Iberdomide plus daratumumab and dexamethasone in patients with newly diagnosed multiple myeloma by renal function: a subgroup analysis of the CC-220-MM-001 trial

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Introduction

- Lenalidomide (LEN) plus an anti-CD38 monoclonal antibody and dexamethasone (DEX) is a standard-of-care treatment for patients with transplant-ineligible (TNE) newly diagnosed (ND) multiple myeloma (MM)[1]
  - Less than one third of patients achieved minimal residual disease (MRD) negativity in the MAIA and BENEFIT trials, highlighting an ongoing unmet need in this population[2,3]
- Iberdomide (IBER) is an oral CELMoD™ agent with greater potency and specificity compared with LEN[4]
  - IBER uniquely and effectively binds cereblon (CRBN) with a higher affinity, inducing higher rates of CRBN closed/active status, leading to greater and faster Ikaros/Aiolos degradation and superior killing of MM cells and immune stimulation[4-8]
- IBER, combined with daratumumab (DARA) and DEX (IberDd) has shown notable MRD negativity (64.0%) and a predictable and tolerable safety profile in TNE NDMM in the ongoing phase 1/2 CC-220-MM-001 trial (NCT02773030)[8-10]
- Prior analysis showed that renal impairment (RI) did not influence clinical outcomes in patients with relapsed/refractory (RR) MM treated with IBER + DEX[9]

Objective

- To assess whether renal impairment impacts efficacy, safety, and pharmacokinetics (PK) of IberDd in patients with TNE or transplant-deferred NDMM in the CC-220-MM-001 trial

Methods

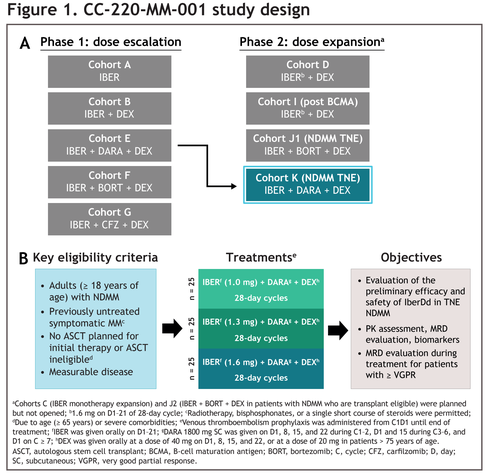
Study design and treatment

- CC-220-MM-001 is a phase 1/2, multicenter, open-label study evaluating IBER with different treatment combinations in patients with MM (**Figure 1A**)
- Key eligibility criteria, treatments, and endpoints are shown in **Figure 1B**

PK analysis

- Baseline creatinine clearance (CrCl) was used to stratify patients into the following subgroups: no RI (≥ 90 mL/min), mild RI (60 to < 90 mL/min), or moderate RI (30 to < 60 mL/min)
  - IBER doses were not modified based on renal impairment
- Oral IBER apparent clearance (CL/F) was estimated from an integrated population PK (popPK) model
- Logistic regression analyses were performed to investigate the correlation between renal impairment and key efficacy (≥ complete response [CR]) and safety endpoints (dose reductions, neutropenia)

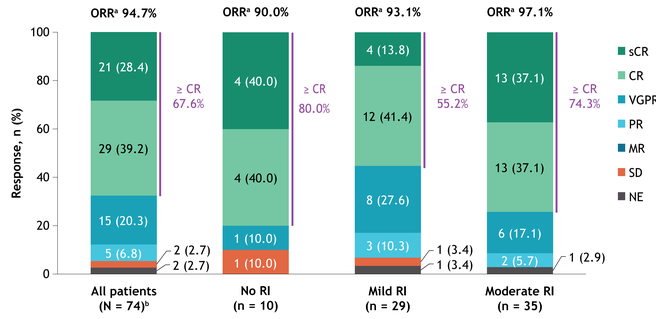
Figure 1. CC-220-MM-001 study design



[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 cycle; [c]Radiotherapy, bisphosphonates, or a single short course of steroids were permitted; [d]Due to age (≥ 65 years) or severe comorbidities; [e]Venous thromboembolism prophylaxis was administered from C1D1 until end of treatment; [f]IBER was given orally on D1-21; [g]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; [h]DEX was given orally at a dose of 40 mg on D1, 8, 15, and 22, or at a dose of 20 mg in patients > 75 years of age.
ASCT, autologous stem cell transplant; BCMA, B-cell maturation antigen; BORT, bortezomib; C, cycle; CFZ, carfilzomib; D, day; SC, subcutaneous; VGPR, very good partial response.

Renal impairment does not affect the efficacy or safety of IberDd in patients with TNE NDMM, with high ORRs (≥ 90.0%) and similar grade 3/4 TEAEs across subgroups

Figure 2. Best overall response by subgroup



Percentages might not total 100% due to rounding. Data cutoff: March 3, 2025. [a]PR or better; [b]74/75 patients were eligible for RI analysis.
MR, minimal response; NE, not evaluable; sCR, stringent CR; SD, stable disease.

Table 4. Safety summary

Grade 3/4 TEAEs of interest, n (%)	All patients (N = 74)[a]	No RI (n = 10)	Mild RI (n = 29)	Moderate RI (n = 35)
Any grade 3/4 event, n (%)	72 (97.3)	10 (100)	29 (100)	33 (94.3)
Hematologic TEAEs, n (%)				
Neutropenia	58 (78.4)	6 (60.0)	22 (75.9)	30 (85.7)
Febrile neutropenia	9 (12.2)	0	4 (13.8)	5 (14.3)
Lymphopenia	15 (20.3)	3 (30.0)	4 (13.8)	8 (22.9)
Anemia	11 (14.9)	1 (10.0)	3 (10.3)	7 (20.0)
Leukopenia	10 (13.5)	2 (20.0)	5 (17.2)	3 (8.6)
Thrombocytopenia	3 (4.1)	0	1 (3.4)	2 (5.7)
Non-hematologic TEAEs				
Fatigue	1 (1.3)	0	1 (3.4)	0
Diarrhea	0	0	0	0
Constipation	0	0	0	0
Rash[b]	24 (32.4)	4 (40.0)	8 (27.6)	12 (34.3)
Infections	39 (52.7)	5 (50.0)	17 (58.6)	17 (48.6)
Pneumonia[c]	29 (39.2)	4 (40.0)	12 (41.4)	13 (37.1)
COVID-19[d]	4 (5.4)	1 (10.0)	1 (3.4)	2 (5.7)

Data cutoff: March 3, 2025. [a]74/75 patients were eligible for RI analysis; [b]Including maculo-papular rash, macular rash, follicular rash, and pruritic rash; [c]Including influenzal pneumonia, bacterial pneumonia, cryptococcal pneumonia, *Pneumocystis jirovecii* pneumonia, parainfluenzae viral pneumonia, *Legionella* pneumonia, pneumococcal pneumonia, and respiratory syncytial viral pneumonia; [d]Including COVID-19 pneumonia.

Results

Patients

- At data cutoff (March 3, 2025), 75 patients had received IberDd (25 patients at each dose level)
- Baseline patient characteristics are shown in **Table 1**
  - Median age was 75 years (range, 44-90) and 31 (41.3%) patients had high-risk cytogenetics
- Median follow-up was 22.3 months (range, 0.4-28.5) (**Table 2**)
  - 50 (66.7%) patients remained on therapy and median duration of treatment was 22.4 months
  - No differences were observed in median duration of treatment across subgroups
- Patients across all IBER dose levels were evenly distributed per subgroup (**Table 3**)

Safety

- Grade 3/4 treatment emergent AEs (TEAEs) were similar across subgroups, occurring in 100% (no RI and mild RI) and 94.3% (moderate RI) of patients (**Table 4**)
  - TEAEs were mostly hematologic, with neutropenia being the most frequent grade 3/4 TEAE
  - The incidence of grade 3/4 neutropenia was 60.0% in the no RI, 75.9% in the mild RI, and 85.7% in the moderate RI subgroups
  - Grade 3/4 infections were observed in 50.0% (no RI), 58.6% (mild RI), and 48.6% (moderate RI) of patients
  - Rates of other non-hematologic grade 3/4 TEAEs were low
- Patients requiring dose modifications were comparable between subgroups (**Table 5**)
  - Dose reductions occurred in 50.0% (no RI), 58.6% (mild RI), and 37.1% (moderate RI) of patients (**Table 5**)
  - Among subgroups, median relative dose intensity was 87.9% (no RI), 78.3% (mild RI), and 87.5% (moderate RI)

Efficacy and MRD negativity

- The overall response rate (ORR; defined as partial response [PR] or better) for each subgroup was 90.0% (no RI), 93.1% (mild RI), and 97.1% (moderate RI) (**Figure 2**)
- ≥ CR was achieved by 80.0% (no RI), 55.2% (mild RI), and 74.3% (moderate RI) of patients (**Figure 2**)
- MRD-negativity rates at any time were 80.0% (no RI), 48.3% (mild RI), and 71.4% (moderate RI)
- Median duration of response was not reached in any of the subgroups

Table 1. Baseline characteristics

Characteristic	IberDd TNE NDMM (N = 75)
Age, median (range), years	75 (44-90)
≥ 75 years of age, n (%)	44 (58.7)
Sex, n (%)	
Male	42 (56.0)
Race, n (%)	
White	53 (70.7)
Asian	11 (14.7)
Black or African American	4 (5.3)
Other or not reported	7 (9.3)
Time since diagnosis, median (range), years	0.1 (0-11.3)
ECOG PS score, n (%)	
0	23 (30.7)
1	43 (57.3)
2	9 (12.0)
ISS stage at study entry,[a] n (%)	
I	30 (40.0)
II	30 (40.0)
III	14 (18.7)
Presence of plasmacytomas,[b] n (%)	6 (8.0)
High-risk cytogenetics,[c,d] n (%)	31 (41.3)

Data cutoff: March 3, 2025. [a]For 1/75 patients, these data were missing; [b]Including parasseous and extramedullary lesions; [c]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; [d]For 9/75 patients, this was missing or not evaluable.
ECOG PS, Eastern Cooperative Oncology Group performance status; ISS, International Staging System.

Table 2. Treatment disposition

Treatment disposition	IberDd TNE NDMM (N = 75)
Follow-up, median (range), months	22.3 (0.4-28.5)
Ongoing, n (%)	50 (66.7)
Duration of treatment, median (range), months	22.4 (0.3-29.0)
IBER cycles received, median (range)	23.0 (1.0-31.0)
Discontinued, n (%)	25 (33.3)
AE[a]	9 (12.0)
Progressive disease	7 (9.3)
Patient withdrawal	4 (5.3)
Death[b]	3 (4.0)
Physician decision	2 (2.7)

Data cutoff: March 3, 2025. [a]Nine patients discontinued due to AEs: 3 general physical health deterioration, 1 cytomegalovirus chorioretinitis, 1 acute kidney injury, 1 hypoxia, 1 anemia/neutropenia, 1 peripheral neuropathy, and 1 peripheral sensory neuropathy; [b]Three patients died during the treatment period due to grade 5 AEs: 1 intestinal ischemia, 1 aspiration pneumonia with sepsis, and 1 death from unknown cause.
AE, adverse event.

Table 3. Distribution of patients across IBER dose levels per subgroup

IBER dose level, n (%)	No RI (n = 10)	Mild RI (n = 29)	Moderate RI (n = 35)
1.0 mg	4 (40.0)	10 (34.5)	11 (31.4)
1.3 mg	1 (10.0)	9 (31.0)	14 (40.0)
1.6 mg	5 (50.0)	10 (34.5)	10 (28.6)

Data cutoff: March 3, 2025; 74/75 patients were eligible for RI analysis.

Table 5. Dose modifications

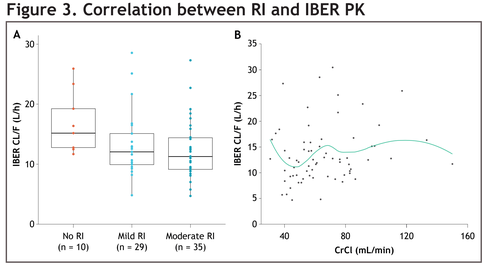
	All patients (N = 74)[a]	No RI (n = 10)	Mild RI (n = 29)	Moderate RI (n = 35)
Patients with ≥ 1 IBER dose interruption, n (%)	72 (97.3)	10 (100)	28 (96.6)	34 (97.1)
Dose interruptions, median (range), n	5.0 (1-36)	4.5 (1-13)	6.0 (1-36)	5.0 (1-34)
Time to first dose interruption,[b] median (range), days	36.0 (5-661)	95.5 (7-545)	24.0 (8-351)	42.0 (5-661)
Patients with ≥ 1 IBER dose reduction, n (%)	35 (47.3)	5 (50.0)	17 (58.6)	13 (37.1)
Dose reductions, median (range), n	1.0 (1-3)	1.0 (1-3)	1.0 (1-3)	2.0 (1-3)
Time to first dose reduction,[c] median (range), days	127.0 (28-735)	358.0 (114-708)	113.0 (28-561)	127.0 (29-735)

Data cutoff: March 3, 2025. [a]74/75 patients were eligible for RI analysis; [b]Time from the date of the first dose of the study medication to the date of the first dose interruption; [c]Time from the date of the first dose of the study medication to the date of the first dose reduction.

PopPK analysis

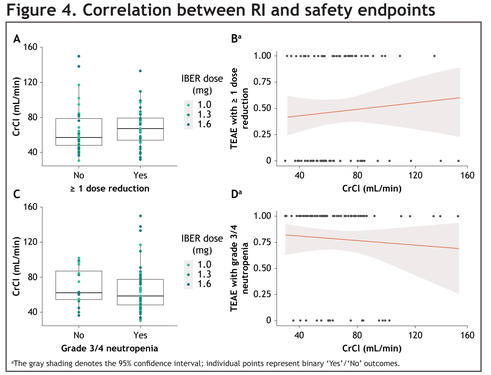
- Baseline CrCl and RI category had no significant impact on CL/F (**Figure 3**)

Figure 3. Correlation between RI and IBER PK



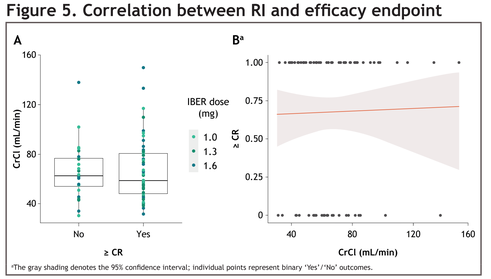
- Logistic regression analyses suggested that there was no significant correlation between baseline CrCl and key safety endpoints (TEAE with ≥ 1 dose reduction and TEAE with grade 3/4 neutropenia) (**Figure 4**)
- There was no clear trend between baseline CrCl and the key efficacy endpoint ≥ CR (**Figure 5**)

Figure 4. Correlation between RI and safety endpoints



[a]The gray shading denotes the 95% confidence interval; individual points represent binary 'Yes'/'No' outcomes.

Figure 5. Correlation between RI and efficacy endpoint



[a]The gray shading denotes the 95% confidence interval; individual points represent binary 'Yes'/'No' outcomes.

Conclusions

- This study suggests that:
  - Renal impairment does not impact clinical outcomes in patients with TNE NDMM treated with IberDd
  - IBER dose modifications are not required for patients with mild-to-moderate renal impairment
- Logistic regression analyses showed no correlation between baseline CrCl and key efficacy and safety endpoints in patients with TNE NDMM receiving IberDd
  - While there was a trend for higher rates of grade 3/4 neutropenia in patients with worse renal function, this did not result in noticeable differences in infection rates between subgroups
- These data are consistent with previous observations in patients with RRMM receiving IBER + DEX[7]

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