# Longitudinal analysis of MRD negativity and immune dynamics in patients with transplant-ineligible newly diagnosed multiple myeloma treated with iberdomide, daratumumab, and dexamethasone from the CC-220-MM-001 trial

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## Introduction

- Iberdomide (IBER) is an oral CELMoD™ agent that delivers superior multiple myeloma (MM) cell killing and immune stimulation by uniquely and more effectively binding cereblon, inducing greater and faster target protein degradation than immunomodulatory drug (IMiD®) agents[1,2]
- Preclinical studies demonstrate that IBER enhances both antibody-dependent and complement-dependent cellular cytotoxicity of daratumumab (DARA) and exhibits greater anti-myeloma synergy when combined with DARA and dexamethasone (DEX; IberDd), compared with combinations involving IMiD agents[3]
- CC-220-MM-001 (NCT02773030; EudraCT number: 2016-000860-40) is a phase 1/2 trial evaluating IBER with different treatment combinations in patients with transplant-ineligible newly diagnosed MM (TNE NDMM)[4] (**Figure 1A**)
- IberDd demonstrated strong preliminary efficacy including sustained and deepening responses in patients with TNE NDMM with nearly 2 years of follow-up
  - Rates of complete response (CR) or better improved from 44% to 68%, and rates of very good partial response (VGPR) or better increased from 83% to 88% over 12 months[4]

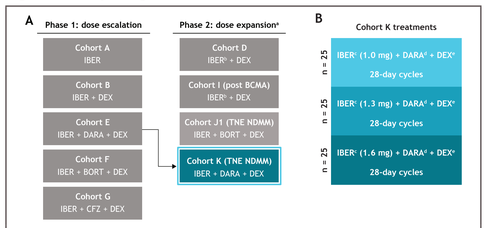
## Objective

- To investigate the rates and sustainability of minimal residual disease (MRD) negativity, correlation with progression-free survival (PFS), and immunomodulatory effects of IberDd in patients with TNE NDMM in the CC-220-MM-001 trial

## Methods

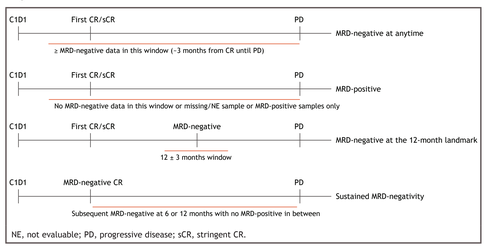
- Patients in cohort K received IBER at different doses, in combination with DARA and DEX (**Figure 1B**)
- MRD was evaluated using next generation flow cytometry in patients achieving VGPR or better (**Figure 2**)
  - MRD analysis had a sensitivity threshold of $10^{-5}$ and was performed as shown previously in the EVIDENCE meta-analysis[5]

**Figure 1. Study design of the CC-220-MM-001 trial**




[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]IBER was given orally on D1-21; [d]DARA-1800 mg SC was given on D1, 8, 15, and 22 during C1-2, D1 and 15 during C3-6, and D1 on C ≥ 7; [e]DEX was given orally at a dose of 40 mg on D1, 8, 15, and 22, or a dose of 20 mg in patients > 75 years of age. BCMA, B-cell maturation antigen; BORT, bortezomib; CFZ, carfilzomib; C, cycle; D, day; SC, subcutaneous.

**Figure 2. Classification of MRD**




NE, not evaluable; PD, progressive disease; sCR, stringent CR.

## In patients with TNE NDMM, IberDd demonstrated robust activity that deepened over time, with high rates of MRD-negativity that correlated with PFS

**Figure 4. Time to MRD-negativity over 27 months**

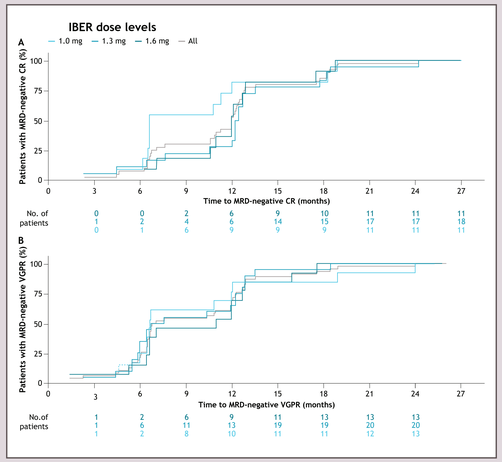
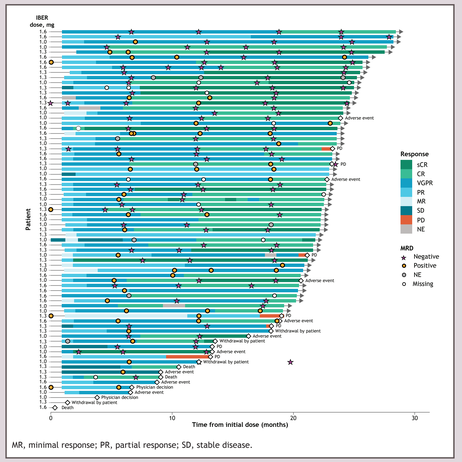
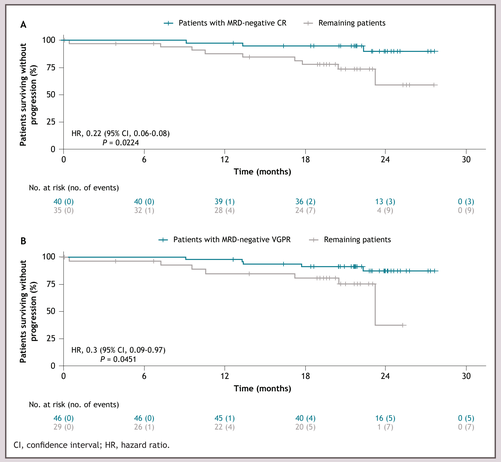



**Figure 5. Response rates over time**




MR, minimal response; PR, partial response; SD, stable disease.

**Figure 6. MRD-negative CR and MRD-negative VGPR correlation with PFS**

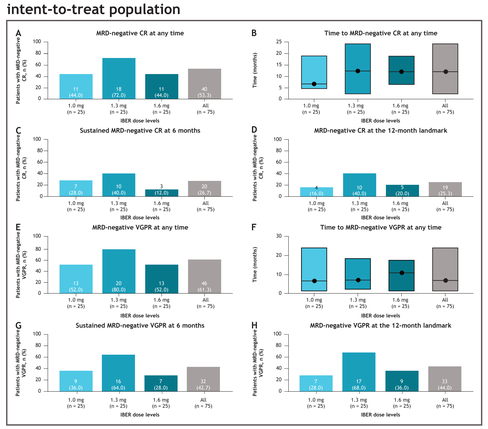



CI, confidence interval; HR, hazard ratio.

## Results

- The rate of patients achieving MRD negativity with CR or better (MRD-negative CR) at any time was 53.3% (**Figure 3A**)
  - The median time to MRD-negative CR was 12 months (**Figure 3B**), 26.7% and 25.3% of patients achieved MRD-negativity at 6 months and the 12-month landmark, respectively (**Figures 3C** and **3D**)
- 61.3% of patients achieved MRD negativity with VGPR or better (MRD-negative VGPR) at any time (**Figure 3E**)
  - The median time to MRD-negative VGPR was 6.7 months (**Figure 3F**), 42.7% and 44.0% of patients achieved MRD-negativity at 6 months and the 12-month landmark, respectively (**Figures 3G** and **3H**)

**Figure 3. MRD-negative CR and MRD-negative VGPR rates in the intent-to-treat population**



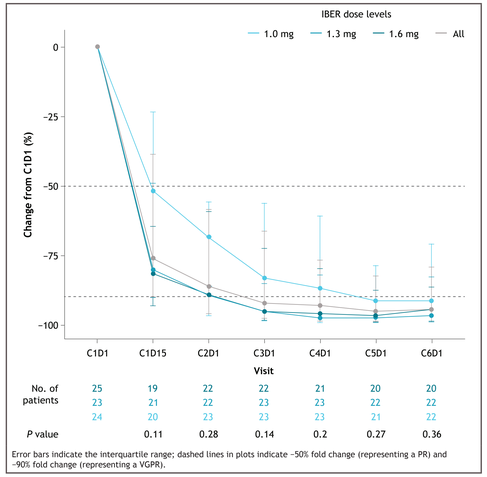

- The proportion of patients who achieved MRD-negative CR and MRD-negative VGPR increased over time, with the most substantial increase observed between 12 and 15 months of treatment (**Figures 4A** and **4B**)
- The rates of MRD-negativity were comparable between patients based in the US and those in the rest of the world (ROW; **Table 1**)
  - Of those achieving MRD-negative CR, 53.6% were based in the US and 53.2% were based in the ROW
  - Of those achieving MRD-negative VGPR, 64.3% were based in the US and 59.6% were based in the ROW
- A swimmer plot describing the survival of each patient shows MRD-negative CR rates increasing over time (**Figure 5**)
- Correlations were found between PFS and MRD-negativity for patients who achieved ≥ CR ($P = 0.0224$; **Figure 6A**) and ≥ VGPR ($P = 0.0451$; **Figure 6B**)

**Table 1. MRD assessments for patients in the US and the ROW**

| Parameter | IBER dose levels | | | | | Chi-square *P* value (US vs ROW) |
|---|---|---|---|---|---|---|
| | 1.0 mg (US) (n = 8) | 1.3 mg (US) (n = 9) | 1.6 mg (US) (n = 11) | All (US) (n = 28) | All (ROW) (n = 47) | |
| MRD-negative CR rate at any time, n (%) | 4 (50) | 6 (66.7) | 5 (45.5) | 15 (53.6) | 25 (53.2) | 1.0000 |
| CR/sCR rate, n (%) | 4 (50) | 6 (66.7) | 8 (72.7) | 18 (64.3) | 33 (70.2) | 0.7823 |
| MRD-negative VGPR rate at any time, n (%) | 5 (62.5) | 7 (77.8) | 6 (54.5) | 18 (64.3) | 28 (59.6) | 0.8728 |
| VGPR rate, n (%) | 5 (62.5) | 9 (100) | 10 (90.9) | 24 (85.7) | 42 (89.4) | 0.9181 |

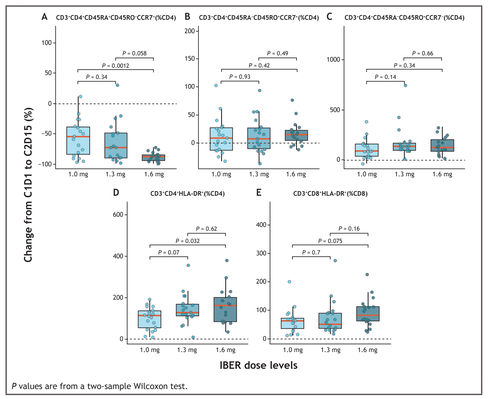
- The anti-tumor activity of IberDd was shown by the decrease in serum free light chains (sFLCs)
  - This response was maintained by all three doses and sustained until C6D1 (**Figure 7**)
- IberDd demonstrated a change in the proportion of circulating immune cells at all three doses (**Figure 8**)
- MRD status does not appear to be associated with the observed immune pharmacodynamic changes of IberDd (**Figure 9**)

**Figure 7. Effect of IberDd treatment on sFLCs**



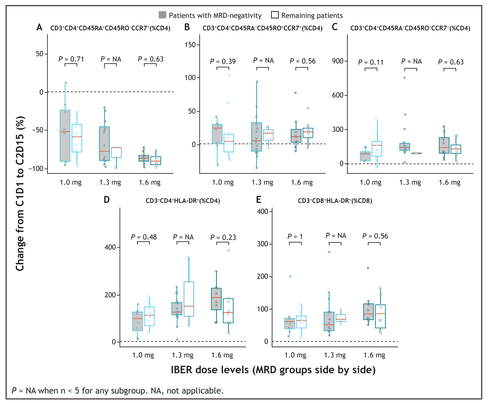

Error bars indicate the interquartile range; dashed lines in plots indicate −50% fold change (representing a PR) and −90% fold change (representing a VGPR).

**Figure 8. Effect of IBER dose on proportion of circulating immune cells**




*P* values are from a two-sample Wilcoxon test.

**Figure 9. Effect of IBER dose on circulating T cells and correlation with MRD-negativity**




*P* = NA when n < 5 for any subgroup. NA, not applicable.

## Conclusions

- IberDd treatment was associated with deep and durable responses in patients with TNE NDMM in the CC-220-MM-001 trial
- A high proportion of patients achieved MRD-negative CR and MRD-negative VGPR, which was maintained at the 12-month follow-up landmark
- These data support the potential of IberDd as an effective treatment for patients with TNE NDMM

## References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