Iberdomide, daratumumab, and dexamethasone in transplant-ineligible newly diagnosed multiple myeloma: results from the phase 1/2 CC-220-MM-001 trial

MM-101

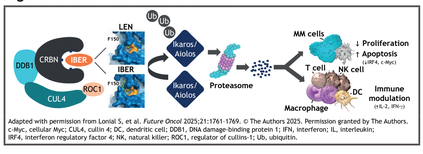
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Introduction

- Lenalidomide (LEN) in combination with daratumumab (DARA) and dexamethasone (DEX) is a standard of care for patients with transplant-ineligible (TNE) newly diagnosed multiple myeloma (NDMM)[1]
- Iberdomide (IBER), an oral CELMoD™ agent, may provide additional therapeutic benefit when given with DARA and DEX
  - IBER binds cereblon (CRBN) with higher affinity and unique interactions that induce CRBN conformational changes more efficiently than pomalidomide (POM) and LEN, leading to enhanced degradation of Ikaros and Aiolos, and higher multiple myeloma (MM) cell killing and immune stimulation[2] (**Figure 1**)
  - In preclinical studies, IBER has shown greater synergistic activity with DEX and DARA (IberDd) compared with immunomodulatory drug (IMiD®) agents in vitro[2]
- IBER is being investigated in different combination regimens for patients with MM in the phase 1/2, multicenter, open-label, dose-escalation and dose-expansion CC-220-MM-001 clinical trial (NCT02773030)[3]
  - IberDd has shown meaningful clinical activity and safety in patients with relapsed/refractory MM (RRMM), including in patients treated with LEN or POM[4]

Figure 1. IBER mechanism of action



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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

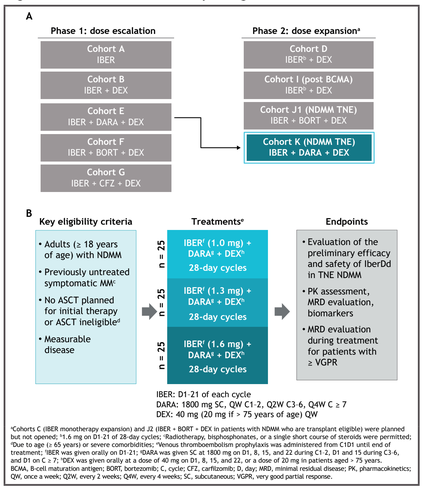
- To report the first results from the IberDd dose-expansion cohort of the CC-220-MM-001 trial in patients with NDMM who are TNE or not receiving autologous stem cell transplant (ASCT) as their first therapy

Methods

Study design

- CC-220-MM-001 is a phase 1/2 trial evaluating IBER with different treatment combinations in MM (**Figure 2A**)
- Adult patients with NDMM who were TNE or who had no ASCT planned for initial therapy were enrolled (**Figure 2B**)

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



IBER: D1-21 of each cycle
DARA: 1800 mg SC, QW C1-2, Q2W C3-6, Q4W C ≥ 7
DEX: 40 mg (20 mg if > 75 years of age) QW

[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]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 was given SC at 1800 mg 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 a dose of 20 mg in patients aged > 75 years.
BCMA, B-cell maturation antigen; BORT, bortezomib; C, cycle; CFZ, carfilzomib; D, day; MRD, minimal residual disease; PK, pharmacokinetics; QW, once a week; Q2W, every 2 weeks; Q4W, every 4 weeks; SC, subcutaneous; VGPR, very good partial response.

Endpoints

- Trial endpoints included the evaluation of preliminary efficacy, safety, PK, MRD, and biomarkers in patients with TNE NDMM receiving IberDd
  - MRD was evaluated during treatment for patients with ≥ VGPR

Results

Baseline characteristics

- Patient baseline characteristics are shown in **Table 1**
  - Median age was 75 (range, 44-90) years, and 44 (58.7%) patients were ≥ 75 years of age
  - Thirty-one (41.3%) patients had high-risk cytogenetics, which included 1q amplification

Table 1. Baseline characteristics

Characteristic[a]	IberDd TNE NDMM (N = 75)
Age, median (range), years	75 (44-90)
≥ 75 years of age, n (%)	44 (58.7)
Sex, male, n (%)	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, n (%)	
0	23 (30.7)
1	43 (57.3)
2	9 (12.0)
ISS stage at study entry,[b] n (%)	
I	30 (40.0)
II	30 (40.0)
III	14 (18.7)
Presence of plasmacytomas,[c] n (%)	6 (8.0)
High-risk cytogenetics,[d,e] n (%)	31 (41.3)

[a]Data cutoff: May 29, 2024; [b]For 1/75 patients, these data were missing; [c]Including paraosseous and extramedullary lesions; [d]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; [e]For 9/75 patients, this was missing or not evaluable. ECOG PS, Eastern Cooperative Oncology Group performance status; ISS, International Staging System.

Treatment disposition

- At data cutoff (May 29, 2024), 82.7% of patients remained on therapy (**Table 2**)
- Three deaths occurred during the treatment period, none of which were attributed to study treatment
- Only 1 patient discontinued treatment due to disease progression

Table 2. Treatment disposition

Treatment disposition[a]	IberDd TNE NDMM (N = 75)
Follow-up, median (range), months	13.9 (0.4-19.4)
Ongoing, n (%)	62 (82.7)
Discontinued, n (%)	13 (17.3)
AE[b]	5 (6.7)
Death[c]	3 (4.0)
Patient withdrawal	2 (2.7)
Physician decision	2 (2.7)
Progressive disease	1 (1.3)

[a]Data cutoff: May 29, 2024; [b]5 patients discontinued due to AEs: 1 cytomegalovirus chorioretinitis, 1 acute kidney injury, 1 general physical health deterioration; 1 hypoxia, and 1 anemia/neutropenia; [c]3 patients died during the treatment period due to grade 5 AEs: 1 intestinal ischemia, 1 pneumonia aspiration, and 1 death from unknown cause. AE, adverse event.

Dose modifications and treatment exposure

- Almost all (92.0%) patients had ≥ 1 IBER dose modification (**Table 3**)
- Over the course of around 14 months of treatment, few patients discontinued IBER due to AEs
- The median treatment duration was 13.5 (range, 0.3-19.6) months

Table 3. Dose modifications and treatment exposure

Dose modifications[a]	IberDd TNE NDMM (N = 75)
Patients with ≥ 1 IBER dose modification, n (%)	69 (92.0)
IBER dose interruptions due to TEAEs, n (%)	60 (80.0)
IBER dose reductions due to TEAEs, n (%)	28 (37.3)
Treatment exposure[a]	
Treatment duration, median (range), months	13.5 (0.3-19.6)
Cycles received, median (range), n	14 (1-21)
RDI of IBER, % (range)	85.7 (16.7-199.4)

[a]Data cutoff: May 29, 2024. RDI, relative dose intensity; TEAE, treatment-emergent AE.

Safety

- Neutropenia was the most frequent hematologic TEAE, occurring in 60 (80.0%) of patients (all grade), and was mostly grade 3/4 (56 [74.7%] of patients)
- Few grade 3/4 non-hematologic TEAEs occurred (**Table 4**)
  - Grade 3/4 diarrhea was not reported as of the data cutoff
  - Infections occurred in 63 (84.0%) patients (all grade), including COVID-19 in 24 (32.0%) patients; 29 (38.7%) patients experienced grade 3/4 infections
    - Grade 3/4 pneumonia was reported in 19 (25.3%) of patients

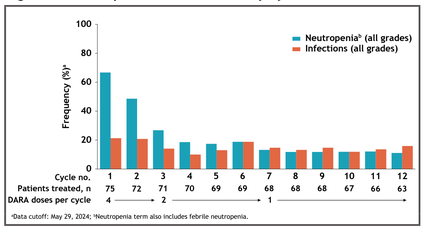
Table 4. Most common (≥ 25% all grade) TEAEs

Most common (≥ 25% all grade) TEAEs and events of interest,[a] n (%)	IberDd TNE NDMM (N = 75)		
	All grade	Grade 3	Grade 4
Any TEAE	75 (100)	35 (46.7)	36 (48.0)
Hematologic TEAEs			
Neutropenia	60 (80.0)	26 (34.7)	30 (40.0)
Febrile neutropenia	9 (12.0)	9 (12.0)	0
Anemia	25 (33.3)	8 (10.7)	0
Lymphopenia	24 (32.0)	10 (13.3)	5 (6.7)
Leukopenia	17 (22.7)	8 (10.7)	3 (4.0)
Thrombocytopenia	16 (21.3)	2 (2.7)	1 (1.3)
Non-hematologic TEAEs			
Constipation	26 (34.7)	0	0
Rash[b]	24 (32.0)	2 (2.7)	0
Fatigue	20 (26.7)	1 (1.3)	0
Pyrexia	20 (26.7)	2 (2.7)	0
Peripheral edema	20 (26.7)	0	0
Nausea	19 (25.3)	2 (2.7)	0
Diarrhea	17 (22.7)	0	0
Infections	63 (84.0)	26 (34.7)	3 (4.0)
COVID-19[c]	24 (32.0)	4 (5.3)	0
Pneumonia[d]	19 (25.3)	17 (22.7)	2 (2.7)

[a]Data cutoff: May 29, 2024; [b]Including maculopapular rash, macular rash, and pruritic rash; [c]Including COVID-19 pneumonia; [d]Including influenzal pneumonia, bacterial pneumonia, cryptococcal pneumonia, parainfluenzae viral pneumonia, pneumococcal pneumonia, and respiratory syncytial viral pneumonia.

- Grade 3/4 neutropenia was more frequent in the first 2 cycles, consistent with the more frequent DARA dosing, and decreased over time (**Figure 3**)
- Infection rates remained low, the risk did not increase over time, and appeared independent of neutropenia (**Figure 3**)
  - Beyond cycle 3, both neutropenia and infection rates were < 20%

Figure 3. Neutropenia and infections by cycle

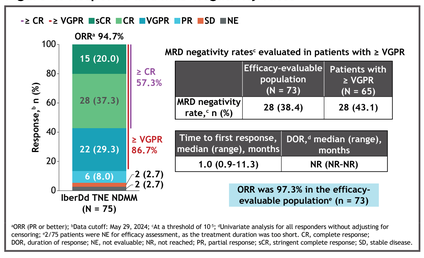


[a]Data cutoff: May 29, 2024; [b]Neutropenia term also includes febrile neutropenia.

Efficacy

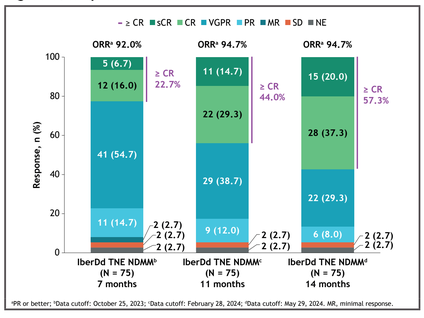
- Overall response rate (ORR) was 94.7% overall (N = 75), and 97.3% in the efficacy-evaluable population (N = 73) (**Figure 4**)
  - Two patients were NE for efficacy assessment, as the treatment duration was too short
  - Overall, 57.3% of patients achieved ≥ CR, and 86.7% achieved ≥ VGPR
- Among patients who achieved ≥ VGPR (N = 65), 28 (43.1%) reached MRD negativity (10^{-5} threshold)
- Responses to IberDd deepened over time (**Figure 5**)

Figure 4. Response and MRD negativity rates



[a]ORR (PR or better); [b]Data cutoff: May 29, 2024; [c]At a threshold of 10^{-5}; [d]Univariate analysis for all responders without adjusting for censoring; [e]2/75 patients were NE for efficacy assessment, as the treatment duration was too short. CR, complete response; DOR, duration of response; NE, not evaluable; NR, not reached; PR, partial response; sCR, stringent complete response; SD, stable disease.

Figure 5. Responses over time

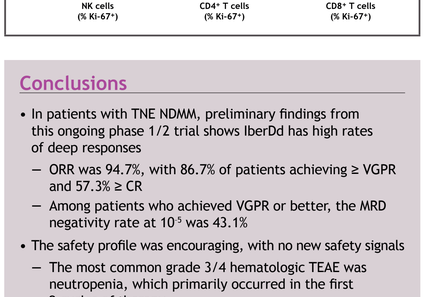


[a]PR or better; [b]Data cutoff: October 25, 2023; [c]Data cutoff: February 28, 2024; [d]Data cutoff: May 29, 2024. MR, minimal response.

Pharmacodynamics

- Immunostimulatory activity was comparable across all doses tested, suggesting maximal pharmacodynamic activity was achieved at the 1.0 mg dose (**Figure 6**)

Figure 6. Induction of NK and T cell proliferation by C2D15



Conclusions

- In patients with TNE NDMM, preliminary findings from this ongoing phase 1/2 trial shows IberDd has high rates of deep responses
  - ORR was 94.7%, with 86.7% of patients achieving ≥ VGPR and 57.3% ≥ CR
  - Among patients who achieved VGPR or better, the MRD negativity rate at 10^{-5} was 43.1%
- The safety profile was encouraging, with no new safety signals
  - The most common grade 3/4 hematologic TEAE was neutropenia, which primarily occurred in the first 2 cycles of therapy
  - Grade 3/4 non-hematologic TEAEs were minimal or absent
  - 29 (38.7%) of patients experienced grade 3/4 infections, most of which were ≤ grade 3
  - Few patients discontinued IBER and 82.7% are still on treatment
  - 3 deaths occurred on study due to TEAEs; none were considered related to study treatment
- These results support the continued evaluation of IberDd in patients with TNE NDMM
  - IberDd is also being investigated in the ongoing phase 3 EXCALIBER-RRMM trial (NCT04975997)[5]

References

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Acknowledgments

- The patients and families who are making the study possible
- The clinical study teams who participated
- 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 Emma Rathbone, PhD, of Excerpta Medica, funded by Bristol Myers Squibb

Presented at the Society of Hematologic Oncology (SOHO) 2025 Annual Meeting; September 3-6, 2025; Houston, TX, USA.
Previously presented at the Journal of Advanced Practitioner in Oncology (JADPRO) 2024 Annual Congress; November 14-17, 2024; Grapevine, TX, USA.

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