Initial Results of a Phase 1 First-in-Human Study of CFT7455 (Cemsidomide), a Novel MonoDAC® Degrader, with Dexamethasone (Dex) in Patients with Relapsed/Refractory Multiple Myeloma (RRMM)

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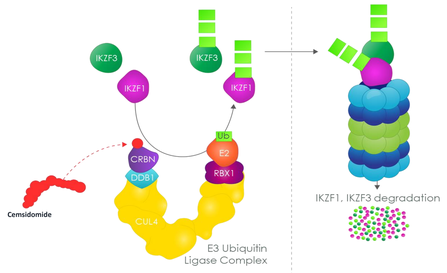
Introduction

- Cemsidomide is a novel, potent, cereblon-based IKZF1/3 MonoDAC® degrader rationally designed with the following properties:
  - Class-leading catalytic activity to enable rapid and deep target degradation
  - High binding affinity to overcome low cereblon levels that drive resistance to lenalidomide and pomalidomide
  - Improved pharmacologic profile to promote tumor residence time and sustained IKZF1/3 degradation with a 14/14 dosing schedule
  - Preclinical rationale for combinability with SoC therapies (Dex) and novel therapies (PIs, CD-38 mAbs, bi-specific T-cell engagers)[1]
- Cemsidomide binds to cereblon creating a new surface that facilitates the recruitment and ubiquitination of IKZF1/IKZF3, leading to the proteasomal degradation of both proteins (Figure 1)

Figure 1: Mechanism of Action for Cemsidomide



IKZF1/3 Degradation Induces:

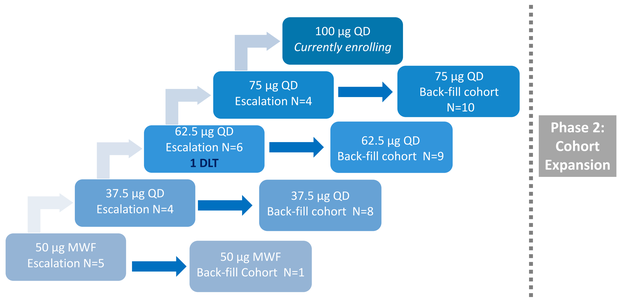
- MM and NHL cell death
- Immune stimulation
  - Activates fully differentiated T-cells, preventing T-cell exhaustion
  - Promotes secretion of key immune stimulating cytokines (e.g., IL-2)
- On-target neutropenia
  - Disrupts hematopoietic stem cell differentiation

Methods

CFT7455-1101 Study Design[2]

- 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

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



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

*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; 2 patients at 100 µg are excluded as they had not completed cycle 1 as of the data cut off date

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Results

Patients

- At the data cutoff date (October 11, 2024), 47 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 6 prior lines of therapy, (range 3-22)
  - 66% of patients had received a CAR-T or TCE and 70% had received a prior BCMA therapy

Table 1: Baseline Characteristics

Characteristics	Safety Population (N=47)
Age, median (range)	67 (39-82 years)
Male, n (%)	25 (53)
Time since initial diagnosis, median (range)	7 (2-18 years)
ECOG performance status, n (%) 0 1 2	 10 (21) 34 (72) 3 (7)
Black or African American, n (%) **White, n (%)** **Other, n (%)**	9 (19) 33 (70) 5 (11)
Revised ISS at screening, n (%) Stage 1 Stage 2 Stage 3 Missing	 21 (45) 15 (32) 5 (11) 6 (13)
Presence of EMD, n (%)	14 (30)

Table 2: Prior Therapies

Characteristics	Safety Population (N=47)
Prior therapies, median (range)	6 (3-22)
Prior lenalidomide, n (%)	47 (100)
Prior pomalidomide, n (%)	46 (98)
Prior anti-CD38 mAB, n (%)	47 (100)
Prior CAR-T therapy, n (%)	19 (40)
Prior T-cell engager therapy, n (%)	21 (45)
Prior CAR-T or T-cell engager therapy, n (%)	31 (66)
Prior BCMA therapy, n (%)	33 (70)
Triple-class exposed*, n (%)	47 (100)
Penta-class exposed†, n (%)	40 (85)

*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=47)
Ongoing	21 (45)
Discontinued	26 (55)
Progressive disease	15 (32)
Withdrawal of consent	6 (13)
Death	3 (6)*
Physician decision	1 (2)
Other	1 (2)†
Adverse event	0

- Treatment disposition is shown on Table 3 with treatment ongoing for 21 patients (45%)
- The primary reason for discontinuation was progressive disease (15/26)

*All deaths were considered unrelated to cemsidomide; deaths were due to disease progression, subdural hematoma (related to a fall), and sepsis; †Subject 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=15)	75 µg QD (N=14)	Total (N=47)
TEAEs	6 (100)	12 (100)	15 (100)	11 (79)	44 (94)
TEAEs possibly related to cemsidomide	3 (50)	11 (92)	13 (87)	7 (50)	34 (72)
TESAEs	3 (50)	6 (50)	4 (27)	4 (29)	17 (36)
TESAEs possibly related to cemsidomide	0	3 (25)	1 (7)	3 (21)	7 (15)
Any Grade ≥3 TEAEs	5 (83)	9 (75)	11 (73)	8 (57)	33 (70)
Any Grade ≥3 TEAEs possibly related to cemsidomide	2 (33)	8 (67)	7 (47)	7 (50)	24 (51)
TEAEs leading to discontinuation*	0	1 (8)	0	1 (7)	2 (4)
TEAEs leading to reduction	0	0	0	0	0

*Primary reason for discontinuation for patient at 37.5 µg was withdrawal of consent; patient at 75 µg discontinued due to death deemed unrelated to cemsidomide

- 33/47 (70%) of patients experienced a Grade 3/4 TEAE
- 1 patient had a DLT: Grade 4 neutropenia >7 days at 62.5 µg QD
- No patient had a cemsidomide dose reduction due to TEAEs

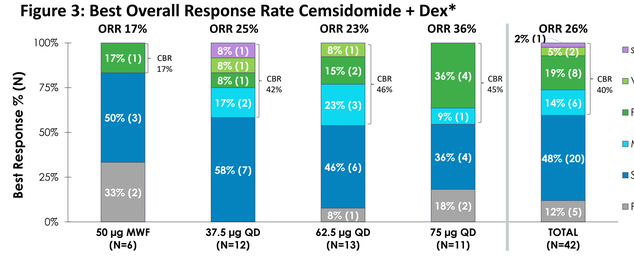
Table 5: Treatment Emergent Adverse Events by Grade

Common (>20% All Grades) TEAEs and Events of Interest, n (%)	All Grades (N=47)	Grade 3 (N=47)	Grade 4 (N=47)	Grade 5 (N=47)
Neutropenia	22 (47)	6 (13)	12 (26)	0
Infections	18 (38)	7 (15)	0	1(2)
Pneumonia	5 (11)	5 (11)	0	0
Upper Respiratory Tract Infection	7 (15)	1 (2)	0	0
Septic Shock	1 (2)	0	0	1(2)
Anemia	17 (36)	10 (21)	0	0
Fatigue	14 (30)	0	0	0
Thrombocytopenia	10 (21)	3(6)	2 (4)	0
Diarrhea	10 (21)	0	0	0
Lymphopenia	9 (19)	6 (13)	0	0
Febrile Neutropenia	3 (6)	3 (6)	0	0

- 2 patients experienced Grade 5 AEs (septic shock and subdural hematoma), both unrelated to cemsidomide
- 18/47 (38%) 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
  - 12/47 (26%) of patients received G-CSF with the majority of use (9/12) in patients from enrichment cohorts[3]

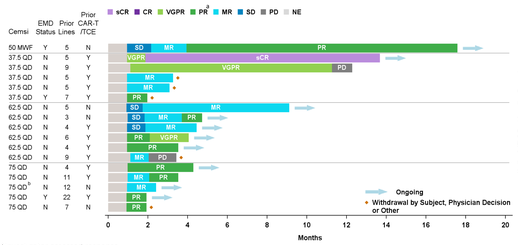
Anti-Myeloma Activity

Figure 3: Best Overall Response Rate Cemsidomide + Dex*



- ORR of 26% (11/42) was achieved across all dose levels with a clinical benefit rate of 40% (Figure 3)
- The ORR at the highest dose level of cemsidomide 75 µg 14/14 + Dex was 36% with a clinical benefit rate of 45%
- Figure 4 shows a swimmer plot with patients achieving an MR or better
- Figure 5 represents the greatest dFLC reduction from baseline
  - Cemsidomide + Dex induced dFLC decreases in 69% (24/35) of patients, with 40% of patients having a reduction of ≥ 50%
  - Cemsidomide demonstrated anti-myeloma activity across a broad range of doses

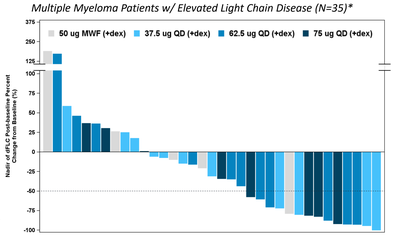
Figure 4: Best Response and Exposure (MR or Better)*



*Investigator assessed response

Figure 5: Best % Change in dFLC from Baseline

*Multiple Myeloma Patients w/ Elevated Light Chain Disease (N=35)**

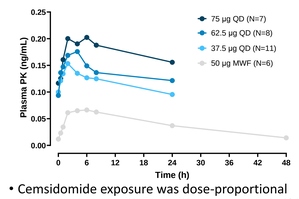


*Only includes treated subjects who meet both criterion (A) and (B): (A) baseline kappa free light chain value >19.4 mg/L or baseline lambda free light chain value >26.3 mg/L; (B) ratio of baseline free light chain kappa over baseline free light chain value lambda >4:1 or <1:2.

[1]1 patient in the 37.5 µg cohort achieved a PR based on light chains, no follow up M protein available; 1 patient in the 62.5 µg cohort had an unconfirmed PR as of the data cut off date; 1 patient in the 75 µg cohort had an unconfirmed PR; [2]Patient came off study due to unrelated death

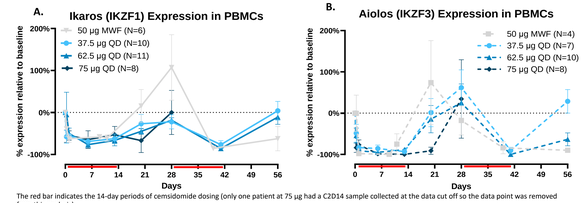
Pharmacokinetics and Pharmacodynamics

Figure 6: Cemsidomide + Dex PK at Steady-state



- Cemsidomide exposure was dose-proportional when combined with Dex with a geometric half-life estimate of approximately 2 days

Figure 7: Cemsidomide + Dex induces IKZF1 and IKZF3 degradation



The red bar indicates the 14-day periods of cemsidomide dosing (only one patient at 75 µg had a C2D14 sample collected at the data cut off so the data point was removed from this analysis)

- Cemsidomide + Dex achieves more than 50% and 80% degradation of IKZF1 (A) and IKZF3 (B), respectively, as assessed by mass spectrometry in human peripheral blood mononuclear cells

Conclusions

- Cemsidomide plus Dex was well tolerated with a safety profile conducive to additional combinations
  - Only 1 DLT occurred as of the data cutoff date
  - 38% of patients experienced Grade 3/4 neutropenia, which was manageable, and no cases resulted in discontinuation or dose reductions
- Cemsidomide plus Dex demonstrated compelling anti-myeloma activity across a broad range of doses, highlighting a wide therapeutic range
  - A 36% ORR was observed at the highest dose to date at 75 µg QD and a 26% ORR was observed across all dose levels
- Cemsidomide plus Dex displays a differentiated PK profile with a 2-day half-life and induces potent IKZF1/3 degradation
- Cemsidomide is well suited for further development across multiple lines of treatment and in combination with other anti-myeloma agents, including proteosome inhibitors, monoclonal antibodies, antibody-drug conjugates, and T-cell engagers

Abbreviations

AE, adverse events; **BCMA**, B-cell maturation antigen; **CAR-T**, chimeric antigen receptor-T cell therapy; **CBR**, clinical benefit rate (≥MR); **CR**, complete response; **CRBN**, cereblon; **Dex**, dexamethasone; **dFLC**, difference between involved and uninvolved free light chains; **DLT**, dose-limiting toxicity; **ECOG**, Eastern Cooperative Oncology Group; **EMD**, extramedullary disease; **G-CSF**, granulocyte colony-stimulating factor; **IFN-γ**, interferon gamma; **IKZF1**, Ikaros zinc finger protein 1; **IKZF3**, Ikaros zinc finger protein 3; **IL-2**, interleukin 2; ; **IL-6**, interleukin 6; **ISS**, international staging system; **mAbs**, monoclonal antibodies; **MM**, multiple myeloma; **MR**, minimal response; **MTD**, maximum tolerated dose; **MWF**, Monday Wednesday Friday; **NE**, not evaluable; **ORR**, overall response rate (≥PR); **PBMCs**, peripheral blood mononuclear cells; **PD**, progressive disease; **PI**, proteasome inhibitor; **PK**, pharmacokinetics; **PR**, partial response; **QD**, daily; **R/R**, relapsed/refractory; **RP2D**, recommended Phase 2 dose; **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; **TNFα**, tumor necrosis factor alpha; **VGPR**, very good partial response; **14/14**, 14 days on/14 days off

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