Pharmacokinetic (PK) Profile of a Novel IKZF1/3 Degrader, CFT7455, Enables Significant Potency Advantage over Other IKZF1/3 Degraders in Models of Multiple Myeloma (MM) and the Results of the Initial Treatment Cohort from a First-in-Human (FIH) Phase 1/2 Study of CFT7455 in MM

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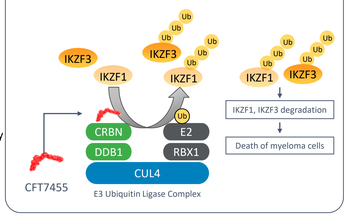
BACKGROUND

CFT7455 BACKGROUND

- The goal in designing CFT7455 was to develop an IKZF1/3 Monofunctional Degradation Activating Compound (MonoDAC™) with the following properties[1]:
  - Class-leading catalytic activity to enable potent, rapid, and deep target degradation
  - High binding affinity to overcome IMiD (immunomodulatory imide drug) resistance
  - Selective to reduce off-target liabilities
  - Improved pharmacologic profile to enable sustained IKZF1/3 degradation through elongated pharmacokinetics at exposure
- In preclinical models, we have observed differentiated PK and anti-tumor activity when comparing CFT7455 to pomalidomide and CC-92480 (Abstract#7922, presented on Monday 04/11)
- The initial clinical data suggests that the differentiated preclinical activity of CFT7455 observed in mouse models is translated into the clinical setting, and at 50 µg, half-life and depth of target degradation are greater than anticipated

Figure 1. Mechanism of Action for CFT7455

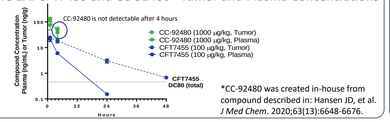


PRECLINICAL DATA

Single Dose PK/PD in H929 Xenografts Differentiates CFT7455 from CC-92480

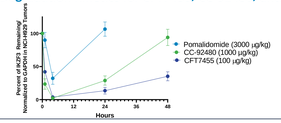
- Figure 2A: Plasma and tumor concentrations are maintained above the DC80 (i.e., the concentration required to effect 80% degradation of target) for almost the full 24-hour period after a single dose of 100 µg/kg CFT7455
- CC-92480 is rapidly cleared after a single dose of 1000 µg/kg is administered (Figure 2A)
- Figure 2B: Shows the resulting pharmacodynamics, and the following are noted from this figure:
  - At the clinically translated pomalidomide dose of 3000 mg/kg, ~50% degradation is observed by 4 hours, but by 24 hours, complete target recovery is observed
  - At 1000 µg/kg, CC-92480 results in complete target degradation but in the setting of more rapid clearance, recovery is observed by 24 hours and near-complete target recovery results at 48 hours
  - In contrast, CFT7455, given at 1/10th the dose of CC-92480 (1000 µg/kg), results in complete target degradation at 4 hours which is more durable

Figure 2A. CFT7455 and CC-92480* Tumor and Plasma Concentrations



*CC-92480 was created in-house from compound described in: Hansen JD, et al. *J Med Chem*. 2020;63(13):6648-6676.

Figure 2B. Degradation Kinetics for CFT7455, CC-92480, and POM



CFT7455 Demonstrates Superior Efficacy in NCI-H929 MM Xenograft Model

- In comparison to CC-92480, CFT7455 achieves equivalent efficacy at 1/100th of the dose (Figure 2C)
- In the NCI-H929 xenograft model, 100 µg/kg/day of CFT7455 resulted in durable tumor regressions (Figure 2D)

Figure 2C. CFT7455 vs. Comparators

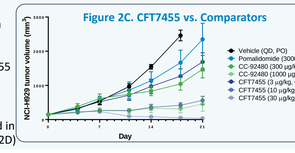
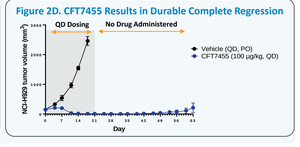


Figure 2D. CFT7455 Results in Durable Complete Regression



CFT7455 is Highly Efficacious in a Model of Systemic Multiple Myeloma

- In a model of systemic multiple myeloma (MM1.S), CFT7455 treatment resulted in complete tumor regression at 100 µg/kg/day
- The superior efficacy observed in this bone marrow-based myeloma model, in comparison to pomalidomide and CC-92480, suggests that the consistently observed increase in *in vivo* potency is clinically translatable

Figure 3A. CFT7455 vs. Comparators in a Model of Systemic MM

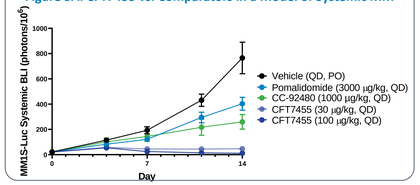
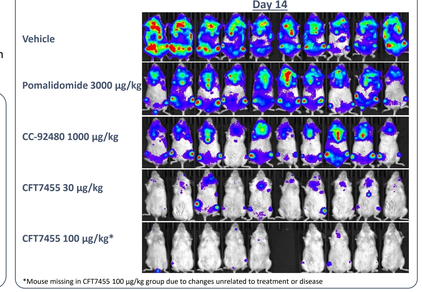


Figure 3B. CFT7455 vs. Comparators in a Model of Systemic MM Day 14



*Mouse missing in CFT7455 100 µg/kg group due to changes unrelated to treatment or disease

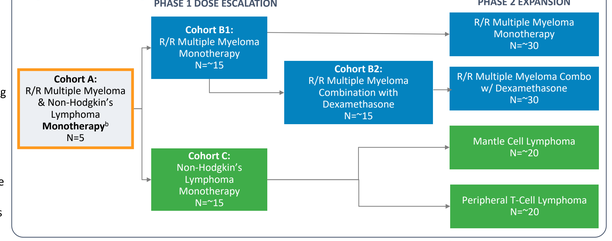
STUDY DESIGN[1]

- Open-label, multicenter, Phase 1/2 clinical trial with dose escalation and dose expansion phases[a] (NCT04756726)
- The dose escalation phase, beginning with a starting dose of 50 µg daily, may include single-participant cohorts at initial dose levels; after dose escalating, 3-6 patients are enrolled per cohort using a BLRM

Key Eligibility Criteria (MM)

- RRMM
- ≥ 3 prior therapies and must not be a candidate for regimens known to provide clinical benefit
- Disease progression on or within 60 days of last antimyeloma therapy
- Refractory to an IMiD agent, a PI, a glucocorticoid, and a CD38 mAb

Figure 4. Study Design



[a]CFT7455 is dosed orally in 28-day cycles, on a 21 day on, 7 day off schedule, until disease progression or intolerable toxicity; [b]28-day cycle / dose limiting toxicity (DLT) window

BASELINE CHARACTERISTICS

Table 1. Patient and Disease Characteristics

N (%) of patients unless stated	N=5
Age in years, median (range)	63 (51,73)
Sex, male	3 (60)
Time since initial diagnosis, median (range), years	11 (4,21)
ECOG PS	
0	2 (40)
1	2 (40)
2	1 (20)
R-ISS stage at screening, n (%)	
Stage I	1 (20)
Stage II	1 (20)
Stage III	2 (40)
Missing	1 (20)
Presence of extramedullary plasmacytoma	3 (60)
Presence of light chain disease	5 (100)

Table 2. Prior Treatment

N (%) of patients unless stated	N=5
Number of lines of prior therapy, median (range)	5 (4-14)
Prior stem cell transplantation	3 (60)
IMiD agent refractory	
POM	5 (100)
LEN	5 (100)
PI refractory	
BORT	4 (80)
CFZ	5 (100)
Prior anti-CD38 antibody	5 (100)
Prior CAR-T	2 (40)
Prior ADC	1 (20)
Prior bispecific antibody	1 (20)
Triple-class refractory*	5 (100)

*≥ 1 IMiD, ≥ 1 PI, and ≥ 1 anti-CD38 antibody

Treatment Exposure

- Data cutoff date: January 14th, 2022
- All patients had heavily pretreated and highly refractory disease
- Among the 5 patients who completed cohort A, single agent CFT7455 was administered 50ug/day for 21 days on-7 days off to 4 patients
- Of the 4 patients who started on 50ug/day, 2 were dose reduced to 25ug/day
  - 1 patient was dose reduced in cycle 2 due to neutropenia
  - 1 patient was dose reduced in cycle 1 due to recommendation of the SRC
- The 5th patient was enrolled at 25 ug/day 21days on-7days off based on SRC recommendation

RESULTS

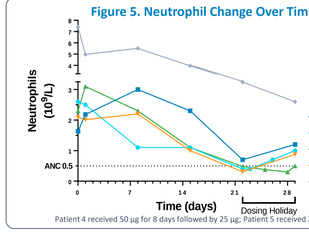
SAFETY DATA

Table 3. Incidence of All Adverse Events

All TEAEs n (%)	Grade 1 (N=5)	Grade 2 (N=5)	Grade 3 (N=5)	Grade 4 (N=5)
Blood and lymphatic system disorders				
Neutropenia	0	0	1(20)	3 (60)
Thrombocytopenia*	1 (20)	1 (20)	1 (20)	0
Anemia	0	0	1(20)	0
Leukopenia	0	0	1 (20)	0
Investigations				
Aspartate aminotransferase increased	2 (40)	0	0	0
Alanine aminotransferase increased	1 (20)	0	0	0
Gastrointestinal disorders				
Diarrhea	1 (20)	0	0	0
General disorders and administration site conditions				
Fatigue	1 (20)	0	0	0
Pyrexia	1(20)	0	0	0
Infections and infestations				
Rhinitis	1 (20)	0	0	0
Upper respiratory tract infection	1 (20)	0	0	0
Nervous system disorders				
Balance disorder	1 (20)	0	0	0
Headache	1 (20)	0	0	0
Renal and urinary disorders				
Nephrolithiasis	0	1 (20)	0	0

*Thrombocytopenia includes the preferred term thrombocytopenia and platelet decreased

Figure 5. Neutrophil Change Over Time



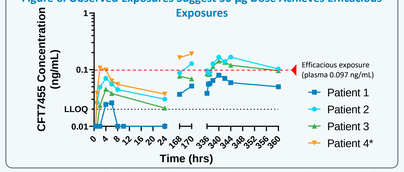
Patient 4 received 50 µg for 8 days followed by 25 µg; Patient 5 received 25 µg dose

- Table 3 represents all AEs reported, including related and unrelated AEs
- There were no SAEs reported and no AEs resulted in treatment discontinuation nor in death
- No patient experiencing neutropenia had a concurrent infection or fever
- Two dose-limiting toxicities (DLTs) were observed due to neutropenia
  - DLT #1 (Patient 3) was Grade 4 neutropenia lasting 8 days, GCSF was administered to this patient and CFT7455 was restarted when the ANC recovered to Grade 3
  - DLT #2 (Patient 4) occurred following recovery of a Grade 4 neutropenia to a Grade 3 neutropenia, the investigator elected to delay initiation of cycle 2 for 14 days to allow for recovery of ANC to ≥ 1000 cells/µl
- As depicted in Figure 5, neutropenia occurred following day 15 and recovery was incomplete during the 7-day dosing holiday
- Due to the pattern of neutropenia and recovery, the mechanism is considered an on-target effect of degrading IKZF1, resulting in the downstream decrease in PU.1 causing transient neutrophil maturation arrest[2-4]

PHARMAKOKINETICS AND PHARMACODYNAMICS

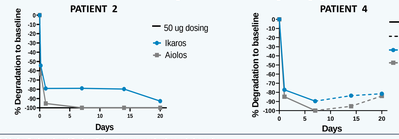
- 10 µg/kg dose in mouse (C_{avg} 0.097 ng/mL) is the dose where tumor stasis was observed
  - This translated to a projected human dose of ~43 µg (Figure 6)
- The plasma half-life ($t_{1/2}$): 2 days; T_{max} 4 hours; 40-60% CV on AUC; $AUC_{0\text{-}24h}$ increased 3- to 4-fold from day 1 to day 15
- After a dosing holiday prior to cycle 2, concentrations returned to below the limit of quantification (BLQ) levels

Figure 6. Observed Exposures Suggest 50 µg Dose Achieves Efficacious Exposures



*Patient 4 received 50 µg for 8 days followed by 25 µg for 13 days followed by the regular 7- day rest period in C1, subsequent cycles continued at 25µg 21 days on and 7 days off in a 28 -day cycle; Data not available for Patient 5

Figure 7. CFT7455 Target Engagement and Degradation of Ikaros and Aiolos

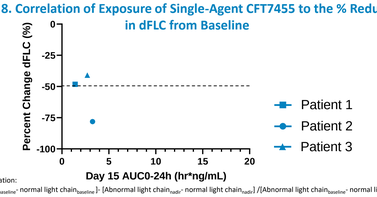


Data not available for Patient 1 and Patient 3 due to compromised sample integrity

- IKZF1/3 degradation was evaluated on C1D1, 4 hours post CFT7455; D7; D14; and D21 using mass spectrometry analysis of total PBMC population
- Deep degradation in initial patients treated with both 50 and 25 µg/day was observed
- The degradation data suggests that there is an early signal for a dose response in IKZF1/3 degradation
- IKZF3 degradation was deeper in human PBMCs at 50 and 25 µg/day than was projected based on observed pre-clinical IKZF3 degradation of ~70% at equivalent exposures, which are associated with tumor stasis in xenograft models (H929)[1]

EFFICACY: REDUCTION IN dFLC

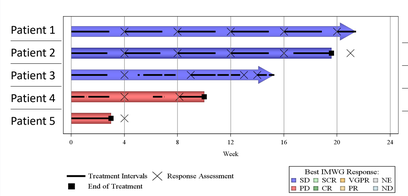
Figure 8. Correlation of Exposure of Single-Agent CFT7455 to the % Reduction in dFLC from Baseline



% change in dFLC equation: [Abnormal light chain$_{baseline}$- normal light chain$_{baseline}$]- [Abnormal light chain$_{nadir}$- normal light chain$_{nadir}$] /[Abnormal light chain$_{baseline}$- normal light chain$_{baseline}$] * 100

- Figure 8 demonstrates the reduction in dFLC at nadir, correlated with the day 15 steady state CFT7455 drug exposures
- Reductions in dFLC were observed in the 3 patients for whom data is available (all dosed at 50 µg)
- Patient 4 had an increase in dFLC of 56%, however is not plotted as exposure data is not available; patient 5 sample was not obtained
- Decreases in dFLC were observed at lower exposures in comparison to other clinical stage IKZF1/3 degraders[5]

Figure 9. CFT7455-1101: Arm A Responses*



First Dose (µg)	Extramedullary Disease	% Change at Nadir in dFLC*
50	No	▼ 48.2
50	Multiple Plasmacytomas	▼ 78.1
50	Lytic Bone Lesions	▼ 41.0
50	No	▲ 56.3
25	Plasmacytomas and Bone Lesions	N/A

- Only patient 5 had measurable serum M protein, and it was assessed at baseline only
- The best recorded response in 3 out of 5 patients were reported per the investigator's assessed response as SD
- Patient 2 experienced a drop in % change at nadir in dFLC of 78.1% but met criteria for SD (rather than PR) due to the presence of multiple plasmacytomas assessed as radiologically SD

SIMULATION DATA

- Due to the observed PK in animal models and the observed clinical potency of single agent CFT7455 in the setting of neutropenia, an alternative dosing regimen may increase the therapeutic index
- Different potential dosing regimens were simulated using a PK-PD model developed based on the clinical PK data (Figure 6) and mouse xenograft data for IKZF3 degradation in tumor (Figure 2B)

Figure 10A. Modeling Based on Initial Dosing Schedule

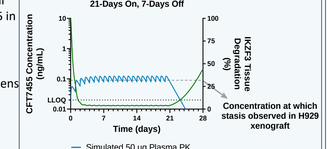
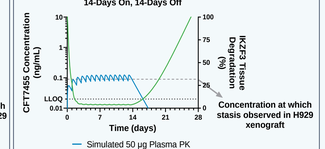


Figure 10B. Modeling Based on Planned Dosing Schedule



- Figure 10A suggests that due to drug accumulation and prolonged half-life, there is insufficient time for neutrophil recovery during the 21 days on, 7 days off dosing schedule.
- Dosing 2 weeks on, 2 weeks off (Figure 10B) may facilitate neutrophil maturation and recovery while achieving sufficient target degradation to maintain efficacy

CONCLUSION

- Preclinically, single-agent CFT7455 demonstrates increased activity *in vivo* in comparison to CC-92480
  - CFT7455 has longer exposure compared to CC-92480, resulting in sustained IKZF1/3 degradation in preclinical models
  - After 21 days of QD dosing, CFT7455 100 µg/kg/day resulted in durable tumor regressions for a prolonged period after drug discontinuation
- Clinically, CFT7455 was rapidly absorbed with a plasma T1/2 of approximately 2 days; accumulation of drug was observed up to 4-fold by day 15 and achieved exposures at 50 µg that are equivalent to predicted efficacious exposures from nonclinical studies
- Neutropenia was observed, including 3 patients with Grade 4 neutropenia resulting in two DLTs
- Early pharmacodynamic data suggests a deep degradation of the primary targets, IKZF1 and IKZF3, at lower plasma exposure levels than initially projected
- Preliminary evidence of single-agent CFT7455 activity was observed in this cohort of heavily pretreated patients, including meaningful decreases in dFLC
- Modeling of this data set suggests that alternative dosing regimens may increase the therapeutic index by allowing time for adequate neutrophil maturation during the days off drug while maximizing the efficacy potential of single-agent CFT7455
- Due to the greater-than-expected differentiated and potent pharmacologic properties observed, patients are currently being enrolled in Cohorts B1 and C of the clinical study on alternative dosing regimens

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Abbreviations
AE, adverse events; BLQ, below the limit of quantification; BLRM, Bayesian logistic regression model; CR, complete response; CRBN, cereblon E3 ligase; dFLC, difference between involved FLC and uninvolved FLC; DLT, dose-limiting toxicity; GCSF, granulocyte colony stimulating factor; IKZF 1/3, Ikaros family zinc finger proteins 1/3; IMiD, Immunomodulatory imide drugs; Len, lenalidomide; mAb, monoclonal antibody; MM, multiple myeloma; MonoDac, monofunctional degradation activating compound; ND, not done; NE, non-evaluable; NHL, non-Hodgkin's Lymphoma; PBMC, peripheral blood mononuclear cells; PD, progressive disease; PD-PK, pharmacodynamics-pharmacokinetics; Pom, pomalidomide; PR, partial response; SAE, serious adverse events; SCR, stringent complete response; SD, stable disease; sFLC, serum free light-chain assay; VGPR, very good partial response.

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