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REVIEW

The Role of CELMoD Agents in Multiple Myeloma

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Abstract: Although recent decades have seen continued improvements in survival for patients with multiple myeloma, the disease remains largely incurable, and most patients will experience relapse and/or become refractory to treatment. There thus remains an urgent unmet need for novel treatments, particularly for those patients with relapsed or refractory multiple myeloma. Novel treatment modalities, such as targeted protein degradation, have attracted particular interest due to their ability to expand the range of druggable protein targets in myeloma cells. Iberdomide (CC-220) and mezigdomide (CC-92480) are promising oral CELMoD™ agents currently being evaluated for the treatment of patients with multiple myeloma. Preclinical data from lenalidomide- and pomalidomide-resistant cell lines and mouse models suggest that iberdomide and mezigdomide have the potential to provide therapeutic benefit even in patients who are refractory to lenalidomide and pomalidomide. The optimized specificity, potency, and safety profile of iberdomide and mezigdomide supports their clinical use and aligns with the need for longer durations of a well-tolerated oral CELMoD agent with synergistic combinability with other immune approaches (such as anti-CD38 monoclonal antibodies) and proteasome inhibitors (such as bortezomib and carfilzomib). Although neither iberdomide or mezigdomide has yet received regulatory approval for the treatment of multiple myeloma, based on their mechanism of action and the data available to date, we propose that both drugs may be attractive options for the treatment of patients with relapsed or refractory multiple myeloma; based on their efficacy and safety profiles, iberdomide is likely better suited for use in newly diagnosed, first relapse, or maintenance settings, whereas mezigdomide may also be better suited for use in patients with early relapse or a greater number of prior antimyeloma treatments. Iberdomide and mezigdomide are currently being evaluated for the treatment of patients with multiple myeloma in several trials, and results so far are promising.

Keywords: iberdomide, mezigdomide, cereblon, treatment, multiple myeloma

Introduction

Recent decades have seen continued improvements in survival for patients with multiple myeloma.[1–4] This effect has largely been due to the introduction of more effective and less toxic novel therapeutic agents such as proteasome inhibitors (including bortezomib and carfilzomib), IMiD® agents (primarily lenalidomide and pomalidomide), and anti-CD38 monoclonal antibodies (eg, daratumumab and isatuximab).[1,5] Nevertheless, multiple myeloma remains incurable, with most patients relapsing or becoming refractory to treatment and many patients experiencing numerous cycles of relapse and remission, with each cycle of therapy being associated with more aggressive disease and shorter response intervals.[3,4]

Relapsed or refractory multiple myeloma is generally difficult to treat as patients have fewer treatment options, are less likely to achieve durable responses, and report significant impacts on their health-related quality of life, including physical, cognitive, emotional, and social effects.[3,6,7] Patients with relapsed or refractory multiple myeloma report that the experience of relapse often has a greater emotional and psychological impact than their initial diagnosis, and in the absence of curative treatment options, patients may also prioritize treatments that prolong life expectancy with minimal side effects.[3,7] To minimize disruptions to everyday life, patients desire therapy that provides the opportunity for treatment-free or "off-treatment" intervals.[7] Multiple

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myeloma also primarily affects older patients, who may be more likely to have comorbidities and susceptibility to toxicities compared with younger patients.[6] There thus remains an unmet need for novel treatments that are effective and tolerable for patients with multiple myeloma, particularly in those who have experienced relapse or who are refractory to other treatment options. In this review, we provide a comprehensive, up-to-date overview of the CELMoD™ agents iberdomide and mezigdomide in the treatment of multiple myeloma, highlighting their mechanisms of action, preclinical and clinical data, and their potential roles within the evolving therapeutic landscape.

Targeted Protein Degradation in Multiple Myeloma by CELMoD Compounds

Given their critical role in many cellular processes and pathways, protein–protein interactions remain a promising target for therapeutic interventions. Historically, most therapeutic agents have targeted proteins with easily accessible active sites to disrupt activity.[8–10] Targeted protein degradation is a novel treatment modality that does not require a protein pocket or active site to which the drug can bind, and therefore has the potential to expand the range of targetable proteins beyond those previously deemed "druggable".[10]

Targeted protein degradation leverages the cell's natural protein degradation machinery to mark specific target proteins for degradation by the proteasome.[8,9,11] This process requires the ubiquitin proteasome system, a key component of the cellular proteostasis network.[11,12] E3 ubiquitin ligases, of which the cullin-RING ubiquitin ligases (CRLs) are the largest family, transfer ubiquitin to the target protein marking it for degradation.[13,14]

IMiD agents and CELMoD agents act as molecular glue by promoting interaction of the E3 ubiquitin ligase with its target protein of interest.[15–17] Similar to IMiD agents, CELMoD agents bind cereblon, a substrate receptor for the CRL4 ubiquitin ligase complex, and modulate its activity to induce ubiquitin-mediated proteasomal degradation of specific target proteins (Figure 1A);[17] however, CELMoD agents also bind cereblon outside of the tri-tryptophan pocket, thus inducing allosteric rearrangement that more efficiently induces its active, "closed" conformation, which is required for efficient and maximal substrate ubiquitination (Figure 1B).[17,18] In multiple myeloma, this leads to enhanced recruitment and subsequent degradation of the transcription factors Ikaros (IKZF1) and Aiolos (IKZF3) which are highly expressed in multiple myeloma and the downregulation of which has been shown to inhibit proliferation and induce apoptosis in multiple myeloma cells through sequential downregulation of c-Myc and IRF4.[19–21] As different substrates are degraded by the proteasome pathway, the binding affinity between CELMoD agents and cereblon and the ability to induce allosteric rearrangement is believed to impact the amount of target degradation.[17,22] CELMoD agents therefore have the potential to remain effective even in the presence of low levels of functional cereblon.

Iberdomide: A CELMoD Agent for Multiple Myeloma

Iberdomide (CC-220) is an oral CELMoD agent that is currently being evaluated in several clinical trials for the treatment of patients with newly diagnosed multiple myeloma (EXCALIBER-Maintenance trial; NCT05827016),[23] for patients with relapsed or refractory multiple myeloma who have received one to two prior lines of antimyeloma therapy (EXCALIBER-RRMM; NCT04975997),[24] and for patients with relapsed or refractory multiple myeloma who were heavily pretreated (CC-220-MM-001; NCT02773030).

Like lenalidomide and pomalidomide, iberdomide contains a glutarimide ring and an isoindolinone ring, allowing for interaction with the tri-tryptophan pocket of cereblon and with cereblon and its substrates, respectively.[22] However, iberdomide contains additional phenyl and morpholino moieties that permit more interactions with cereblon or protein substrates.[22] Correspondingly, iberdomide has a differentiated profile relative to both lenalidomide and pomalidomide.[25,26] Iberdomide has significantly higher cereblon-binding affinity when compared with lenalidomide and pomalidomide, as well as faster and more potent degradation of the target substrates Ikaros and Aiolos.[25] Iberdomide also induces more efficient allosteric rearrangement of the cereblon binding site than lenalidomide and pomalidomide, promoting the active/closed conformation needed for substrate recruitment.[17]

Promisingly, iberdomide has also shown activity in lenalidomide-resistant and pomalidomide-resistant cell lines.[25] Unlike lenalidomide and pomalidomide, iberdomide has been shown to induce rapid depletion of Ikaros and Aiolos in pomalidomide-resistant cell lines.[25] Preclinical analyses using peripheral blood mononuclear cells also show that iberdomide is more potent than either lenalidomide or pomalidomide in overcoming bortezomib-induced immunosuppression.[26] Patients with relapsed

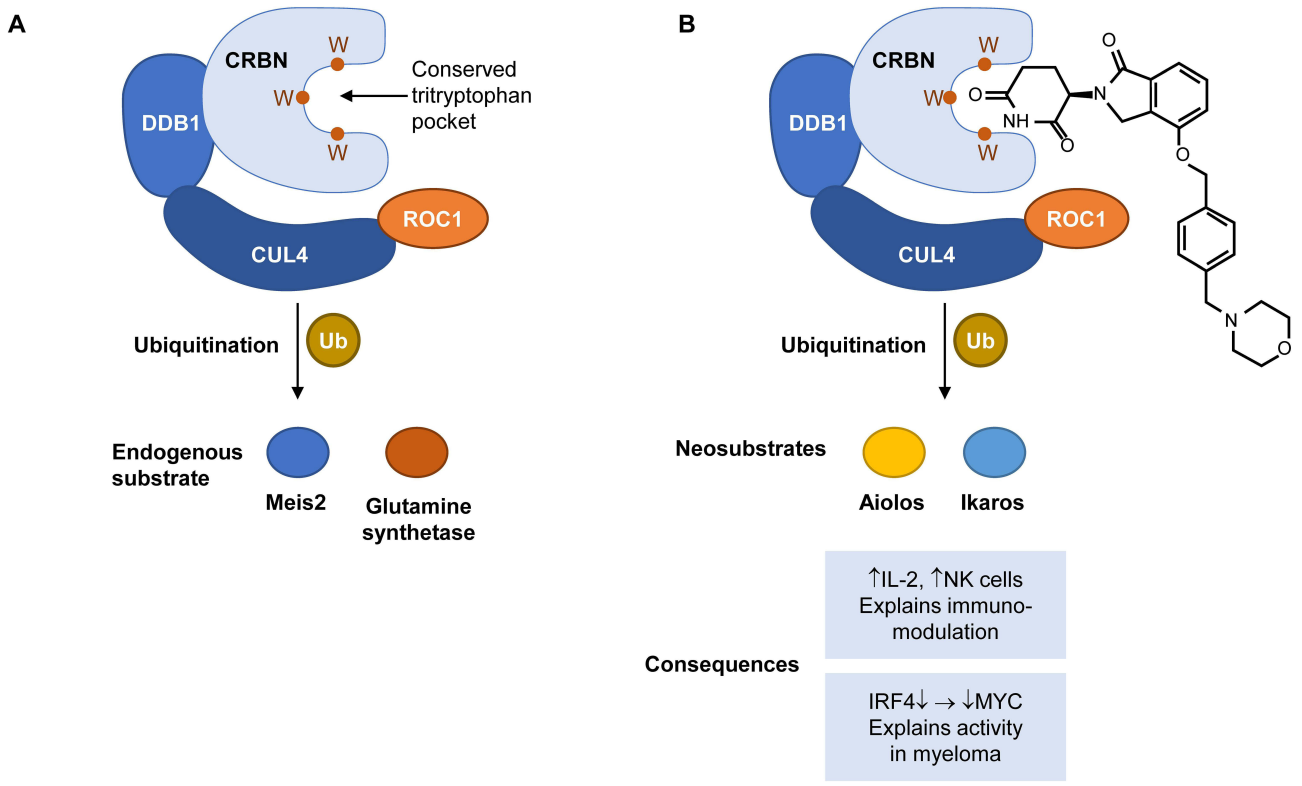

Figure 1 CELMoD agents redirect the CRBN pathway to degrade target proteins. (**A**) The CRBN complex ubiquitinates endogenous substrates to maintain protein homeostasis. (**B**) CELMoD agents, such as iberdomide (depicted) and mezigdomide, bind to and alter the conformation of CRBN, redirecting the protein degradation pathway to the neosubstrates Ikaros and Aiolos and resulting in downstream immunomodulatory effects. Adapted from Collins I, Wang H, Caldwell JJ, Chopra R. Chemical approaches to targeted protein degradation through modulation of the ubiquitin–proteasome pathway. Biochem J 2017;474(7):1127–1147. © 2017 The Author(s). This is an open access article published by Portland Press Limited on behalf of the Biochemical Society and distributed under the Creative Commons Attribution License 4.0 (CC BY).[15] Adapted from Richardson PG, Mateos MV, Vangsted AJ et al. The role of E3 ubiquitin ligase in multiple myeloma: potential for cereblon E3 ligase modulators in the treatment of relapsed/refractory disease. Expert Rev Proteomics. 2022;19(4–6):235–246. © 2022, Taylor & Francis Ltd.[16]
Abbreviations: CRBN, cereblon; CUL4, cullin 4; DDB1, DNA damage-binding protein 1; IL-2, interleukin-2; IRF4, interferon regulatory factor 4; MYC, myelocytomatosis oncogene; NK, natural killer; ROC1, regulator of cullins-1; Ub, ubiquitin; W, tryptophan.

or refractory multiple myeloma receiving iberdomide, either as monotherapy or in combination with dexamethasone, show increased immunostimulatory activity, with enhanced proliferation of natural killer (NK), CD4+, and CD8+ T cells in the peripheral blood.[27] Mass cytometry and immunophenotyping analyses revealed that iberdomide induces innate and adaptive immune cell activation, including effector T cells and NK cells, in the bone marrow tumor microenvironment of patients with relapsed or refractory multiple myeloma.[28]

Iberdomide has been shown to retain its immune-stimulatory effects in patients with late-line multiple myeloma, despite the higher levels of immunosuppression and T cell exhaustion in these patients, and shift the T cell compartment to an activated/effector memory phenotype.[29,30] Preclinical data have demonstrated that iberdomide exerts synergistic immune stimulation in combination with the proteasome inhibitors bortezomib and carfilzomib, as well as with monoclonal antibodies such as daratumumab, and elotuzumab.[31–33] In co-culture systems of myeloma and immune cells, iberdomide has been shown to significantly increase antibody-dependent cellular cytotoxicity of daratumumab.[33] In patients with newly diagnosed multiple myeloma, iberdomide combined with daratumumab was shown to drive deep responses, including minimal residual disease negativity; responses were also observed in patients with high levels of baseline T cell exhaustion and high-risk gene expression signatures.[34]

Recent preclinical data have also suggested that the antitumor activity of T cell-redirecting therapies could be improved when combined with iberdomide. Iberdomide enhanced the activity of the anti-B-cell maturation antigen (BCMA) bispecific antibody alnuctamab toward multiple myeloma cells, which was not seen with pomalidomide,[35] and also increased the proliferation and cytotoxic activity of anti-BCMA chimeric antigen receptor (CAR) T cells in vitro.[36]

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Iberdomide in Clinical Trials

Iberdomide is being evaluated in several clinical trials. CC-220-MM-001 (NCT02773030) is an ongoing phase 1/2 study evaluating iberdomide in different treatment combinations in patients with relapsed or refractory multiple myeloma and newly diagnosed multiple myeloma.[37–39] The study consists of two parts, part 1 is a dose-escalation study to determine the recommended phase 2 dose for iberdomide monotherapy, iberdomide with dexamethasone, iberdomide with daratumumab and dexamethasone (IberDd), iberdomide with bortezomib and dexamethasone (IberVd), and iberdomide with carfilzomib and dexamethasone (IberKd). Part 2 evaluates the recommended phase 2 dose for iberdomide with dexamethasone in relapsed or refractory multiple myeloma, and IberDd and IberVd for newly diagnosed multiple myeloma. Eligible patients in the iberdomide plus dexamethasone, IberDd, and IberKd cohorts had received two or more prior treatment regimens for multiple myeloma, and eligible patients in the IberVd had received at least one prior regimen.[37] In the IberDd, IberVd, and IberKd cohorts, despite high levels of refractoriness to proteasome inhibitors (82%, 67%, and 71%) and anti-CD38 monoclonal antibodies (47%, 79%, and 71%), the overall response rates of at least partial response in this dose-escalation phase were 41%, 58%, and 57%, respectively.[37] In a post hoc dose-escalation cohort subgroup analysis of 37 patients who were triple-class refractory and had received at least three previous lines of therapy, 11 patients achieved either a complete or partial response to iberdomide plus dexamethasone.[39] A recommended phase 2 dose of 1.6 mg was therefore selected for the iberdomide plus dexamethasone dose-expansion cohort of 107 patients who were triple-class refractory and received at least three previous lines of therapy, and the overall response rate in that cohort was 26%.[39] Data from Cohort I of the CC-220-MM-001 trial showed that in patients treated with iberdomide plus dexamethasone who had received prior anti-BCMA therapy, the overall response rate was 37%.[40]

Initial results from the IberDd cohort indicate that iberdomide in combination with daratumumab and dexamethasone was associated with mostly hematologic adverse events, and the incidence of nonhematologic adverse events was low.[37,38] The most common grade 3/4 adverse event was neutropenia, which occurred in 45% of patients in the iberdomide plus dexamethasone cohort,[39] 63% of patients in the IberDd cohort, 29% of patients in the IberVd cohort, and 43% of patients in the IberKd cohort. Nonhematologic grade 3/4 adverse events were low, where six patients in the iberdomide plus dexamethasone cohort experienced gastrointestinal disorders, three experienced fatigue, and three experienced rash;[39] grade 3 fatigue and grade 3 diarrhea (IberDd cohort) and grade 3 diarrhea and grade 3 rash (IberVd cohort) were each experienced by one patient.[41] Subsequent dose-expansion data from patients with newly diagnosed multiple myeloma in the IberDd cohort (75 patients) and the IberVd cohort (18 patients) produced response rates of 97% (IberDd) and 89% (IberVd), with 85% (IberDd) and 78% (IberVd) of patients achieving a very good partial response or better.[42,43] At the time of data cutoff, deep ongoing responses were being observed at 14 months of median follow-up for both cohorts, with 83% (IberDd) and 72% (IberVd) patients remaining on treatment.

In patients with mild to moderate renal impairment, iberdomide in combination with dexamethasone did not require dosing adjustments and demonstrated similar efficacy to patients with no renal impairment.[44]

The efficacy of iberdomide was further studied by comparing 34 patients with cereblon dysregulation and 48 patients with wild-type cereblon; 18% (6/34) of the patients with cereblon dysregulation responded to iberdomide plus dexamethasone while 27% (13/48) patients with wild-type cereblon responded.[30] Further analysis of responders revealed that both patients with dysregulation versus those with wild type had similar median duration of response (9.5 vs 9.4 months), respectively.[30]

The EXCALIBER-RRMM trial (CC-220-MM-002; NCT04975997) is a multicenter, open-label, phase 3 study assessing the efficacy and safety of iberdomide in combination with daratumumab and dexamethasone (IberDd) in patients with early-line relapsed or refractory multiple myeloma.[45] This trial compares IberDd with daratumumab, bortezomib, and dexamethasone (DVd). EXCALIBER-RRMM is currently recruiting, and adult patients with progressive disease who have received one to two prior lines of antimyeloma therapy are eligible for participation. Stage 1 of the study involved dose optimization, with three iberdomide doses assessed. Stage 2 is ongoing and assesses the efficacy and safety of the selected iberdomide dose in combination with daratumumab and dexamethasone versus DVd. The dual primary endpoints of the study are progression-free survival and minimal residual disease-negative complete response at any time;[24] key secondary endpoints include overall response rate, overall survival, and safety. The estimated primary completion date for the EXCALIBER-RRMM trial is March 2026.[24]

The EMN26 trial (NCT04564703) is a multicohort phase 2 study assessing the safety and efficacy of three different iberdomide doses (0.75 mg, 1.0 mg, and 1.3 mg) as a maintenance treatment post-transplant in patients with newly diagnosed multiple myeloma.[46,47] Eligible patients are those who had achieved a partial response or better after induction therapy containing a proteasome inhibitor plus IMiD agent, followed by single or double autologous stem cell transplantation (ASCT) ± consolidation. Patients showed a similar deepening of response improvement at 6 months at all doses tested (~ 45%), which appears to be higher than what has been historically reported for lenalidomide maintenance (26%).[46] The safety profile of iberdomide in the EMN26 trial was manageable with the most common grade ≥ 3 adverse events of neutropenia, infections, and fatigue/asthenia and no occurrences of thrombocytopenia, anemia, or diarrhea. Additional follow-up in the EMN26 trial will contribute to define the recommended maintenance dose used in the EXCALIBER-Maintenance trial (NCT05827016).[23]

The EXCALIBER-Maintenance trial is a randomized, phase 3 head-to-head study of iberdomide versus lenalidomide for the treatment of patients with newly diagnosed multiple myeloma after ASCT.[48] The EXCALIBER-Maintenance trial is currently recruiting. Stage 1 of the study involves dose optimization, with three iberdomide doses assessed. Stage 2 assesses the efficacy and safety of the selected iberdomide versus lenalidomide. Eligible patients have newly diagnosed multiple myeloma and have received three to six cycles of induction therapy that included a proteasome inhibitor and an immunomodulatory drug or VCD (bortezomib, cyclophosphamide, and dexamethasone), followed by a single or tandem ASCT. Primary completion of the EXCALIBER-Maintenance trial is expected in March 2029.[23]

Mezigdomide: Maximal Protein Degradation

Like iberdomide, mezigdomide (CC-92480) is an oral CELMoD agent that is currently being evaluated for the treatment of multiple myeloma. Mezigdomide was specifically developed to have maximal and rapid protein degradation of target proteins in the context of low cereblon levels while avoiding off-target binding.[13,17,49] Mezigdomide is highly potent due to its ability to induce an active closed conformation of the cereblon binding site in 100% of cereblon molecules, compared with approximately 50% induced by iberdomide and approximately 20% induced by pomalidomide; since the active closed conformation is required for substrate degradation, mezigdomide demonstrates maximal substrate-binding capacity.[17]

Mezigdomide has been shown to have a higher binding affinity when compared with lenalidomide and pomalidomide and promotes recruitment of Ikaros to the cereblon E3 ligase complex more effectively than pomalidomide.[50] Mezigdomide is also associated with a more extensive ubiquitination of Ikaros and more efficient depletion of Ikaros and Aiolos when compared with pomalidomide.[50] Mezigdomide was shown to induce degradation of Ikaros and in various multiple myeloma cell lines, including cells with acquired lenalidomide or pomalidomide resistance.[50] Preclinical data suggest that mezigdomide has potent antiproliferative and proapoptotic effects in multiple myeloma cells, including those that are resistant to lenalidomide or pomalidomide.[50]

In addition to the antiproliferative and proapoptotic effects induced in multiple myeloma cells, mezigdomide has been demonstrated to activate exhausted and senescent bone marrow T cells and NK cells;[51] patients with relapsed or refractory multiple myeloma who received mezigdomide treatment had expanded NK and NK T cell populations in their bone marrow aspirate samples with a greater number of effector CD4 and CD8 T cells and a reduced number of senescent cells.[51] Further, mezigdomide treatment was shown to reverse T cell exhaustion by downregulating exhaustion markers and upregulating proinflammatory cytokines, demonstrating the immunomodulatory properties of mezigdomide.[52]

Mezigdomide Acts Synergistically with Other Multiple Myeloma Therapies

Mezigdomide was shown to act synergistically with dexamethasone, bortezomib, carfilzomib, and daratumumab, suggesting its potential for use in combination therapies with these agents. In a preclinical study of multiple myeloma cell lines, mezigdomide in combination with dexamethasone was shown to reduce myeloma cell viability and potentiate dexamethasone-induced apoptosis; notably, mezigdomide and dexamethasone when used in combination demonstrated activity at concentrations that had only minimal activity when they were used as single agents.[53] In the same study, the combination of mezigdomide and dexamethasone significantly inhibited tumor growth in a lenalidomide-resistant xenograft mouse model, with a higher efficacy than either agent alone.[53] Importantly, mezigdomide was also shown to maintain protein degradation activity in the presence of proteasome-inhibiting concentrations of bortezomib, and the combination of mezigdomide and bortezomib showed greater cytotoxic effects to multiple myeloma cells than either agent alone.[53] When treated with

daratumumab, multiple myeloma cell lines pretreated with mezigdomide showed increased antibody-dependent cellular toxicity and antibody-dependent cellular phagocytosis when compared with cells treated with DMSO.[53] Mezigdomide was also shown to work synergistically with the anti-BCMA bispecific antibody alnuctamab by enhancing alnuctamab-mediated antitumor activity and T cell infiltration in a multiple myeloma xenograft mouse model; among mezigdomide, iberdomide, and pomalidomide, mezigdomide exerted the greatest effect on reversing T cell exhaustion in an in vitro multiple myeloma model.[35] Further studies are needed to determine whether mezigdomide could be combined with other novel cellular therapies, such as the bispecific antibody talquetamab, which induces the killing of GPRC5D-expressing myeloma cells via the recruitment and activation of T cells.[54]

Mezigdomide in Clinical Trials

Mezigdomide is being evaluated in a number of clinical trials. CC-92480-MM-001 (NCT03374085) is an open-label phase 1/2 study evaluating the safety, pharmacokinetics, and efficacy of mezigdomide as a monotherapy and in combination with dexamethasone in patients with relapsed or refractory multiple myeloma.[55] The CC-92480-MM-001 study is being conducted in two parts: phase 1 evaluated the pharmacokinetics and safety of mezigdomide at different schedules and escalating doses with a fixed dose of dexamethasone and aimed to determine the maximum tolerated dose and recommended phase 2 dose of mezigdomide; phase 2 evaluated the efficacy of mezigdomide at the recommended phase 2 dose in combination with dexamethasone, as measured by overall response (defined as partial response or better). Eligible patients had received at least three previous lines of therapy and had progression of disease during the 60 days after the final dose of their last antimyeloma therapy. Eligible patients enrolled in phase 2 were also refractory to lenalidomide, pomalidomide, or both, a glucocorticoid, a proteasome inhibitor, and an anti-CD38 antibody; 30% of patients had previously received anti-BCMA therapy. The most common dose-limiting toxicities in phase 1 were neutropenia and infections. Based on the results of phase 1, a mezigdomide dose of 1.0 mg was selected, administered once daily in combination with weekly dexamethasone for 21 days followed by 7 days off, in 28-day cycles. The most common adverse events in phase 2 were neutropenia, which occurred in 77% of patients, and infection, which occurred in 65% of patients. Other nonhematologic adverse events of any grade included fatigue in 36% of patients and diarrhea in 31% of patients. The overall response rate was 41% with a median duration of response of 7.6 months, and median progression-free survival was 4.4 months. Responses were also observed in patients who had received prior anti-BCMA therapy, with an overall response rate of 50%, and median progression-free survival of 5.4 months. Patients with plasmacytomas, including extramedullary plasmacytomas, in the dose-expansion cohort achieved an overall response rate of 30%.[55] Mild to moderate renal impairment did not influence clinical outcomes with mezigdomide and dexamethasone, and dose adjustments are likely not required for these patients.[56]

CC-92480-MM-002 (NCT03989414) is an ongoing phase 1/2 study evaluating mezigdomide in various combinations with standard treatments in patients with relapsed or refractory multiple myeloma.[57] Eligible patients had received two to four prior lines of therapy with a minimal response or better to at least one prior regimen and had experienced disease progression during or after their last therapy. None of the patients in the mezigdomide, daratumumab, and dexamethasone (MeziDd) arm were refractory to daratumumab,[58] and none of the patients in the mezigdomide, elotuzumab, and dexamethasone (MeziEd) arm were refractory to elotuzumab (data on file). In the mezigdomide, dexamethasone, and bortezomib (MeziVd) and mezigdomide, dexamethasone, and carfilzomib (MeziKd) dose-escalation cohorts, patients were heavily pretreated and all were previously exposed to an IMiD agent.[59] Preliminary data showed that the most common grade 3/4 adverse events were hematologic, with neutropenia occurring in 54% (MeziDd), 67% (MeziEd), 36% (MeziVd), and 44% (MeziKd) of patients.[57,59] The incidence of nonhematologic grade 3/4 adverse events was low; grade 3/4 infections occurred in 20% (MeziDd), 33% (MeziEd), 18% (MeziVd), and 33% (MeziKd) of patients and were considered manageable in all cases. The overall response rate for MeziDd was 75%, compared with 45% (MeziEd), 75% (MeziVd), and 85% (MeziKd).[57,59]

CA057-003 (NCT05372354) is another ongoing phase 1/2 study evaluating triplet combination regimens of mezigdomide and dexamethasone (MEZId) plus a novel agent in patients with relapsed or refractory multiple myeloma.[60] The novel agents, each targeting an oncogenic pathway, include tazemetostat (TAZ), an enhancer of zeste homolog 2 (EZH2) inhibitor; BMS-986158, a bromodomain and extraterminal (BET) inhibitor; and trametinib (TRAM), a mitogen-activated

extracellular signal-regulated kinase (MEK) inhibitor. Eligible patients had documented progressive disease, Eastern Cooperative Oncology Group performance status score of ≤ 1, and were intolerant to/ineligible for all available therapies. The overall response rates were 54% (MEZId + TAZ), 36% (MEZId + BMS-986158), and 92% (MEZId + TRAM); neutropenia was the most common grade 3/4 adverse event, ranging from 43%–73%.[60]

Results from the CC-92480-MM-001, CC-92480-MM-002, and CA057-003 trials are encouraging, with all trials reporting mainly hematologic grade 3/4 adverse events which were manageable and predictable, and few nonhematologic grade 3/4 adverse events to date; notable nonhematologic toxicities included fatigue, nausea, diarrhea, and rash.[55,59,60] However, since the incidence of neutropenia is relatively high, the management of neutropenia will be a priority in patients treated with mezigdomide.

SUCCESSOR-1 (NCT05519085) is an ongoing, phase 3, two-stage study of the efficacy and safety of mezigdomide in combination with bortezomib and dexamethasone (MeziVd) versus pomalidomide, bortezomib, and dexamethasone combination therapy (PomVd) in patients with relapsed or refractory multiple myeloma who have been previously treated with one to three lines of antimyeloma therapy, including a lenalidomide-containing regimen.[61,62] To be eligible for enrollment, patients must be at least 18 years of age, have achieved minimal response or better to at least one prior therapy, have progressive disease during or after the last regimen, not have prior pomalidomide exposure, and not be refractory to a proteasome inhibitor. Stage 1 will consist of 140 patients randomized 1:1:1:1 to receive 0.3-, 0.6-, or 1.0-mg doses of mezigdomide plus bortezomib and dexamethasone or PomVd for mezigdomide dose selection, and stage 2 will randomize 620 additional patients 1:1 to MeziVd or PomVd to assess efficacy and safety.[61]

SUCCESSOR-2 (NCT05552976) is an ongoing, phase 3, two-stage study comparing the efficacy and safety of mezigdomide in combination with carfilzomib and dexamethasone (MeziKd) versus carfilzomib and dexamethasone (Kd) in patients with relapsed or refractory multiple myeloma with progressive disease who have received at least one prior line of antimyeloma therapy including lenalidomide and an anti-CD38 monoclonal antibody.[62,63] Eligible patients must be at least 18 years of age, had to achieve minimal response or better to at least one prior therapy, and could not have received previous carfilzomib therapy. Stage 1 of the trial will consist of at least 128 patients randomized 3:3:3:2 to receive mezigdomide at 0.3-, 0.6-, or 1.0-mg doses and Kd versus the Kd arm for dose selection of mezigdomide in stage 2. Stage 2 will consist of 397 additional patients randomized 3:2 to receive MeziKd versus Kd.[63]

Both the SUCCESSOR-1 and SUCCESSOR-2 clinical trials have a primary endpoint of progression-free survival, a secondary endpoint including minimal residual disease, and are currently undergoing dose selection for stage 2.[62,64,65]

Iberdomide and Mezigdomide in the Multiple Myeloma Treatment Landscape

Neither iberdomide or mezigdomide has yet received regulatory approval for the treatment of multiple myeloma, and it is not yet clear which combination therapies would be best suited for the treatment of patients with this disease. Based on their mechanism of action and the data available to date, it seems likely that both drugs would be particularly attractive options in the treatment of patients who have experienced relapse or who are refractory to other treatment options or to improve outcomes for patients with newly diagnosed multiple myeloma. Iberdomide and mezigdomide have similar yet distinct profiles (Table 1).[66] The specificity, potency, and safety profile of iberdomide supports its use in early stages of multiple myeloma such as the newly diagnosed, early relapse, or maintenance setting, whereas the maximized potency of mezigdomide may better support its use in patients with more advanced disease, including those with extramedullary disease and a greater number of prior antimyeloma treatments including prior anti-BCMA therapy, and those with early relapse who are refractory to standard antimyeloma therapies. This aligns with the need for longer durations of a well-tolerated CELMoD agent with synergistic combinability with other immune approaches (such as anti-CD38 monoclonal antibodies), since longer treatment durations are more beneficial in providing meaningful responses in patients with limited disruptions to daily life. In addition, the convenience of oral therapies like iberdomide and mezigdomide may be a particularly attractive treatment option for all patients, particularly elderly or frail populations or those living in rural areas without access to specialized hospitals. Both iberdomide and mezigdomide have been described as a "potential new backbone" for myeloma treatment, thanks to their activity and encouraging safety profiles with no new safety events compared with other immunomodulatory drugs in relapsed or refractory multiple myeloma.[55,67] Given the immune-stimulatory effects of iberdomide and mezigdomide, it is possible that their combination with T cell-redirecting therapies

Table 1 Relative Properties of Iberdomide and Mezigdomide

	Iberdomide	Mezigdomide
Cereblon binding	++	+++
Targeted protein degradation	++	+++
Tumor antiproliferation	++	+++
Tumor apoptosis	++	+++
Immune stimulation	+++	+++
Synergistic combinations	+++	+++
Neutropenia	++	+++

Notes: + indicates the relative extent of each preclinical property for each compound. Adapted from Hartley-Brown et al[66] published under a Creative Commons Attribution License (CC BY) https://creativecommons.org/licenses/by/4.0/legalcode.

such as bispecific antibodies and CAR T cell therapy could augment their antitumor effects; this may be particularly effective in late-line relapsed or refractory multiple myeloma, where these therapies are less effective due to increased dysregulation in the CD4+ T cell compartment, which is essential for the activity of T cell-redirecting therapies.[30,68–70]

The most common adverse events observed to date with iberdomide and mezigdomide are hematologic, with neutropenia, anemia, and infections being among the most reported grade 3/4 adverse events in a number of trials and minimal or absent grade 3/4 nonhematologic adverse events. Neutropenia appears to be particularly common, occurring in more than half of patients in a number of treatment cohorts and more frequently with mezigdomide, and was managed by dosing schedule adjustments and treatment with granulocyte colony-stimulating factor.[37,58] The frequent occurrence of neutropenia with CELMoD compounds is not unexpected, given that the modulation of cereblon by CELMoD compounds has been shown to mediate the decrease of transcription factors required for neutrophil maturation.[71] Neutropenia management has been highlighted as a treatment burden by patients with relapsed or refractory multiple myeloma, with the steps taken to minimize the associated risk of infection negatively affecting patient quality of life; risk-minimizing behaviors such as avoiding crowds may contribute to feelings of isolation among patients with multiple myeloma.[3] Whilst low rates of MEZI discontinuation due to neutropenia were observed, careful consideration will need to be given to the management of adverse events, particularly neutropenia.

Ongoing phase 3 trials will provide important information on how iberdomide and mezigdomide might improve patient care, and where they might fit in the multiple myeloma treatment landscape. Given their more potent preclinical profiles than IMiD agents, it seems possible that iberdomide and mezigdomide could in the future form a standard of care in different disease settings, from maintenance to heavily pretreated multiple myeloma.

Limitations of the Current Evidence

As discussed, iberdomide and mezigdomide have shown promising efficacy and safety in patients with multiple myeloma. Nonetheless, the current evidence is primarily derived from early-phase clinical trials; these trials have small sample sizes and limited duration of follow-up in addition to having the potential for selection bias resulting in a patient population that is not fully representative of the broader real-world population. Further, given the open-label nature of these studies and variation between the patient populations with regards to factors such as number of prior lines of therapy and refractory status, generalizability of the findings is limited. The ongoing phase 3 EXCALIBER-RRMM, EXCALIBER-Maintenance, SUCCESSOR-1, and SUCCESSOR-2 trials are expected to provide more robust data and therefore help address these limitations, thereby facilitating more definitive conclusions regarding long-term efficacy and safety of CELMoD agents in the treatment of multiple myeloma.[23,24,64,65]

Conclusion

There remains an unmet need for novel treatment options in multiple myeloma, particularly for patients who have experienced relapse or who have become refractory to other antimyeloma treatments, to also improve the outcomes of patients with newly diagnosed multiple myeloma, and for more effective and less toxic maintenance therapies. Novel treatment modalities, such as targeted protein degradation by CELMoD compounds, have attracted particular interest due to their ability to expand the range of druggable protein targets in myeloma cells and the convenience of oral administration. Two oral CELMoD agents, iberdomide and mezigdomide, have the potential to provide therapeutic benefit even in patients who are refractory to lenalidomide and pomalidomide as well as other novel therapies, as evidenced by preclinical data from lenalidomide- and pomalidomide-resistant cell lines and mouse models. Importantly, iberdomide and mezigdomide are currently being evaluated for the treatment of patients with multiple myeloma in a number of trials, and results are so far encouraging, confirming the activity of these agents in relapsed and refractory patients with manageable side effects and favorable tolerability, and taken together, support the translation of these promising results to real-world practice.[72]

Abbreviations

ASCT, autologous stem cell transplantation; BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CRL, cullin-RING ubiquitin ligases; Dvd, daratumumab, bortezomib, and dexamethasone; IberDd, iberdomide with daratumumab and dexamethasone; IberKd, iberdomide with carfilzomib and dexamethasone; IberVd, iberdomide with bortezomib and dexamethasone; IMiD, immunomodulatory drug; MeziDd, mezigdomide, daratumumab, and dexamethasone; MeziEd, mezigdomide, elotuzumab, and dexamethasone; MeziKd, mezigdomide, dexamethasone, and carfilzomib; MeziVd, mezigdomide, dexamethasone, and bortezomib; NK, natural killer; PomVd, pomalidomide, bortezomib, and dexamethasone; TAZ, tazemetostat; TRAM, trametinib; VCD, bortezomib, cyclophosphamide, and dexamethasone.

Data Sharing Statement

No datasets were generated or used in the development of this manuscript.

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Author Contributions

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References

1. Goel U, Usmani S, Kumar S. Current approaches to management of newly diagnosed multiple myeloma. *Am J Hematol*. 2022;97(Suppl 1):S3–S25. doi:10.1002/ajh.26512
2. Kumar SK, Dispenzieri A, Lacy MQ, et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. *Leukemia*. 2014;28(5):1122–1128. doi:10.1038/leu.2013.313
3. Parsons JA, Greenspan NR, Baker NA, McKillop C, Hicks LK, Chan O. Treatment preferences of patients with relapsed and refractory multiple myeloma: a qualitative study. *BMC Cancer*. 2019;19(1):264. doi:10.1186/s12885-019-5467-x
4. van de Donk N, Pawlyn C, Yong KL. Multiple myeloma. *Lancet*. 2021;397(10272):410–427. doi:10.1016/S0140-6736(21)00135-5
5. Nooka AK, Kastritis E, Dimopoulos MA, Lonial S. Treatment options for relapsed and refractory multiple myeloma. *Blood*. 2015;125(20):3085–3099. doi:10.1182/blood-2014-11-568923
6. Larocca A, Cani L, Bertuglia G, Bruno B, Bringhen S. New strategies for the treatment of older myeloma patients. *Cancers (Basel)*. 2023;15(10):2693. doi:10.3390/cancers15102693
7. Crawford R, Gries KS, Valluri S, et al. The patient experience of relapsed refractory multiple myeloma and perspectives on emerging therapies. *Cancer Rep*. 2022;5(11):e1603. doi:10.1002/cnr2.1603
8. Chamberlain PP, D'Agostino LA, Ellis JM, et al. Evolution of cereblon-mediated protein degradation as a therapeutic modality. *ACS Med Chem Lett*. 2019;10(12):1592–1602. doi:10.1021/acsmedchemlett.9b00425
9. Thompson JW, Clayton T, Khambatta G, et al. Profiling CELMoD-mediated degradation of cereblon neosubstrates. *Methods Mol Biol*. 2021;2365:283–300. doi:10.1007/978-1-0716-1665-9_15
10. Raina K, Crews CM. Targeted protein knockdown using small molecule degraders. *Curr Opin Chem Biol*. 2017;39:46–53. doi:10.1016/j.cbpa.2017.05.016
11. Zheng N, Shabek N. Ubiquitin ligases: structure, function, and regulation. *Annu Rev Biochem*. 2017;86:129–157. doi:10.1146/annurev-biochem-060815-014922
12. Klaips CL, Jayaraj GG, Hartl FU. Pathways of cellular proteostasis in aging and disease. *J Cell Biol*. 2018;217(1):51–63. doi:10.1083/jcb.201709072
13. Shortt J. Mezigdomide and multiple myeloma. *N Engl J Med*. 2023;389(11):1046–1050. doi:10.1056/NEJMe2307370
14. Nguyen HC, Wang W, Xiong Y. Cullin-RING E3 ubiquitin ligases: bridges to destruction. *Subcell Biochem*. 2017;83:323–347. doi:10.1007/978-3-319-46503-6_12
15. Collins I, Wang H, Caldwell JJ, Chopra R. Chemical approaches to targeted protein degradation through modulation of the ubiquitin-proteasome pathway. *Biochem J*. 2017;474(7):1127–1147. doi:10.1042/BCJ20160762
16. Richardson PG, Mateos MV, Vangsted AJ, et al. The role of E3 ubiquitin ligase in multiple myeloma: potential for cereblon E3 ligase modulators in the treatment of relapsed/refractory disease. *Expert Rev Proteomics*. 2022;19(4–6):235–246. doi:10.1080/14789450.2022.2142564
17. Watson ER, Novick S, Matyskiela ME, et al. Molecular glue CELMoD compounds are regulators of cereblon conformation. *Science*. 2022;378(6619):549–553. doi:10.1126/science.add7574
18. Thakurta A, Pierceall WE, Amatangelo MD, et al. Developing next generation immunomodulatory drugs and their combinations in multiple myeloma. *Oncotarget*. 2021;12(15):1555–1563. doi:10.18632/oncotarget.27973
19. Krönke J, Udeshi ND, Narla A, et al. Lenalidomide causes selective degradation of IKZF1 and IKZF3 in multiple myeloma cells. *Science*. 2014;343(6168):301–305. doi:10.1126/science.1244851
20. Lu G, Middleton RE, Sun H, et al. The myeloma drug lenalidomide promotes the cereblon-dependent destruction of Ikaros proteins. *Science*. 2014;343(6168):305–309. doi:10.1126/science.1244917

21. Bjorklund CC, Lu L, Kang J, et al. Rate of CRL4(CRBN) substrate Ikaros and Aiolos degradation underlies differential activity of lenalidomide and pomalidomide in multiple myeloma cells by regulation of c-Myc and IRF4. *Blood Cancer J*. 2015;5(10):e354. doi:10.1038/bcj.2015.66
22. Matyskiela ME, Zhang W, Man HW, et al. A cereblon modulator (CC-220) with improved degradation of Ikaros and Aiolos. *J Med Chem*. 2018;61 (2):535–542. doi:10.1021/acs.jmedchem.6b01921
23. Bristol Myers Squibb. A study to compare iberdomide maintenance versus lenalidomide maintenance therapy following autologous stem cell transplant in participants with newly diagnosed multiple myeloma. Available from: https://clinicaltrials.gov/study/NCT05827016. Accessed February 14, 2025.
24. Celgene. Open-label study comparing iberdomide, daratumumab and dexamethasone (IberDd) versus daratumumab, bortezomib, and dexamethasone (DVd) in participants with relapsed or refractory multiple myeloma (RRMM) (EXCALIBER-RRMM). Available from: https://clinicaltrials.gov/study/NCT04975997. Accessed February 14, 2025.
25. Bjorklund CC, Kang J, Amatangelo M, et al. Iberdomide (CC-220) is a potent cereblon E3 ligase modulator with antitumor and immunostimulatory activities in lenalidomide- and pomalidomide-resistant multiple myeloma cells with dysregulated CRBN. *Leukemia*. 2020;34(4):1197–1201. doi:10.1038/s41375-019-0620-8
26. Lonial S, Amatangelo M, Popat R, et al. Translational and clinical evidence of a differentiated profile for the novel CELMoD, iberdomide (CC-220). *Blood*. 2019;134(Suppl 1):3119. doi:10.1182/blood-2019-124298
27. Amatangelo M, Van Oekelen O, Rahman AH, et al. Multidimensional single cell analysis shows increased T/NK cell subsets in both blood and bone marrow of iberdomide (CC-220) treated relapsed/refractory multiple myeloma patients. *Blood*. 2019;134(Suppl 1):1775. doi:10.1182/blood-2019-126146
28. Van Oekelen O, Amatangelo M, Guo M, et al. Iberdomide increases innate and adaptive immune cell subsets in the bone marrow of patients with relapsed/refractory multiple myeloma. *Cell Rep Med*. 2024;5(6):101584. doi:10.1016/j.xcrm.2024.101584
29. Amatangelo M, Flynt E, Stong N, et al. RRMM and post-BCMA treated subjects from the CC-220-MM-001 study show increased genomic aberrations associated with high-risk and significant dysfunction in CD4+ T-cell compartment compared to NDMM subjects. *Blood*. 2023;142 (Suppl 1):4665. doi:10.1182/blood-2023-178912
30. Amatangelo M, Flynt E, Stong N, et al. Pharmacodynamic changes in tumor and immune cells drive iberdomide's clinical mechanisms of activity in relapsed and refractory multiple myeloma. *Cell Rep Med*. 2024;5(6):101571. doi:10.1016/j.xcrm.2024.101571
31. Amatangelo M, Bjorklund C, Kang J, et al. Preclinical and translational support for clinical development of iberdomide in combination with proteasome inhibitors: mechanism of synergy in clinical trial CC-220-MM-001. *Blood*. 2020;136(Suppl 1):8–9. doi:10.1182/blood-2020-137710
32. Amatangelo M, Bjorklund C, Ma P, et al. Preclinical and translational data support development of iberdomide in combination with CD38- and SLAMF7-directed monoclonal antibodies: evidence for rational combinations. *Blood*. 2020;136(Suppl 1):9–10. doi:10.1182/blood-2020-137667
33. Amatangelo M, Bjorklund CC, Kang J, Polonskaia A, Viswanatha S, Thakurta A. Iberdomide (CC-220) has synergistic anti-tumor and immunostimulatory activity against multiple myeloma in combination with both bortezomib and dexamethasone, or in combination with daratumumab in vitro. *Blood*. 2018;132(Suppl 1):1935. doi:10.1182/blood-2018-99-113383
34. Amatangelo M, Stong N, Maciag P, et al. Iberdomide, daratumumab, and dexamethasone shows deep antimyeloma activity across molecular patient subsets with transplant-ineligible newly diagnosed multiple myeloma from the CC-220-MM-001 trial. *Blood*. 2024;144(Suppl 1):1973. doi:10.1182/blood-2024-199016
35. Paiva B, Gaffney B, Burnett K, et al. Synergistic antitumor activity of alnuctamab (ALNUC; BMS-986349; CC-93269), a BCMA 2+1 T cell engager (TCE), and CELMoD agents in multiple myeloma (MM) preclinical models. *Blood*. 2022;140(Suppl 1):7054–7055. doi:10.1182/blood-2022-157987
36. Aleman A, Kogan-Zadjman A, Upadhyaya B, et al. Improving anti-BCMA CAR-T functionality with novel immunomodulatory agent iberdomide (CC220) in multiple myeloma. *Clin Lymphoma Myeloma Leuk*. 2023;23(Suppl 2):S131–S132. doi:10.1016/S2152-2650(23)01793-7
37. Lonial S, Richardson PG, Popat R, et al. Iberdomide (IBER) in combination with dexamethasone (DEX) and daratumumab (DARA), bortezomib (BORT), or carfilzomib (CFZ) in patients (pts) with relapsed/refractory multiple myeloma (RRMM). *HemaSphere*. 2021;5(Suppl 2):49. doi:10.1097/HS9.0000000000000566
38. van de Donk NWCJ, Popat R, Larsen J, et al. First results of iberdomide (IBER; CC-220) in combination with dexamethasone (DEX) and daratumumab (DARA) or bortezomib (BORT) in patients with relapsed/refractory multiple myeloma (RRMM). *Blood*. 2020;136(Suppl 1):16–17. doi:10.1182/blood-2020-137743
39. Lonial S, Popat R, Hulin C, et al. Iberdomide plus dexamethasone in heavily pretreated late-line relapsed or refractory multiple myeloma (CC-220-MM-001): a multicentre, multicohort, open-label, phase 1/2 trial. *Lancet Haematol*. 2022;9(11):e822–e832. doi:10.1016/S2352-3026(22)00290-3
40. Lonial S, Abdallah A-O, Anwer F, et al. Iberdomide (IBER) in combination with dexamethasone (DEX) in relapsed/refractory multiple myeloma (RRMM): results from the anti-b-cell maturation antigen (BCMA)-exposed cohort of the CC-220-MM-001 trial. *Blood*. 2022;140(Suppl 1):4398–4400. doi:10.1182/blood-2022-158180
41. Lonial S, Richardson PG, Popat R, et al. Iberdomide (IBER) in combination with dexamethasone (DEX) and daratumumab (DARA), bortezomib (BORT), or carfilzomib (CFZ) in patients (pts) with relapsed/refractory multiple myeloma (RRMM). Oral presentation at: 26th Congress of the European Hematology Association; June 9-17, 2021; virtual.
42. White D, Lipa B, Gironella M, et al. Iberdomide, bortezomib, and dexamethasone (IberVd) in transplant-ineligible newly diagnosed multiple myeloma (NDMM): results from the CC-220-MM-001 trial. *Clin Lymphoma Myeloma Leuk*. 2023;23(Suppl 2):S25. doi:10.1016/S2152-2650(23)01608-7
43. Sureda Balari A, Khan A, Oriol A, et al. Iberdomide, daratumumab, and dexamethasone (IberDd) in transplant-ineligible (TNE) newly diagnosed multiple myeloma (NDMM): results from the CC-220-MM-001 trial. *Clin Lymphoma Myeloma Leuk*. 2024;24(Suppl 2):S35. doi:10.1016/S2152-2650(24)01896-2
44. van de Donk N, Raab M, Besemer B, et al. Efficacy, safety, and pharmacokinetics of iberdomide plus dexamethasone in patients with relapsed/refractory multiple myeloma by renal function: a subgroup analysis of the CC-220-MM-001 trial. *Clin Lymphoma Myeloma Leuk*. 2022;22:S191–S192. doi:10.1016/S2152-2650(22)00609-7
45. Lonial S, Quach H, Dimopoulos MA, et al. EXCALIBER-RRMM: a phase 3, two-stage study of iberdomide, daratumumab, and dexamethasone (IberDd) versus daratumumab, bortezomib, and dexamethasone (DVd) in patients (pts) with relapsed/refractory multiple myeloma (RRMM). *J Clin Oncol*. 2023;41(Suppl 16):TPS8069. doi:10.1200/JCO.2023.41.16_suppl.TPS8069
46. van de Donk NWCJ, Touzeau C, Trudeau E, et al. Iberdomide maintenance after autologous stem-cell transplantation in newly diagnosed MM: first results of the phase 2 EMN26 study. *Blood*. 2023;142(Suppl 1):208. doi:10.1182/blood-2023-177564

47. Gay F, Touzeau C, Terpos E, et al. Iberdomide maintenance after autologous stem-cell transplantation in patients with newly diagnosed multiple myeloma: an update from the phase 2 EMN26 trial. *HemaSphere*. 2024;8(Suppl 1):1703–1704 doi:10.1002/hem3.104.
48. Gay F, Dimopoulos M, Huang X, et al. A phase 3, two-stage, randomized study of iberdomide maintenance versus lenalidomide maintenance post autologous stem cell transplantation in newly diagnosed multiple myeloma: EXCALIBER-maintenance. *Clin Lymphoma Myeloma Leuk*. 2023;23 (Suppl 1):S111. doi:10.1016/S2152-2650(23)01755-X
49. Hansen JD, Correa M, Nagy MA, et al. Discovery of CRBN E3 ligase modulator CC-92480 for the treatment of relapsed and refractory multiple myeloma. *J Med Chem*. 2020;63(13):6648–6676. doi:10.1021/acs.jmedchem.9b01928
50. Lopez-Girona A, Havens CG, Lu G, et al. CC-92480 is a novel cereblon E3 ligase modulator with enhanced tumoricidal and immunomodulatory activity against sensitive and resistant multiple myeloma cells. *Blood*. 2019;134(Suppl 1):1812. doi:10.1182/blood-2019-124338
51. Chen LY, Van Oekelen O, Amatangelo M, et al. Mezigdomide treatment in relapsed-refractory myeloma patients shifts bone marrow NK and T cell populations from exhaustion to activation. *Blood*. 2023;142(Suppl 1):4686. doi:10.1182/blood-2023-187748
52. Chiu H, Zhao J, Ortiz Estevez M, Hagner PR, Gandhi AK. Mezigdomide reverses T-cell exhaustion through degradation of Aiolos/Ikaros and reinvigoration of cytokine production pathways. *Blood*. 2023;142(Suppl 1):335. doi:10.1182/blood-2023-189445
53. Wong L, Narla RK, Leisten J, et al. CC-92480, a novel cereblon E3 ligase modulator, is synergistic with dexamethasone, bortezomib, and daratumumab in multiple myeloma. *Blood*. 2019;134(Suppl 1):1815. doi:10.1182/blood-2019-124345
54. Chari A, Minnema MC, Berdeja JG, et al. Talquetamab, a T-cell-redirecting GPRC5D bispecific antibody for multiple myeloma. *N Engl J Med*. 2022;387(24):2232–2244. doi:10.1056/NEJMoa2204591
55. Richardson PG, Trudel S, Popat R, et al. Mezigdomide plus dexamethasone in relapsed and refractory multiple myeloma. *N Engl J Med*. 2023;389 (11):1009–1022. doi:10.1056/NEJMoa2303194
56. Trudel S, Bahlis NJ, Popat R, et al. Impact of renal impairment (RI) on pharmacokinetics (PK) and clinical outcomes with mezigdomide plus dexamethasone (DEX) in relapsed/refractory multiple myeloma (RRMM). *J Clin Oncol*. 2024;42(Suppl 16):7539. doi:10.1200/JCO.2024.42.16_suppl.7539
57. Richardson PG, Sandhu I, Hofmeister CC, et al. Mezigdomide (MEZI) plus dexamethasone (DEX) and daratumumab (DARA) or elotuzumab (ELO) in patients (pts) with relapsed/refractory multiple myeloma (RRMM): results from the CC-92480-MM-002 trial. *Blood*. 2023;142(Suppl 1):1013. doi:10.1182/blood-2023-174443
58. Richardson PG, Sandhu I, Hofmeister CC, et al. Mezigdomide (MEZI) plus dexamethasone (DEX) and daratumumab (DARA) or elotuzumab (ELO) in patients (pts) with relapsed/refractory multiple myeloma (RRMM): results from the CC-92480-MM-002 trial. Oral presentation at the 65th American Society of Hematology Annual Meeting; December 9-12, 2023; San Diego, CA, USA.
59. Sandhu I, Richardson PG, Oriol A, et al. Mezigdomide (MEZI) plus dexamethasone (DEX) and bortezomib (BORT) or carfilzomib (CFZ) in patients (pts) with relapsed/refractory multiple myeloma (RRMM): updated results from the CC-92480-MM-002 trial. *Blood*. 2024;144(Suppl 1):1025. doi:10.1182/blood-2024-198408
60. Costa LJ, Popat R, Siegel D, et al. Mezigdomide (MEZI) in novel-novel combinations for relapsed or refractory multiple myeloma (RRMM): preliminary results from the CA057-003 trial. *Blood*. 2024;144(Suppl 1):677. doi:10.1182/blood-2024-198403
61. Richardson PG, Badelita SN, Besemer B, et al. A phase III, two-stage, randomized study of mezigdomide, bortezomib, and dexamethasone (MeziVd) versus pomalidomide, bortezomib, and dexamethasone (PVd) in relapsed/refractory multiple myeloma (RRMM): SUCCESSOR-1. *Clin Lymphoma Myeloma Leuk*. 2023;23(Suppl 1):S228. doi:10.1016/S2152-2650(23)00876-5
62. Dimopoulos M, Badelita S, Schjesvold F, et al. Phase 3, two-stage, randomized trials of mezigdomide-based regimens versus standard regimens in relapsed/refractory multiple myeloma (RRMM): SUCCESSOR-1 (MeziVd vs PVd) and SUCCESSOR-2 (MeziKd vs Kd). *Clin Lymphoma Myeloma Leuk*. 2024;24(Suppl 2):S258. doi:10.1016/S2152-2650(24)02291-2
63. Richardson PG, Amatangelo M, Berenson JR, et al. A phase 3, two-stage, randomized study of mezigdomide, carfilzomib, and dexamethasone (MeziKd) versus carfilzomib and dexamethasone (Kd) in relapsed/refractory multiple myeloma (RRMM): SUCCESSOR-2. *J Clin Oncol*. 2023;41 (Suppl 16):TPS8070. doi:10.1200/JCO.2023.41.16_suppl.TPS8070
64. Bristol Myers Squibb. A study to evaluate mezigdomide, bortezomib and dexamethasone (MEZIVd) versus pomalidomide, bortezomib and dexamethasone (PVd) in participants with relapsed or refractory multiple myeloma (RRMM) (SUCCESSOR-1). Available from: https://clinicaltrials.gov/study/NCT05519085. Accessed May 14, 2025.
65. Bristol Myers Squibb. A study to evaluate mezigdomide in combination with carfilzomib and dexamethasone (MeziKD) versus carfilzomib and dexamethasone (Kd) in participants with relapsed or refractory multiple myeloma (SUCCESSOR-2). Available from: https://clinicaltrials.gov/study/NCT05552976. Accessed May 14, 2025.
66. Hartley-Brown MA, Mo CC, Nadeem O, et al. Mezigdomide—a novel cereblon E3 ligase modulator under investigation in relapsed/refractory multiple myeloma. *Cancers (Basel)*. 2024;16(6):1166. doi:10.3390/cancers16061166
67. Rodriguez-Otero P, San-Miguel JF. Iberdomide with dexamethasone: a new backbone for myeloma treatment? *Lancet Haematol*. 2022;9(11):e799–e801. doi:10.1016/S2352-3026(22)00322-2
68. Kravtsov DS, Erbe AK, Sondel PM, Rakhmilevich AL. Roles of CD4+ T cells as mediators of antitumor immunity. *Front Immunol*. 2022;13:972021. doi:10.3389/fimmu.2022.972021
69. Wang D, Aguilar B, Starr R, et al. Glioblastoma-targeted CD4+ CAR T cells mediate superior antitumor activity. *JCI Insight*. 2018;3(10):e99048. doi:10.1172/jci.insight.99048
70. Perez-Diez A, Joncker NT, Choi K, et al. CD4 cells can be more efficient at tumor rejection than CD8 cells. *Blood*. 2007;109(12):5346–5354. doi:10.1182/blood-2006-10-051318
71. Li S, Fu J, Wang H, et al. IMiD compounds affect CD34(+) cell fate and maturation via CRBN-induced IKZF1 degradation. *Blood Adv*. 2018;2 (5):492–504. doi:10.1182/bloodadvances.2017010348
72. Richardson PG, San Miguel JF, Moreau P, et al. Interpreting clinical trial data in multiple myeloma: translating findings to the real-world setting. *Blood Cancer J*. 2018;8(11):109. doi:10.1038/s41408-018-0141-0