Iberdomide, bortezomib, and dexamethasone in transplant-ineligible newly diagnosed multiple myeloma: updated results from the CC-220-MM-001 trial

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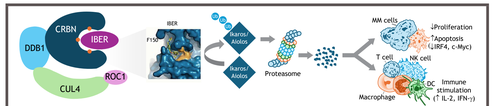
Introduction

- Lenalidomide (an immunomodulatory drug [IMiD®] agent) in combination with dexamethasone (DEX) and bortezomib (BORT) is an approved first-line treatment for patients with newly diagnosed multiple myeloma (NDMM) who are not planned to receive or are ineligible for autologous stem cell transplantation (ASCT)[1]
- CELMoD™ agents provide better therapeutic outcomes than IMiD agents, and they bind cereblon (CRBN) with higher affinity due to their distinct binding features[2]
- Iberdomide (IBER) is an oral CELMoD agent (**Figure 1**), which modulates CRBN activity to induce enhanced degradation of Ikaros and Aiolos target proteins, leading to higher MM cell killing and immune stimulation versus IMiD agents[3-5]
- IBER has shown synergistic antiproliferative activity and apoptosis of MM cell lines in combination with BORT and DEX[3,4]
- IBER in combination with BORT and DEX (IberVd) has shown meaningful efficacy and safety in patients with transplant-ineligible (TNE) NDMM in the ongoing phase 1/2 CC-220-MM-001 trial (NCT02773030)[6]

Figure 1. Mechanism of action and downstream effects of IBER



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c-Myc, cellular Myc; CUL4, cullin 4; DC, dendritic cell; DDB1, DNA damage-binding protein 1; IFN, interferon; IL, interleukin; IRF4, interferon regulatory factor 4; NK, natural killer; ROC1, regulator of cullins-1; Ub, ubiquitin.

Objective

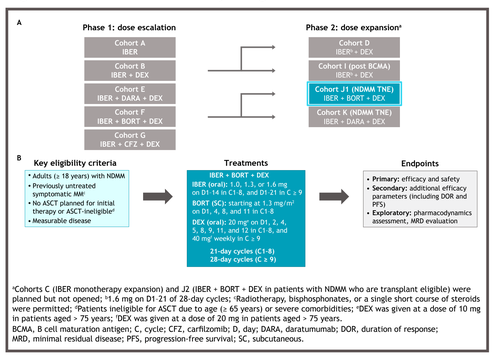
- To report updated results from the dose-expansion cohort of the CC-220-MM-001 trial evaluating IberVd in patients with NDMM who are TNE or are not receiving ASCT as their first therapy

Methods

Study design and treatment

- CC-220-MM-001 is a phase 1/2 study evaluating IBER with different treatment combinations in patients with MM (**Figure 2**)
- In Cohort J1, patients received oral IBER at 1.0 mg or 1.6 mg on D1-14 of each 21-day cycle in C1-8 and on D1-21 of each 28-day cycle in C ≥ 9
- Endpoints included efficacy, safety, pharmacokinetics, and MRD assessment by next-generation flow cytometry
- Bone marrow samples were collected from patients who achieved a response of very good partial response (VGPR) or better at D1C7, and at 12, 18, 24 months, and annually thereafter

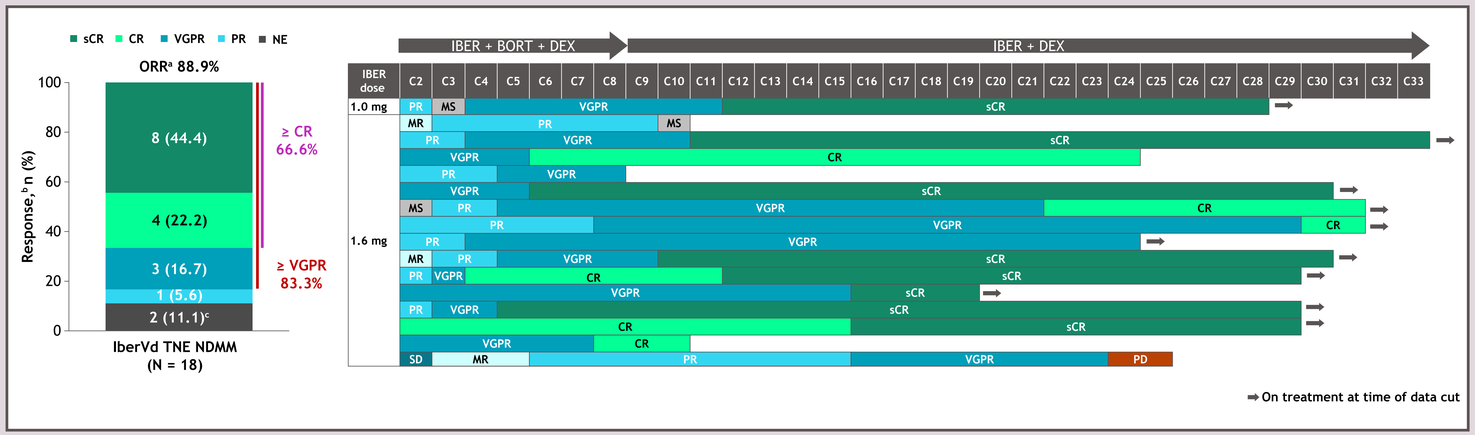
Figure 2. CC-220-MM-001 study design



[a]Cohorts C (IBER monotherapy expansion) and J2 (IBER + BORT + DEX in patients with NDMM who are transplant eligible) were planned but not opened; [b]1.6 mg on D1-21 of 28-day cycles; [c]Radiotherapy, bisphosphonates, or a single short course of steroids were permitted; [d]Patients ineligible for ASCT due to age (≥ 65 years) or severe comorbidities; [e]DEX was given at a dose of 10 mg in patients aged > 75 years; [f]DEX was given at a dose of 20 mg in patients aged > 75 years.
BCMA, B cell maturation antigen; C, cycle; CFZ, carfilzomib; D, day; DARA, daratumumab; DOR, duration of response; MRD, minimal residual disease; PFS, progression-free survival; SC, subcutaneous.

IberVd demonstrates deep and durable responses in patients with TNE NDMM over 2 years of treatment

Figure 3. Efficacy of IberVd in patients with TNE NDMM (ITT population)



[a]Defined as PR or better; [b]Data cutoff: May 29, 2024; [c]Non-evaluable patients discontinued prior to completing 1 treatment cycle due to consent withdrawal or were lost to follow-up. ITT, intent-to-treat; MR, minimal response; MS, missing; SD, stable disease.

Results

Patients

- At data cutoff (May 29, 2024), 18 patients had received IberVd (1 patient at 1.0 mg, 17 patients at 1.6 mg)
- Baseline patient characteristics are shown in **Table 1**
  - Median age was 77.5 years (range, 57-84) and 11 (61.1%) patients had high-risk cytogenetics
  - 11 (61.1%) patients remain on treatment and median follow-up was 25.0 months (range, 0.7-29.5) (**Table 2**)
  - 3 patients discontinued due to withdrawal, 2 due to AEs (peripheral neuropathy and shingles), 1 due to PD, and 1 due to physician decision
  - 1 patient died during follow-up (stroke)

Table 1. Baseline characteristics

Characteristic[a]	IberVd TNE NDMM (N = 18)
Age, median (range), years	77.5 (57-84)
Patients aged ≥ 75 years, n (%)	11 (61.1)
Male sex, n (%)	12 (66.7)
Race, n (%)	
White	17 (94.4)
Not collected or reported	1 (5.6)
Time since diagnosis, median (range), years	0.1 (0-0.4)
ECOG performance status, n (%)	
0	3 (16.7)
1	11 (61.1)
2	4 (22.2)
ISS stage, n (%)	
I	7 (38.9)
II	9 (50.0)
III	2 (11.1)
High-risk cytogenetics,[b] n (%)	11 (61.1)[c]

[a]Data cutoff: May 29, 2024; [b]Defined as the presence of any abnormality for del(17p), and/or translocation t(4,14), and/or translocation t(14,16), and/or amplification 1q21; [c]2/18 patients were not evaluable.
ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System.

Table 2. Patient disposition

Patient disposition[a]	IberVd TNE NDMM (N = 18)
Follow-up, median (range), months	25.0 (0.7-29.5)
Ongoing treatment, n (%)	11 (61.1)
Discontinued treatment, n (%)	7 (38.9)
Patient withdrawal	3 (16.7)[b]
AE	2 (11.1)[c]
PD	1 (5.6)
Physician decision	1 (5.6)[d]

[a]Data cutoff: May 29, 2024; [b]2 patients withdrew consent and 1 patient stopped attending site and was lost to follow up; [c]Due to peripheral neuropathy and shingles; [d]Due to suboptimal response. AE, adverse event; PD, progressive disease.

Treatment received

- Of 17 evaluable patients, all 17 (100%) experienced ≥ 1 IBER dose modification, and 10 patients (58.8%) had ≥ 1 treatment-emergent AE (TEAE) that led to an IBER dose reduction (**Table 3**)
  - Patients received a median of 25.0 (range, 1.0-34.0) cycles, with a median IBER RDI of 74.6% (range, 45.0-100)

Table 3. Dose modifications and treatment exposure

Dose modifications[a]	IberVd TNE NDMM (N = 17)[b]
Patients with ≥ 1 IBER dose modification, n (%)	17 (100)
IBER dose interruptions due to TEAEs, n (%)	14 (82.4)
Patients with ≥ 1 TEAE leading to IBER dose reduction, n (%)	10 (58.8)
TEAEs leading to DEX dose reductions, n (%)	13 (76.5)
TEAEs leading to BORT dose reductions, n (%)	7 (41.2)
Treatment exposure[a]	
Treatment duration, median (range), months	24.9 (0.7-29.5)
Cycles received, median (range), n	25.0 (1.0-34.0)
RDI of IBER, median (range), %	74.6 (45.0-100)

[a]Data cutoff: May 29, 2024; [b]1 patient was enrolled but not included in the safety population due to self-withdrawal (appointment absence).
RDI, relative dose intensity.

Safety

- 14 of 17 (82.4%) patients in the safety population had grade 3/4 TEAEs (**Table 4**)

Table 4. Most common (≥ 25% all grade) TEAEs

Most common (≥ 25% all grade) TEAEs and events of interest,[a] n (%)	IberVd TNE NDMM (N = 17)[b]		
	All grade	Grade 3	Grade 4
Hematologic TEAEs			
Neutropenia	7 (41.2)	2 (11.8)	3 (17.6)
Thrombocytopenia	6 (35.3)	2 (11.8)	1 (5.9)
Anemia	6 (35.3)	1 (5.9)	0
Lymphopenia	5 (29.4)	1 (5.9)	0
Non-hematologic TEAEs			
Peripheral edema	12 (70.6)	1 (5.9)	0
Peripheral neuropathy[c]	12 (70.6)	2 (11.8)	0
Constipation	10 (58.8)	1 (5.9)	0
Insomnia	8 (47.1)	1 (5.9)	0
Fatigue	7 (41.2)	2 (11.8)	0
Decreased appetite	7 (41.2)	0	0
Pain in extremity	6 (35.3)	0	0
Rash[d]	6 (35.3)	0	0
Dyspnea	6 (35.3)	1 (5.9)	0
Abdominal pain	5 (29.4)	0	0
Agitation	5 (29.4)	0	0
Dysgeusia	5 (29.4)	0	0
Infections	14 (82.4)	6 (35.3)	2 (11.8)
Pneumonia[e]	4 (23.5)	3 (17.6)	1 (5.9)
COVID-19[f]	8 (47.1)	2 (11.8)	0

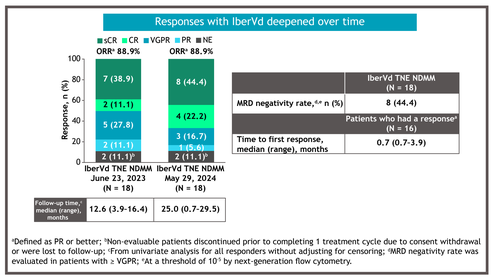
[a]Data cutoff: May 29, 2024; [b]1 patient was enrolled but not included in the safety population due to self-withdrawal (appointment absence); [c]Includes peripheral sensory neuropathy and peripheral motor neuropathy; [d]Includes rash, maculo-papular rash, macular rash, follicular rash, and pruritic rash; [e]Includes pneumonia; [f]Includes COVID-19 and COVID-19 pneumonia.

- Grade 3/4 TEAEs were primarily infections (47.1%), including pneumonia (23.5%) and COVID-19 (11.8%)
- The most common hematologic grade 3/4 TEAE was neutropenia (29.4%)
- 2 (11.8%) patients experienced grade 3/4 peripheral neuropathy
- Other grade 3/4 non-hematologic TEAEs, including fatigue, were rare
- No pulmonary embolism events were reported during treatment; 1 patient experienced deep-vein thrombosis
- The most common TEAEs leading to dose reductions were peripheral neuropathy (23.5%), neutropenia (11.8%), and thrombocytopenia (11.8%)
- TEAEs were manageable with dose modifications or interruptions and granulocyte colony-stimulating factor use

Efficacy

- The overall response rate (ORR) was 88.9%: 8 patients achieved stringent complete response (sCR), 4 complete response (CR), 3 VGPR, and 1 partial response (PR); 2 patients were not evaluable (NE) for response (**Figure 3**)
- The ORR in the efficacy-evaluable population was 100%, with 93.8% of patients achieving VGPR or better, and 75.0% of patients achieving CR or better (not shown)
- Median time to response was 0.7 months (0.7-3.9) while median DOR was not reached (not shown), and 5 patients experienced deepening of response post 1 year of treatment (**Figure 4**)
- MRD negativity at 10^{-5} was reported in 8 (44.4%) patients, all of which had CR or better

Figure 4. Response rates over time, time to first response, and MRD negativity



[a]Defined as PR or better; [b]Non-evaluable patients discontinued prior to completing 1 treatment cycle due to consent withdrawal or were lost to follow-up; [c]From univariate analysis for all responders without adjusting for censoring; [d]MRD negativity rate was evaluated in patients with ≥ VGPR; [e]At a threshold of 10^{-5} by next-generation flow cytometry.

Conclusions

- In this cohort of mostly older patients (median age 77.5 years) with TNE NDMM, longer follow-up confirmed that treatment with IberVd is associated with deep, durable responses
  - The ORR in the ITT population was 88.9% with 12 (66.6%) patients achieving CR or better
  - The ORR in the efficacy-evaluable population was 100%, with 93.8% of patients achieving VGPR or better, and 75.0% of patients achieving CR or better
  - MRD negativity at 10^{-5} was reported in 8 (44.4%) patients, and all had CR or better; 1 (5.6%) patient has converted to MRD negative status after an additional 1 year of follow-up
- IberVd was well-tolerated, with no new safety signals during continued IBER treatment
  - Most grade 3/4 TEAEs were hematologic and the occurrence of grade 3/4 non-hematologic TEAEs was low
  - Only 2 patients discontinued treatment due to an AE (1 due to peripheral neuropathy and 1 due to shingles)
- These data support further evaluation of IBER combinations, including IberVd, in the frontline setting

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Acknowledgments

- The patients and families who made this study possible
- The clinical study teams who participated
- The investigators of the CC-220-MM-001 study
- The study was supported by Celgene, a Bristol-Myers Squibb Company
- All authors contributed to and approved the presentation; writing and editorial assistance were provided by Mauro Locati, PhD, of Excerpta Medica, funded by Bristol Myers Squibb

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Presented at the 30th European Hematology Association (EHA) Congress; June 12-15, 2025; Milan, Italy.
Previously presented at the American Society of Clinical Oncology (ASCO) Annual Meeting; May 30-June 3, 2025; Chicago, IL, USA & Online.