treatment scheme | Patients | Key trials or studies | Efficacy | Notable adverse effects | (Refs.) |
|---|---|---|---|---|---|
| VRD | NDMM | Phase 3 clinical trial (NCT01863550) | Median PFS, 34.4 months | Upper respiratory tract infection:<br>• Any grades AEs, 59%<br>• ≥3 Grade AEs, 5%<br>Fatigue, 6%<br>Hyperglycemia, 4%<br>Peripheral neuropathy, 8%<br>Dyspnea, 2%<br>Diarrhoea, 5%<br>Thrombotic events, 2%<br>Serious AEs, 22% | (56) |
| KRD | | | Median PFS, 34.6 months | Fatigue, 6%<br>Hyperglycemia, 6%<br>Peripheral neuropathy, <1%<br>Dyspnea, 7%<br>Diarrhoea, 3%<br>Thrombotic events, 5%<br>Serious AEs, 45% | |
| KRD + ASCT + KRD | NDMM | Phase 2 multicenter investigation (NCT01816971) | sCR, 76%<br>PFS rate in 5 years, 72%<br>OS rate in 5 years, 84% | Neutropenia, 34%<br>Lymphocytopenia, 32%<br>Infection, 22%<br>Cardiac events, 3% | (57) |
| KRD + ASCT + R | NDMM | Phase 2 study (NCT02405364) | Median PFS, 56.4 months<br>CR, 64.3%<br>sCR, 61.9% | Hematogenous, 74%<br>Infectious, 22% | (58) |
| KRD<br>RD | RRMM | Randomized controlled study (NCT01080391) | Median OS, 48.3 months<br>Median OS, 40.4 months | ≥3 Grade AEs, 87%<br>≥3 Grade AEs, 83.3% | (59) |
| KRD | RRMM | Multicenter real-world investigation | ORR, 68.2%<br>Median PFS, 8.8 months<br>Median OS, 29 months | ≥3 Grade AEs, 48% | (60) |
| KRD | RRMM | Study on the use of KRD reinduction | VGPR, 57% | Data not available | (61) |
| KRD + HDCT/ASCT | | | VGPR, 77%<br>Median PFS, 23.3 months | | |

[a]In the subsequent phase 2 clinical trial (NCT01450215), patients with RRMM who responded to first-line RD in the observational study (NCT01430546) received R or RD as extended treatment. [b]In the Griffin trial (NCT02874742), patients were randomized 1:1 to Dara-VRD or VRD induction (4 cycles), ASCT, Dara-VRD or VRD consolidation (2 cycles), and R or R plus Dara maintenance (26 cycles). [c]The data in this table from three phase I/II studies NCT01217957 and NCT01383928. [d]The patients had received ASCT. [e]A total of 66.7% of patients had the IgG type. RD-R, lenalidomide monotherapy after receiving RD; RD, lenalidomide and dexamethasone; VRD, bortezomib and RD; Dara-VRD, CD38 monoclonal antibody, daratumumab, and VRD; IRD, ixazomib and RD; KRD, carfilzomib and RD; Dara-KRD, carfilzomib, daratumumab and RD; NDMM, newly diagnosed multiple myeloma; EFS, event-free survival; PFS, progression-free survival; OS, overall survival; RRMM, relapsed refractory multiple myeloma; CR, complete response; VGPR very good partial response; PR, partial response; TTP, time to progress; AE, adverse effect; RR, relative risk; ASCT, autologous-hematopoietic stem cell transplantation; MRD, measurable residual disease; sCR, strict complete response; ORR, overall response rate; TEAEs, treatment-emergent adverse events; HDCT/ASCT, high-dose chemotherapy plus autologous hematopoietic stem cell transplantation.

In previous research (42,43), sequential ASCT was administered to 751 of the 1,000 consecutive patients receiving VRD induction therapy. The median PFS and OS for this population were 63 and 123.4 months, respectively. The most recent

data from the Griffin trial and German-Speaking Myeloma Multicenter Group (GMMG-HD7) trial (44,45,67) investigations indicated that in patients deemed eligible for ASCT, the reaction rate of adding CD38 monoclonal antibody, isatuximab to VRD, and the negative rate of measurable residual disease (MRD) were both improved. Although the Griffin trial recently showed that the combination of these four medications offers considerable benefits in terms of PFS (45), neither research included data on PFS or OS. Therefore, the CD38 monoclonal antibody and VRD quadruple induction procedure may become the norm for patients with MM who are deemed ASCT candidates. The pursuit of negative MRD may also be advantageous for patients who have reached VGPR. Specifically, an analysis of patients who participated in the PETHEMA/GEM 2012 trial (68) established that negative MRD can improve the prognosis of high-risk patients with cytogenetics. However, the use of the VRD scheme for consolidation treatment after ASCT is still debatable. The published ASCT investigations on consolidation therapy with the VRD scheme (46), however, were performed throughout two cycles, which revealed improved VGPR and CR after consolidation.

The median age of the study participants was 73 years (range 65-91 years) in a phase 2 study of lenalidomide combined with bortezomib and dexamethasone for treating transplant-ineligible patients with MM (47). The total effective rate was 86 and 66% of the patients achieved VGPR or improved remission. The median OS was not attained, the mean PFS was 35.1 months (95% CI, 30.9-not reached), and the mean follow-up period was 30 months. Additionally, a phase 2 study (JCOG0904) (48) revealed that patients with RRMM undergoing VRD treatment exhibited satisfactory 1-year PFS (45.5%) and 3-year OS (70%) outcomes.

*Application of lenalidomide combined with ixazomib and dexamethasone in MM.* A reversible PI called ixazomib (I) with oral bioavailability was produced by Millenium Pharmaceuticals, Inc. (now Takeda Oncology) (69). The drug functions by binding to and inhibiting the subunits of the 20S proteasome. The FDA approved its use in combination with lenalidomide and dexamethasone (IRD) in November 2015 for treating patients with MM who have already undergone at least a single therapy. Globally, however, clinical trials involving ixazomib for NDMM and real-world research applications are still ongoing.

In a previous study, a total of 25 patients with NDMM receiving weekly IRD, as well as 18 other patients receiving twice-weekly IRD, then received ≥1 dose of ixazomib maintenance (49). The median PFS for the weekly IRD group was 25.8 months (95% CI, 9.2-34.8), and for twice-weekly IRD group, it was 26.3 months (95% CI, 5.7-not reached). Patients in the two groups showed a 3-year OS of 96 and 77%, respectively. A study by Kumar *et al* (50) treated patients with NDMM using ixazomib for maintenance after examining the long-term effectiveness and safety of the weekly complete oral combination of IRD. In the study, induction was halted in 23 patients and ASCT was performed. The remaining 42 patients showed an overall response rate (ORR) of 80%, of which 63% had VGPR and 32% had CR. This finding reveals that the IRD procedure can be administered for a considerable amount of time without any signs of cumulative toxicity. Furthermore, a double-blind, placebo-controlled TOURMALINE-MM2 clinical trial (NCT01850524) (51) was conducted, which involved patients with NDMM who were not candidates for or were unable to undergo ASCT. The median PFS of the IRD group was 35.3 months and the median follow-up duration was 53.3 months; 63% had VGPR and 26% had CR.

The response rates of the patients following ASCT increased over time, which was partly due to the advantages of lenalidomide maintenance that were noted in the previous trial. This finding led the researchers to add ixazomib to 64 patients with NDMM after ASCT, to compare the effects of R and IR (52). The median survival time was not attained, the CR/strict CR (sCR) was 43%, and the median follow-up period was 62 months (25-82 months). The median PFS of the patients was 73 months. The addition of lenalidomide to the maintenance of the drug resulted in a superior PFS than anticipated, and it was safe and was well tolerated when compared with the historical usage of lenalidomide alone.

A double-blind, placebo-controlled TOURMALINE-MM1 phase 3 clinical trial (53) for treating patients with relapsed and refractory MM revealed that there were no new or worse safety concerns. Moreover, among patients with RRMM, the OS rate of those taking IRD was statistically improved compared with those taking placebo-RD. According to a multicenter real-world study conducted by Japanese researchers using the Kansai Myeloma Forum database (https://myeloma.jp/), IRD treatment exhibited stronger efficacy than other types of treatments in patients with IgG-type RRMM in actual clinical practice (54), but no additional clinical trials and studies are available to support these findings.

*Application of lenalidomide combined with carfilzomib, dexamethasone and CD38 monoclonal antibody, daratumumab (Dara), in MM.* In 2012, the FDA authorized carfilzomib (K) for the treatment of MM. The drug, which is a tetrapeptide epoxy ketone, specifically targets and permanently inhibits the proteasome (70). The FDA originally authorized the single medication therapy for patients with MM who had received at least two treatments in 2012. Later, the FDA approved the use of lenalidomide with dexamethasone or carfilzomib in conjunction with dexamethasone to treat RRMM (71). Furthermore, several clinical studies on carfilzomib are concurrently being performed on patients with NDMM.

The effectiveness of Dara in combination with carfilzomib, lenalidomide, and dexamethasone (Dara-KRD) in treating patients with NDMM was explored in an open phase 1b research (55). Regardless of fulfilling the transplantation requirements, 22 patients received Dara-KRD treatment for up to 13 cycles that lasted 28 days or until ASCT. An ORR of 95% was achieved, of which 86% was PR and 67% was CR. Hence, Dara-KRD appears to be well tolerated. In another multicenter, open-label, phase 3 randomized controlled trial (56), patients with NDMM who did not immediately receive ASCT were compared in terms of VRD and KRD data. The median PFS was 34.4 months [95% CI, 30.1-not estimable (NE)] for VRD and 34.6 months (95% CI, 28.8-37.8) for KRD; KRD did not

increase the PFS in patients with NDMM in this randomized phase 3 study.

Patients with NDMM who were eligible for transplantation underwent four cycles of KRD induction, ASCT, four cycles of KRD consolidation, and ten cycles of KRD maintenance in a phase 2 multicenter investigation that evaluated the use of KRD and ASCT in the treatment of NDMM (57); sCR was the major endpoint after eight cycles of KRD. In total, 76 patients were enrolled in the study, their median age ranged from 40 to 76 years. Furthermore, the sCR rate after eight cycles was 60%. The sCR rate was 76% in the intention to treat (ITT) population. The 5-year PFS and OS rates of ITT were 72 and 84% after a median follow-up of 56 months. In patients with NDMM treated with KRD and ASCT, there was a significant incidence of negative sCR and MRD at the end of the consolidation of KRD. PFS and OS may be extended by prolonging the consolidation treatment for KRD, and safety and tolerance can be effectively managed. Another phase 2 study on KRD and ASCT (58) involved eight KRD treatments, ASCT for all patients, and a year-long course of lenalidomide, with the primary objective of sCR. Poor cytogenetics affected 21% of the 46 individuals. Of the 42 patients assessed following consolidation, 26 patients (61.9%) and 27 patients (64.3%) had sCR and CR, respectively. In conclusion, eight cycles of KRD resulted in a quick and favorable response in patients with NDMM who qualified for transplantation, however, of note cardiovascular side effects need to be constantly monitored.

Eligible patients were randomly assigned in a ratio of 1:1 to receive KRD or RD treatment for 28 days in a randomized controlled study on RRMM (59). In patients who had previously received a single therapy, the median OS was extended by 11.4 months for KRD compared with RD, and in patients who had previously received two therapies, the median OS was extended by 6.5 months for KRD compared with RD. Hence, it can be surmised that in RRMM, KRD has a markedly lower risk of mortality and a higher survival rate compared with RD. The therapeutic benefit of KRD is, however, most apparent during the initial recurrence. Similar findings were obtained by Japanese researchers conducting a multicenter real-world investigation using the Kansai Myeloma Forum database (60). They identified that 107 patients had received KRD therapy. The ORR was 68.2% and the median PFS and OS were 8.8 and 29 months, respectively. The results of 44 patients who had salvage high-dose chemotherapy (HDCT) plus ASCT following KRD reinduction were examined in a study on the use of KRD reinduction and salvage ASCT after first-line transplantation for RRMM (61). All patients had first-line high-dose chemotherapy plus ASCT (HDCT/ASCT), with a median progression time of 2.9 (1.2-13.5) years. After reinduction and before the salvage transplantation, 25/44 patients (57%) achieved VGPR; however, after salvage HDCT/ASCT, the percentage increased to 34/44 (77%). Given that the median PFS following rescue HDCT/ASCT was 23.3 months, KRD considerably prolonged PFS following rescue HDCT/ASCT and was enhanced by maintenance treatment.

## 5. Safety and tolerability

*Neutropenia, thrombocytopenia and anemia*. The Myeloma XI experiment was conducted at 110 National Health Service hospitals in England, Wales, and Scotland. It was an open-label, randomised, phase 3 adaptive design trial with three selection steps (72). Hematological adverse effects (AEs), such as neutropenia [362 (33%) patients], thrombocytopenia [72 (7%) patients], and anemia [42 (4%) patients], were the most frequent grade 3 or 4 AEs among lenalidomide users. Compared with 150 (17%) of the 874 individuals under observation, 494 (45%) of the 1,097 patients receiving lenalidomide experienced serious AEs. Therefore, complete blood counts, including white blood cells and their counts, platelet counts, hemoglobin, and hematocrit, should be checked weekly at baseline and during the first 8 weeks of lenalidomide treatment, and monthly thereafter. If neutropenia is present, physicians should consider treating the patient with growth factors (G-CSF). Dose adjustments in the event of grade 3 or 4 thrombocytopenia or neutropenia should be made by an experienced physician with reference to the medication package insert. Following the development of hematologic toxicity, if continued lenalidomide therapy results in improved bone marrow function (no hematologic toxicity for at least two consecutive cycles and an absolute neutrophil count $\geq 1.5 \times 10^9$/l and platelet count $\geq 100 \times 10^9$/l at the start of a new cycle using the current dose level), and the lenalidomide dose can be reinstated to the original level.

*Thyroid dysfunction*. Cases of hypothyroidism and hyperthyroidism have been reported in patients taking lenalidomide (73). Effective management of comorbidities affecting thyroid function should be achieved prior to treatment with lenalidomide. The authors recommend continuous monitoring of thyroid function at baseline and during treatment.

*Peripheral neuropathy*. One of the main reasons that has caused numerous physicians to abandon the use of thalidomide is peripheral neuropathy (74). No worsening of peripheral neuropathy was observed in patients with NDMM treated with long-term lenalidomide (37). In a prospective clinical and neurophysiological study of long-term neurotoxicity of lenalidomide applications, investigators confirmed that the neuropathy induced by lenalidomide is usually subclinical or mild. Neurotoxicity was independent of cumulative lenalidomide dose and hematologic response (75).

*Tumor lysis syndrome*. Due to the antitumor activity of lenalidomide, the complication of tumor lysis syndrome (TLS) may occur. However, there have been rare reports of TLS in patients with MM treated with lenalidomide. Nonetheless, caution should be exercised when administering lenalidomide to patients with a high pre-treatment tumor load, and these patients should be closely monitored, with particular attention to the first cycle, and appropriate precautions taken.

*Severe skin reactions (including allergic reactions)*. Angioedema, hypersensitivity, and severe skin reactions, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reactions with eosinophilia and systemic symptoms (DRESS), have been reported with the use of lenalidomide (76-78). DRESS may be associated with skin reactions (for example, rash or epidermal exfoliative dermatitis), eosinophilia, fever, and/or systemic complications

of lymphadenopathy, such as hepatitis, nephritis, pneumonia, myocarditis, and/or pericarditis (78). These events can have fatal consequences. In addition, lenalidomide should be avoided in patients who have experienced a grade 4 rash with prior thalidomide use. If a grade 2-3 rash occurs, suspending or discontinuing the drug should be considered. If angioedema, hypersensitivity, grade 4 rash, exfoliative or maculopapular rash, or suspected SJS, TEN, and DRESS occur, the drug must be discontinued and must not be restarted after these reactions have resolved.

*Second primary tumor.* In a retrospective pooled analysis of 11 clinical trials of lenalidomide for RRMM, the overall incidence rate (IR, events per 100 patient-years) of second primary malignancies (SPM) was 3.62. The IR for aggressive SPM (hematologic and solid tumors) was 2.08, which was in line with background cancer incidence. Non-invasive second primary tumors include basal cell or squamous cell skin cancers. In another analysis, pooled data from pivotal phase 3 trials of relapsed or refractory MM (N=703) showed an IR of 3.98 (95% CI, 2.51-6.31) for SPM with lenalidomide/dexamethasone and 1.38 (95% CI, 0.44-4.27) for placebo/dexamethasone (79). When considering treatment with lenalidomide, the physician should weigh both the potential benefit of lenalidomide and the risk of a second primary malignancy.

*Hepatotoxicity.* Liver failure, including death, has been reported in patients treated with lenalidomide in combination with other drugs (80,81). The mechanism of drug-induced severe hepatotoxicity is not known, but in some cases, preexisting viral liver disease, elevated baseline liver enzymes and treatment with antibiotics may also be a risk factor. Commonly, abnormal liver function test values were reported, which were generally asymptomatic and reversible with suspension of dosing. Once parameters return to baseline values, treatment at a lower dose may be considered. Lenalidomide is excreted through the kidneys (36). Dose adjustment in patients with renal insufficiency is particularly important to avoid higher hematological adverse effects or hepatotoxicity that may result from elevated blood levels. Hepatic function monitoring may be indicated by the clinician, particularly if there has been a history of viral liver infection or concurrent viral liver infection, or if lenalidomide is used in combination with medications known to cause abnormalities in liver function.

*Infections.* Patients with MM are more likely to develop infections, including pneumonia (72). For patients with NDMM, treatment with lenalidomide in combination with dexamethasone was associated with a higher incidence of infection in the former compared with treatment with melphalan, prednisone, and thalidomide (MPT) (82,83). For patients with NDMM previously treated with ASCT, maintenance therapy with lenalidomide was associated with a higher incidence of infection in the former compared with placebo (84). All patients should seek immediate medical attention at the first sign of infection (for example, cough and fever) for empirical anti-infective treatment by a hematologist. Cases of viral reactivation, including severe cases of re-inactivation of herpes zoster (85) or hepatitis B virus (HBV) (86), have been reported in patients treated with lenalidomide. Some cases of herpes zoster turn into disseminated herpes zoster, herpes zoster meningitis, or ocular herpes zoster, requiring suspension or permanent discontinuation of lenalidomide therapy and adequate antiviral therapy. Patients with prior HBV infection and treated with lenalidomide have progressed to acute liver failure in some cases, leading to discontinuation of lenalidomide and adequate antiviral therapy. HBV status should be clarified prior to initiating lenalidomide therapy. For patients who have tested positive for HBV infection, it is recommended to consult a specialist experienced in the treatment of hepatitis B. Lenalidomide should be used with caution in patients with a history of HBV infection, including those who are anti-HBc antibody-positive but HBsAg-negative. These patients should be closely monitored for signs and symptoms of active HBV infection throughout the course of treatment.

*Venous and arterial thromboembolism.* Lenalidomide combined with dexamethasone for the treatment of patients with MM increases the risk of venous thrombosis (especially the risk of deep vein thrombosis and pulmonary embolism) (87). Clinicians routinely apply aspirin or rivaroxaban to prevent thrombosis (88). Lenalidomide in combination with dexamethasone for the treatment of patients with MM increases the risk of arterial thrombosis (especially myocardial infarction and cerebrovascular events), and the risk of arterial thrombosis is lower when lenalidomide is combined with melphalan and prednisone. Lenalidomide monotherapy is associated with a lower risk of arterial thrombosis than lenalidomide in combination with other drugs for the treatment of MM (89).

*Teratogenicity.* Thalidomide, the first-generation IMiD, was once recommended as a sedative antiemetic for pregnant women to reduce their pregnancy reactions before being used as a therapeutic agent for MM (90), which was withdrawn due to its teratogenicity (91). Lenalidomide has been shown to be teratogenic, as its predecessor, thalidomide (92). Hui *et al* used pregnant cynomolgus monkeys to study the teratogenic potential of lenalidomide (93). All of the fetuses of the lenalidomide-treated group had deformities upon external fetal inspection, including anomalies of the upper and lower limbs. Therefore, lenalidomide is contraindicated in pregnant women and women who are likely to become pregnant if all contraceptive requirements have not been met.

*Tolerability.* Cereblon (CRBN) is the central target molecule for lenalidomide. It is suggested that the emergence of lenalidomide resistance is influenced by low CRBN expression, CRBN mutations, and genes encoding downstream proteins (94). In addition, in a prospective multicenter, single-arm clinical trial, researchers combined longitudinal single-cell RNA sequencing (scRNA-seq) to study the molecular dynamics of MM resistance mechanisms. This study revealed new MM molecular resistance pathways including hypoxia tolerance, protein folding and mitochondrial respiration, and it was identified that peptidyl prolyl isomerase A (PPIA), a central enzyme in the protein folding reaction pathway, may be a new target for drug-resistant MM. CRISPR-Cas9 deletion of PPIA or inhibition of PPIA with a small-molecule inhibitor (cyclosporine) markedly

sensitized MM tumor cells to proteasome inhibitors (95). Hematological grade 4 or nonhematological grade 3/4 AEs and drug resistance are the main factors that lead to lenalidomide discontinuation in clinical research and in clinical practice (37,96).

## 6. Dosage in special populations

*Medications for patients with renal insufficiency*. No dose adjustment is required for patients with creatinine clearance (CLcr) ≥60 ml/min. Dose adjustments should be made for patients with CLcr <60 ml/min at the start of treatment. Lenalidomide can be administered at a full dose of 25 mg per day 21/28 (daily on days 1-21 of each repetitive 28-day cycle) in patients with a CLcr >30 and can be given daily to patients with a CLcr <30, even on dialysis, at a dose of at least 15 mg per day (97).

*Elderly patients*. In a multicenter, open-label, phase 3 FIRST trial (MM-020/IFM07-01), of the 1,623 patients receiving medication in the present study, 94% (1,521/1,623) were 65 years or older and 35% (561/1,623) were 75 years or older. The 1,623 were randomly assigned to the following three groups: Rd in 28-day cycles until disease progression (Rd pers), to the same combination for 18 cycles (Rd18), or to MPT for 72 weeks. The proportion of patients >75 years of age was similar across study groups (Rd pers, 33%; Rd18, 34%; MPT, 33%). The incidence of most adverse reaction categories (for example, all adverse reactions, grade 3/4 AEs, serious adverse reactions) was higher in older subjects (>75 years of age) than in younger subjects (≤75 years of age) in all treatment groups. Grade 3/4 AEs were consistently reported at higher rates for systemic disease and site-of-administration status body systems in older subjects than in younger subjects in all groups (difference of at least 5%). The incidence of grade 3 or 4 AEs for infections and contagions, cardiac diseases (including heart failure and congestive heart failure), skin and subcutaneous tissue diseases, and renal and urologic diseases (including renal failure) was consistently slightly higher in older subjects than in younger subjects in all groups (<5% difference). These trends were not clear with respect to the incidence of grade 3/4 adverse reactions in other body systems (for example, blood and lymphatic system disorders, infections and infectious heart disease, and vascular disease). The incidence of serious adverse reactions was generally higher in older subjects than in younger subjects in all groups (83). In another study, the population pharmacokinetic analysis included patients of advanced age, and the results of the analysis showed no effect of age on the clearance (plasma exposure) of lenalidomide (98). Because elderly patients are more likely to have decreased renal function, caution should be exercised in dose selection and renal function should be monitored.

*Pregnant and lactating women*. As already mentioned, lenalidomide should be contraindicated during pregnancy. Women who are at risk of becoming pregnant should use effective contraception. If a female patient becomes pregnant while using lenalidomide, treatment must be discontinued and she is asked to seek evaluation and advice from a physician with expertise or experience in teratology. It is uncertain whether lenalidomide is secreted through human milk; therefore, it is recommended that breastfeeding women discontinue breastfeeding during treatment with lenalidomide.

## 7. Conclusion

Lenalidomide, a second-generation IMiD, is highly regarded in the treatment of patients with NDMM and RRMM owing to its several advantages over thalidomide, which is a first-generation immunosuppressant. Lenalidomide kills MM cells in diverse ways, including through direct induction and immune modulation. Lenalidomide is an oral medication that is quickly and well absorbed; however, the renal function of the patient taking it is affected in terms of the plasma exposure concentration. Lenalidomide has a variety of uses in the treatment of MM, including induction therapy and maintenance therapy. It can also be used in combination with other medications such as dexamethasone, PIs, and CD38 monoclonal antibodies. Although several clinical trials have revealed positive outcomes with lenalidomide, there is less real-world research evidence for NDMM relative to RRMM. Despite the fact that the neurological side-effects of lenalidomide, particularly those affecting the peripheral nerves, are markedly reduced compared with those of thalidomide, the clinical application of lenalidomide should be cautious, especially in relation to its performance in the blood system, infections, thrombosis, teratogenic potential and other unpleasant responses.

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## Availability of data and materials

Not applicable.

## Authors' contributions

CWZ was responsible for the conception and writing of the article. YNW collected information and XLG approved the articles and performed modifications with regard to language editing. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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