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

MM-488

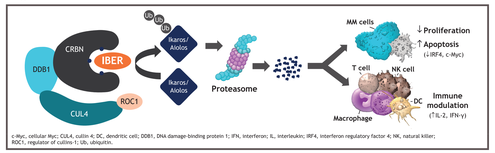
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## Introduction

- In patients with newly diagnosed multiple myeloma (NDMM), the immunomodulatory drug (IMiD®) lenalidomide (LEN) forms a standard of care in combination with bortezomib (BORT) and dexamethasone (DEX), and more recently, with daratumumab (DARA) and DEX[1]
- Iberdomide (IBER) is a novel, potent oral CELMoD™ agent with increased tumoricidal activity and immune-modulatory effects compared with IMiD agents[2,3] (**Figure 1**)
- In preclinical studies, IBER in combination with BORT and DEX (Vd) demonstrates synergistic antiproliferative activity and deeper apoptosis of myeloma cell lines compared with either LEN or pomalidomide + Vd[3,4]
- In the ongoing phase 1/2 CC-220-MM-001 trial (ClinicalTrials.gov: NCT02773030), IberVd has shown promising preliminary efficacy and safety in patients with relapsed/refractory multiple myeloma[5]

**Figure 1. Mechanism of action and downstream effects of IBER**




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

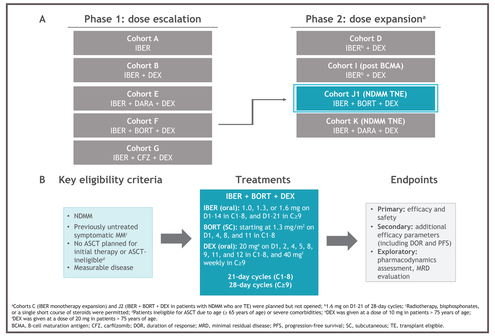
- To report updated results from the dose-expansion cohort of the CC-220-MM-001 trial evaluating IberVd in patients with NDMM who are not intended for transplant (ie, patients who are transplant-ineligible [TNE] or not receiving autologous stem cell transplant [ASCT] as their first therapy)

## Methods

### Study design and treatment

- CC-220-MM-001 is a phase 1/2 study evaluating IBER with different treatment combinations in multiple myeloma (MM) (**Figure 2A**)
- Patients received oral IBER (1.0, 1.3, or 1.6 mg) for 14 days over 21-day cycles in cycles 1-8 with BORT and DEX, and for 21 days over 28-day cycles from ≥ cycle 9+ with DEX
- Key eligibility criteria, treatment, and endpoints are shown in **Figure 2B**

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



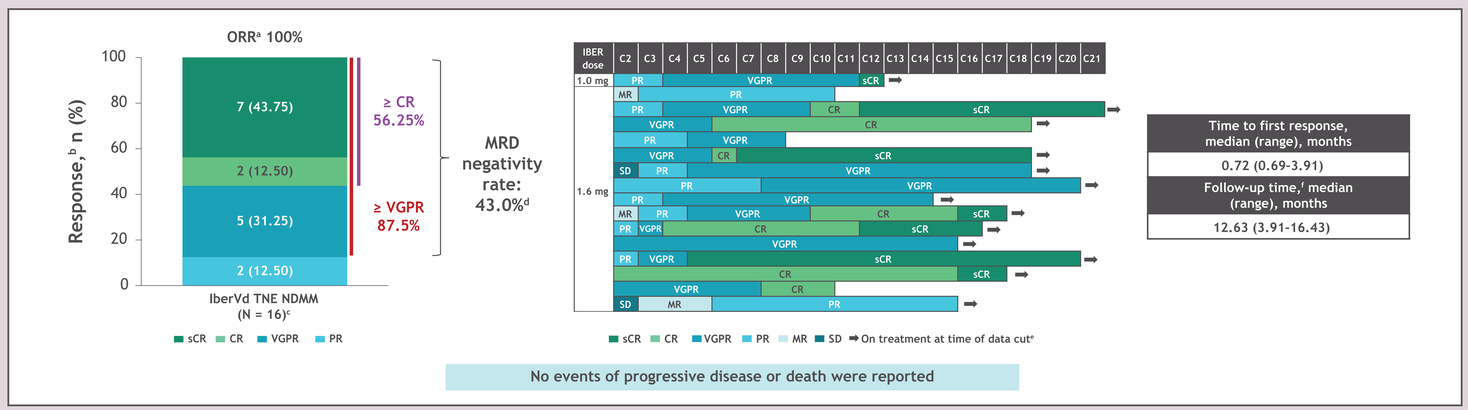

[a]Cohorts C (IBER monotherapy expansion) and J2 (IBER + BORT + DEX in patients with NDMM who are TE) were planned but not opened; [b]1.6 mg on D1-21 of 28-day cycles; [c]Radiotherapy, bisphosphonates, or a single short course of steroids were permitted; [d]Patients ineligible for ASCT due to age (≥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

### Pharmacodynamics

- Patient bone marrow (BM) samples were collected at screening and on cycle 2 day 11 (C2D11) for analysis of Aiolos expression by immunohistochemistry
- Peripheral blood (PB) samples were collected from patients at baseline (C1D1) and C4D8 for immunophenotyping by multicolor flow cytometry

## IberVd demonstrates high efficacy (ORR 100%) with deep responses in patients with TNE NDMM

**Figure 3. Efficacy of IberVd in patients with TNE NDMM**




| Time to first response, median (range), months |
|---|
| 0.72 (0.69-3.91) |
| **Follow-up time,[f] median (range), months** |
| 12.63 (3.91-16.43) |

No events of progressive disease or death were reported

[a]ORR (PR or better); [b]Data cutoff: June 23, 2023; [c]Efficacy-evaluable population; [d]At a threshold of 10-5; [e]BORT was administered during C1-8 only; [f]From univariate analysis for all responders without adjusting for censoring.
CR, complete response; MR, minimal response; ORR, overall response rate; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

## Results

### Patients

- At data cutoff (June 23, 2023), 18 patients had received IberVd
  - Seventeen patients received IBER at 1.6 mg, 1 patient received IBER at 1.0 mg, and no patients received IBER at 1.3 mg (due to slow recruitment; enrollment closed before any patients were enrolled to this dose level)
- Baseline characteristics are shown in (**Table 1**), and patient disposition shown in (**Table 2**)
  - Median age was 77.5 (range, 57-84) years and 11 (61.1%) patients had high-risk cytogenetics
  - Median follow-up was 14.0 (range, 0.7-18.0) months

**Table 1. Baseline characteristics**

| Characteristic[a] | IberVd TNE NDMM (N = 18) |
|---|---|
| **Age, median (range), years** | 77.5 (57-84) |
| **Sex, n (%)** | |
| Male | 12 (66.7) |
| **Race, n (%)** | |
| White | 17 (94.4) |
| Not collected or reported | 1 (5.6) |
| **Time since diagnosis, median (range), years** | 0.1 (0.0-0.4) |
| **ECOG PS, n (%)** | |
| 0 | 3 (16.7) |
| 1 | 11 (61.1) |
| 2 | 4 (22.2) |
| **ISS stage at study entry, 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: June 23, 2023; [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]18 patients were not available.
ECOG PS, Eastern Cooperative Oncology Group performance status; ISS, International Staging System.

- Thirteen (72.2%) patients continued on treatment, with the most common reason for discontinuation being patient withdrawal
- Only 1 patient discontinued treatment due to an AE of peripheral neuropathy

**Table 2. Patient disposition**

| Patient disposition[a] | IberVd TNE NDMM (N = 18) |
|---|---|
| **Follow-up, median (range), months** | 14.0 (0.7-18.0) |
| **Ongoing treatment, n (%)** | 13 (72.2) |
| **Discontinued treatment, n (%)** | 5 (27.8) |
| Patient withdrawal | 3 (16.7) |
| AE[b] | 1 (5.6) |
| Physician decision | 1 (5.6) |

[a]Data cutoff: June 23, 2023; [b]1 patient was enrolled but not included in the safety population due to self-withdrawal (appointment absence).
RDI, relative dose intensity; TEAE, treatment-emergent AE.

- TEAEs led to IBER dose interruptions in 13 (76.5%) patients and IBER dose reductions in 8 (47.1%) patients (**Table 3**)
  - Peripheral neuropathy was the main cause of dose reductions due to TEAEs for both IBER (4 [23.5%] patients) and BORT (4 [23.5%] patients)
  - Patients received a median of 16 cycles (range, 1.0-21.0), with an IBER RDI of 83.9% (range, 55.1-100.0) (**Table 3**)

**Table 3. Dose modifications and treatment exposure**

| Dose modification[a] | IberVd TNE NDMM (N = 17)[b] |
|---|---|
| **Patients with ≥ 1 IBER dose modification, n (%)** | 16 (94.1) |
| **IBER dose interruptions due to TEAEs, n (%)** | 13 (76.5) |
| **IBER dose reductions due to TEAEs, n (%)** | 8 (47.1) |
| **Treatment exposure[a]** | |
| **Treatment duration, median (range), months** | 14.0 (0.7-18.0) |
| **Cycles received, median (range), n** | 16.0 (1.0-21.0) |
| **RDI of IBER, % (range)** | 83.9 (55.1-100.0) |

[a]Data cutoff: June 23, 2023; [b]1 patient was enrolled but not included in the safety population due to self-withdrawal (appointment absence).
RDI, relative dose intensity; TEAE, treatment-emergent AE.

### Safety

- All patients experienced ≥ 1 TEAE; 13 (76.5%) patients had a grade 3/4 TEAE (**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 |
| **Any TEAE** | 17 (100) | 9 (52.9) | 4 (23.5) |
| **Hematologic TEAEs** | | | |
| Neutropenia | 6 (35.3) | 2 (11.8) | 2 (11.8) |
| Thrombocytopenia | 5 (29.4) | 1 (5.9) | 1 (5.9) |
| Anemia | 4 (23.5) | 1 (5.9) | 0 |
| Lymphopenia | 4 (23.5) | 0 | 0 |
| **Non-hematologic TEAEs** | | | |
| Peripheral edema | 11 (64.7) | 1 (5.9) | 0 |
| Peripheral sensory neuropathy | 11 (64.7) | 1 (5.9) | 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 |
| Pain in extremity | 6 (35.3) | 0 | 0 |
| Dyspnea | 6 (35.3) | 0 | 0 |
| Decreased appetite | 6 (35.3) | 0 | 0 |
| Agitation | 5 (29.4) | 0 | 0 |
| Dysgeusia | 5 (29.4) | 0 | 0 |
| **Infections** | 13 (76.5) | 5 (29.4) | 1 (5.9) |
| COVID-19 | 5 (29.4) | 1 (5.9) | 0 |
| Pneumonia | 3 (17.6) | 2 (11.8) | 1 (5.9) |

[a]Data cutoff: June 23, 2023; [b]1 patient was enrolled but not included in the safety population due to self-withdrawal (appointment absences).
COVID-19, coronavirus disease 2019.

- Neutropenia and infections were the most common grade 3/4 TEAEs, respectively
  - Neutropenia occurred in 6 (35.3%) patients, with grade 3/4 neutropenia occurring in 4 (23.5%) patients
  - Infections occurred in 13 (76.5%) patients, with 6 (35.3%) patients experiencing grade 3/4 infections
    - COVID-19 occurred in 5 (29.4%) patients, which was mild in most cases, and 3 (17.6%) patients had pneumonia
- Overall, non-hematologic grade 3/4 TEAEs were relatively low

### Efficacy

- All patients in the efficacy evaluable population had a response to IberVd (**Figure 3**)
  - The ORR was 100%, 14 (87.5%) patients achieved a VGPR or better, and 9 (56.25%) patients achieved a CR or better
- The median time to first response was 0.72 (range, 0.69-3.91) months, and the median follow-up was 12.63 (range, 3.91-16.43) months
- Patients treated with IberVd had deep and durable responses

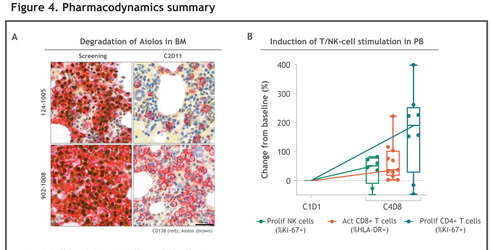
### MRD negativity rate

- The MRD negativity rate (at a threshold of $10^{-5}$) in patients achieving a VGPR or better was 43.0% (**Figure 3**)

### Pharmacodynamics summary

- IberVd led to robust Aiolos degradation (median > 50.0% decrease) in patient BM samples (**Figure 4A**)
- IberVd induced activation of CD8+ T cells and proliferation of CD4+ T cells and NK cells (**Figure 4B**)
  - A median increase of 177% in T-cell proliferation was observed with IberVd treatment

**Figure 4. Pharmacodynamics summary**




Act., activated; HLA-DR, human leukocyte antigen - DR isotype; Prolif., proliferating.

## Conclusions

- In this cohort of patients with TNE NDMM, IberVd showed high efficacy with deep, ongoing responses
  - The ORR in the efficacy-evaluable population was 100%, with 87.5% of patients achieving VGPR or better, and 56.25% of patients achieving CR or better
  - Among patients who achieved VGPR or better, 6/14 (43%) patients were MRD-negative at $10^{-5}$
  - 68.8% of patients responded in < 6 weeks
  - At data cutoff, no events of documented progressive disease or death were reported
- The safety profile was manageable with no new safety signals
  - Most grade 3/4 TEAEs were hematologic and the occurrence of other grade 3/4 non-hematologic TEAEs was low
  - Only 1 patient discontinued treatment due to an AE of peripheral neuropathy
- IBER induced robust Aiolos degradation and immune stimulation in combination with Vd
- These data support further assessment of IBER combinations in the frontline setting

## References

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