Updated Results of a Phase 1 First-in-Human Study of Cemsidomide, a Novel MonoDAC® Degrader, with Dexamethasone (DEX) in Patients (pts) with Relapsed/Refractory Multiple Myeloma (RRMM)

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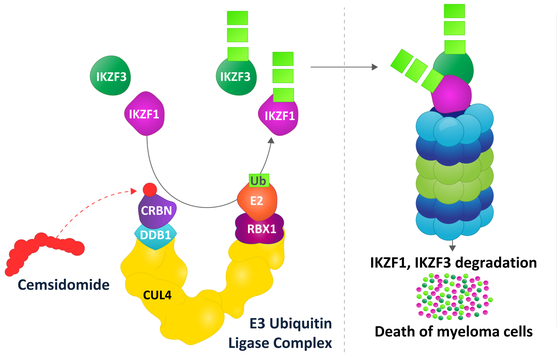
Introduction

- Cemsidomide is a novel, highly potent, cereblon-based, IKZF1/3 MonoDAC® degrader, having a similar mechanism of action as BMS's IMiD® or CELMoD® degraders for MM
- Cemsidomide displays catalytic activity enabling rapid and deep target degradation with high binding affinity to overcome resistance due to low cereblon levels
- Cemsidomide binds to cereblon to facilitate the recruitment and ubiquitination of IKZF1/3 leading to the proteasomal degradation of both proteins (Figure 1)
- IKZF1/3 degradation induces multiple myeloma cell death, activation of fully differentiated T-cells which prevents T-cell exhaustion and promotes secretion of key immune stimulating cytokines[1]

Figure 1: Mechanism of Action of Cemsidomide[2]



IKZF1/3 Degradation Induces:

- Multiple Myeloma cell death
- Immune stimulation
  - Activates fully differentiated T-cells, preventing T-cell exhaustion
  - Promotes secretion of key immune stimulating cytokines (e.g., IL-2)
- On-target neutropenia
  - Disrupts hematopoietic stem cell differentiation

Methods

CFT7455-1101 Study Design[3]

- Open-label, multicenter, phase 1/2 clinical trial with dose escalation and expansion phases (NCT04756726)*
- Dose escalation phase, beginning with a starting oral dose of 50 µg MWF 14 days on/14 days off, following a Bayesian logistic regression model until determination of the MTD and/or RP2D
  - Escalation cohorts enrolled 3-6 patients, once dose was declared safe by SRC, additional patients were eligible to enroll at the dose deemed safe
    - G-CSF and transfusions were not allowed in cycle 1 for dose escalation subjects
    - Once a dose was declared safe, additional patients at each dose level were allowed G-CSF use at any timepoint

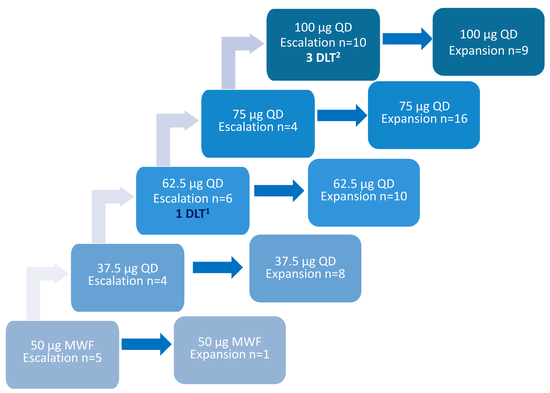
KEY INCLUSION CRITERIA

- Adults with MM, R/R to at least 3 prior lines of therapy that have included lenalidomide, pomalidomide, a proteasome inhibitor, a glucocorticoid, and an anti-CD38 monoclonal antibody
- Nonresponsive to or progressed within 60 days of prior therapy
- Creatinine clearance ≥40 mL/min
- ECOG ≤2

Phase 1 Study Endpoints

- Primary: assess safety, tolerability and define the RP2D/MTD
- Secondary: assess PK, PD, and preliminary anti-tumor activity

Figure 2: Phase 1 Dose Escalation Cemsidomide 14/14 + Dex*



*CFT7455 administered as 14 days on/14 days off in a 28-day cycle; Dex was dosed on days 1, 8, 15, and 22 at doses of 40 mg orally for patients ≤75 years old and 20 mg orally for patients >75 years old; [1]DLT in the 62.5 µg QD was due to grade 4 neutropenia lasting >7 days; [2]Three patients in the 100 µg QD escalation had 5 DLT events (G4 neutropenia, G3 pneumonia in 2 subjects, G3 ALT increase, G3 febrile neutropenia)

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Results

Patients

- At the data cutoff date (February 27, 2026), 73 patients had received cemsidomide + dexamethasone
- Baseline characteristics are shown in Table 1, and prior therapies are shown in Table 2
  - Patients were heavily pre-treated, having received a median of 7 prior lines of therapy (range 3-22)
  - 75% of patients had received a CAR-T or TCE and 75% had received a prior BCMA therapy

Table 1: Baseline Characteristics

Characteristics	Safety Population (N=73)
Age, median (range)	67 (39-90 years)
Male, n (%)	43 (59)
Time since initial diagnosis, median (range)	7 (2-22 years)
ECOG performance status, n (%)	
0	18 (25)
1	52 (71)
2	3 (4)
Asian	1 (1)
Black or African American, n (%)	15 (21)
White, n (%)	50 (69)
Other, n (%)	7 (10)
Revised ISS at screening, n (%)	
Stage 1	24 (33)
Stage 2	31 (43)
Stage 3	9 (12)
Missing	9 (12)
Presence of EMD, n (%)	23 (32)

Table 2: Prior Therapies

Characteristics	Safety Population (N=73)
Prior therapies, median (range)	7 (3-22)
3L, n (%)	3 (4)
4L, n (%)	11 (15)
≥ 5L, n (%)	59 (81)
Prior stem cell transplant, n (%)	45 (62)
Prior lenalidomide, n (%)	73 (100)
Prior pomalidomide, n (%)	72 (99)
Prior anti-CD38 mAb, n (%)	73 (100)
Prior CAR-T therapy, n (%)	37 (51)
Prior T-cell engager therapy, n (%)	40 (55)
Prior CAR T or T-cell engager therapy, n (%)	55 (75)
Prior CAR T and T-cell engager therapy, n (%)	22 (30)
Prior BCMA therapy, n (%)	55 (75)
Prior GPRC5D therapy, n (%)	35 (48)
Triple-class exposed*, n (%)	73 (100)
Penta-drug exposed†, n (%)	59 (81)

*Defined as exposed to ≥1 immunomodulatory agent, ≥ 1 proteasome inhibitor, and 1 anti-CD38 monoclonal antibody; †Defined as exposed to ≥2 immunomodulatory agents, ≥ 2 proteasome inhibitors, and 1 anti-CD38 monoclonal antibody

Table 3: Treatment Disposition

Patient Disposition, n (%)	Safety Population (N=73)
Ongoing	7 (10)
Discontinued	66 (90)
Progressive disease	51 (70)
Withdrawal of consent	8 (11)
Adverse event	2 (3)*
Death	2 (3)#
Physician Decision	2 (3)
Other	1 (1)†

- Treatment disposition is shown on Table 3 with treatment ongoing for 7 patients (10%)
- The primary reason for discontinuation was progressive disease (51/66)
- Median time on treatment was 3.4 months

*2 patients discontinued due to an AE of septic shock and an AE of partial seizures (unrelated to cemsidomide)
#Death in a 62.5 µg cohort patient was due to subdural hematoma (related to a fall), unrelated to cemsidomide; death in a 100 µg cohort patient was due to T cell lymphoma (unrelated to cemsidomide); †A patient in the 50 µg MWF cohort was transferred to hospice, did not meet IMWG definition of progressive disease

Safety

Table 4: Overall Treatment Emergent Adverse Events

Adverse Events, n (%)	50 µg MWF (N=6)	37.5 µg QD (N=12)	62.5 µg QD (N=16)	75 µg QD (N=20)	100 µg QD (N=19)	Total (N=73)
TEAEs	6 (100)	12 (100)	16 (100)	20 (100)	19 (100)	73 (100)
TEAEs possibly related to cemsidomide	3 (50)	11 (92)	12 (75)	14 (70)	16 (84)	56 (77)
TESAEs	3 (50)	6 (50)	7 (44)	7 (35)	9 (47)	32 (44)
TESAEs possibly related to cemsidomide	0	4 (33)	3 (19)	5 (25)	4 (21)	16 (22)
Any grade ≥3 TEAEs	5 (83)	8 (67)	12 (75)	18 (90)	16 (84)	59 (81)
Any grade ≥3 TEAEs possibly related to cemsidomide	3 (50)	8 (67)	9 (56)	12 (60)	13 (68)	45 (62)
TEAEs leading to discontinuation	0	0	0	1 (5)	2 (11)	3 (4)*
TEAEs leading to reduction	0	0	0	1 (5)#	4 (21)§	5 (7)

*3 patients discontinued due to a grade 5 AE of septic shock, grade 5 AE of T cell lymphoma, grade 5 AE of partial seizures, all deemed unrelated to cemsidomide
#A patient in the 75 µg cohort had grade 4 thrombocytopenia possibly related to cemsidomide resulting in dose reduction; §A patient in the 100 µg cohort had grade 3 pneumonia and another patient at 100µg had grade 3 neutropenia, both AEs possibly related to cemsidomide resulting in dose reduction, a patient in the 100 µg cohort had a dose reductions after an AE of arthralgia, deemed possibly related to cemsidomide, a patient in the 100 µg cohort had two dose reductions after two events of pseudomonal bacteremia, deemed unrelated to cemsidomide.

- 4 DLTs: 1 patient at 62.5 µg had grade 4 neutropenia >7 days; 3 patients at 100 µg had 5 DLT events (grade 4 neutropenia >7 days, grade 3 ALT increase, grade 3 febrile neutropenia, grade 3 pneumonia in 2 subjects)
- No patient had a related TEAE leading to cemsidomide discontinuation

Table 5: Treatment Emergent Adverse Events by Grade

Hematologic and Infection TEAEs, n (%)	All Grades (N=73)	Grade 3 (N=73)	Grade 4 (N=73)	Grade 5 (N=73)
Neutropenia	45 (62)	16 (22)	26 (36)	0
Infections	46 (63)	21 (29)	1 (1)	1 (1)
Pneumonia	13 (18)	11 (15)	0	0
URTI	13 (18)	2 (3)	0	0
Septic Shock	1 (1)	0	0	1 (1)
Sepsis	2 (3)	2 (3)	0	0
PML*	1 (1)	0	1 (1)	0
Anemia	28 (38)	17 (23)	1 (1)	0
Leukopenia	22 (30)	10 (14)	8 (11)	0
Thrombocytopenia	14 (19)	5 (7)	3 (4)	0
Lymphopenia	12 (16)	7 (10)	1 (1)	0
Febrile Neutropenia	4 (6)	3 (4)	1 (1)	0

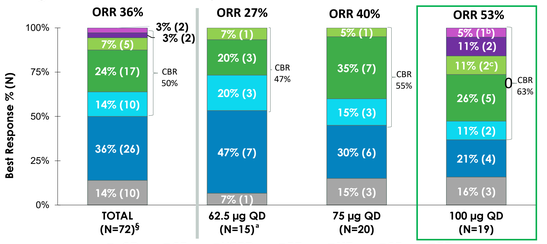
TEAEs (>20%) and Events of Interest, n (%)	All Grades (N=73)	Grade 3 (N=73)	Grade 4 (N=73)	Grade 5 (N=73)
Fatigue	29 (40)	0	0	0
Diarrhea	26 (36)	1 (1)	0	0
Cough	21 (29)	1 (1)	0	0
Insomnia	20 (27)	1 (1)	0	0
Constipation	19 (26)	0	0	0
Pyrexia	19 (26)	0	0	0
Nausea	18 (25)	0	0	0
Arthralgia	18 (25)	0	0	0
Dyspnea	17 (23)	2 (3)	0	0
Hypertension	17 (23)	5 (7)	1 (1)	0

*Grade 4 PML considered possibly related but occurred in the setting of pre-existing chronic lymphopenia and prior exposure to immunosuppressive therapies, including therapies that have been associated with PML. Patient had recurrent seizures in the setting of a brain lesion with a negative CSF for PML. After withdrawal of care due to recurrent seizures and ultimately death, autopsy report indicated a brain lesion consistent with PML diagnosis.

- 4 patients experienced grade 5 AEs (septic shock, subdural hematoma, T-Cell lymphoma and partial seizures), all deemed unrelated to cemsidomide
- G-CSF support was not allowed during cycle 1 for patients in dose escalation cohorts
- 42/73 (58%) of patients experienced grade 3/4 neutropenia, an anticipated on-target effect of IKZF1/3 degradation
  - Neutropenia was manageable with treatment interruptions and G-CSF use when permitted
  - Across all doses, 45% (33/73) of patients received G-CSF

Anti-Myeloma Activity

Figure 3: Best Overall Response Rate Cemsidomide + Dex*

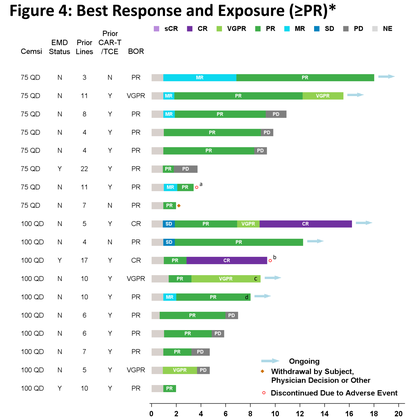


*1 patient in the 62.5µg cohort did not have a post-baseline assessment; §Patient went from VGPR to sCR after data cut. ᵃPatient went from PR to VGPR after data cut.

Table 6 : ORR Subgroups (All Dose Levels and 100 µg dose)

	Response/Subjects	ORR % (95% CI)
Prior CAR-T or TCE		
All doses	20/54	37.0% (24.3, 51.3)
100 µg (RP2D)	**9/17**	**52.9% (27.8, 77.0)**
Prior BCMA		
All doses	18/54	33.3% (21.1, 47.5)
100 µg (RP2D)	**7/15**	**46.6 % (21.3, 73.4)**
> 5 Prior Lines of Therapy		
All doses	16/48	33.3% (20.4, 48.4)
100 µg (RP2D)	**7/15**	**46.7% (21.3, 73.4)**

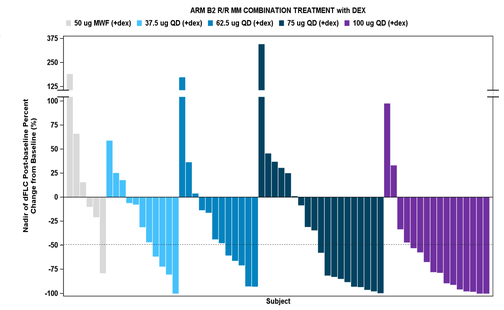
Figure 4: Best Response and Exposure (≥PR)*



*Investigator assessed response
ᵃPatient at 75µg discontinued due to grade 5 AE of septic shock, deemed unrelated to cemsidomide; ᵇPatient at 100 ug discontinued due to grade 5 recurrent seizures, deemed unrelated to cemsidomide; ᶜPatient went from VGPR to sCR after data cut; ᵈPatient went from PR to VGPR after data cut.

Figure 5: Best % Change in dFLC from Baseline

*Multiple Myeloma Patients w/ Elevated Light Chain Disease (N=64)**



*Only includes treated subjects who meet both criterion (A) and (B): (A) baseline kappa free light chain value >19.4 mg/L or baseline lambda free light chain value >26.3 mg/L; (B) ratio of baseline free light chain kappa over baseline free light chain value lambda >4:1 or <1:2.

- ORR at the highest dose level of cemsidomide (100 µg) was 53% with a clinical benefit rate of 63% (Figure 3)
  - MRD negativity achieved in 2 patients who achieved a sCR and CR at the highest dose level of cemsidomide (100 µg)
- ORR is consistent across subgroups irrespective of prior therapies (Table 6)
- Median PFS across all dose levels was 3.9 months (95% CI, 3.2–5.6)
- Median DOR across all dose levels was 7.9 months (95% CI, 3.0–NE)
- Figure 5 represents the greatest dFLC reduction from baseline
  - Cemsidomide + Dex induced a ≥ 50% decrease in dFLC in 50% (32/64) of patients
  - Cemsidomide demonstrated anti-myeloma activity across a broad range of doses

Conclusions

- Cemsidomide 14/14 plus Dex demonstrated durable anti-myeloma activity at increasing dose levels in a heavily pretreated patient population
  - A 53% ORR was observed at the highest dose of 100 µg QD, with a 36% ORR observed across all dose levels
  - 100 µg 14/14 QD was established as the RP2D and MTD
  - Responses were durable and continued to deepen over time at the 75 µg and 100 µg dose levels
  - **ORR was consistent across subgroups, with patients receiving prior CAR-T or TCE having a 53% ORR at the RP2D**
- Cemsidomide 14/14 plus Dex was well tolerated across dose levels
  - TEAEs were manageable with minimal treatment discontinuations or reductions
- Cemsidomide data strongly support further development across multiple lines of treatment and in combination with other anti-myeloma agents, including PIs, CD-38 mAB, ADCs, and TCEs
- Based on these results, cemsidomide 14/14 plus Dex is currently being assessed in the phase 2 MOMENTUM study in the 4L+ patient population and in a phase 1b study in combination with elranatamab (BCMA TCE)

Abbreviations

AE, adverse event; **ALT**, alanine aminotransferase; **BCMA**, B-cell maturation antigen; **BMS**, Bristol Myers Squibb; **CAR-T**, chimeric antigen receptor-T cell therapy; **CBR**, clinical benefit rate (≥MR); **CD38**, cluster of differentiation 38; **CI**, confidence interval; **CR**, complete response; **CRBN**, cereblon; **CSF**, cerebrospinal fluid; **CUL4**, cullin 4; **DDB1**, damage-specific DNA binding protein 1; **Dex**, dexamethasone; **dFLC**, difference between involved and uninvolved free light chains; **DLT**, dose-limiting toxicity; **DOR**, duration of response; **ECOG**, Eastern Cooperative Oncology Group; **EMD**, extramedullary disease; **G-CSF**, granulocyte colony-stimulating factor; **IKZF1**, Ikaros zinc finger protein 1; **IKZF3**, Ikaros zinc finger protein 3; **IL-2**, interleukin 2; **IMWG**, International Myeloma Working Group; **mAb**, monoclonal antibody; **MM**, multiple myeloma; **MR**, minimal response; **MRD**, minimal residual disease; **MTD**, maximum tolerated dose; **MWF**, Monday Wednesday Friday; **NE**, not evaluable; **ORR**, overall response rate; **PD**, progressive disease; **PFS**, progression-free survival; **PI**, proteasome inhibitor; **PK**, pharmacokinetics; **PML**, progressive multifocal leukoencephalopathy; **PR**, partial response; **QD**, daily; **R-ISS**, revised international staging system; **R/R**, relapsed/refractory; **RBX1**, ring-box 1; **RP2D**, recommended Phase 2 dose; **RRMM**, relapsed/refractory multiple myeloma; **sCR**, stringent complete response; **SD**, stable disease; **SOC**, standard of care; **SRC**, safety review committee; **TCE**, T-cell engager; **TEAEs**, treatment emergent adverse events; **TESAEs**, treatment emergent serious adverse events; **URTI**, upper respiratory tract infection; **VGPR**, very good partial response; **14/14**, 14 days on/14 days off

References

1. Dhakal B, et al. *Clinical Lymphoma, Myeloma & Leukemia*, Vol. 25, No. S2, S35, 2025
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