First-in-human phase 1 study of the novel CELMoD agent CC-92480 combined with dexamethasone in patients with relapsed/refractory multiple myeloma

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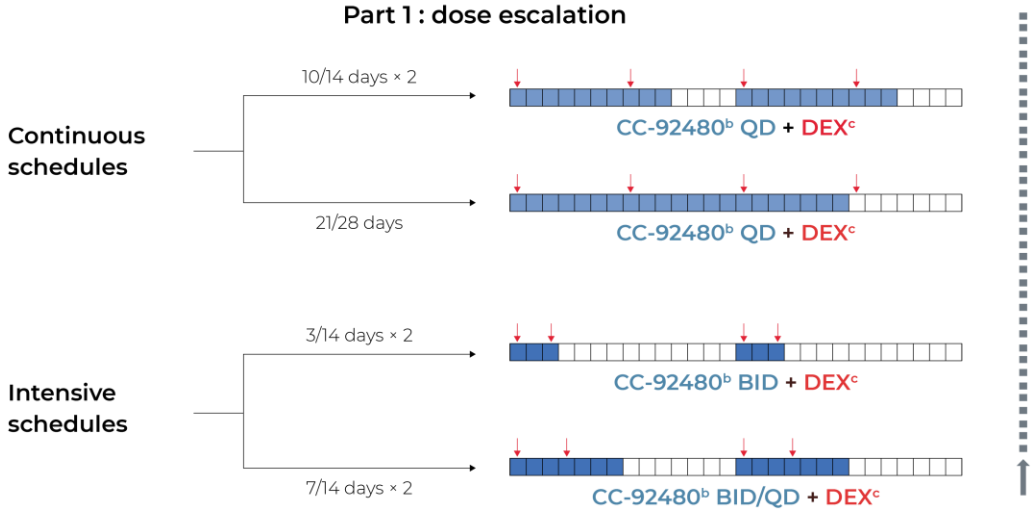
CC-92480-MM-001 phase 1 trial (NCT03374085): study design

Key eligibility criteria

- RRMM
- Resistant or intolerant to, or not otherwise candidates for currently available therapies[a]
- Progression on or within 60 days of last antimyeloma therapy

Study endpoints

- **Primary:** assess PK, safety, and define the MTD/RP2D
- **Secondary:** assess preliminary efficacy



Part 2: cohort expansion

[a]Including LEN, POM, a PI, a glucocorticoid, and/or anti-CD38 mAb, according to local availability; [b]Administered orally; [c]DEX given at a dose of 40 mg (20 mg in patients aged ≥ 75 years).

BID, twice daily; DEX, dexamethasone; LEN, lenalidomide; MTD, maximum tolerated dose; PD, pharmacodynamics; PK, pharmacokinetics; QD, once daily; RP2D, recommended phase 2 dose; RRMM, refractory/relapsed multiple myeloma.

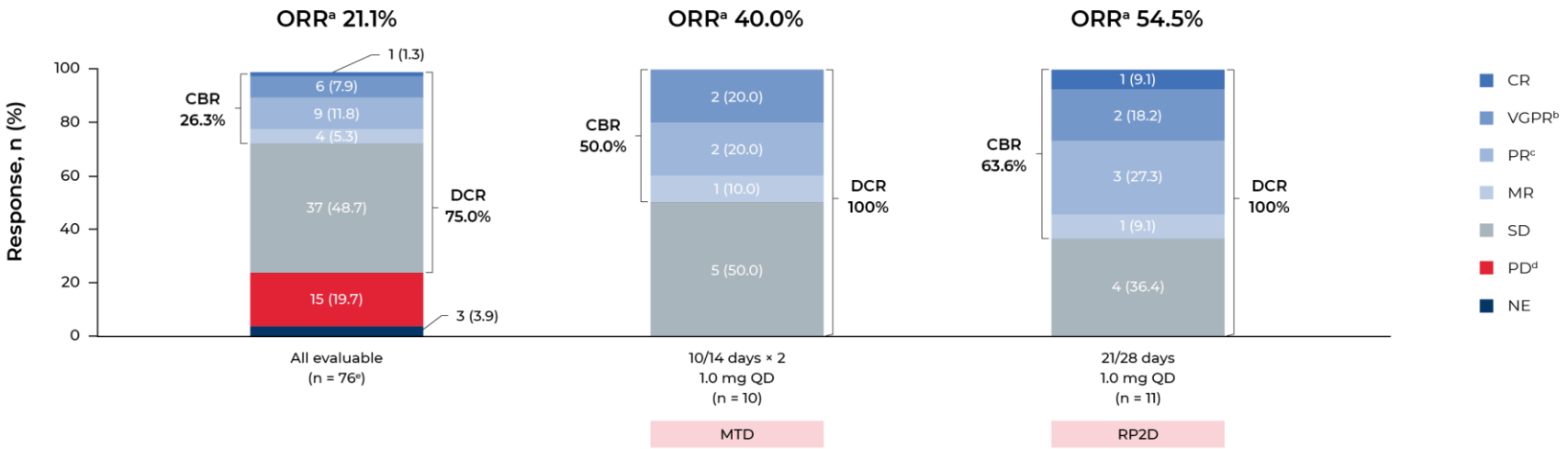
TEAEs all cycles

Common (> 20 % all grade) TEAEs and events of interest, n (%)	All doses (N = 76)		
	All grade	Grade 3	Grade 4
Neutropenia	56 (73.7)	23 (30.3)	26 (34.2)
Febrile neutropenia	6 (7.9)	4 (5.3)	1 (1.3)
Anemia	42 (55.3)	24 (31.6)	-
Thrombocytopenia	33 (43.4)	5 (6.6)	7 (9.2)
Infections	54 (71.1)	25 (32.9)	2 (2.6)
Pneumonia[a]	13 (17.1)	11 (14.5)	-
Fatigue	29 (38.2)	7 (9.2)	-
Pyrexia	17 (22.4)	3 (3.9)	-
Peripheral sensory neuropathy	4 (5.3)	-	-
Diarrhea	18 (23.7)	1 (1.3)	-
Nausea	17 (22.4)	1 (1.3)	-
Deep vein thrombosis	1 (1.3)	-	-

- Prophylactic G-CSF was not permitted during Cycle 1
- Neutropenia was managed with dose interruption/reduction and G-CSF
- Dose reductions of CC-92480 occurred in 17 (22.4%) patients
- No patients discontinued due to treatment-related AEs

[a]Includes Medical Dictionary for Regulatory Activities Terminology version 22.0 preferred terms pneumonia, pneumocystis jirovecii pneumonia, respiratory syncytial viral pneumonia, and staphylococcal pneumonia.
AE, adverse event; G-CSF, granulocyte colony-stimulating factor; MTD, maximum tolerated dose; TEAE, treatment-emergent adverse event.

Best response



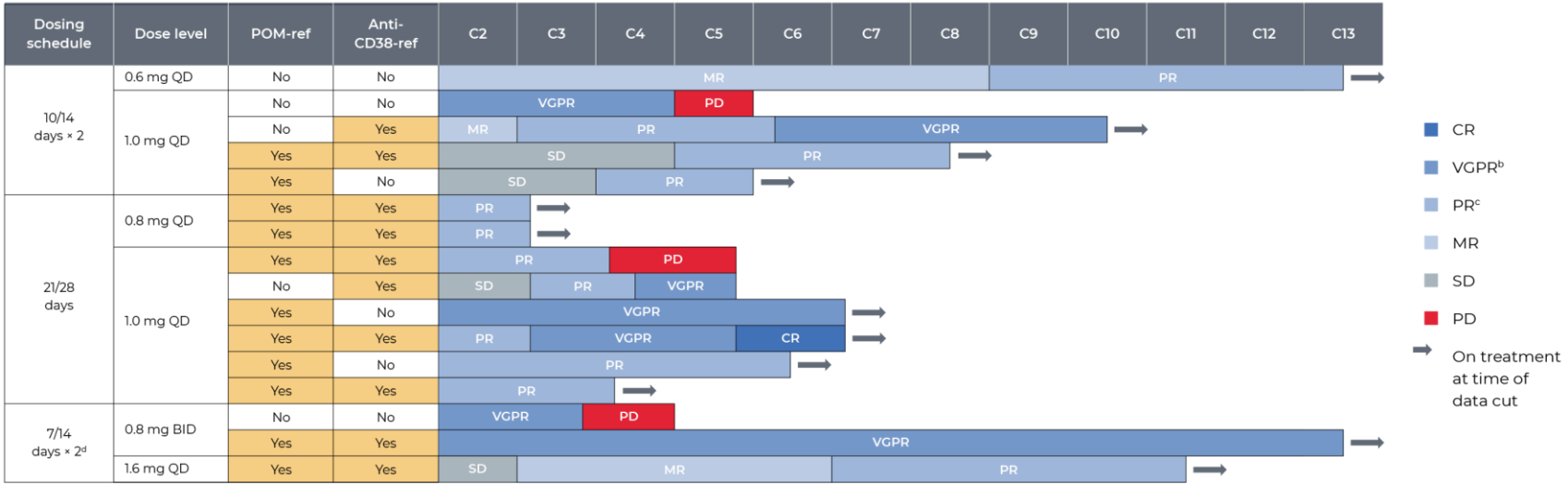
- At the RP2D 1.0 mg QD 21/28 days, 7 out of 11 patients were triple-class-refractory[f]
  - 1 patient had CR, 1 VGPR, 2 PR, and 1 MR

[a]PR or better; [b]1 patient in the 21/28-day 1.0 mg QD cohort had an unconfirmed VGPR as of the data cutoff date; [c]2 patients in the 21/28-day 0.8 mg QD cohort had an unconfirmed PR as of the data cutoff date; [d]1 patient in the 21/28-day 0.8 mg QD cohort had an unconfirmed PD as of the data cutoff date; [e]1 patient had a pending response assessment at data cutoff date; [f]Defined as refractory to ≥ 1 IMiD agent, 1 PI, and 1 anti-CD38 mAb.

CBR, clinical benefit rate; CR, complete response; DCR, disease control rate; MR, minimal response; MTD, maximum tolerated dose; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; QD, once daily; RP2D, recommended phase 2 dose; SD, stable disease; VGPR, very good partial response.

Responders (PR or better) by dose level

- Majority of responders were dual-IMiD-refractory[a] (10 out of 16 patients [63%])



[a] Refractory to both LEN and POM; [b]1 patient in the 21/28 1.0 mg QD cohort had an unconfirmed VGPR as of the data cutoff date; [c]2 patients in the 21/28 0.8 mg QD cohort had an unconfirmed PR as of the data cutoff date; [d]No response at 2.0 mg QD 7/14 days × 2.

C, cycle; CR, complete response; IMiD, immunomodulatory drug; MR, minimal response; PD, progressive disease; PR, partial response; QD, once daily; ref, refractory; SD, stable disease; VGPR, very good partial response.

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Conclusions and future directions

- CC-92480 is a novel CELMoD agent with enhanced antiproliferative and tumoricidal activity in MM cell lines, including those resistant to LEN and POM[1,2]
- CC-92480 + DEX showed a manageable safety profile in patients with heavily pretreated RRMM
  - MTD was 1.0 mg QD for both 10/14-day × 2 and 21/28-day schedules
  - TEAEs were mainly related to myelosuppression
- Innovative study design employed PK/PD data to optimize dose and schedule selection to achieve a preclinically defined differentiated profile of CC-92480
- Promising activity at therapeutic doses was observed in MM patients refractory to SoC, including POM- and triple-class-refractory patients, and in patients with extramedullary disease
- The study is ongoing with a dose-expansion cohort planned at the RP2D (1.0 mg QD 21/28 days)
- A Phase 1/2 study evaluating the safety and efficacy of CC-92480 in combination with standard treatments in patients with MM is ongoing (CC-92480-MM-002, NCT03989414)[3]

DEX, dexamethasone; LEN, lenalidomide; MM, multiple myeloma; MTD, maximum tolerated dose; POM, pomalidomide, QD, once daily; RP2D, recommended phase 2 dose; RRMM, relapsed/refractory multiple myeloma; SoC, standard of care; TEAE, treatment-emergent adverse event.

1. Hansen J et al. *J. Med. Chem*. 2020. 2. Lopez-Girona A, et al. *Blood*. 2019;134:abstract 1812. 3. NCT0398414. https://clinicaltrials.gov/ct2/show/NCT03989414.