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

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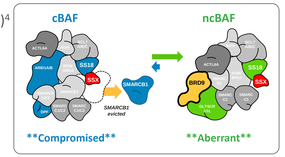
BACKGROUND

- SMARCB1-perturbed cancers are dependent on the chromatin factor BRD9[1,2]
  - 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 ~10% of all soft tissue sarcomas[2]
- SMARCB1-null tumor types include malignant rhabdoid tumor (MRT), poorly differentiated chordoma, and epithelioid sarcoma[3]
- 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 ~60%)[4]
- Mechanism of disease
  - SS18-SSX fusion protein and SMARCB1 deletion both result in perturbation of the cBAF complex (Figure 1)[1] causing oncogenic dependency on the ncBAF complex
  - Tumor specific ncBAF dependency results in a synthetic lethal dependency on BRD9
  - The DUF subdomain of BRD9 is a critical mediator of its oncogenicity[5]

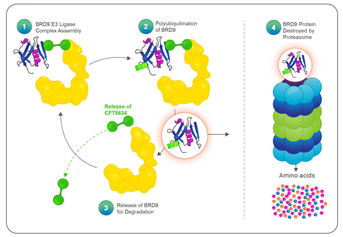
Figure 1: Oncogenic SS18-SSX Fusion Leads to BRD9 Dependency in Synovial Sarcoma[1]



CFT8634 BACKGROUND

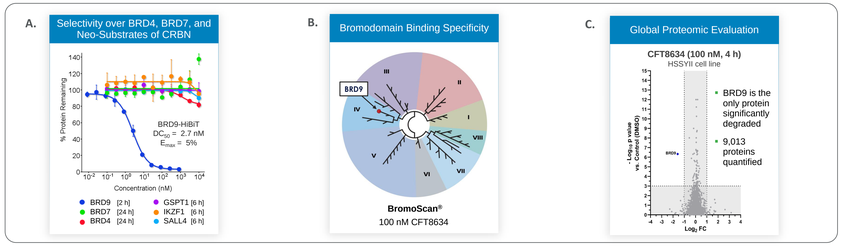
- Bromodomain inhibitors are insufficient to ablate BRD9 oncogenicity, because the DUF domain is critical, while a degrader approach achieves efficacy[2]
- CFT8634 is an orally bioavailable selective bifunctional degradation activating compound, or BiDAC™ degrader, of BRD9
  - CFT8634 was synthesized using C4 Therapeutics' TORPEDO® platform
- Mechanism of action (Figure 2)
  - CFT8634 induces a ternary complex formation with BRD9 and cereblon E3 ligase (step 1)
  - BRD9 is ubiquitinated and subsequently degraded by the proteasome (steps 2-4)
- 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 vitro and in vivo models of SMARCB1-perturbed cancers (Figures 5-6)

Figure 2: Mechanism of Action for CFT8634[6]



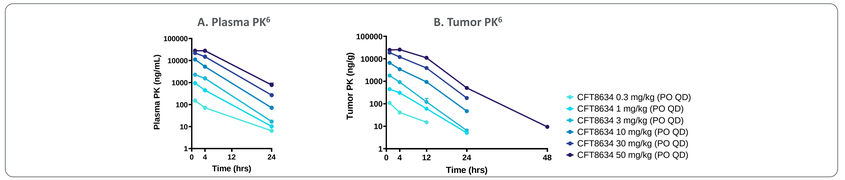
PRE-CLINICAL DATA: IN VITRO

Figure 3: CFT8634 is a Highly Selective BRD9 Degrader[6]



PRE-CLINICAL DATA: IN VIVO IN CDX

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



PRE-CLINICAL DATA: IN VIVO IN PDX

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

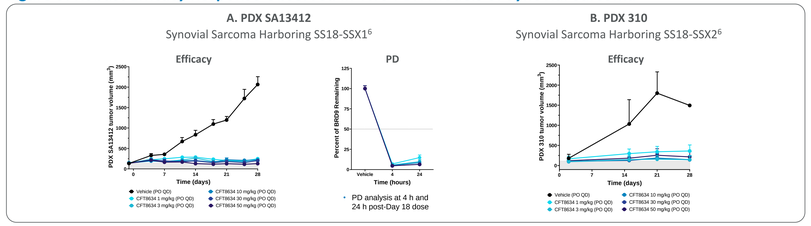
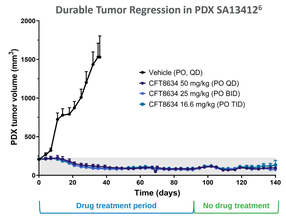


Figure 6: Durable Response Observed in a PDX Model of Synovial Sarcoma



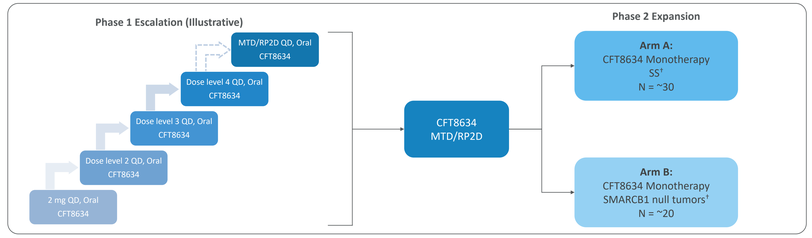
- Treatment administered for 89 days followed by 51-day observation period
- Tumor regressions were durable with no regrowth observed

These pre-clinical results provide the rationale for a Phase 1 study (first-in-human) to evaluate CFT8634 in synovial sarcoma and SMARCB1-null tumors

Phase 1/2: FIRST-IN-HUMAN CLINICAL STUDY DESIGN[7]

- 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)
- N=110 patients (approximately) at 10 US sites will be enrolled
- Registered on ClinicalTrials.gov as NCT05355753, study is open for enrollment

Figure 7: CFT8634 Study Design



*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.

FIRST-IN-HUMAN STUDY DESIGN[7]

KEY ELIGIBILITY CRITERIA

KEY INCLUSION CRITERIA

- SS or SMARCB1-null tumors confirmed by immunohistochemistry, fluorescent in situ hybridization, or other equivalent tests like gene mutation 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 confer clinical benefit and must be ≥18 years of age, or ≥16 years old and weigh ≥50 kg

KEY EXCLUSION CRITERIA

- Systemic anti-neoplastic therapy within 14 days or 5 half-lives, whichever is shorter, prior to the planned first dose of CFT8634
- Patient should not have received another BRD9 degrader

STUDY ENDPOINTS[7]

PRIMARY ENDPOINT

- Frequency and severity of AEs and SAEs of CFT8634
- Changes between baseline and post baseline safety assessments
- ORR (Phase 2)
- Changes from baseline in ECG parameters
- Frequency of dose interruptions and dose reductions
- Incidence of DLTs during escalation

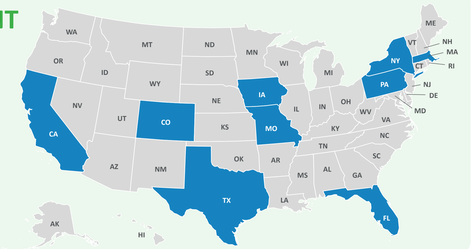
SECONDARY ENDPOINTS

- Assessment of PK and PD
- ORR (Phase 1)
- DoR
- PFS
- 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[7]
- Trial registration: NCT05355753
- As of 09/27/2022, 5 sites have initiated recruitment
- Contact information: *clinicaltrials@C4therapeutics.com*

*Blue colored states indicate clinical trial sites



Abbreviations

AE, adverse event; **BID**, twice daily; **BRD4**, bromodomain containing 4; **BRD7**, bromodomain containing 7; **BRD9**, bromodomain containing 9; **cBAF**, canonical BAF; **CDX**, cell line-derived xenograft; **CRBN**, cereblon; **DoR**, duration of response; **DLT**, dose limiting toxicities; **ECG**, electrocardiogram; **HiBiT**, high affinity bioluminescent tag; **MTD**, maximum tolerated dose; **ncBAF**, noncanonical BAF; **ORR**, overall response rate; **OS**, overall survival; **pBAF**, polybromoBAF; **PD**, pharmacodynamics; **PDX**, patient-derived xenografts; **PFS**, progression free survival; **PK**, pharmacokinetics; **PO**, by mouth; **QD**, once daily; **RP2D**, recommended phase 2 dose; **SAE**, serious adverse event; **SMARCB1**, SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1; **SS**, synovial sarcoma; **TID**, thrice daily

Disclosures

BVT: leadership: Polaris; honoraria: Bionest Partners, Horizon CME, Research to Practice, Targeted Oncology; consulting or advisory role: Adaptimmune, ADRx, Apexigen, Ayala Pharmaceuticals, Bayer, Cytokinetics, Daiichi Sankyo, Deciphera, EMD Serono, Epizyme, GlaxoSmithKline, Immune Design, IntelliSphere, Lilly, Novartis, Pfizer; speakers' bureau at Adaptimmune, GlaxoSmithKline, Lilly, Novartis; research funding: GlaxoSmithKline, Merck, Pfizer, TRACON Pharma; patents, royalties, other intellectual property: Accuronix Therapeutics - Licensing agreement, Sigma-2 Receptor Ligands and Therapeutic uses therefor (006766), Modular Platform for Targeted Therapeutic Delivery (006755), Sigma-2 Receptor Ligand Drug Conjugates as Antitumor Compounds, Methods of synth; patent on ALEXT3102; patent on the use of ME1 as a biomarker; expert testimony: Health Advances; travel, accommodations, expenses: Adaptimmune, Advenchen Laboratories, GlaxoSmithKline, Lilly. **WT**: research funding: AmMax Bio, Atropos Therapeutics, Ayala Pharmaceuticals, Bayer, Certis Oncology Solutions, Cogent Biosciences, Connecting Humans in Health, Daiichi Sankyo, Deciphera, Eli Lilly, Epizyme, Foghorn Therapeutics, Kowa Research Institute, MedPacto, Novo Holdings A/S. **RR**: stock and other ownership interests: Johnson & Johnson, Medtronic; honoraria: touchIME; consulting or advisory role: Epizyme; research funding: Ayala Pharmaceuticals, Bayer, Epizyme, SpringWorks Therapeutics; travel, accommodations, expenses: SpringWorks Therapeutics. **SA**: research funding: Desmoid Tumor Research Foundation, AB Science, TRACON Pharma, Bayer, Novartis, Lilly, Karyopharm Therapeutics, Epizyme, Blueprint Medicines, Genmab, CBA Pharma, Merck, Philogen, Gradalis, Deciphera, Takeda, Incyte, SpringWorks, Adaptimmune, Advenchen Laboratories, Bavarian Nordic, BTG, PTC Therapeutics, GlaxoSmithKline, FORMA Therapeutics, TRACON Pharma, Ayala Pharmaceuticals, Trillium Therapeutics, Boehringer Ingelheim, Salarius Pharmaceuticals, Theseus Pharmaceuticals, Monopar Therapeutics, C4 Therapeutics, Inhibrx, Noxopharm and Rain Therapeutics. **AE**: no disclosures. **VM**: research funding: Amgen, Forma Therapeutics, GSK, Deciphera, Trillium, Astex Pharma, Prelude Therapeutics, Pfizer, Oblato, Hutchison; advisory role: Forma Therapeutics and Astex Pharmaceuticals. **LH**: no disclosures. **MA**: consulting or advisory role: Lilly, Adaptimmune, Regeneron, AstraZeneca, BMS, Bayer, Deciphera; research funding: Exelixis. **GS:** stock and other ownership interests: GenCirq, Bionauts Labs, January Therapeutics; consulting or advisory role: Bionaut Labs, Ellipses Pharma, GenCirq, Epizyme, Array BioPharma, Apexigen, Oncogenuity, OnCusp, Concarlo, Shanghai Pharma, Astex, January Therapeutics, Sellas Life Sciences, Purtech, Killys Therapeutics; research funding: Astex Pharmaceuticals, Incyte, Calithera Biosciences, Lilly, Daiichi Sankyo, Fortress, Karyopharm Therapeutics, Oxford BioTherapeutics, Astex Pharmaceuticals, TopAlliance BioSciences, Adaptimmune, SpringWorks Therapeutics, TRACON Pharma; travel, accommodations, expenses: Array Biopharma and Epizyme. **AA**: employed by and equity holder in C4 Therapeutics. **RL**: employed by and equity holder in C4 Therapeutics. **IM:** employed by and equity holder in C4 Therapeutics. **OSK**: consultancy at C4 Therapeutics. **EH:** employed by and equity holder in C4 Therapeutics. **KN:** employed by and equity holder in C4 Therapeutics. **GC:** research funding: Servier Pharmaceuticals, Epizyme, PharmaMar, MacroGenics, Eisai, Merck, Bavarian Nordic, Bayer, SpringWorks Therapeutics, Repare Therapeutics, Foghorn Therapeutics, SMP Oncology, Jazz Pharmaceuticals, RAIN Therapeutics, BioAtla, InhibitRX, Ikena, C4 Therapeutics.

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