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

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KEY ELIGIBILITY CRITERIA

KEY INCLUSION CRITERIA

- 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-CRBN antibody

- Non-Hodgkin Lymphoma Patients
  - Histologically/cytologically confirmed NHL that is R/R
  - Patients may be candidates for regimens known to provide clinical benefit, defined as the requisite prior lines of therapy according to an indication-specific basis

STUDY ENDPOINTS

- **PRIMARY ENDPOINTS**
  - 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 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
- This trial is registered with ClinicalTrials.gov as NCT04756728
- As of 11/3/2021, 8 sites have initiated recruitment
- Contact information: clinicaltrials@c4therapeutics.com

PRE-ClinICAL DATA: IN VITRO

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

STUDY-ENDPOINT Diagrams

**FIRST-IN-HUMAN STUDY DESIGN**

- Open-label, multi-center, Phase 1/2 clinical trial with dose-escalation and dose-expansion phases*
- The dose-escalation phase, beginning with a starting dose of 3 mg 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 NCT04756728; enrollment is ongoing

**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

**FIRST-IN-HUMAN STUDY DESIGN**

- **KEY ELIGIBILITY 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-CRBN antibody

- **KEY INCLUSION CRITERIA**
  - Histologically/cytologically confirmed MM that is R/R
  - Patients may 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, B-cell prolymphocytic leukemia, syringoid syndrome and lympholastic lymphoma)

**STUDY ENDPOINTS**

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**PRE-ClinICAL DATA: IN VIVO IN NHL**

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

**Figure 1: Mechanism of Action for CFT7455**

- 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 IRF-1 and Janssen.
- The high-DNB binding affinity (IC50 = 0.01 nM) of CFT7455 enables rapid and deep degradation of IKZF1/3, resulting in potency activity in MM and several subtypes of NHL in both in vitro and in vivo xenograft models.

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

- A. CFT7455 Promotes Durable Tumor Regression
- B. CFT7455 Promotes Durable Tumor Regression: 100 µg/kg

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

- A. MCL1
- B. MCL1
- C. DLBCL2

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

- A. Multiple Myeloma
- B. DLBCL
- C. MCL
- D. PTCL

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

- A. Dose-Dependent IKZF3 Degradation
- B. Dose-Dependent Efficacy
- C. Loss of BCL-2 via IKZF3 Degradation

**Figure 6: CFT7455-1101 Study Design**

- Open-label, multi-center, Phase 1/2 clinical trial with dose-escalation and dose-expansion phases*
- The dose-escalation phase, beginning with a starting dose of 3 mg 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 NCT04756728; enrollment is ongoing

**First Study Diagrams**

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