A Phase 1/2 Study Of CFT1946, A Novel Bifunctional Degradation Activating Compound, or BiDAC™ Degrader, of Mutant BRAF V600 as Monotherapy and in Combination with Trametinib, in Mutant BRAF V600 Solid Tumors

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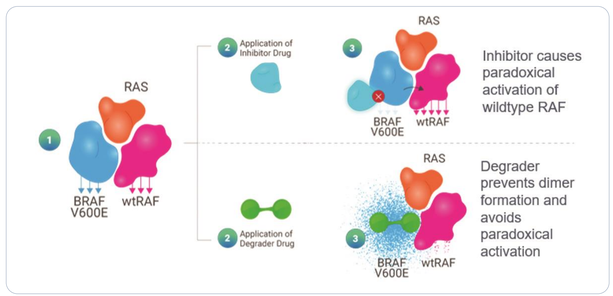
BACKGROUND

- BRAF is a protein kinase that acts as a signal transducer/amplifier in receptor tyrosine kinase (RTK) signaling pathways, specifically, the mitogen activated protein kinase (MAPK) pathway that promotes cell proliferation and survival when activated through extracellular signals[1,2]
- Constitutively active mutated BRAF, specifically BRAF with valine 600 mutations (BRAF V600), is capable of uncontrolled signaling which signals as a monomer, resulting in hyperactivation of MEK, ERK, and dysregulation of cellular proliferation[2]
- BRAF V600 is a clinically validated oncology target in the follow tumor types[1-3]
  - Melanoma, colorectal cancer (CRC), non-small cell lung cancer (NSCLC), and anaplastic thyroid carcinoma (ATC)
- Currently approved BRAF inhibitors (BRAFi) result in paradoxical RAF activation as the mutant BRAF protein is still able to dimerize with wtBRAF, resulting in a dimeric signaling complex[4] (Figure 1)

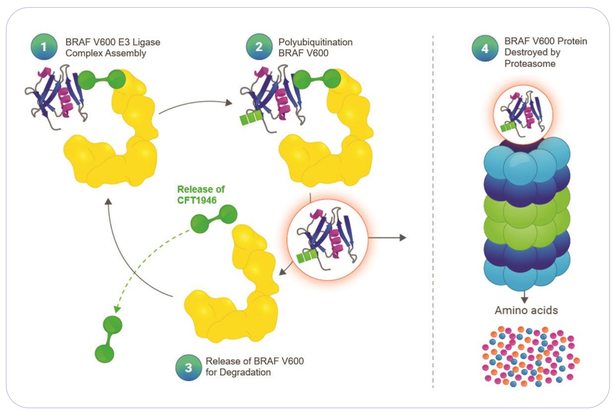
Figure 1: Utilizing a Degrader Approach to Overcome Limitations of BRAF Inhibition[5]



CFT1946 BACKGROUND[5]

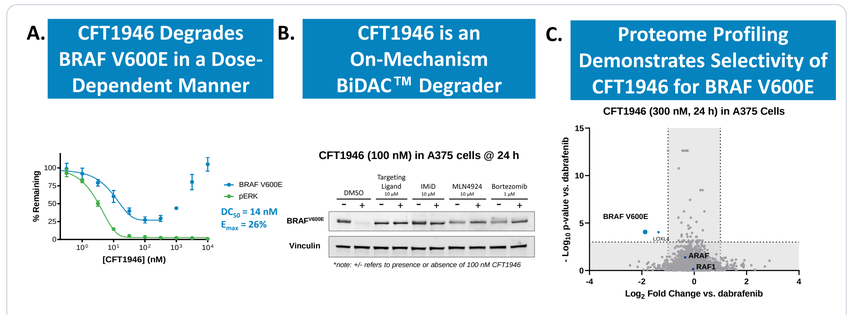
- CFT1946 is a novel, orally bioavailable, bifunctional degradation activating compound, or BiDAC™ degrader
  - CFT1946 selectively inhibits and degrades mutant BRAF V600 protein
  - Distinct from approved BRAFi, CFT1946 avoids paradoxical RAF activation as the degraded BRAF V600 mutant protein can no longer incorporate into a dimeric signaling complex (Figure 1)
  - CFT1946 is selective for the mutant protein and spares wtBRAF V600
  - Mechanism of action (Figure 2)
    - i. CFT1946 induces ternary complex formation with BRAF and cereblon E3 ligase (step 1)
    - ii. BRAF V600 is ubiquitinated and subsequently released for degradation in the proteasome (steps 2-4)
- CFT1946 has demonstrated preclinical activity in BRAF V600 mutant in vitro and in vivo models, including models resistant to BRAFi (Figures 3-5)

Figure 2: Mechanism of Action for CFT1946 Compound[5]



PRE-CLINICAL DATA: IN VITRO

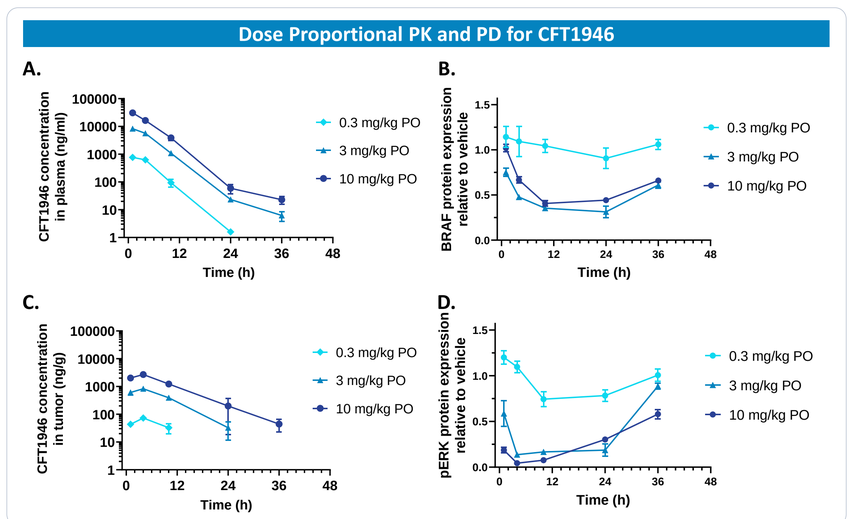
Figure 3: CFT1946 Is an On-Mechanism, CRBN-Based, Highly Selective BRAF V600X BiDAC™ Degrader[5]



- CFT1946 acts as both an inhibitor and a degrader of BRAF V600E as demonstrated in HiBiT assay in panel A. Phospho-ERK levels decrease in a CFT1946 dose-dependent manner. BRAF V600E levels decrease in a CFT1946 dose-dependent manner until "hook effect" concentrations are achieved. Panel B demonstrates that CFT1946 is on-mechanism for a CRBN-based BiDAC™ degrader and Panel C shows the selectivity of CFT1946 in A375 cells using global proteomic profiling.

PRE-CLINICAL DATA: IN VIVO

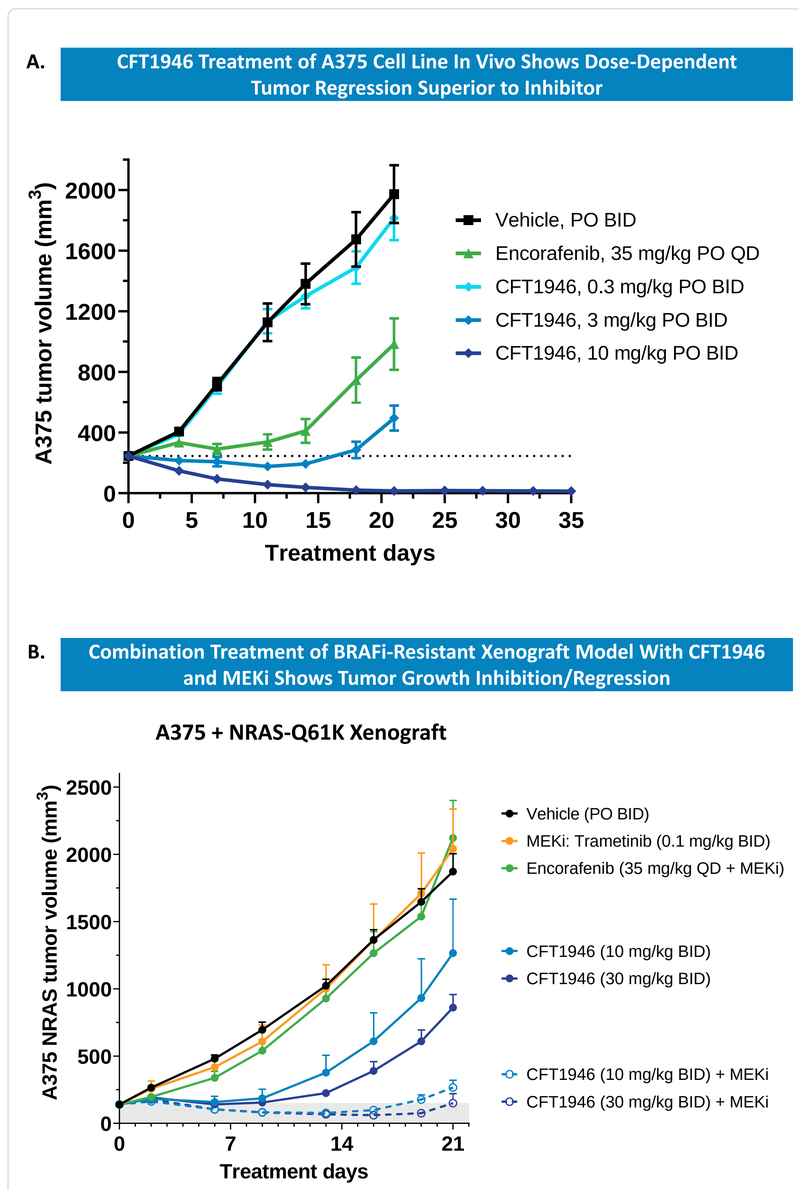
Figure 4: Dose Proportional PK and PD Profile in the BRAF V600E A375 Xenograft Mouse Model for CFT1946 Compound[5]



- Pharmacodynamic data demonstrates a dose-proportional loss of BRAF V600E protein and decreased signaling through the MAPK pathway as determined by loss of phospho-ERK (pERK). As CFT1946 degrades BRAF V600 mutant protein and results in decreases phospho-ERK levels, some MAPK pathway inhibition occurs prior to maximal loss of BRAF V600E protein.

PRE-CLINICAL DATA: IN VIVO (continued)

Figure 5: CFT1946 Induces Tumor Regression in the A375 (homozygous BRAF V600E) Xenograft Mouse Model as a Single Agent and in Combination With the MEK Inhibitor, Trametinib, in a BRAF Inhibitor-Resistant Xenograft Mouse Model[5]



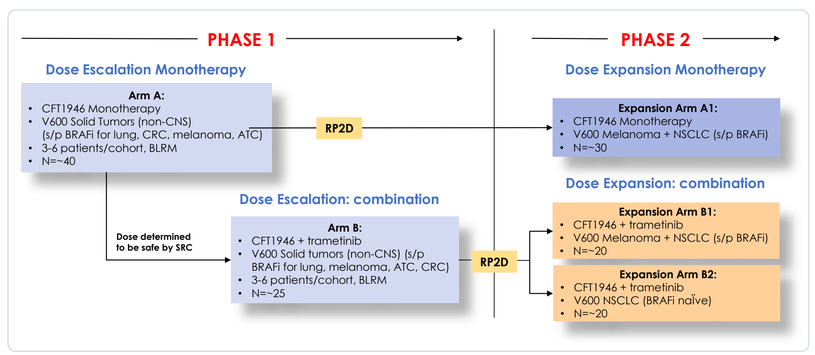
A. In the A375 mouse xenograft model, CFT1946 showed dose-dependent tumor growth inhibition (TGI) when administered PO at 0.3 mg/kg and 3 mg/kg BID, and immediate and sustained tumor regression at 10 mg/kg PO BID.
B. In the BRAFi-resistant A375+NRAS-Q61K xenograft model, CFT1946 showed dose-dependent TGI when administered PO as a single agent at 10 mg/kg (TGI ~35%) and 30 mg/kg (TGI ~60%) BID. When CFT1946 at 10 and 30 mg/kg BID was combined with 0.1 mg/kg trametinib, combination treatment resulted in tumor regression up to Day 16 and Day 19, respectively, with slight tumor re-growth emerging at Day 19 and Day 21, respectively.

These preclinical data provide rationale for a first-in-human (FIH) study to evaluate CFT1946 in BRAF V600 mutant solid tumors

PHASE 1/2: FIRST-IN-HUMAN CLINICAL STUDY DESIGN[5,6]

- Open-label, multicenter, Phase 1/2 clinical trial with dose escalation and expansion phases*
- Dose escalation Phase 1 comprises CFT1946 (Arm A) with a starting oral dose of 20 mg twice daily and CFT1946+trametinib (Arm B)
- Dose expansion Phase 2 comprises CFT1946 (Arm A1) and CFT1946+trametinib (Arms B1 and B2)†
  - Arms A1 and B1 will include BRAF V600 mutant melanoma and NSCLC with prior BRAFi therapy while Arm B2 will enroll BRAF V600 mutant NSCLC who are BRAFi-naïve
- N=135 (approximately) across 11 US and European sites will be enrolled
- Registered on ClinicalTrials.gov as NCT05668585, study is open for enrollment

Figure 6: CFT1946 Study Design[5‡]



*CFT1946 is administered orally in 28-day cycles until disease progression or intolerable toxicity.
†Phase 2 will be initiated once the RP2D has been identified. Eligible subjects are ≥18 years-old with documented BRAF V600 mutant cancers who have received ≥1 prior therapy.
‡Phase 2 expansion study design will be updated based on Health Authority feedback.

FIRST-IN-HUMAN STUDY DESIGN

KEY ELIGIBILITY CRITERIA[6]

KEY INCLUSION CRITERIA

- ≥18 years of age at time of informed consent
- Documented evidence of a BRAF V600 mutation obtained from tumor tissue or liquid biopsy
- Received ≥1 prior line of SoC therapy for unresectable locally advanced or metastatic disease, NSCLC, CRC, ATC or other BRAF V600 mutation-positive tumors
- Adequate bone marrow, liver, renal, and cardiac organ function

KEY EXCLUSION CRITERIA

- Subject has had major surgery within 21 days prior to the planned first dose. Minor surgery is permitted within 21 days prior to enrollment
- Subject with CNS involvement (primary tumor or metastatic disease), except if clinically stable
- Subject with known malignancy other than trial indication that is progressing or has required treatment within the past 3 years, except for conditions that have undergone potentially curative therapy

STUDY ENDPOINTS[6]

PRIMARY ENDPOINTS

- Frequency and severity of AEs and SAEs of CFT1946 (Phase 1)
- Incidence of DLTs (Phase 1)
- Number of participants with changes between baseline and post-baseline safety assessments (Phase 1)
- Frequency of dose interruptions and dose reductions (Phase 1)
- Frequency of AEs leading to discontinuation (Phase 1)
- ORR (Phase 2)
- PFS
- DOR

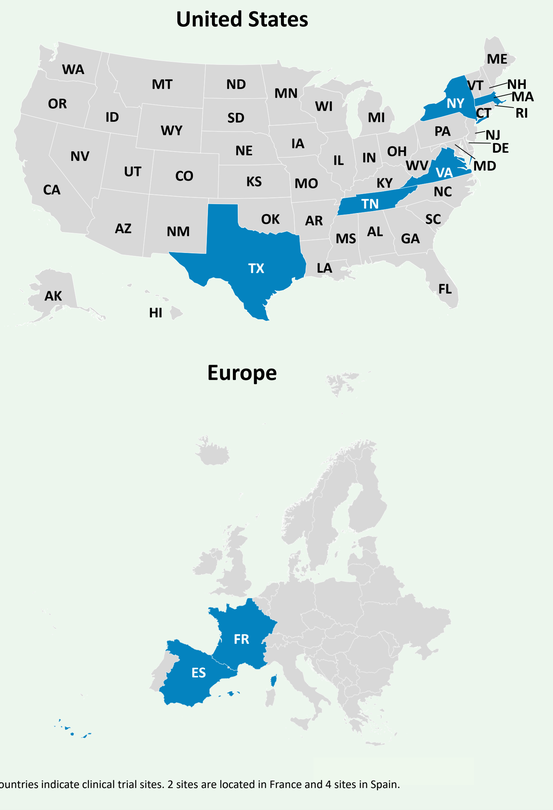
SECONDARY ENDPOINTS

- Frequency and severity of AEs and SAEs of CFT1946 (Phase 2)
- Number of participants with changes between baseline and post-baseline safety assessments (Phase 2)
- Frequency of dose interruptions and dose reductions (Phase 2)
- Assessment of PK and PD
- PK-QTcF relationship
- ORR (Phase 1 and 2)
- DCR

STUDY STATUS/ENROLLMENT[6]

The study opened to accrual in December 2022 and will be recruiting ~N=135patients from 11 sites* in the US and Europe

- Trial registration: NCT05668585
- As of 05/15/2023, all 5 US sites have initiated recruitment
- Contact information: *clinicaltrials@C4therapeutics.com*



*Blue-colored US states and EU countries indicate clinical trial sites. 2 sites are located in France and 4 sites in Spain.

Abbreviations
AE, adverse event; **ATC**, anaplastic thyroid carcinoma; **BID**, twice daily; **BiDAC™**, bifunctional degradation activating compound; **BLRM**, Bayesian logistic regression model; **BRAF**, v-raf murine sarcoma viral oncogene homolog B1; **BRAFi**, BRAF inhibitor, **Bx**, biopsy; **CNS**, central nervous system; **CRBN**, cereblon; **CRC**, colorectal cancer; **DCR**, disease control rate; **DLT**, dose limiting toxicities; **DOR**, duration of response; **ERK**, extracellular signal-regulated kinases; **FIH**, first-in-human; **HiBiT**, high affinity bioluminescent tag; **IMiD**, immunomodulatory imide drug; **MAPK**, mitogen-activated protein kinase; **MEK**, mitogen-activated protein kinase kinase; **MEKi**, MEK inhibitor; **MTD**, maximum tolerated dose; **NRAS**, neuroblastoma ras; **NSCLC**, non-small cell lung cancer; **ORR**, overall response rate; **pERK**, phospho-ERK; **PD**, pharmacodynamics; **PDX**, patient-derived xenografts; **PFS**, progression-free survival; **PK**, pharmacokinetics; **PO**, by mouth; **PoM**, proof of mechanism; **QD**, once daily; **QTcF**, Fridericia heart-rate-corrected QT interval; **RAF**, rapidly accelerated fibrosarcoma; **RP2D**, recommended phase 2 dose; **RTK**, receptor tyrosine kinase; **SAE**, serious adverse event; **s/p**, status post; **SoC**, standard-of-care; **SRC**, Safety Review Committee; **TGI**, tumor growth inhibition; **wt**, wild-type.

Disclosures
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