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First Results of Iberdomide (IBER; CC-220) in Combination with Dexamethasone (DEX) and Daratumumab (DARA) or Bortezomib (BORT) in Patients with Relapsed/Refractory Multiple Myeloma (RRMM)

Niels W.C.J. Van De Donk[1], *Rakesh Popat*[2]*, *Jeremy Larsen*[3], *Monique C. Minnema*[4], *Sundar Jagannath, MD*[5]*, *Albert Oriol*[6]*, *Jeffrey Zonder*[7], *Paul G. Richardson, MD*[8], *Paula Rodriguez-Otero, MD, PhD*[9]*, *Ashraf Z. Badros, MD*[10], *Edward Stadtmauer*[11]*, *Sara Bringhen, MD*[12], *Erica Campagnaro, MD*[13]*, *David S. Siegel, MD*[14], *Barbara Gamberi*[15]*, *Mercedes Gironella Mesa*[16]*, *Pieter Sonneveld, MD, PhD*[17], *Tuong Vi Nguyen*[18]*, *Antonia Di Micco*[19]*, *April Sorrell*[18]*, *Min Chen*[18]*, *Michael Amatangelo*[18]*, *Elisabeth Kueenburg*[19]* *and Sagar Lonial, MD*[20]

[1]Department of Hematology, Cancer Center Amsterdam, Amsterdam UMC, VU University Medical Center, Amsterdam, Netherlands
[2]NIHR UCLH Clinical Research Facility, University College London Hospitals NHS Foundation Trust, London, United Kingdom
[3]Mayo Clinic, Scottsdale, AZ
[4]Department of Hematology, University Medical Center Utrecht, Utrecht University, Utrecht, Netherlands
[5]The Mount Sinai Hospital, New York, NY
[6]Institut Josep Carreras and Institut Català d'Oncologia, Hospital Germans Trias i Pujol, Badalona, Spain
[7]Karmanos Cancer Institute, Detroit, MI
[8]Dana-Farber Cancer Institute, Boston, MA
[9]Clínica Universidad de Navarra, CIMA, IDISNA, CIBERONC, Pamplona, Spain
[10]The University of Maryland Marlene and Stewart Greenebaum Comprehensive Cancer Center, University of Maryland Medical Center, Baltimore, MD
[11]University of Pennsylvania, Philadelphia, PA
[12]Myeloma Unit, Division of Hematology, University of Torino, Azienda-Ospedaliero Universitaria Città della Salute e della Scienza di Torino, Torino, Italy
[13]Michigan Medicine Hematology Clinic, University of Michigan Rogel Cancer Center, Ann Arbor, MI
[14]Division of Multiple Myeloma, John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ
[15]Hematology Unit, AUSL-IRCSS, Reggio Emilia, Italy
[16]University Hospital Vall d'Hebron, Barcelona, Spain
[17]Erasmus Medical Center Rotterdam, Rotterdam, Netherlands
[18]Bristol Myers Squibb, Princeton, NJ
[19]Celgene International Sàrl, a Bristol-Myers Squibb Company, Boudry, Switzerland
[20]Winship Cancer Institute of Emory University, Atlanta, GA

*signifies non-member of ASH

Introduction: IBER is an oral, potent novel cereblon E3 ligase modulator (CELMoD) agent with marked synergistic tumoricidal and immune-stimulatory effects in combination with BORT or DARA in preclinical models. CC-220-MM-001 is a phase 1/2 study evaluating dose escalations of IBER with different treatment combinations in independent cohorts, in patients (pts) with RRMM (NCT02773030); the IBER + DEX cohort showed a favorable safety profile with promising efficacy and a selected IBER RP2D of 1.6 mg 21/28 days (D). Here, we present results from the IBER + DARA + DEX (IberDd) and IBER + BORT + DEX (IberVd) cohorts.

Methods: Eligible pts had received ≥ 2 prior regimens in the IberDd cohort, and ≥ 1 prior regimen in the IberVd cohort, containing at least lenalidomide or pomalidomide, and a proteasome inhibitor (PI), and had experienced disease progression on or within 60 days of last MM therapy. Escalating doses of IBER were given orally, in the IberDd cohort on D1–21, with DARA (16 mg/kg) on D1, D8, D15, and D22 (cycles [C]1–2), D1 and D15 (C3–6), and D1 (C ≥ 7), of each 28-day cycle; in the IberVd cohort, on D1–14, with BORT (1.3 mg/m^2) on D1, D4, D8, and D11 (C1–8), and on D1 and D8 (C ≥ 9), of each 21-day cycle. In both cohorts DEX was given weekly. Primary objectives were to evaluate MTD, RP2D, and safety separately for each cohort; a key secondary objective was preliminary assessment of efficacy. Immune profiling was evaluated by flow cytometry from pt peripheral blood at C1D1, C2D15, C4D1, and C4D15.

Results: As of June 18, 2020, 19 pts had received IberDd and 21 pts IberVd. Baseline characteristics for the 2 independent cohorts are shown in the table. All pts were refractory to their last prior regimen, and exposure to prior regimens was heterogeneous. IBER doses ranged from 1.0 to 1.6 mg; the MTD/RP2D has not been reached in either cohort. Median follow-up was 5 (0–14) and 3 (0–11) months, 10 (53%) and 13 (62%) pts continue on treatment, median cycles received was 5 (1–14) and 4.5 (1–17), with IberDd and IberVd, respectively.

Grade (Gr) 3–4 treatment-emergent adverse events (TEAEs) were reported in 14 (78%) pts with IberDd, and in 13 (65%) pts with IberVd. Most frequent Gr 3–4 TEAEs of interest included neutropenia (50%), leukopenia (22%), and anemia (22%) with IberDd; and neutropenia (20%) and thrombocytopenia (20%) with IberVd. In both cohorts, neutropenia was managed with G-CSF. One pt (IberDd; 1.2 mg dose) had Gr 4 neutropenic sepsis. Occurrence of Gr 3–4 non-hematological TEAEs was low in both cohorts. One pt had Gr 2 infusion-related reaction with IberDd, and 3 pts had Gr 1–2 peripheral neuropathy with IberVd. Six (33%) and 4 (20%) pts had IBER dose reductions with IberDd and IberVd, respectively.

In the IberDd cohort, with 12/19 (63%) DARA-refractory pts and 11 (58%) quad-class-refractory pts, the overall response rate (ORR) was 35% across all dosing groups (2 very good partial responses [VGPRs], 4 partial responses [PRs]); the clinical benefit rate (CBR) was 47% and disease control rate (DCR) was 88%. In the IberVd cohort, with 16/21 (76%) PI-refractory pts, 9 (43%) BORT-refractory pts, and 10 (48%) quad-class refractory pts, ORR was 50% (1 complete response, 3 VGPRs, 6 PRs); CBR was 65% and DCR was 85%. Responses with IberDd and IberVd were observed irrespective of DARA- and BORT-refractoriness, respectively. Median time to response was 4.1 (4.1–12.0) and 4.9 (3.0–13.1) weeks, in the IberDd and IberVd cohorts, respectively; median duration of response was not reached in both cohorts.

Immune profiling showed dose-dependent decreases in B cells and increases in activated and differentiated T cells, in both cohorts. Except for reductions in CD38+ T cells in pts receiving IberDd, these observations were similar in pts treated with IBER + DEX.

Conclusions: IberDd and IberVd showed a favorable tolerability profile in heavily pretreated RRMM pts, with promising clinical activity, even among pts refractory to the last prior regimen and previously exposed to IMiD agents, PIs, and CD38 antibodies. Immune-profiling data confirm that IBER + DEX was pharmacodynamically active in triplet combination and not augmented by the addition of DARA or BORT. The study is ongoing with continued enrollment at the 1.6 mg dose level for both cohorts. Updated results, including the MTD/RP2D, will be presented at the meeting. These results support the further development of IBER-based regimens in MM; phase 3 trials are planned to further evaluate these combinations.

Table. Baseline characteristics and prior therapies

	IberDd (n = 19)	IberVd (n = 21)
Age, median (range), years	66 (40–77)	65 (47–81)
Time since initial diagnosis, median (range), years	8.0 (3.4–19.1)	7.6 (3.0–16.0)
ISS at study entry, n (%)		
Stage I	11 (57.9)	12 (57.1)
Stage II	5 (26.3)	9 (42.9)
Stage III	2 (10.5)	0
Presence of EMP, n (%)	3 (15.8)	4 (19.0)
Prior therapies, median (range)	4 (2–12)	6 (1–14)
ASCT, n (%)	16 (84.2)	17 (81.0) [a]
BORT, n (%)	19 (100)	20 (95.2)
CFZ, n (%)	14 (73.7)	11 (52.4)
LEN, n (%)	19 (100)	21 (100)
POM, n (%)	14 (73.7)	16 (76.2)
DARA, n (%)	13 (68.4)	17 (81.0)
Anti-BCMA, n (%)	2 (10.5)	2 (9.5)
> 8 prior regimens, n (%)	4 (21.1)	3 (14.3)
IMiD-refractory,[b] n (%)	18 (94.7)	16 (76.2)
PI-refractory, n (%)	14 (73.7)	16 (76.2)
Anti-CD38 mAb-refractory, n (%)	12 (63.2)	16 (76.2)
Quad-class refractory,[c] n (%)	11 (57.9)	10 (47.6)

[a]Four patients received both autologous and allogenic stem cell transplant.
[b]Defined as refractory to LEN or POM.
[c]Defined as refractory to ≥ 1 IMiD, 1 PI, 1 anti-CD38 mAb, and 1 glucocorticoid.
ASCT, autologous stem cell transplant; BCMA, B-cell maturation antigen; BORT, bortezomib; CFZ, carfilzomib; DARA, daratumumab; DEX, dexamethasone; EMP, extramedullary plasmacytoma; IberDd, IBER + DARA + DEX; IberVd, IBER + BORT + DEX; ISS, International Staging System; IMiD, immunomodulatory drug; LEN, lenalidomide; mAb, monoclonal antibody; POM, pomalidomide.

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Springer Healthcare Ibérica S.L.
Rosario Pino, 14 - 4ª Planta. 28020 Madrid. Spain
Tel.: +34 91 555 40 62. Fax: +34 91 555 76 89
E-mail: Miguel.Quesada@springer.com
www.springerhealthcare.com
www.springernature.com

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