Initial Results From A Phase 1 Study of CFT8634, A Novel Bifunctional Degradation Activating Compound (or BIDAC™ Degrader) of BRD9, in Synovial Sarcoma and *SMARCB1*-Null Tumors

Mark Agulnik, MD[1], William D. Tap, MD[2], Gregory M. Cote, MD, PhD[3], Ravin Ratan, MD, M.Ed[4], Shaheer A Khan, D.O.[5], Sant P. Chawla, MD[6], Steven Attia, D.O.[7], Anthony Elias, MD[8], Mohammed Milhem, MBBS[9], Joseph G. Pressey, MD[10], Amro Ali, PharmD[11], Ingrid Mintautas, B.A[11], Riadh Lobbardi, PhD[11], Joseph Pariseau, PharmD[11], Huan Liu, M.A[11], Eunju Hurh, PhD[11], Kathleen Neville, MD[11], and Brian A. Van Tine, MD, PhD[12]

[1]City of Hope, Duarte, CA; [2]Memorial Sloan Kettering Cancer Center, New York, NY; [3]Massachusetts General Cancer Center, Boston, MA; [4]University of Texas MD Anderson Cancer Center, Houston, TX; [5]Columbia University Herbert Irving Comprehensive Cancer Center, New York, NY; [6]Sarcoma Oncology Center, Santa Monica, CA; [7]Division of Oncology, Mayo Clinic, Jacksonville, FL; [8]University of Colorado Cancer Center, Aurora, CO; [9]University of Iowa Hospitals and Clinics, Iowa City, IA; [10]Cincinnati Children's Hospital, Cincinnati, OH; [11]C4 Therapeutics, Inc., Watertown, MA; [12]Washington University School of Medicine, St. Louis, MO

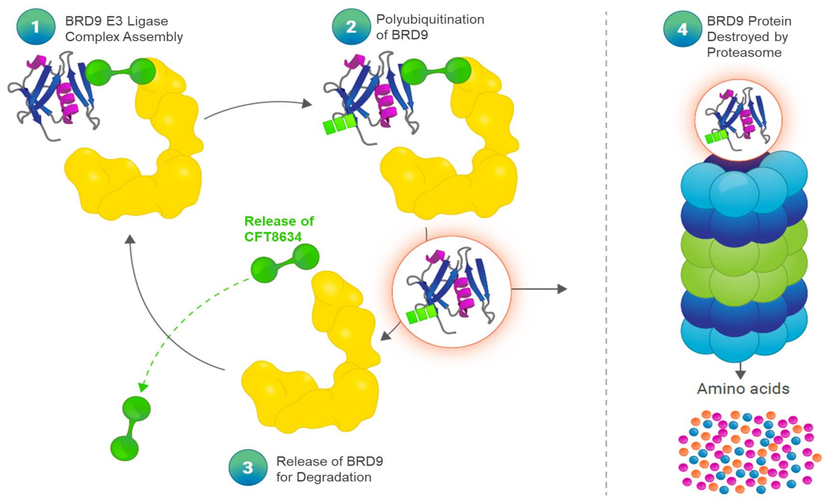
BACKGROUND

- Bromodomain-containing protein 9 (BRD9) belongs to the non-canonical SWI/SNF complex and is essential to the proliferation of SMARCB1-perturbed cancers[1,2]
  - SMARCB1-perturbed cancers include synovial sarcoma, defined by the SS18-SSX fusion, and *SMARCB1*-null tumors such as epithelioid sarcoma[2,3]
- Synovial sarcoma is a rare soft tissue malignancy comprising ~10% of all soft tissue sarcomas[2]
  - In the metastatic setting, therapeutic options are limited, and outcomes are poor with a median OS of 17.0 months and 1-year survival rate of ~60%[4]

CFT8634 BACKGROUND[5]

- CFT8634 is an orally bioavailable selective bifunctional degradation activating compound, or BiDAC™ degrader of BRD9
  - CFT8634 was developed using C4 Therapeutics' TORPEDO® platform
- Mechanism of Action (**Figure 1**)
  - i. CFT8634 induces ternary complex formation with BRD9 and cereblon E3 ligase (step 1)
  - ii. BRD9 is ubiquitinated and subsequently released for degradation in the proteasome (steps 2-4)
- CFT8634 leads to robust and dose-dependent degradation of BRD9 in in vitro and in vivo models of SMARCB1-perturbed cancer, which translates to significant and dose-dependent anti-tumor activity in patient-derived preclinical xenograft models (**Figures 2**)

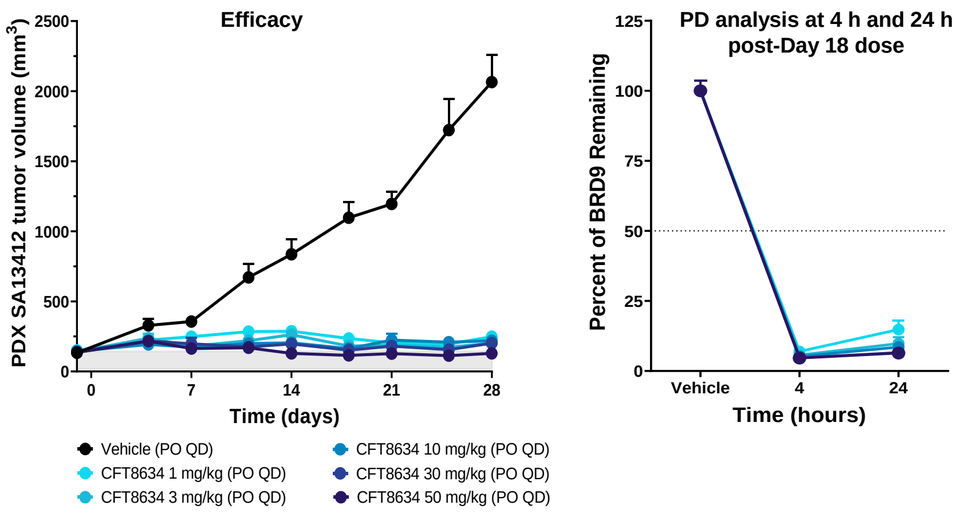
Figure 1: Mechanism of Action for CFT8634[5]



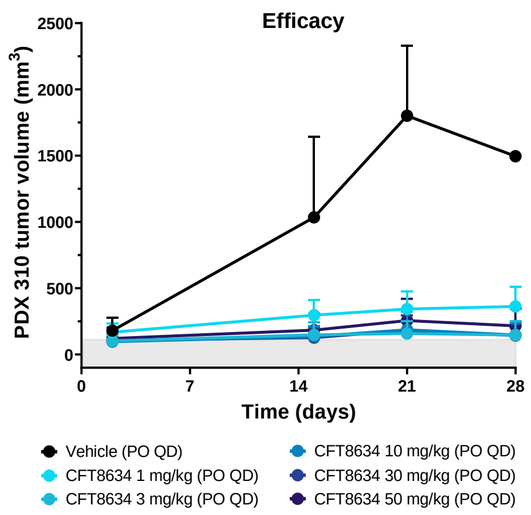
PRE-CLINICAL DATA: IN VIVO IN PATIENT-DERIVED XENOGRAFTS (PDX)[5]

Figure 2: Robust Efficacy Response Observed in Two PDX Models of Synovial Sarcoma[5]

A. PDX SA13412
Synovial Sarcoma Harboring SS18-SSX1[5]



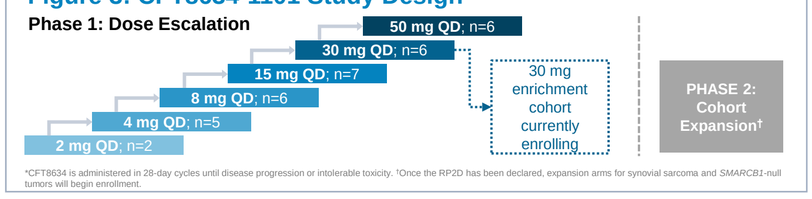
B. PDX 310
Synovial Sarcoma Harboring SS18-SSX2[5]



PHASE 1/2 STUDY DESIGN[6]

- 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, follows a Bayesian logistic regression model until determination of the MTD and/or RP2D
  - Escalation will enroll patients with synovial sarcoma and *SMARCB1*-null solid tumors (N = ~40)
  - Enrichment cohort currently enrolling at 30 mg, additional enrichment cohorts may be added

Figure 3: CFT8634-1101 Study Design[6]



*CFT8634 is administered in 28-day cycles until disease progression or intolerable toxicity. †Once the RP2D has been declared, expansion arms for synovial sarcoma and *SMARCB1*-null tumors will begin enrollment.

KEY ELIGIBILITY CRITERIA[6]

KEY INCLUSION CRITERIA

- Must be ≥18 years of age, or ≥16 years old and weigh ≥50 kg with measurable disease per RECIST v1.1
- Synovial sarcoma or *SMARCB1*-null tumors with unresectable or metastatic disease, following at least 1 prior line of standard-of-care systemic therapy
- Patients must not be candidates for available therapies that are known to confer clinical benefit

PHASE 1 STUDY ENDPOINTS[6]

PRIMARY ENDPOINT
- Assessment of safety and tolerability
- Defining the RP2D/MTD

SECONDARY
- Assessment of PK and pharmacodynamics
- Assessment of preliminary anti-tumor activity

BASELINE CHARACTERISTICS

Data cut off date: August 29, 2023

Table 1: Baseline Patient and Disease Characteristics[5]

N (%) of patients unless stated	N=32
Age in years, median (range)	39.5 (19,65)
Sex, male	17 (53.1)
Sex, female	15 (46.9)
ECOG PS	
0	16 (50)
1	16 (50)
2	0 (0)
Race, n (%)	
White	28 (87.5)
Asian	4 (12.5)
Primary tumor type, n (%)	
Synovial sarcoma	23 (71.9)
Epithelioid sarcoma	6 (18.8)
Poorly differentiated chordoma	1 (3.1)
Yolk sac tumor	1 (3.1)
Renal medullary carcinoma	1 (3.1)

Table 2: Disease History[5]

N (%) of patients unless stated	N=32
Number of lines of prior therapy, n (%)	
1	3 (9.4)
2	2 (6.2)
≥3	27 (84.4)
Time since initial diagnosis (years), median (range)	3.4 (1,18)
Largest target lesion diameter (mm), median (range)	42 (4,188)
Prior doxorubicin	29 (90.6)
Prior ifosfamide	27 (84.4)
Prior pazopanib	17 (53.1)
Prior tazemetostat	6 (18.8)

Table 3: Treatment Disposition[5]

N (%) of patients unless stated	N=32
Ongoing	9 (28.1)
Discontinued	
Progressive disease	17 (53.1)
Death	3 (9.4)
Adverse event‡	2 (6.2)
Withdrawal by patient	1 (3.1)
Duration of treatment (months), Median (range)	1.8 (0,11)

‡1 patient each discontinued due to a dysphagia and respiratory failure, both deemed unlikely related to drug

RESULTS

SAFETY DATA

Incidence of AEs, SAEs and Grade ≥3 AEs were consistent across all cohorts

Table 4: Overview of AEs Across Cohorts[5]

	2 mg QD (N=2) n (%)	4 mg QD (N=5) n (%)	8 mg QD (N=6) n (%)	15 mg QD (N=7) n (%)	30 mg QD (N=6) n (%)	50 mg QD (N=6) n (%)	Total (N=32) n (%)
Patients with ≥1 TEAE	2 (100.0)	5 (100.0)	6 (100.0)	7 (100.0)	6 (100.0)	6 (100.0)	32 (100.0)
Patients with ≥1 TESAE	2 (100.0)	2 (40.0)	2 (33.3)	4 (57.1)	1 (16.7)	2 (33.3)	13 (40.6)
≥1 TESAE related to CFT8634	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (33.3)	2 (6.3)
≥1 TESAE leading to death	1 (50.0)	1 (20.0)	0 (0.0)	2 (28.6)	0 (0.0)	0 (0.0)	4 (12.5)
Patients with ≥1 possibly related TEAE	2 (100.0)	3 (60.0)	6 (100.0)	4 (57.1)	5 (83.3)	6 (100.0)	26 (81.3)
Patients with ≥1 TEAE with CTCAE Grade ≥ 3	2 (100.0)	3 (60.0)	3 (50.0)	5 (71.4)	4 (66.7)	4 (66.7)	21 (65.6)

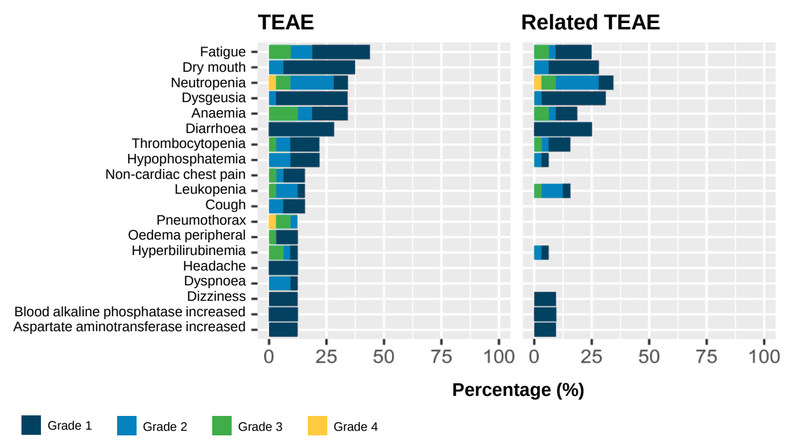
Table 5: TEAEs Occurring in ≥10% or of Interest[5]

System organ class Preferred term	Grade 1 (N=32)	Grade 2 (N=32)	Grade 3 (N=32)	Grade 4 (N=32)	Total (N=32)
General disorders and administration site conditions					
Fatigue	8 (25.0)	3 (9.4)	3 (9.4)	0 (0.0)	14 (43.8)
Non-cardiac chest pain	3 (9.4)	1 (3.1)	1 (3.1)	0 (0.0)	5 (15.6)
Oedema peripheral	3 (9.4)	0 (0.0)	1 (3.1)	0 (0.0)	4 (12.5)
Gastrointestinal disorders					
Dry mouth	10 (31.3)	2 (6.3)	0 (0.0)	0 (0.0)	12 (37.5)
Diarrhoea	9 (28.1)	0 (0.0)	0 (0.0)	0 (0.0)	9 (28.1)
Nervous system disorders					
Dysgeusia	10 (31.3)	1 (3.1)	0 (0.0)	0 (0.0)	11 (34.4)
Dizziness	4 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	4 (12.5)
Headache	4 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	4 (12.5)
Blood and lymphatic system disorders					
Anaemia	5 (15.6)	2 (6.3)	4 (12.5)	0 (0.0)	11 (34.3)
Neutropenia	2 (6.3)	6 (18.8)	2 (6.3)	1 (3.1)	11 (34.3)
Thrombocytopenia	4 (12.5)	2 (6.3)	1 (3.1)	0 (0.0)	7 (21.9)
Leukopenia	1 (3.1)	3 (9.4)	1 (3.1)	0 (0.0)	5 (15.6)
Metabolism and nutrition disorders					
Hypophosphataemia	4 (12.5)	3 (9.4)	0 (0.0)	0 (0.0)	7 (21.9)
Respiratory, thoracic and mediastinal disorders					
Cough	3 (9.4)	2 (6.3)	0 (0.0)	0 (0.0)	5 (15.6)
Dyspnoea	1 (3.1)	2 (6.3)	1 (3.1)	0 (0.0)	4 (12.5)
Pneumothorax	0 (0.0)	1 (3.1)	2 (6.3)	1 (3.1)	4 (12.5)
Investigations					
Aspartate aminotransferase increased	4 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	4 (12.5)
Blood alkaline phosphatase increased	4 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	4 (12.5)
Electrocardiogram QT prolonged	1 (3.1)	0 (0.0)	2 (6.3)	0 (0.0)	3 (9.4)
Neutrophil count decreased	0 (0.0)	2 (6.3)	1 (3.1)	0 (0.0)	3 (9.4)
Electrocardiogram T wave inversion	1 (3.1)	2 (6.3)	0 (0.0)	0 (0.0)	3 (9.4)
Hepatobiliary disorders					
Hyperbilirubinaemia	1 (3.1)	1 (3.1)	2 (6.3)	0 (0.0)	4 (12.5)

- **Table 5** represents all TEAEs reported, including related and unrelated
- Majority of AEs reported are considered mild to moderate in severity
- In review of available AEs, no dose-dependent relationship to incidence/severity of AEs observed
- The most common (occurring in ≥1 patient) TEAEs leading to treatment interruption include QT prolongation, T wave inversion, pneumothorax, and neutropenia

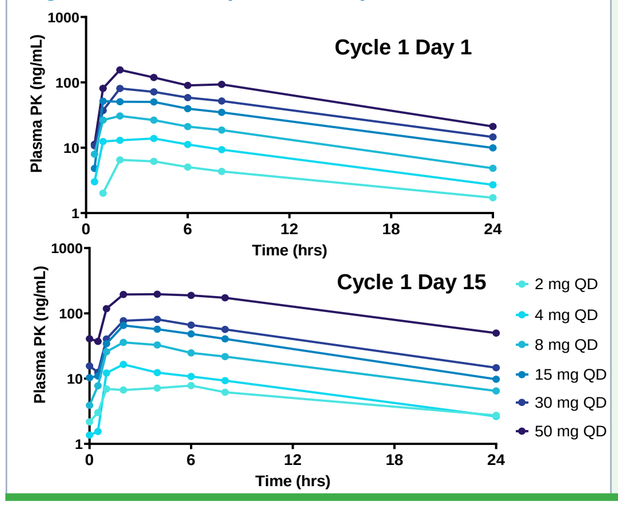
- **Figure 4** represents all TEAEs along with all related TEAEs that occurred in ≥10% of enrolled patients
- The most common treatment related AEs include anemia, fatigue, dry mouth, dysgeusia, and neutropenia
- Majority of AEs were mild and were grade 1/2
- Grade 3 and 4 neutropenia occurred in 1 patient each

Figure 4: TEAEs and Related TEAEs by CTCAE Grade (>10%)[5]



PHARMACOKINETICS[5]

Figure 5: Dose Proportional Exposure and PK Profile[5]

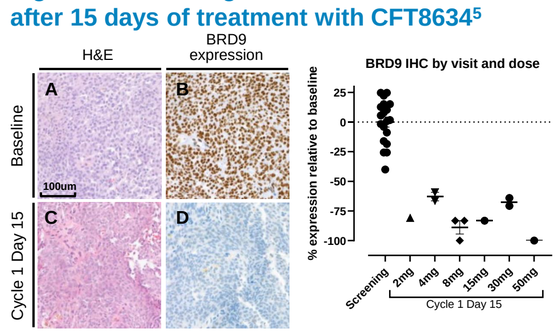


Plasma exposure of CFT8634 increased proportionally with dose after single and repeat oral administration

Mean half-life of 10-14 hours supports once daily oral dosing

PHARMACODYNAMICS[5]

Figure 6: BRD9 degradation on tumor tissue after 15 days of treatment with CFT8634[5]



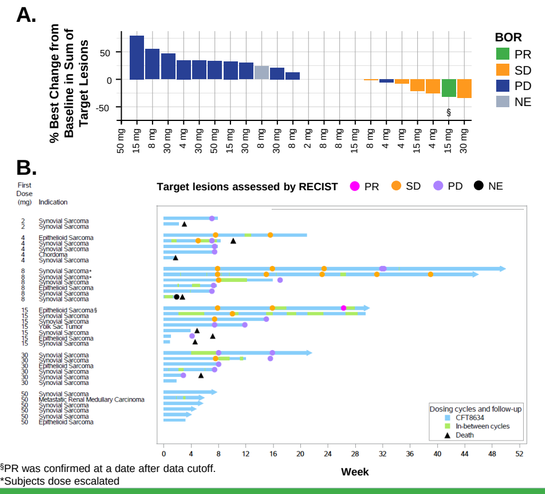
A-D: Staining of fresh tumor biopsy at Baseline and at Cycle 1 Day 15 with Hematoxylin and Eosin (A,C) as well as BRD9 immunohistochemistry (IHC) using clone E4Q3F (B,D) is shown for one patient dosed at 15 mg with CFT8634. CFT8634 degrades BRD9 in tumor tissue as seen at Cycle 1 Day 15 (D) in comparison to Baseline (B).
E: BRD9 H-score was plotted for all patients at different doses and the average of BRD9 H-score at screening (including archival tissue and fresh tumor biopsy) was used to normalize all data. These data show overall a high degradation level of BRD9, consistent at all doses and very comparable to the level of degradation observed in peripheral blood mononuclear cells (PBMCs, data not shown). All IHCs were performed by CellCarta and sections were quantified by a CellCarta histopathologist.

High levels of BRD9 degradation observed at different doses on tumor tissue after 15 days of treatment with CFT8634

Similar observation done by measuring BRD9 expression in PBMCs via Mass Spectrometry

ANTI-TUMOR ACTIVITY[5]

Figure 7: Anti-Tumor Activity[5]



§PR was confirmed at a date after data cutoff.
*Subjects dose escalated

As of the data cutoff, CFT8634 has shown preliminary evidence of anti-tumor activity in patients with synovial sarcoma and *SMARCB1*-null tumors across several dose levels, with eight patients demonstrating a best overall response of stable disease and one patient with a partial response

Figure 7A represents the % best change from baseline in the sum of target legions in all patients that received a follow up PET-CT scan

CONCLUSIONS

- CFT8634 is an orally bioavailable selective bifunctional degrader of BRD9 that demonstrates dose-dependent anti-tumor activity in synovial sarcoma PDX models
- In 32 patients treated with CFT8634 at escalating dose levels at the time of the data cutoff date (08/29/2023), CFT8634 showed a manageable safety profile in patients with pre-treated synovial sarcoma and *SMARCB1*-null tumors
  - Majority of AEs reported were considered mild to moderate in severity
  - No clear dose dependent relationship to incidence/severity of TEAEs was observed
- CFT8634 demonstrated a dose proportional peak concentration and AUC across escalating dose levels
- BRD9 degradation was measured across dose levels in tumor tissues after 15 days of treatment
- CFT8634 has shown preliminary evidence of anti-tumor activity in patients with synovial sarcoma and *SMARCB1*-null tumors
  - Tumor regression was observed across multiple dose levels including an unconfirmed PR in a *SMARCB1*-null tumor patient
  - At the time of data cutoff, 8 patients had stable disease as best response at 8 weeks per RECIST 1.1 criteria

The Phase 1 dose escalation study is currently ongoing and an RP2D has not yet been identified

Abbreviations
AE, adverse event; **BiDAC™**, bifunctional degradation activating compound; **BOR**, best overall response; **BRD9**, bromodomain containing 9; **CTCAE**, Common Terminology Criteria for Adverse Events; **ECOG**, Eastern Cooperative Oncology Group; **H&E**, Hematoxylin and Eosin; **IHC**, immunohistochemistry; **MTD**, maximum tolerated dose; **NE,** not evaluable; **OS**, overall survival; **PBMC**, peripheral blood mononuclear cells; **PD**, progressive disease; **PDX**, patient-derived xenografts; **PET-CT**, Positron Emission Tomography and Computed Tomography; **PK**, pharmacokinetics; **PO**, by mouth; **PR**, partial response; **PS**, performance status; **QD**, once daily; **RESIST**, Response Evaluation Criteria in Solid Tumors; **RP2D**, recommended Phase 2 dose; **SD**, stable disease; **SMARCB1**, SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1; **SS**, synovial sarcoma; **SWI/SNF**, SWItch/Sucrose Non-Fermentable; **TEAE**, treatment emergent adverse event; **TESAE**, treatment emergent serious adverse event; **TORPEDO®**, Target OrIented ProtEin Degrader Optimizer.

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