A Phase 1/2 Study of CFT8634, a Novel Bifunctional Degradation Activating Compound (BDiAC™) Degrader Of BRD9, in Synovial Sarcoma and SMARCB1-null Tumors

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BACKGROUND

• SMARCB1-perturbed cancers are dependent on the chromatin factor BRD91,2
• Two types of genetic alterations disturb SMARCB1: SS18-SSX gene fusion and SMARCB1 loss-of-function (SMARCB1-null)
• The presence of SS18-SSX chromosomal translocation drives the development of synovial sarcoma (SS), a soft tissue malignancy comprising ~25% of all soft tissue sarcomas2
• SMARCB1-null tumor types include malignant rib tumor (MRT), poorly differentiated chondrosarcoma, and epithelioid sarcoma3
• In the metastatic setting, outcomes for many of these SMARCB1-null tumor types are poor with limited therapeutic options (e.g., synovial sarcoma: 1-year survival rate ~68%)4
• Mechanism of disease: SS18-SSX fusion protein and SMARCB1 deletion both result in perturbation of the ccb complex (Figure 1) causing oncogenic dependency on the ccb complex
• Tumor specific ncbAIF4F results in a synthetic lethal dependency on BRD9
• The DUF subdomain of BRD9 is a critical mediator of its oncogenicity

CFT8634 BACKGROUND

• Bromodomain inhibitors are insufficient to obtain BRD9 oncogenicity, because the DUF domain is critical, while a degrader approach achieves efficacy1
• CFT8634 is an orally bioavailable selective bifunctional degradation activating compound, or BDiAC™ degrader, of BRD9
• CFT8634 was synthesized using C4 Therapeutics’ TORDOS® platform
• Mechanism of action (Figure 2) CFT8634 reduces a tertiary complex formation with BRD9 and ccb complex 7.8
• BRD9 is ubiquitinated and subsequently degraded by the proteasome (steps 1-2)
• CFT8634 is highly selective for BRD9 and demonstrates dose proportional exposure in both plasma and cell derived xenograft models (Figures 3-4)
• CFT8634 leads to robust and dose-dependent degradation of BRD9, which translated to significant and dose-dependent anti-tumor activity in preclinical in vivo and in vitro models of SMARCB1-perturbed cancers (Figures 5-6)

PRE-ClinICAL DATA: IN VITRO

Figure 3: CFT8634 is a Highly Selective BRD9 Degrader

Figure 4: Dose Proportional Exposure and Concentrad Cross-Species PK Profile in a Cell-Derived Xenograft (Tomato-SS)

PRE-ClinICAL DATA: IN Vivo IN PDx

Figure 5: Robust Efficacy Response Observed in Two PDX Models of Synovial Sarcoma

Figure 6: Durable Response Observed in a PDX Model of Synovial Sarcoma

Phase 1/2: FIRST-IN-HUMAN CLINICAL STUDY DESIGN

• Open-label, multicenter, Phase 1/2 clinical trial with dose escalation and expansion phases
• Dose escalation phase, beginning with a starting oral dose of 2 mg daily, will follow a Bayesian logistic regression model until determination of the MTD and/or RP2D
• Escalation will include synovial sarcoma and SMARCB1 deleted solid tumors (N = 40)
• UP to 120 patients (approximately) at 10 sites will be enrolled
• Registered on ClinicalTrial.gov as NCT03535753, Study is open for enrollment

Figure 7: CFT8634 Study Design

FIRST-IN-HUMAN STUDY DESIGN

KEY ELIGIBILITY CRITERIA

KEY INCLUSION CRITERIA

• SS or SMARCB1-null tumors confirmed by immunohistochemistry, fluorescence in situ hybridization, or other equivalent tests/tissue gene expression analysis, with unresectable or metastatic disease
• At least 1 prior line of standard of care systemic therapy
• Patients must not be candidates for available therapies that are known to center clinical benefit and must be ≥18 years of age, ≤14 years old and weigh ≥50 kg

STUDY ENDPOINTS

PRIMARY ENDPOINT

• Frequency and severity of AEs and SAEs of CFT8634
• Changes between baseline and post baseline safety assessments
• ORR (Phase 1)
• Changes from baseline in EOG parameters
• Frequency of dose interruptions and dose reductions
• Vindication of CLs during escalation
• Time to next treatment

SECONDARY ENDPOINTS

• Assessment of PK and PD
• ORR (Phase 2)
• DFS
• OS
• Time to next treatment

STUDY STATUS/ENROLLMENT

• The study opened to accrual in March 2022
• and will be recruiting “N=110 patients from 10 sites” in the USA
• Trial registration: NCT03535753
• As of 09/27/2022, 5 sites have initiated recruitment
• Contact information: clinicaltrialsh@C4therapeutics.com

*All patient data is subject to disclosure in clinical trial.