Iberdomide, daratumumab, and dexamethasone shows deep antimyeloma activity across molecular patient subsets with transplant-ineligible newly diagnosed multiple myeloma: results from the phase 1/2 CC-220-MM-001 trial

MM-100

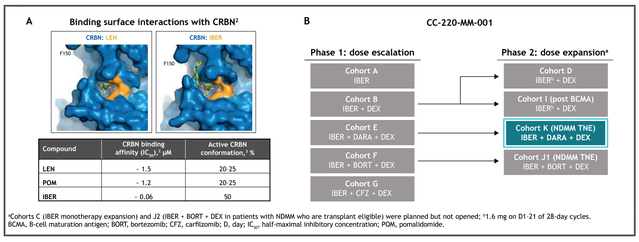
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Introduction

- Daratumumab (DARA) plus lenalidomide (LEN) and dexamethasone (DEX; DRd) treatment has shown impressive outcomes for stem cell transplant non-eligible (TNE) patients with newly diagnosed multiple myeloma (NDMM) and is currently the standard of care in this setting[1]
- Iberdomide (IBER) is an oral CELMoD™ agent that, like LEN, induces ubiquitination and degradation of the hematopoietic transcription factors Ikaros and Aiolos[2]
  - However, IBER binds cereblon (CRBN) with unique interactions and higher affinity than LEN, enabling more efficient allosteric rearrangement of CRBN to the conformation required for Ikaros/Aiolos recruitment, promoting more rapid substrate degradation and greater myeloma cell death and immune stimulation compared with LEN[2,3] (**Figure 1A**)
- In preclinical models, IBER has shown synergistic activity when combined with DARA, inducing deeper antimyeloma cell activity than LEN + DARA[4]
- Preliminary results from the phase 1/2 CC-220-MM-001 study (NCT02773030; **Figure 1B**) showed impressive activity of IBER + DARA + DEX (IberDd) in patients with TNE NDMM[5]

Figure 1. IBER interactions with CRBN (A); CC-220-MM-001 cohorts (B)



Compound	CRBN binding affinity (IC_{50}),[a] µM	Active CRBN conformation,[a] %
LEN	~ 1.5	20-25
POM	~ 1.2	20-25
IBER	~ 0.06	50

[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. BCMA, B-cell maturation antigen; BORT, bortezomib; CFZ, carfilzomib; D, day; IC_{50}, half-maximal inhibitory concentration; POM, pomalidomide.

- While IBER has shown synergistic activity when paired with DARA in preclinical models, inducing deeper antimyeloma cell activity than LEN + DARA, the clinical activity of IberDd in patient populations where DRd treatment may be suboptimal has not been previously reported

Objectives

- To report results from the CC-220-MM-001 dose-expansion cohort of IberDd in patients with TNE NDMM in biomarker-defined patient populations
- To assess the preliminary activity of IberDd and support dose selection of IBER in combination with DARA in this setting

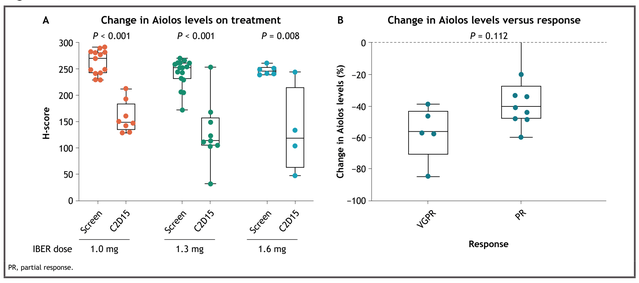
Methods

- Biomarker samples for analysis were collected from eligible patients in the phase 1/2 CC-220-MM-001 clinical study who had untreated symptomatic NDMM with no autologous stem cell transplant planned (TNE or deferred) or were ineligible because of age or comorbidities
- Oral IBER was given at 3 different doses on D1-21 of each 28-day cycle in combination with subcutaneous DARA (1800 mg) on D1, 8, 15, and 22 in cycle (C)1-2, on D1 and 15 in C3-6, and on D1 in C7 or later, plus weekly oral DEX (40 mg; 20 mg if > 75 years of age)
- Analysis of 75 patients with TNE NDMM who received IberDd (1.0 mg, n = 25; 1.3 mg, n = 25; 1.6 mg, n = 25) were performed for the following biomarkers:
  - Measurement of involved serum-free light chains (sFLCs) at the first day of each cycle during treatment
  - Assessment of minimal residual disease (MRD) by EuroFlow assay in patients achieving deep response (≥ very good partial response [VGPR])
  - Immunohistochemistry staining of CD138$^+$ bone marrow (BM) samples for CRBN and Aiolos at screening, which were scored digitally for substrate staining intensity within the CD138$^+$ mask and correlated with best overall responses
  - Flow cytometry of peripheral blood to assess immune cell composition at C1D1 and C2D15 using a panel to measure T, B, and natural killer (NK) cells and expression of activation (HLA-DR), proliferation (Ki-67$^+$), differentiation (CD45RO CCR7$^+$), and exhaustion (PD-1$^+$) markers and correlate with best overall responses (BOR)
  - Assessment of high risk (HR) genomic and gene expression signatures at screening in CD138-enriched BM samples and correlate with BOR and progression-free survival (PFS)

Results

- Changes in involved sFLCs as biomarkers for tumor reduction showed deep and overlapping decreases on treatment across all 3 doses (**Figure 2A**) with the nadir of sFLCs observed at around C3D1 (**Figure 2B**)
- Of those patients attaining a response of ≥ VGPR and with available samples, MRD negativity at 10^{-5} was achieved in 54.6% (41/75) patients treated with IberDd (**Table 1**)
- Across all doses, a significant reduction in substrate protein levels was observed by C2D15, without a dose-dependent trend (**Figure 3A**); deep responders (≥ VGPR) tended to have greater reductions (**Figure 3B**)

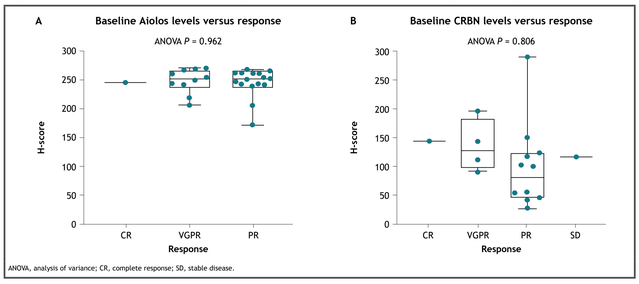
Figure 3. IberDd decreases Aiolos levels at all doses



PR, partial response.

- Baseline CRBN or Aiolos levels were not associated with depth of response (≥ VGPR $P = 0.320$, $P = 0.792$, respectively) (**Figure 4**)

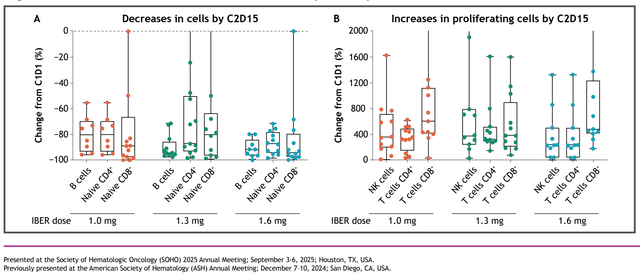
Figure 4. Baseline CRBN and Aiolos expression do not associate with depth of response



ANOVA, analysis of variance; CR, complete response; SD, stable disease.

- In the immune compartment, IberDd treatment resulted in a > 4-fold increase in proliferating T and NK cells and a > 75% decrease in median absolute B cells and naive T cells across all doses (**Figure 5**)

Figure 5. IberDd shows similar immunomodulatory activity at all IBER doses



IberDd induced deep reductions in sFLCs and drove MRD negativity in patients with TNE NDMM

Figure 2. IberDd induced deep antimyeloma activity across all 3 IBER doses

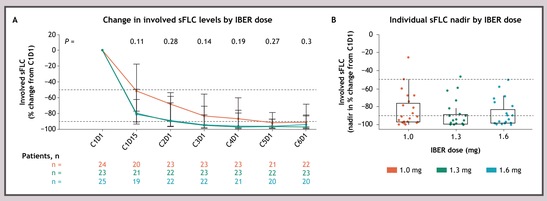


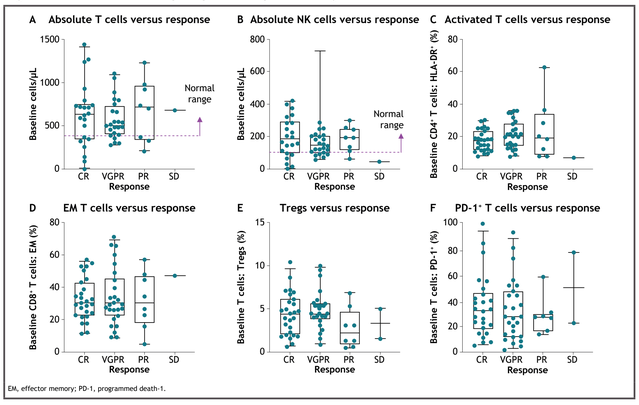
Table 1. IberDd induced MRD negativity[a] in patients at all 3 IBER doses

	IBER dose, mg		
	1.0 (n = 25)[b]	1.3 (n = 25)[b]	1.6 (n = 25)[b]
Patients with MRD sample, n MRD-negative[a] samples, n (%)	18 11 (61.1)	24 19 (79.2)	19 11 (57.9)
MRD negativity[a] in ITT population, %	44.0	76.0	44.0
Median follow-up: ~ 17 months			

Analysis as of September 2024. [a]At 10^{-5}; [b]ITT population. ITT, intent-to-treat.

- Baseline levels of immune parameters previously shown to be associated with poor outcomes in MM (low total T/NK cells, high levels of T-cell activation/differentiation, high regulatory T cells [Tregs], and exhaustion marker expression) did not associate with depth of response to IberDd (**Figure 6**)
  - ≥ VGPR rate below normal CD4$^+$ T cells (441 cells/µL): 82.4%
  - ≥ VGPR rate below normal NK cells (95 cells/µL): 83.3%
  - ≥ VGPR rate above median Tregs (4.4% CD4$^+$): 89.3%
  - ≥ VGPR rate above median PD-1$^+$ T cells (27.2%): 87.1%

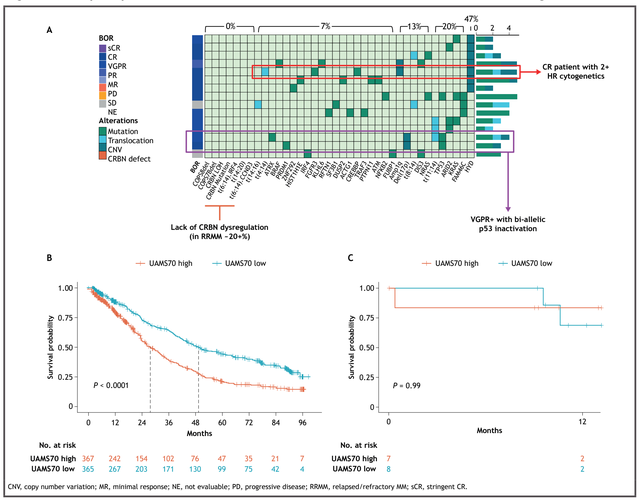
Figure 6. IberDd shows deep responses in patients regardless of immune status at baseline



EM, effector memory; PD-1, programmed death-1.

- Several patients with high-risk markers were identified, including *TP53* mutations (n = 3), del(17p) (n = 2), 1qAMP (n = 2), and t(4;14) (n = 1); all patients responded to IberDd in each subgroup, regardless of HR markers (**Figure 7A**)
  - ≥ VGPR rate HR genomic events: 80%
- Analysis of the HR gene expression signature UAMS70, which was shown by the Multiple Myeloma Research Foundation to be associated with poor response in NDMM, showed similar PFS between patients with high and low scores when treated with IberDd (**Figure 7B, C**)

Figure 7. Deep responses to IberDd and similar PFS observed across molecular HR segments



CNV, copy number variation; MR, minimal response; NE, not evaluable; PD, progressive disease; RRMM, relapsed/refractory MM; sCR, stringent CR.

Conclusions

- IberDd showed deep reductions in sFLCs and drove MRD negativity across all 3 doses (1.0 mg, 1.3 mg, and 1.6 mg) of IBER tested in patients with TNE NDMM from the CC-220-MM-001 study, suggesting all doses of IBER tested were clinically active
- A reduction in Aiolos and Ikaros protein levels was observed in BM MM cells across all 3 doses and an induction of proliferation and activation of T and NK cells, suggesting all doses of IBER tested had similar pharmacological activity
- Notably, responses to IberDd were observed across molecular and immune subgroups, including in patients with HR markers at baseline with evidence of T-cell exhaustion, bi-allelic inactivation of p53, and high UAMS70 gene expression signature scores, providing preliminary evidence of deep and broad activity of IberDd in the TNE NDMM setting

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