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A Review of the Immunomodulatory Activity of Novel Drug Iberdomide (CC-220) for Multiple Myeloma

Sherlyn Anne Cardenas[1], Cristina Jaida Cosio[1], Shen Lee Cua[1], Faith Joy Domingo[1], Donna Rose Gido[1], Alexander Johann Lim III[1], Jacqueline Abiso-Padilla[2]

[1,2]San Pedro College, Davao City, 8000, Philippines

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A B S T R A C T

Iberdomide (CC-220) is a novel immunomodulatory drug currently under investigation for the treatment of multiple myeloma (MM), demonstrating potential therapeutic efficacy in clinical trials. It is a cereblon E3 ligase modulator (CELMoD) that functions by stimulating the ubiquitination and proteasome-dependent degradation of the Ikaros and Aiolos proteins, which leads to tumoricidal and immunomodulatory action in myeloma cells. Preclinical studies demonstrate Iberdomide's potent anti-myeloma and immunomodulatory activities, surpassing established immunomodulatory drugs (IMiDs) like Lenalidomide and Pomalidomide. Iberdomide's enhanced cereblon binding affinity suggests superior efficacy in degrading key transcription factors crucial for MM cell survival. Initial clinical trial data indicate favorable safety profiles and promising efficacy, particularly in combination regimens. Preclinical and initial clinical data suggest its potential to overcome immunomodulatory drug resistance and enhance the immune-mediated killing of MM cells. Ongoing Phase 3 trials and additional studies will be crucial for evaluating long-term efficacy, safety, and optimal dosage, positioning Iberdomide as a transformative agent in refractory and relapsed MM scenarios.

Keywords: Iberdomide, CC-220, Multiple myeloma, MM, Cereblon E3 ligase modulator, CELMoD, Immunomodulatory drugs, IMiD

1. Introduction

Multiple myeloma (MM) is a hematologic malignancy marked by the neoplastic proliferation of plasma cells within the bone marrow, resulting in monoclonal gammopathy, skeletal destruction, and a spectrum of clinical manifestations [1-4]. The condition can result in bone marrow failure, causing anemia, weakened immune function leading to infections, pathological fractures, bone abnormalities, increased blood thickness (hyperviscosity), elevated calcium levels (hypercalcemia), and renal failure [5,6].

According to data from the International Agency for Research on Cancer, the estimated global incidence of multiple myeloma (MM) in 2018 was 160,000 cases, constituting 0.9% of all cancer diagnoses. The global mortality from myeloma was 106,000 patients, accounting for 1.1% of all cancer-related deaths. Among these cases, approximately 90,000 were male and 70,000 were female, resulting in age-standardized incidences of 2.1/100,000 and 1.4/100,000, respectively. The cumulative risk of being diagnosed with MM from birth to age 74 is 0.24% for men and 0.17% for women, indicating a 50% higher likelihood in men [7,8]. Multiple myeloma constitutes 10–15% of new hematological neoplasm diagnoses globally, making it the second most common hematological cancer [9]. Typically affecting older individuals (with a median age of diagnosis at 61 years for men and 62 years for women), the disease can also be diagnosed in younger individuals (15% under 60 years and 2% under 40 years). The incidence is notably higher in African-Americans compared to Caucasians, while Chinese and other Asian populations experience lower rates. Across all racial groups, men have a higher incidence than women [10-13].

In the last few years, the range of treatments for multiple myeloma (MM) has significantly grown, resulting in extended survival rates. Despite these advancements, the majority of patients still face the challenge of a lack of definitive cure [5]. Many individuals will experience periods of remission and relapse until resistance to existing therapies develops [5,14]. Although MM remains incurable, various drug therapies, along with autologous stem cell transplantation, radiation, and, in specific situations, surgical interventions, play a crucial role in managing patients with MM [15,16].

The primary pharmaceutical treatments for multiple myeloma include novel drugs such as proteasome inhibitors, immunomodulatory drugs (IMiDs), monoclonal antibodies, B-cell maturation antigen (BCMA)-targeted therapies, and traditional drugs like corticosteroids. Although these drugs operate through different mechanisms, their common objective is to manage and eliminate multiple myeloma cells. Immunomodulators, an essential class of drugs in standard treatments for multiple myeloma, are used to activate specific immune system cells, impede myeloma cell growth, and even directly cause myeloma cell death. Lenalidomide (Revlimid), pomalidomide (Pomalyst), and the less frequently used thalidomide (Thalomid) are clinically

effective immunomodulatory drugs for cancer therapy, including newly diagnosed and relapsed/refractory multiple myeloma (RRMM). These drugs target cereblon (CRBN), a substrate receptor for the CRL4 (CUL4-DDB1-RBX1) ubiquitin ligase complex [17,18].

Recently, new thalidomide analogs, namely CC-122 (Avadomide), CC-220 (Iberdomide), CC-92480 (Mezigdomide), and CC-885 have been developed and are currently undergoing active clinical trials. This next generation of IMiDs, called CRBN E3 Ligase Modulators (CELMoDs), have broader biological activity sought for their higher efficacy and more favorable toxicity profile. Iberdomide (CC-220) is a thalidomide analog in clinical development for treating relapsed/refractory multiple myeloma (RRMM) and systemic lupus erythematosus (SLE) [19]. Iberdomide exhibits a higher affinity for cereblon than lenalidomide or pomalidomide, as well as increased potency in the cellular degradation of cereblon substrates Ikaros and Aiolos, which are encoded by the genes IKZF1 and IKZF3, respectively. This suggests that Iberdomide has greater effectiveness in degrading zinc finger transcription factors IKZF1 and IKZF3 by tightly binding to the CRL4CRBN E3 ligase. This provides an illustration of how the binding affinity of E3 ligases can influence other endeavors in drug discovery focused on targeted protein degradation [20].

This review article critically examines the immunomodulatory activity of CC-220 (Iberdomide) in the context of its potential application in the treatment of multiple myeloma. By exploring the epidemiology of MM, its clinical manifestations, existing treatment modalities, and the current clinical data on Iberdomide, this review aims to provide a comprehensive analysis of Iberdomide's impact on the immunomodulation of the disease. Understanding Iberdomide's mechanism of action and reviewing it with existing literature on immunomodulatory drugs and multiple myeloma treatments will contribute valuable insights into its therapeutic potential.

2. Methods

The researchers conducted an extensive article review utilizing various reputable databases, including the National Library of Medicine - National Center for Biotechnology Information (NCBI), MEDLINE (PubMed), and Google Scholar. These databases were employed to retrieve systematic reviews and clinical trials related to the novel drug CC-220, also known as Iberdomide, for the treatment of multiple myeloma (MM).

ClinicalTrials.gov and HemaSphere were specifically utilized to obtain clinical trial results. ClinicalTrials.gov is a comprehensive registry and results database of privately and publicly funded clinical studies conducted around the world, providing a valuable source for information on ongoing and completed trials. HemaSphere, on the other hand, is a specialized platform that focuses on hematologic diseases and could provide specific insights into clinical trials related to multiple myeloma.

The analysis of article titles and abstracts obtained through search engines enabled the researchers to determine whether the materials retrieved met the inclusion criteria for the article review. The comprehensive review aimed to present a thorough examination of the potential benefits of employing Iberdomide as a treatment option for multiple myeloma, integrating information from diverse sources to provide a comprehensive overview of the drug's efficiency and safety.

3. Pathogenesis of Multiple Myeloma

Multiple myeloma (MM) is a disease of unknown exact etiology and high heterogeneity, manifesting various symptoms, clinical presentations, and genetic variability [1-4,21]. Malignant plasma cells generate an anomalous antibody known as M protein, the hallmark characteristic of MM, marked by elevated concentrations of this abnormal immunoglobulin [22]. The pathological interplay of dysregulated plasma cell growth and aberrant antibody production underscores the pathophysiological basis of MM [21-22].

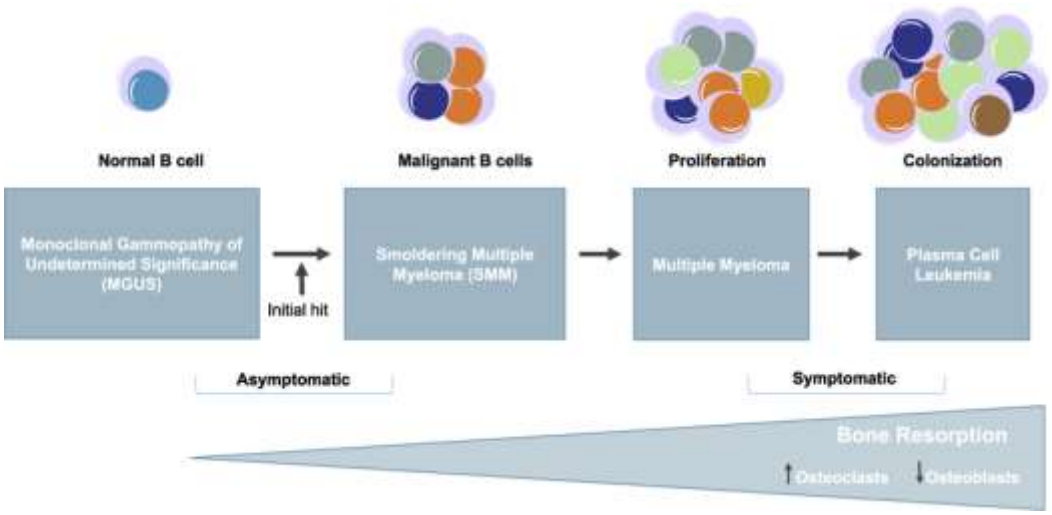


Fig. 1 – Stages of Multiple Myeloma Progression. Adopted from Ullah (2019) [23].

The progression of MM, as seen in Figure 1, typically follows the development of monoclonal gammopathy of undetermined significance (MGUS), a premalignant condition arising from mutations in plasma cells that restore their ability to proliferate where clonal plasma cells constitute less than 10% of the bone marrow, with serum protein levels below 3 g/dL and an absence of myeloma-related organ damage [23-24]. An intermediate stage, termed smoldering MM, is characterized by an M protein level of 3 g/dL or higher, over 10% clonal plasma cells in the bone marrow, and no symptomatic organ damage related to myeloma [23-24]. Various cytogenetic abnormalities are observed in MGUS and MM, wherein roughly half of the cases exhibit hyperdiploid, often with extra copies of odd-numbered chromosomes. The remaining cases are non-hyperdiploid, typically involving a primary translocation of the Ig heavy-chain gene at 14q32 [25]. Dysregulation of the cyclin D/retinoblastoma (cyclin D/RB) pathway is a common factor in nearly all cases, contributing to the genetic diversity associated with the rapid development of drug resistance in MM [25].

MM transitions from an asymptomatic state to a symptomatic one by initially acquiring foundational genetic instability, followed by subsequent genetic and epigenetic changes [23]. This progression amplifies bone resorption and, in advanced stages, extends beyond the bone marrow to extramedullary sites, contributing to increased disease aggressiveness. This expansion may be associated with plasma cell leukemia, characterized by elevated malignant plasma cells in peripheral blood, which concurrently exhibit enhanced bone resorption capabilities by releasing factors inducing bone tissue breakdown [23-25].

Emerging evidence underscores the pivotal role of the bone marrow microenvironment in the pathogenesis of myelomas, leading to an expansion of treatment options [26]. Cytokines, notably interleukin-6 (IL-6), are pivotal in the pathogenesis of MM, inhibiting apoptosis, interacting with factors implicated in MM pathogenesis, including adhesion molecules, tumor suppressor genes, and oncogenes, and neutralizing its effect may lead to tumor regression, with tumor necrosis factor and IL-1b being additional relevant cytokines [27].

CC-220 (Iberdomide)

Iberdomide (CC-220) is an investigational drug being actively developed by Bristol Myers Squibb (BMS) for the treatment of several types of cancer, with a significant focus on multiple myeloma and lymphoma [28]. Iberdomide is an orally available derivative of thalidomide, which binds to the cereblon E3 ubiquitin ligase complex with increased affinity for cereblon (CRBN). It exhibits a unique chemical structure in contrast to other thalidomide analogs (Figure 2), suggesting a potential for broader target specificity [20,29-31]. Initially discovered by Celgene Corporation, a biopharmaceutical company specializing in similar therapies, Iberdomide's ownership transitioned to BMS in 2019 through a major acquisition [32].

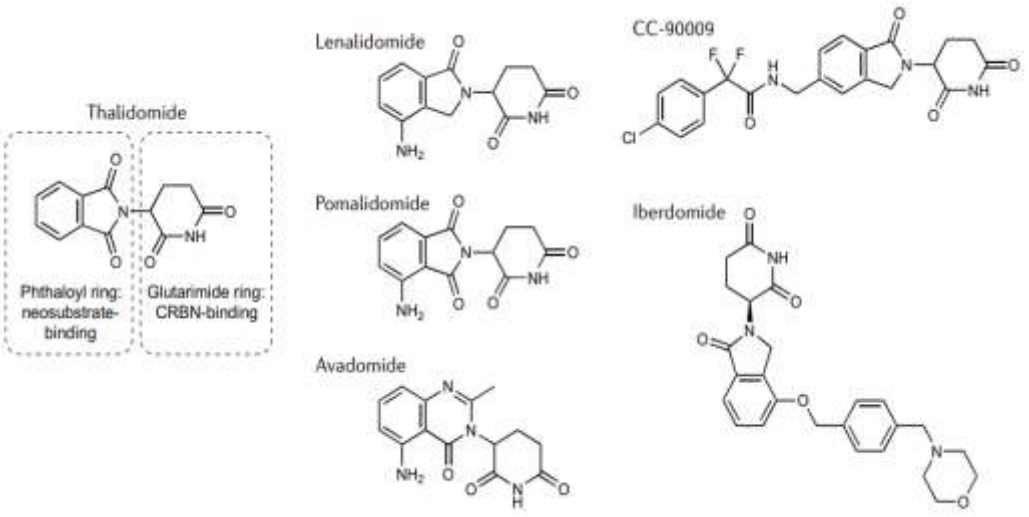
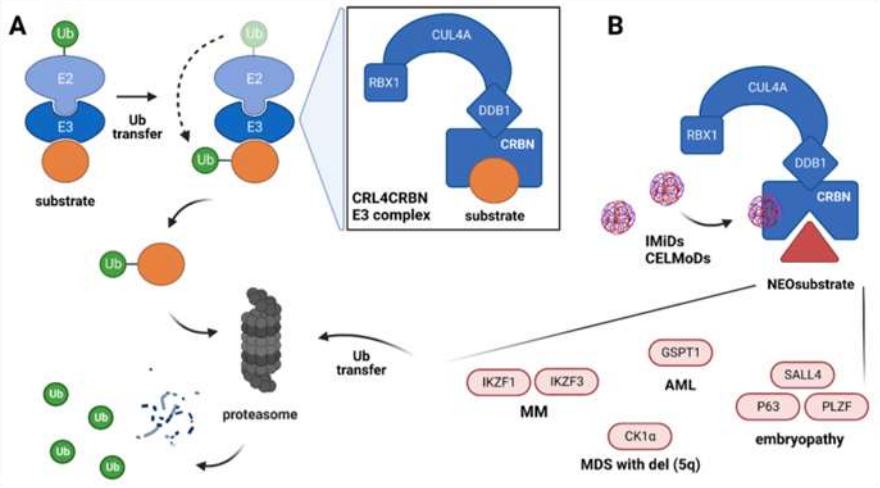


Fig. 2 – Thalidomide Analog Chemical Structures. Adopted from Jan *et al.* (2021) [33].

Bristol-Myers Squibb (BMS) is a globally recognized biopharmaceutical company with a distinct emphasis on developing and commercializing innovative drugs, particularly within the field of oncology; they have cultivated a comprehensive portfolio addressing various malignancies, including lung, melanoma, hematologic, and solid tumors [34]. The company has made notable contributions to cancer treatment through its leadership in immunotherapy, exemplified by successful checkpoint inhibitors like nivolumab (Opdivo) and ipilimumab (Yervoy) [35-36]. BMS has strategically expanded its oncology capabilities through acquisitions and collaborations, as demonstrated by the acquisition of Celgene, reinforcing its position in developing immunomodulatory drugs such as Iberdomide [32].

4.1 Mechanism of Action

Iberdomide (IBER; CC-220) is a Cereblon E3 Ligase Modulator (CELMoD), a novel class of drugs derived from IMiDs. Despite sharing certain mechanistic similarities, CELMoDs exhibit distinct modes of action from IMiDs, leading to differentiated therapeutic profiles [37]. Iberdomide operates by targeting and binding to cereblon (CRBN), a protein that acts as a substrate receptor, within the cullin-ring ligase-4 cereblon (CRL4CRBN) E3 ubiquitin ligase complex. The E3 ubiquitin ligase complex is formed by cereblon (CRBN), damaged DNA binding protein 1 (DDB1), cullin-4A (CUL4A), and RING-box protein 1 (RBX1), also known as a regulator of cullins 1 (ROC1) as shown in Figure 3A [20,38-39].



(A) Overview of the ubiquitination process via CRL4CRBN E3 ligase complex.
(B) Mechanism of CRBN-mediated effects upon exposure to thalidomide and its derivatives.

Fig. 3 – Ubiquination Process and Mechanism of Action of IMiDs and CELMoDs. Adopted from Barankiewicz *et al.* (2022) [38].

Contrary to traditional inhibition, ligand binding to CRBN induces neomorphic and anti-myeloma activity. Binding to CRBN leads to an altered substrate selectivity of the ubiquitin ligase, which facilitates the recruitment of target proteins essential for myeloma cell survival. Substrate proteins essential for myeloma cell survival bound to the CRL4CRBN complex are ubiquitinated, leading to proteolysis by the 26S proteasome [20,39-40]. The key neosubstrates in plasma cells are the Ikaros and Aiolos proteins, which are members of the Ikaros family zinc finger transcription factors encoded by the IKZF1 and IKZF3 genes, respectively. They regulate cell fate in normal lymphopoiesis, plasma cell development, and homeostasis [41-42]. The degradation of IKZF1 and IKZF3 via CRBN-dependent ubiquitination results in the downregulation of IRF4 and c-MYC, both of which are essential oncogenic transcription factors for malignant plasma cell growth in MM (Figure 3B) [37,39,43-44]. In addition to their direct anti-myeloma effects, these drugs exhibit indirect anti-myeloma activity by suppressing the release of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin IL-1, IL-6, IL-12, and IL-16. This cytokine blockade starves MM cells of growth and survival signals, inhibiting proliferation and ultimately promoting apoptosis [37,45-46].

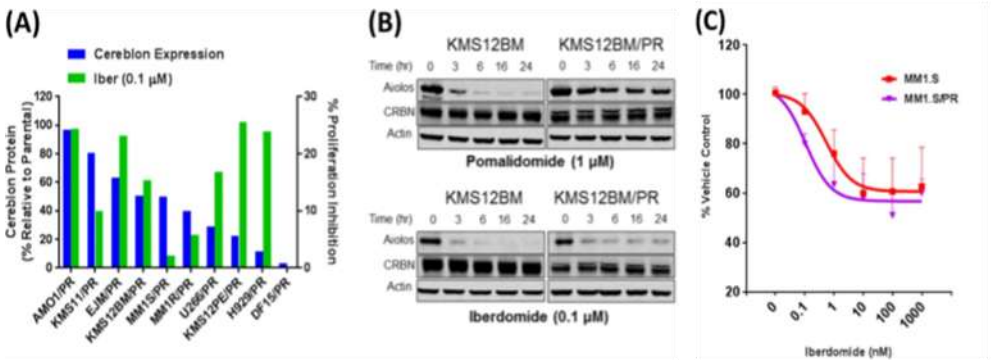
CELMoDs demonstrate superior CRBN binding affinity in comparison to IMiDs, corresponding to the higher degradation of Ikaros' and Aiolos' transcription factors. This translates to enhanced anti-myeloma activity and immunomodulatory effects [20]. Iberdomide exhibits an approximately 10 to 20-fold greater affinity for CRBN as compared to Lenalidomide and Pomalidomide, leading to significantly more potent and efficient degradation of Ikaros and Aiolos [20,38,47]. Analysis of the crystal structure of the Iberdomide-CRBN-DDB1 complex reveals that its enhanced potency is linked to expanded interactions with cereblon outside the predicted binding site of Ikaros and Aiolos [20]. Iberdomide's enhanced CRL4CRBN E3 ligase complex binding affinity, as revealed by its crystal structure, translates to potent Ikaros and Aiolos degradation. This enables the use of lower dosing, minimizing potential off-target effects [48]. The increased potency of CELMoDs explains their enhanced cell-autonomous activity and their effectiveness in situations where the CRBN protein is present in lower amounts or is dysfunctional from IMiD resistance due to mutations or splicing errors [47].

4.2 Pre-Clinical Studies

Preclinical evaluations revealed that Iberdomide (IBER; CC-220) exhibits promising anticancer and immunomodulatory activities, providing a substantial foundation for potential application in MM treatment. Through comprehensive analyses involving POM-sensitive and acquired-resistant MM cell lines, as well as peripheral blood mononuclear cells (PBMCs) from healthy volunteers and bone marrow from RRMM patients, IBER demonstrated its efficacy in inducing potent tumoricidal effects, surpassing established immunomodulatory drugs lenalidomide (LEN) and pomalidomide (POM) [29,49-51].

In specific evaluations targeting LEN- and POM-sensitive and -resistant MM cell lines, IBER demonstrated elevated antiproliferative activity, particularly evident in LEN-sensitive (H929) and acquired LEN-resistant (H929/LR) cell lines (Figure 4A). In a panel of MM cell lines across a range of concentrations, IBER demonstrated pronounced antiproliferative effects, surpassing the impact of lenalidomide and pomalidomide (Figure 4B). Molecular insights into IBER's mechanism of action revealed a distinctive profile characterized by a higher cereblon-binding affinity (IC50 ~150 nM) compared to POM and LEN. This higher affinity suggests a more potent interaction between Iberdomide and cereblon compared to pomalidomide and lenalidomide.

Notably, Iberdomide induced greater apoptosis than pomalidomide across all MM cell lines tested, even at a tenfold lower concentration within the estimated clinical activity range. Additionally, Iberdomide's comparable PBMC-mediated cytotoxicity against both parental MM1.S cells and MM1.S/PR cells in PBMC co-culture killing experiments further emphasizes its consistent and potent immunomodulatory effects across different MM cell scenarios (Figure 4C) [29].



(A) Iberdomide (IBER) activity in POM-resistant cell lines.
(B) Western blot analysis illustrating the effects of either POM (1 μM) or IBER (0.1 μM) on the degradation kinetics of Aiolos in both the parental sensitive KMS 12 BM and POM-resistant KMS12BM/PR.
(C) In PBMC co-culture experiments, CD3-stimulated PBMCs were treated with IBER (0.0001-1 μM) for 72 hours and then combined with either the parental MM1.S (CFSE-stained) or POM-resistant MM1.S/PR (CFSE-stained) cells for the final 4 hours.

Fig. 4 – Iberdomide Comparison to Pomalidomide and Lenalidomide. Adopted from Bjorklund *et al.* (2019) [29].

In combination studies with monoclonal antibodies (mAbs), IBER demonstrated potent immunomodulatory effects. CD3-stimulated PBMCs treated with IBER exhibited a more potent increase in cytokine secretion than immunomodulatory drugs (IMiDs), fostering natural killer (NK) cell proliferation and amplifying immune-mediated killing of MM cell lines. Remarkably, IBER treatment of MM cells induced elevated CD38 protein expression, and its combination with daratumumab (DARA) or elotuzumab (ELO) displayed superior immune-mediated killing of MM cell lines compared to LEN or POM combined with the same mAbs [49]. Further highlighting IBER's potential clinical use, synergistic antiproliferative effects were observed in combination studies with bortezomib and dexamethasone. Immune-mediated cytotoxicity assessments revealed that IBER when combined with DARA, exhibited a greater inhibitory effect on MM cells compared to either drug alone. An ADCC assay emphasized IBER's potent immune-mediated cytotoxicity and its ability to augment daratumumab-mediated ADCC [29,51].

The evaluation of IBER's pharmacological properties highlighted minimal interference with substrate degradation when combined with proteasome inhibitors, highlighting its efficacy in inducing potent tumoricidal activity. These collective findings, supported by synergistic antiproliferative effects and increased apoptosis compared to established drug combinations, present a compelling rationale for continued exploration of IBER as a promising therapeutic strategy for MM. IBER's unique profile, efficacy against resistant cell lines, and potent immunomodulatory properties position it as a promising candidate for further clinical investigation in the treatment of MM [50].

4.3 Clinical Trials

Clinical trials for Iberdomide (CC-220) are ongoing, with an expected completion date between 2026 and 2029. The clinical trial headed by Bristol-Myers Squibb (CC-220-MM-001) is considered the pioneer study for the development of CC-220 as a treatment for multiple myeloma, and currently, it is on its Phase 1b/2a to evaluate the maximum tolerated dose (MTD), recommended phase 2 dose (RP2D), safety, and preliminary efficacy of Iberdomide as monotherapy and in combination with other treatments, specifically with dexamethasone, daratumumab, bortezomib, and carfilzomib. Table 1 shows the preliminary results of the different study arms under the same clinical trial with other cohorts currently enrolling participants or undergoing the study and has yet to produce any results [52].

Efficacy endpoints are pivotal measures in clinical trials, offering comprehensive insights into the impact of treatments on patients with MM. The Overall Response Rate (ORR) signifies the proportion of patients experiencing a substantial reduction in tumor size or disease burden, providing crucial information about the initial treatment response. Clinical Benefit Rate (CBR), a broader metric, encompasses complete and partial responses and stable disease, reflecting the proportion of patients achieving clinically meaningful benefits. Disease Control Rate (DCR) assesses patients responding to treatment or stable disease, portraying a comprehensive picture of disease control. Median Duration of Response (mDoR) measures the average time patients' diseases remain under control or in remission, with a longer mDoR indicating sustained treatment response. Median Progression-Free Survival (mPFS) and median Overall Survival (mOS) provide temporal insights, gauging the duration until disease progression and patient survival. A longer mPFS suggests an effective delay in disease progression, while a lengthened mOS is considered a positive outcome, indicating increased overall survival associated with the treatment. Together, these efficacy endpoints form a cohesive framework for evaluating the multifaceted impact of RRMM treatment regimens [53].

Table 1 – Study Arms Results of CC-220-MM-001 [52].

Date	Regimen	Results		
	(Condition)	**MTD/RP2D**	**Efficacy Endpoints**	
Jan. 2019	IBER + DEX *(RRMM)* [28]	NR	ORR = 31%; CBR = 51%; DCR = 88%	-
Jun. 18, 2020	IBER + DEX + DARA *(RRMM)* [54]	NR	ORR = 35%; CBR = 47%; DCR = 88%	-
	IBER + DEX + BTZ *(RRMM)* [54]	NR	ORR = 50%; CBR = 65%; DCR = 85%	-
Apr. 8, 2021	IBER + DEX + DARA *(RRMM)* [55]	-	ORR = 46%	mDoR NR
	IBER + DEX + BTZ *(RRMM)* [55]	RP2D = 1.6 mg	ORR = 56%	mDoR = 8.3 mos.
	IBER + DEX + CFZ *(RRMM)* [55]	-	ORR = 50%	mDoR NR
Jun. 2, 2021	IBER + DEX *(RRMM)* [56]	-	ORR = 26.2%; CBR = 36.4%; DCR = 79.4%	mDoR = 7.0 (4.5 - 11.3) mos. mPFS = 3.0 (2.8 - 3.7) mos. mOS = 11.2 (9.0 - NR) mos.

Abbreviation: BTZ: *Bortezomib*; CBR: *Clinical Benefit Rate*; CFZ: *Carfilzomib*; DARA: *Daratumumab*; DCR: *Disease Control Rate*; DEX: *Dexamethasone*; DoR: *Duration of Response*; IBER: *Iberdomide*; MTD: *Maximum Tolerated Dose*; mDoR: *Median DoR*; mPFS: *Median PFS*; mOS: *Median OS*; NR: *Not Reached*; ORR: *Overall Response Rate*; OS: *Overall Survival*; PFS: *Progression-Free Survival*; RP2D: *Recommended Phase 2 Dose*; RRMM: *Relapsed/Refractory Multiple Myeloma*.

MTD and RP2D for these particular arms have not yet been reached, indicating that the highest dose tested has not caused dose-limiting toxicities (DLTs) significant enough to determine the MTD. This is an exception for the IberVd cohort with an RP2D of 1.6 mg chosen as a dose that shows promise regarding safety and efficacy and is recommended for further evaluation in phase 2 trials [55]. Cohorts receiving triple combinations involving Iberdomide have demonstrated superior ORR compared to its standalone use or in conjunction with only one drug compound. The most notable outcome was observed in the IberVd cohort (Iberdomide + Dexamethasone + Bortezomib), where the highest ORR reached 56% [55]. Notably, a significant number of patients experienced clinical benefits from the iberdomide-based combination therapy, characterized by achieving a minimal response or stable disease. Specifically, the IberDd cohort exhibited a CBR of 47% and a DCR of 88%, and the IberVD cohort demonstrated a CBR of 65% and a DCR of 85%, emphasizing the efficacy of this treatment approach [54]. The analysis revealed diverse temporal outcomes, with mDoR ranging from non-reported to 8.3 months, mPFS spanning 2.8 to 3.7 months, and mOS exhibiting varied survival outcomes across evaluated cohorts in RRMM treatments [55-56].

The CC-220-MM-001 study also reveals distinct immune profiles between NDMM and RRMM subjects. NDMM shows a less immunodeficient profile with higher CD4+ T-cells, while RRMM displays significant immunosuppression and molecular dysregulation of CRBN [57]. The EMN26 study evaluates Iberdomide post-autologous stem-cell transplantation (ASCT), demonstrating favorable responses at 0.75, 1.0, and 1.3 mg doses, surpassing the null hypothesis. Safety is favorable, with manageable adverse events, and Iberdomide emerges as an effective post-ASCT maintenance strategy, pending phase 3 follow-up [58]. In the health-related quality of life (HRQoL) study, IBER + DEX maintains stable mean HRQoL scores, with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Multiple Myeloma Module (EORTC QLQ-MY20) body image domain showing clinically meaningful improvement. The findings suggest IBER + DEX's potential to enhance HRQoL in triple-class exposed RRMM patients, providing insights beyond traditional efficacy measures [59].

Bristol-Myers Squibb Company is currently conducting the EXCALIBER-RRMM Phase 3 study (CC-220-MM-002) that aims to evaluate and compare the effectiveness and safety of the IberDd cohort against a treatment regimen not involving Iberdomide (DVd: Daratumumab + Bortezomib + Dexamethasone) in participants with RRMM [60].

5. Discussion

The emerging role of CELMoDs presents a promising frontier in cancer therapeutics, particularly in scenarios where cancer cells exhibit resistance to Immunomodulatory drugs (IMiDs) due to mutations in cereblon as their strong binding affinity allows them to function even when cereblon levels are low or dysfunctional. Preclinical results have demonstrated the potential of Iberdomide (IBER/CC-220), a new CELMoD, to overcome IMiD resistance. CC-220 has a twenty times more affinity for cereblon than LEN and POM, resulting in a greater breakdown of Ikaros and Aiolos. Moreover, its immunomodulatory effects, particularly when combined with mAbs, showcase its potential to enhance the immune-mediated killing of MM cells; additionally, IBER with DARA, BTZ, and/or DEX produces a synergistic effect when used together.

In patients with RRMM who had undergone extensive pretreatment and had numerous failed regimens in the past, IBER combined with DEX demonstrated favorable effectiveness and safety. This research is currently underway and looks at using BORT or DARA in combination with IBER. When used in individuals with MM who had received intensive pretreatment, including those whose illness was resistant to immunomodulatory medications, the combination was generally safe and demonstrated considerable therapeutic activity. These findings imply that additional research on IBER and DEX or other conventional antimyeloma treatments is necessary.

According to the initial results of the phase 1b/2a CC-220-MM-001 clinical trial (NCT02773030), triple combinations with iberdomide (CC-220) plus dexamethasone, daratumumab, bortezomib, and/or carfilzomib have demonstrated a favorable safety profile as well as positive clinical activity in heavily pretreated MM patients. LEN- and POM-resistant MM patients may also benefit from the treatment utilized in the same study with different cohorts. When IBER and DEX were combined with DARA or BTZ, the ORR and other efficacy endpoints increased compared to only IBER and DEX. Tolerable safety profiles and promising efficacy were observed in patients with significantly pretreated RRMM who took either IberDd, IberVd, or IberKd regimen. These results support the initiation of phase 3 combination trials and additional development of IBER-based regimens in MM.

Data from the CC-220-MM-001 study, which included RRMM and Post-BCMA Treated Subjects, indicate that subjects with late-line RRMM exhibit significant immunosuppression in comparison to subjects with NDMM, with specific dysfunction in the CD4+ helper T-cell compartment. This suggests that combining immunotherapies with agents that enhance CD4+ T-cell function may enhance the efficacy of immunotherapies in late-line myeloma. Additionally, in RRMM individuals in the CC-220-MM-001 investigation, these findings demonstrate the enrichment of molecular high-risk regions and genomic abnormalities related to CRBN.

The investigation into immune profiles, health-related quality of life, and post-autologous stem-cell transplantation scenarios provides a comprehensive perspective on the diverse dimensions of Iberdomide (IBER; CC-220) in the context of multiple myeloma (MM) therapeutics. This holistic exploration underscores the nuanced potential of Iberdomide to influence not only disease-specific outcomes but also broader aspects of patient well-being. The ongoing clinical trials, marked by meticulous data collection and analysis, are poised to yield crucial insights that have the potential to significantly impact the future landscape of MM treatment paradigms. As these trials progress toward completion, the data generated is anticipated to assume a pivotal role in informing clinical decision-making, potentially positioning Iberdomide as a beacon of hope for individuals confronting refractory and relapsed MM. The multidimensional nature of these investigations augurs well for the prospect of Iberdomide as a transformative agent in reshaping the therapeutic approach to MM, presenting a ray of optimism for patients in challenging clinical scenarios.

6. Conclusion

Iberdomide (CC-220) is a promising investigational drug for the treatment of relapsed/refractory multiple myeloma (RRMM). Preclinical research indicates that Iberdomide exhibits greater antiproliferative efficacy than existing immunomodulatory medications such as Pomalidomide and Lenalidomide. Furthermore, the mechanism of action suggests a possibility for greater effectiveness due to its higher cereblon-binding affinity and effective destruction of targeted proteins.

Positive initial findings from the continuing clinical trials, especially the CC-220-MM-001 study, indicate an excellent safety profile and potential clinical performance in patients with significant medical pretreatment for multiple myeloma. Especially when combined with Dexamethasone, Daratumumab, Bortezomib, or Carfilzomib, where triple combinations containing Iberdomide have reasonable overall response rates (ORR) and clinical benefit rates (CBR). According to the data, Iberdomide may be able to overcome immunomodulatory drug resistance, but it is essential to remember that clinical trials are still in progress. Phase 3 trials and other studies will be required to determine the drug's long-term efficacy, safety, and recommended dosage for specific therapy plans.

As a result, Iberdomide emerges as a prospective therapeutic option for RRMM. However, more research and the conclusion of existing clinical trials will be necessary to assess its efficacy thoroughly. In order to make individualized treatment decisions, it is advised to stay current on the latest study findings and speak with medical professionals.

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