A Phase 1 Study of CFT7455, a Novel Degrader of IKZF1/3, in Multiple Myeloma and Non-Hodgkin Lymphoma

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#1675

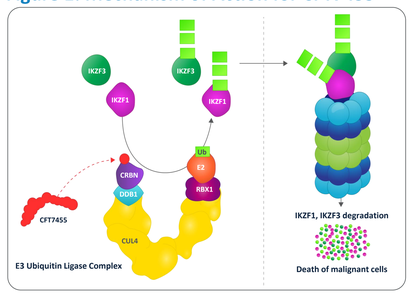
BACKGROUND

- Despite treatment options, multiple myeloma (MM) remains largely incurable with poor outcomes among patients who progress after treatment with a proteasome inhibitor, immunomodulatory drugs (IMiDs), and an anti-CD38 antibody.[1]
- Multiple targeted therapies have been developed for different subtypes of non-Hodgkin lymphoma (NHL); however, these therapies are typically not curative for patients with relapsed/refractory disease.[2]
- IMiDs regulate the ubiquitination of key transcription factors IKZF1/3 and are a standard of care for treatment of MM and are approved for some NHL subtypes.[1,3]
- However, given that most patients treated with these agents develop disease progression, an unmet need remains.[4]

CFT7455 BACKGROUND

- CFT7455 is a novel protein degrader that binds to cereblon (CRBN) E3 ligase, creating a new surface on CRBN, resulting in increased interaction with the transcription factors IKZF1/3 with increased potency compared with other immunomodulatory agents (**Figure 1**).
- CFT7455 selectively degrades IKZF1/3, which are ubiquitinated by the CRBN E3 ligase and degraded by the proteasome.
- The high CRBN binding affinity (IC50 = 0.9 nM) of CFT7455 enables rapid and deep degradation of IKZF1/3, resulting in potent activity in MM and several subtypes of NHL in both in vitro and in vivo xenograft models.

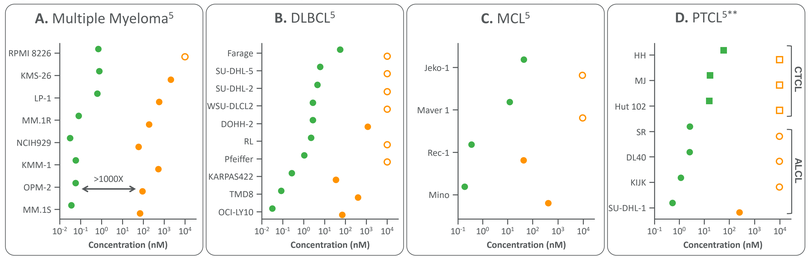
Figure 1: Mechanism of Action for CFT7455



PRE-CLINICAL DATA: IN VITRO

- In vitro and in vivo models of MM and NHL, including diffuse large B-cel lymphoma (DLBCL), mantle cell lymphoma (MCL), and peripheral T-cell lymphoma (PTCL), demonstrated greater activity with CFT7455 than pomalidomide (**Figures 2-5**).

Figure 2: Potent Anticancer Activity in Panels of Myeloma and Lymphoma Cell Lines*



*Open symbols indicate that growth was not inhibited by more than 50% at the highest tested concentration (100 nM or 10 µM for CFT7455 and 10 µM for pomalidomide) and therefore IC50 was not determined. **Circles denote anaplastic large cell lymphoma (ALCL); squares denote cutaneous T-cell lymphoma (CTCL) .

PRE-CLINICAL DATA: IN VIVO IN MULTIPLE MYELOMA

Figure 3: Depth and Duration of IKZF 1/3 Degradation Associated With Dose-Dependent CFT7455 Efficacy in Xenograft Models

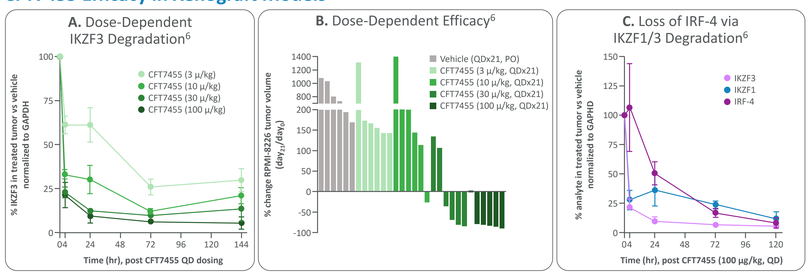
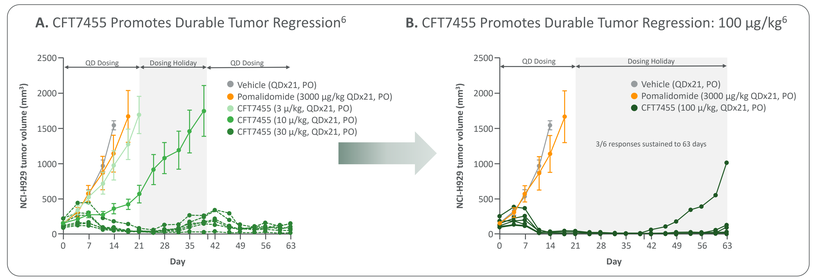
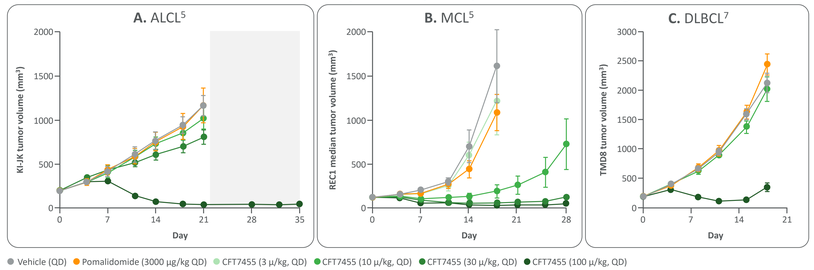


Figure 4: CFT7455 Demonstrates High Potency and Dose-Dependent Efficacy in Multiple Myeloma Xenografts



PRE-CLINICAL DATA: IN VIVO IN NHL

Figure 5: CFT7455 Demonstrates Efficacy in ALCL, MCL, and DLBCL Xenograft Models

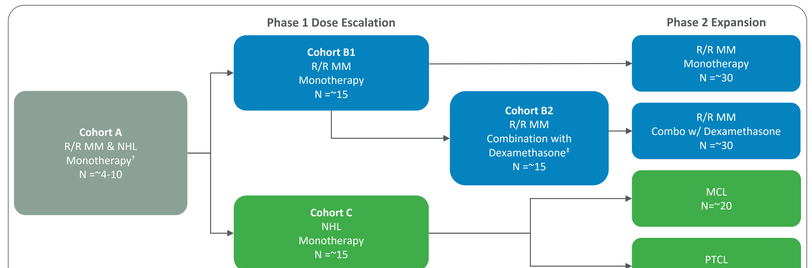


- These results provided rationale for a first-in-human, phase 1 study to evaluate CFT7455

FIRST-IN-HUMAN STUDY DESIGN[8]

- Open-label, multicenter, phase 1/2 clinical trial with dose-escalation and dose-expansion phases*
- 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 will be enrolled per cohort using a Bayesian logistic regression model
- Approximately 164 patients at approximately 13 US sites will be enrolled. This trial is registered with ClinicalTrials.gov as NCT04756726; enrollment is ongoing

Figure 6: CFT7455-1101 Study Design



*CFT7455 is dosed orally in 28-day cycles, on a 21-day on, 7-day off schedule, until disease progression or intolerable toxicity
†28-day cycle / dose limiting toxicity (DLT) window; ‡Combination therapy cohorts will open once the selected CFT7455 dose level has been cleared for safety 6-12 patient food effect enrichment cohort also included during escalation, not pictured in the schema

FIRST-IN-HUMAN STUDY DESIGN

KEY ELIGIBILITY CRITERIA

KEY INCLUSION CRITERIA

Multiple Myeloma Patients

- Histologically/cytologically–confirmed MM that is R/R
- Patients must not be candidates for regimens known to provide clinical benefit, defined as having received ≥3 prior anti-myeloma regimens including ≥2 consecutive cycles of:
  - Lenalidomide
  - Pomalidomide
  - Proteasome inhibitor
  - Glucocorticoid
  - Anti-CD38 antibody

Non-Hodgkin Lymphoma Patients

- Histologically/cytologically–confirmed NHL that is R/R
- Patients must not be candidates for regimens known to provide clinical benefit, defined as the requisite prior lines of therapy according to an indication-specific basis

KEY EXCLUSION CRITERIA

- Presence of central nervous system malignancy, recent venous thromboembolism or inability to undergo its prophylaxis
- Plasma cell leukemia
- Several lymphoma subtypes less likely to benefit are excluded (eg, Richter transformation, Burkitt lymphoma, Sezary syndrome, and lymphoblastic lymphoma)

STUDY ENDPOINTS

PRIMARY ENDPOINT

- Safety and tolerability of CFT7455 as monotherapy and in combination with dexamethasone
- Maximum tolerated dose (MTD) or recommended Phase 2 dose (RP2D) for CFT7455 as monotherapy and in combination with dexamethasone
- Antitumor activity of CFT7455

SECONDARY ENDPOINTS

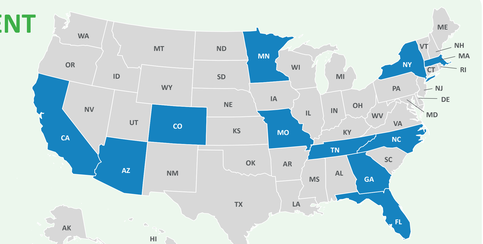
- Assessment of pharmacokinetics

EXPLORATORY ENDPOINTS

- Characterization of target engagement and IKZF1/3 degradation
- Assessment of the immunomodulatory effects of CFT7455

STUDY STATUS/ENROLLMENT

- The study opened to accrual in April 2021 and will be recruiting approximately 164 patients from 13 sites in the United States[8]
- This trial is registered with ClinicalTrials.gov as NCT04756726
- As of 11/3/2021, 8 sites have initiated recruitment
- Contact information: *clinicaltrials@C4therapeutics.com*



Abbreviations
ALCL, anaplastic large cell lymphoma; **CRBN**, cereblon E3 ligase; **CTCL**, cutaneous t-cell lymphoma; **DLBCL**, diffuse large b-cell lymphoma; **IKZF 1**, Ikaros family zinc finger protein 1; **IKZF 1/3**, Ikaros family zinc finger protein 1/3; **IKZF 3**, Ikaros family zinc finger protein 3; **IRF-4**, interferon regulatory factor 4; **IMiDs**, immunomodulatory drugs; **MCL**, mantle cell lymphoma; **MM**, multiple myeloma; **NHL**, non-Hodgkin Lymphoma; **POM**, pomalidomide; **PTCL**, peripheral t-cell lymphoma; **R/R**, relapsed refractory

Disclosures
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