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Preclinical Evaluation of CFT1946

as a Selective Degrader of Mutant BRAF for the Treatment of BRAF Driven Cancers

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Disclosure Information

Mathew E. Sowa, PhD

- I have the following financial relationships to disclose:
  - Stockholder in: C4 Therapeutics
  - Employee of: C4 Therapeutics

Mechanism of Action for BRAF-V600X Driven Human Cancers

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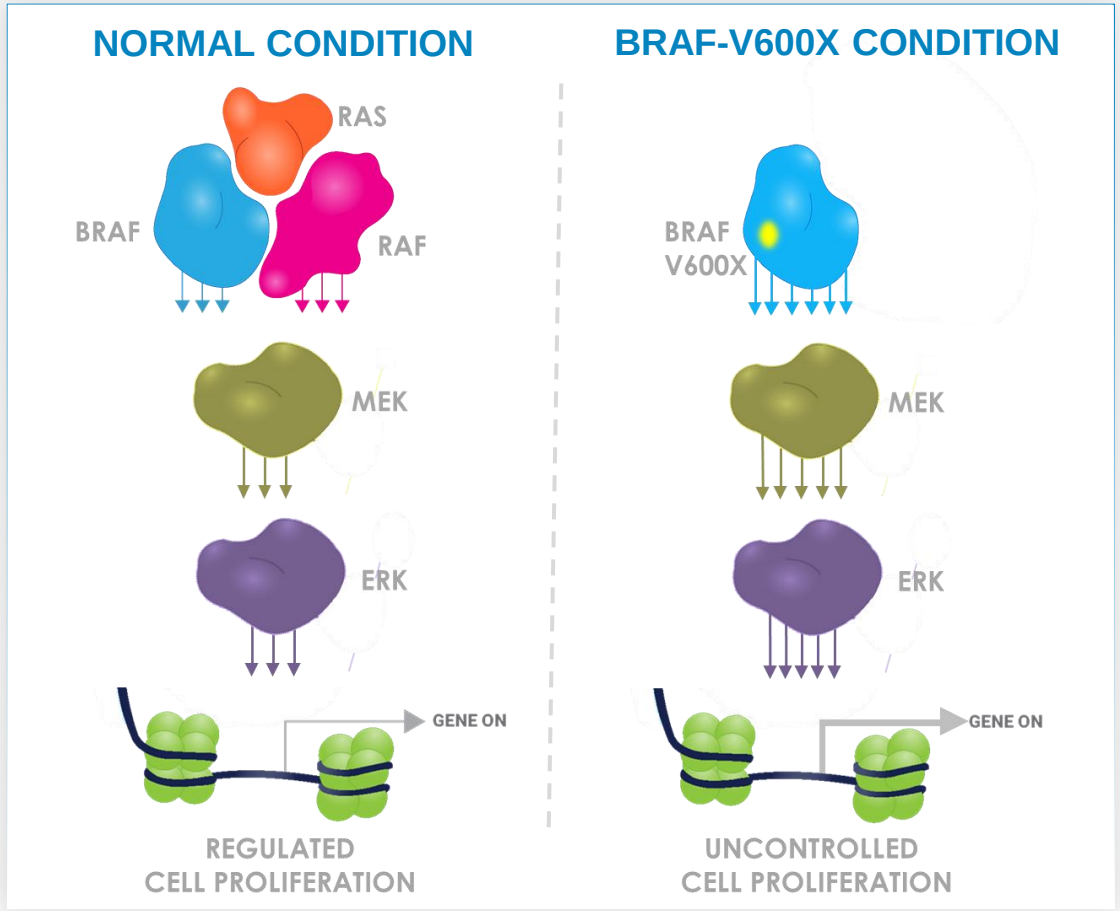

Mechanism of BRAF-V600X Driven Cancer

- BRAF is a serine/threonine protein kinase in the MAPK pathway that promotes cell proliferation and survival when activated through extracellular signals
- Constitutively active BRAF-V600X causes uncontrolled MAPK signaling, leading to tumorigenesis, tumor growth, and maintenance
- Decreasing BRAF-V600X activity in these cancers leads to growth arrest, cell death, and tumor regression
- BRAF-V600X is a clinically validated oncology target, however limitations in currently approved inhibitors highlight the need for additional BRAF-V600X targeted therapies

MAPK, MAP kinase.

Utilizing a Degrader Approach to Overcome Limitations of BRAF Inhibition

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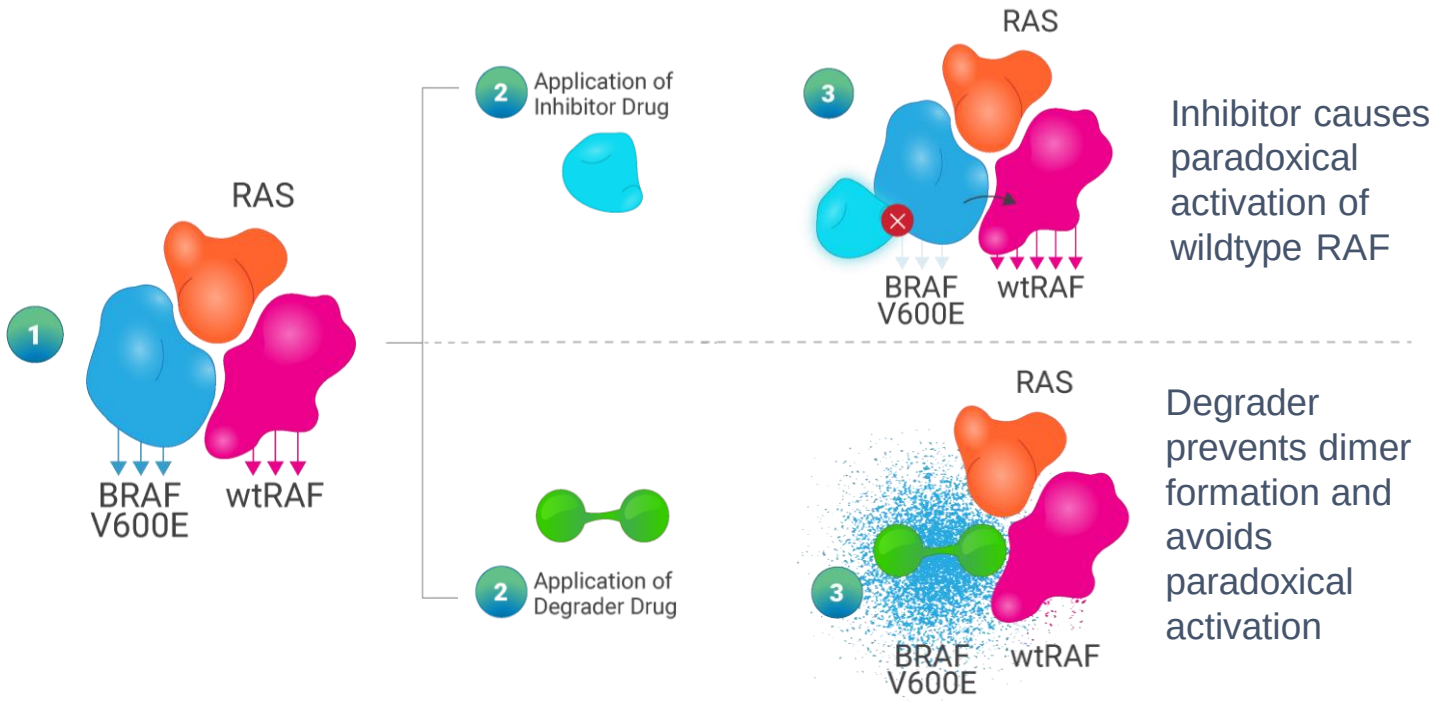
Degrader Rationale



Advantages of BRAF V600X Degradation

- Specifically target mutant BRAF-V600X over wildtype BRAF
- Prevent mutant BRAF-V600X incorporation into RAF dimers
- Avoid paradoxical activation of RAF dimers
- Address failures in inhibitor-based therapy due to resistance mechanisms
- Effect deep elimination of mutant BRAF signaling and create durable responses

CFT1946 is an On-Mechanism, CRBN-Based, BRAF-V600X BiDAC™ Degrader

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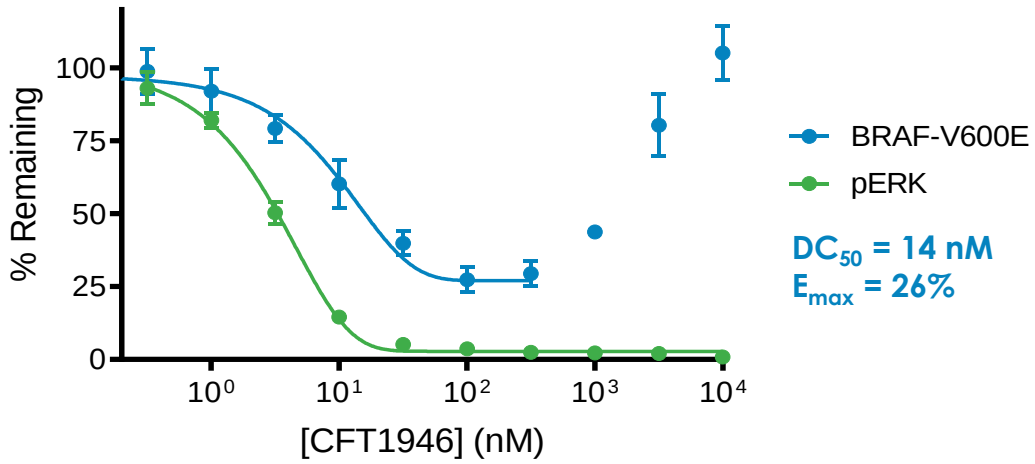
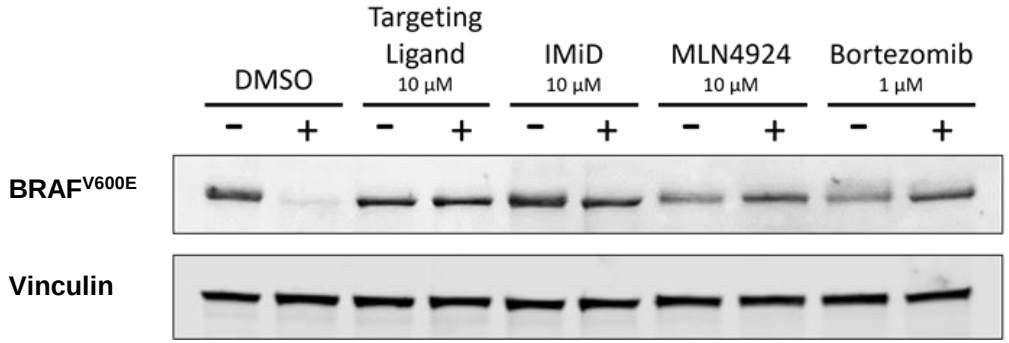
CFT1946 Degrades BRAF-V600E in a Dose Dependent Manner



- HiBiT assay shows BRAF-V600E degradation with CFT1946 treatment in dose-dependent manner
- pERK loss aligns with loss of BRAF-V600E protein demonstrating MAPK pathway inhibition

CFT1946 is an On-Mechanism BiDAC™ Degrader

CFT1946 (100 nM) in A375 cells @ 24 h



**note: +/- refers to presence or absence of 100 nM CFT1946*

- BRAF-V600E degradation with CFT1946
- No BRAF-V600E degradation with ligand competition, CRBN ligand competition, inhibition of CUL4 E3 with MLN4924 or inhibition of the proteasome with bortezomib

BiDAC, bifunctional degradation activating compound; HiBiT; high affinity bioluminescent tag; IMiD, immunomodulatory imide drug.
C4 Therapeutics data on file.

CFT1946 Degrades BRAF-V600E with No Activity on WT-BRAF, CRAF, or ARAF

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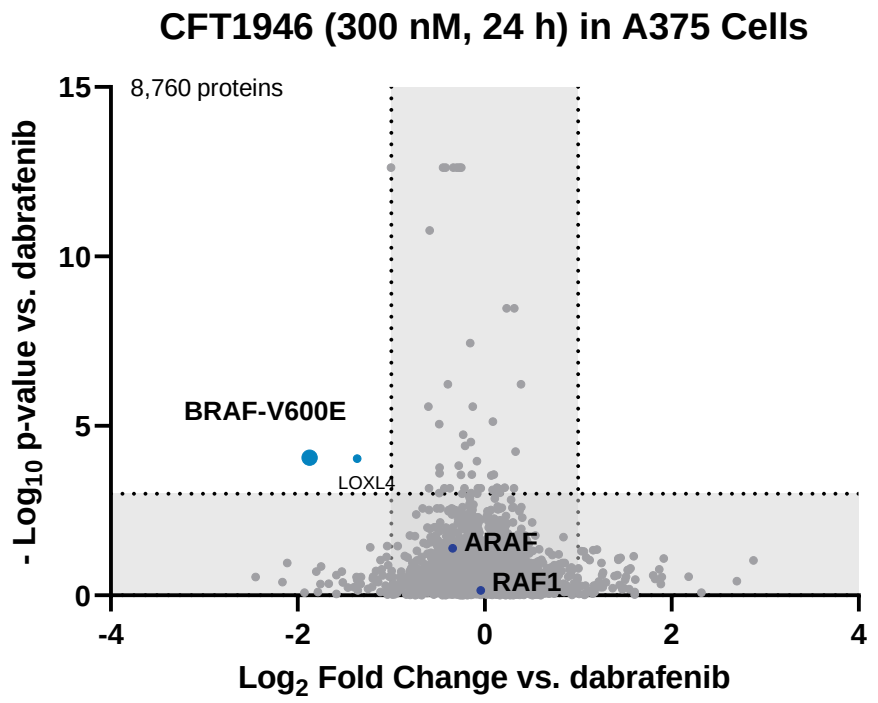
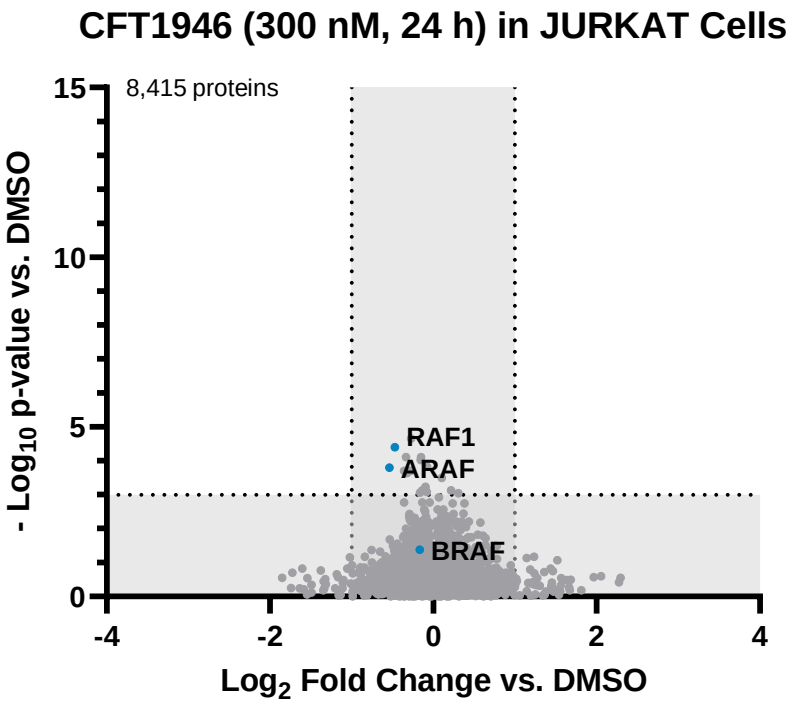
Proteome Profiling Demonstrates Selectivity of CFT1946 for BRAF-V600E



Proteome Profiling in WT-BRAF Cells Demonstrates Selectivity of CFT1946 for mBRAF



C4 Therapeutics data on file.

CFT1946 Causes BRAF-V600E Degradation, Potent Inhibition of MAPK Signaling, & Loss of Viability in BRAF-V600E Cells but Not in WT-BRAF Cells

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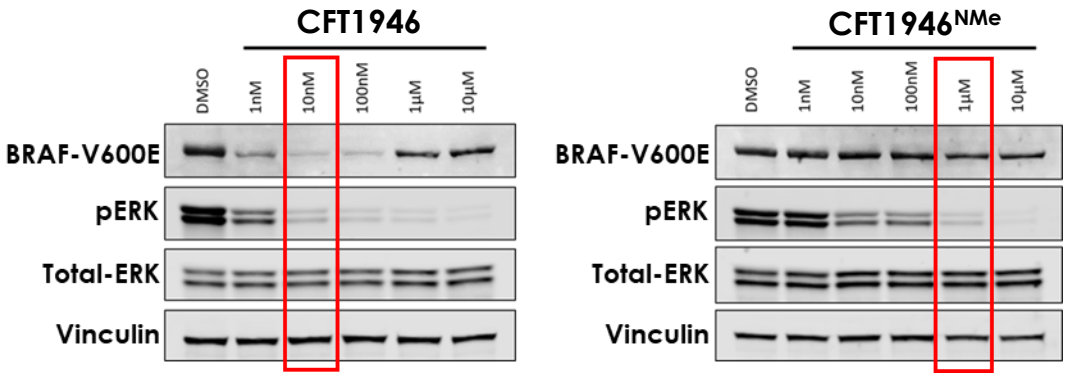
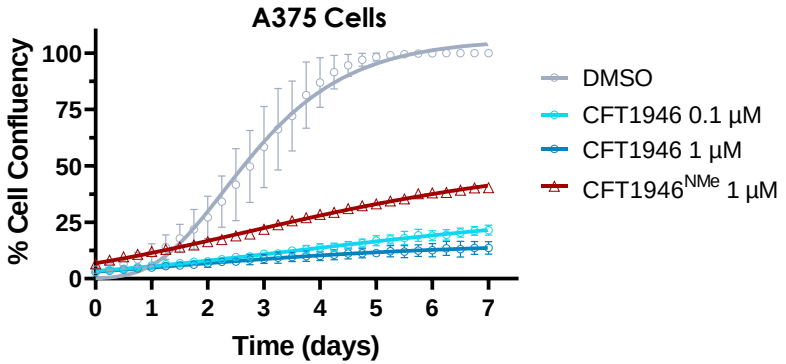
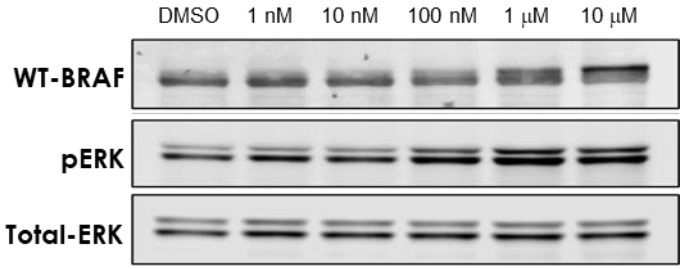
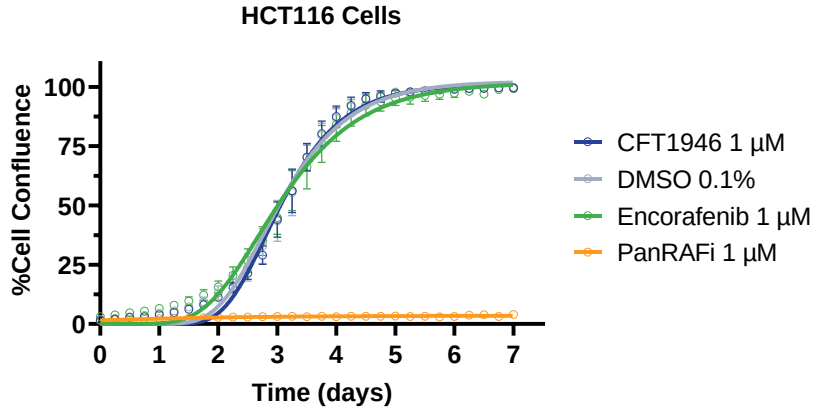
BRAF-V600E Degradation by CFT1946 Causes Loss of MAPK Signaling Superior to Inhibition Alone





CFT1946 Treatment of WT-BRAF Cells Has No Effect on MAPK Pathway and Cell Growth





*note: CFT1946NMe is a non-CRBN binding version of CFT1946; BRAF is BRAF-V600E
MAPK, MAP kinase.
C4 Therapeutics data on file.

CFT1946 Induces Tumor Regression in the BRAF-V600E A375 Xenograft Mouse Model in Accordance with PK/PD Results

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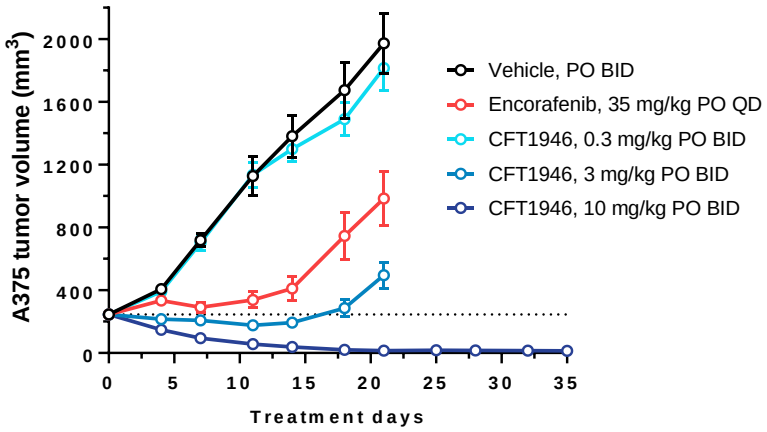
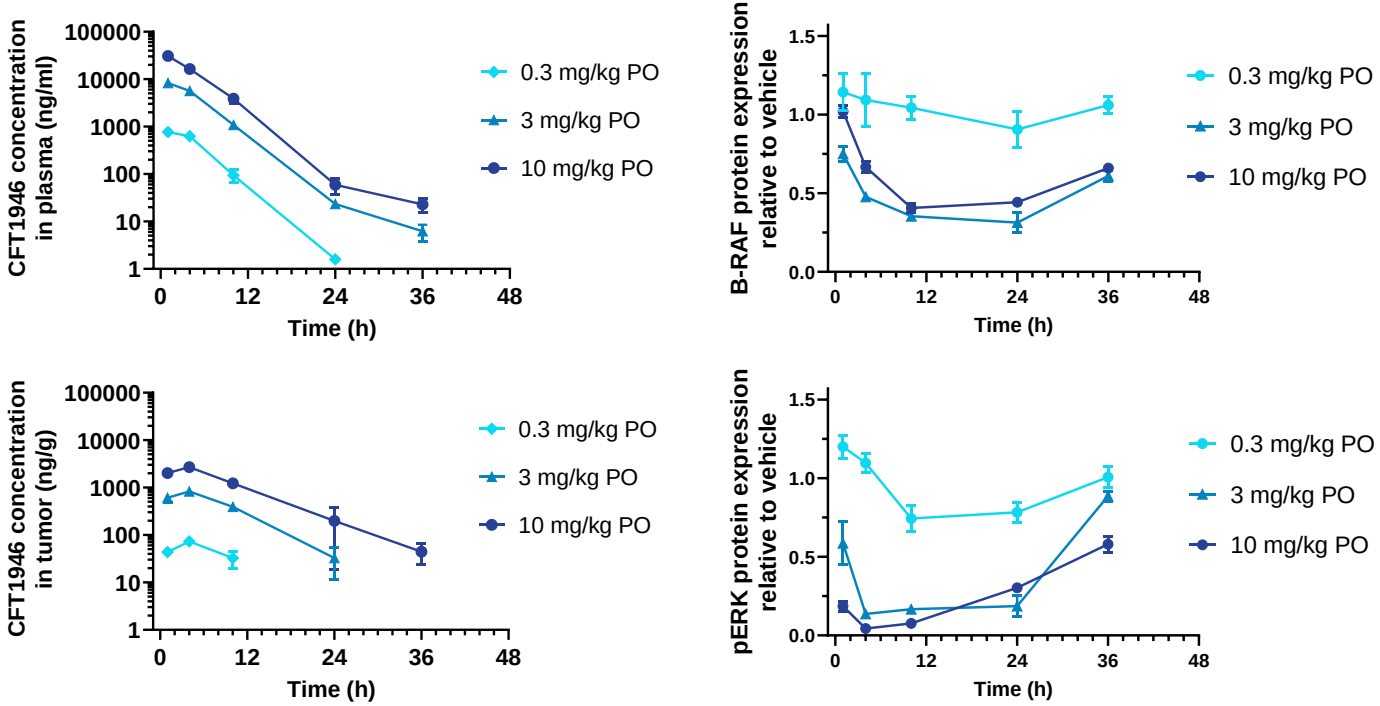
CFT1946 Treatment of A375 Cell Line *in vivo* Shows Dose-Dependent Tumor Regression Superior to Inhibitor



CFT1946 dose-response xenograft data demonstrates that 10 mg/kg BID dose results in sustained tumor regression and is the minimum efficacious dose

Dose Proportional PK and PD for CFT1946



BID, twice a day; MAPK, MAP kinase; PO, by mouth; PK/PD, pharmacokinetics/pharmacodynamics; QD, once daily.
C4 Therapeutics data on file.

CFT1946 is Active in BRAF-V600E/NRAS-Q61K, a Model of Clinical Resistance to BRAF Inhibitors

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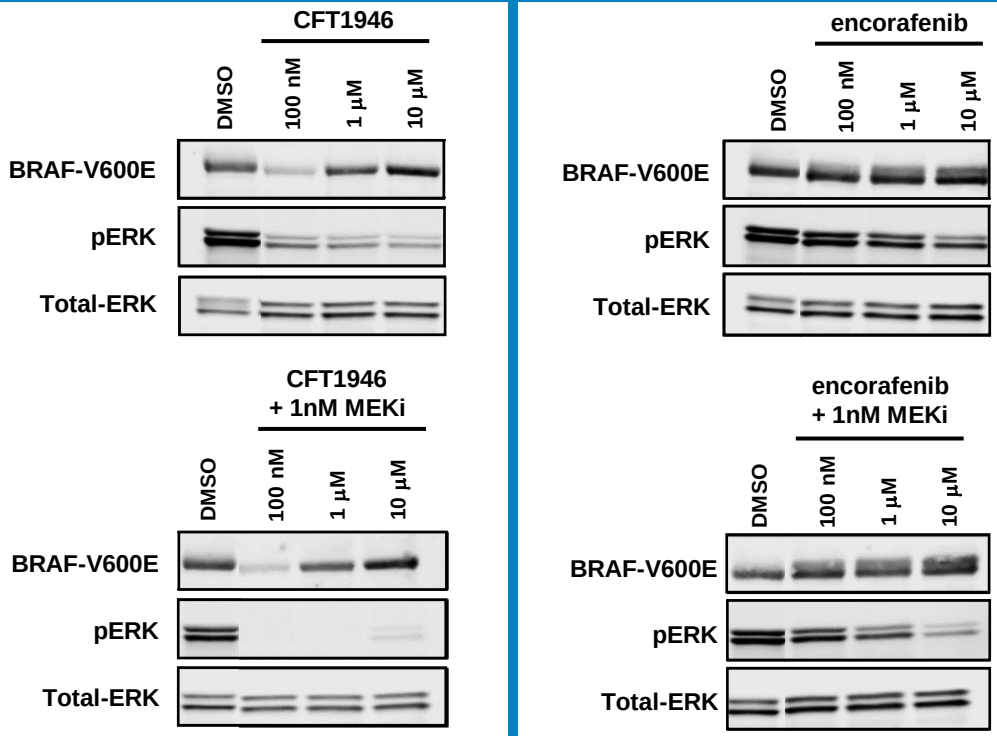
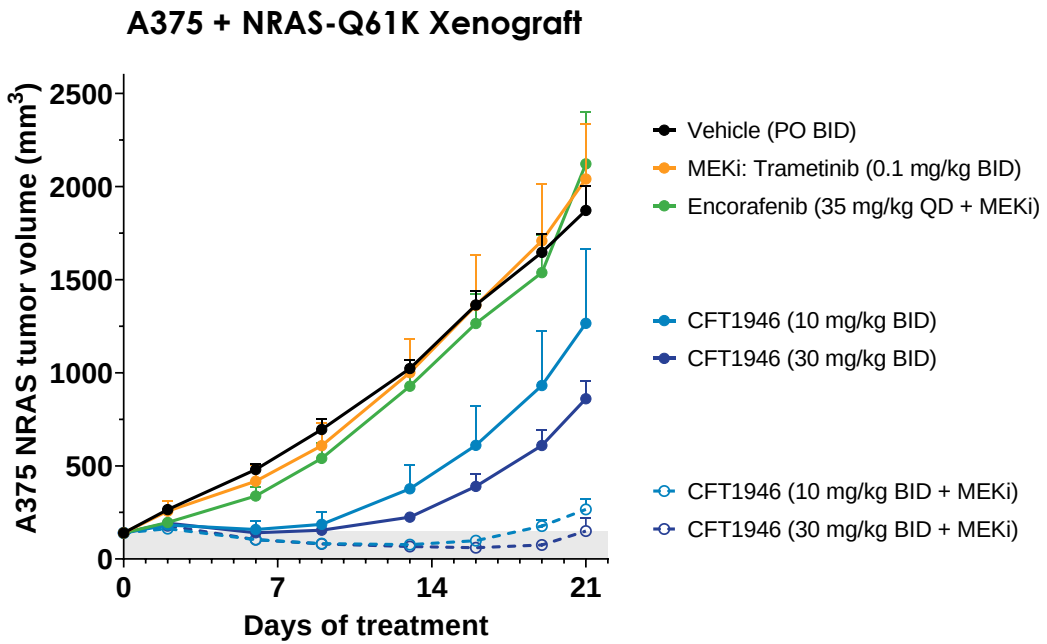
CFT1946 as a Single Agent and in Combination with MEKi is Effective in MAPK Pathway Inhibition, Superior to BRAFi



Combination Treatment of BRAFi Resistant Xenograft Model with CFT1946 and MEKi Shows Tumor Growth Inhibition/Regression



BID, twice a day; BRAFi, BRAF inhibitor; MAPK, MAP kinase; MEKi, MEK inhibitor; PO, by mouth; PK/PD, pharmacokinetics/pharmacodynamics; QD, once daily.
C4 Therapeutics data on file.

CFT1946 Demonstrates Potential of TPD-Based Therapies in non-V600X mBRAF Driven Cancers

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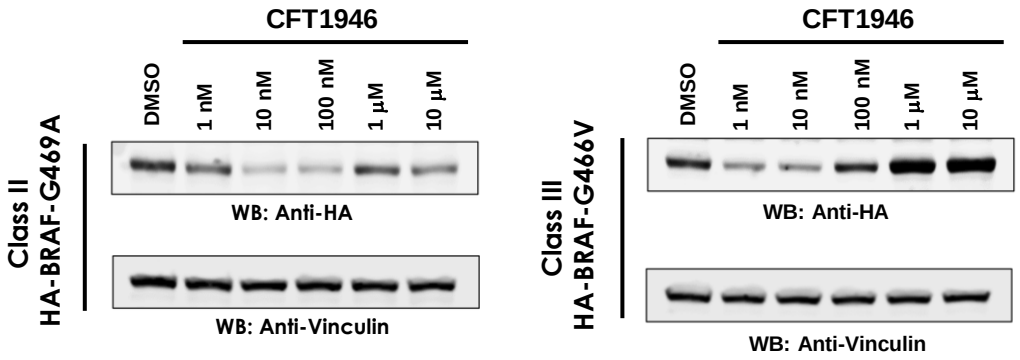
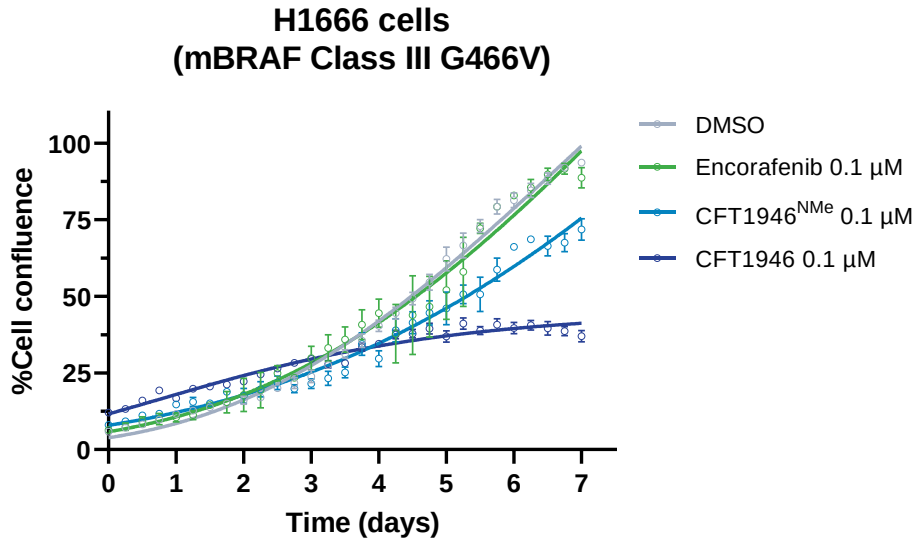
CFT1946 Provides PoC for Degradation of Selected non-V600E mBRAF of Both Class II and Class III



Using an ectopic expression system in HEK293T cells, CFT1946 treatment demonstrates degradation of HA-tagged mBRAF in a dose-dependent manner

CFT1946 Treatment of Class III mBRAF Model Cell Line Shows PoC for TPD-mediated Growth Inhibition Superior to BRAFi



CFT1946 treatment of H1666 cells shows modest growth inhibition, superior to inhibition alone

BRAFi, BRAF inhibitor; MEKi, MEK inhibitor; PoC, proof of concept; TPD, targeted protein degradation.
C4 Therapeutics data on file.

Summary of Findings

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- CFT1946 is a potent and mutant-selective BiDAC™ degrader of BRAF-V600X
- CFT1946 is active *in vitro* and *in vivo* in models with BRAF-V600E–driven disease and in the escape mutant BRAF-V600E/NRAS-Q61K–driven model
- CFT1946 demonstrates that a TPD approach could be developed to address mBRAF Class II and Class III driven cancers
- CFT1946's preclinical profile warrants clinical evaluation in patients with both BRAF-V600X–driven cancers and inhibitor-resistant BRAF-V600X–driven cancers

Acknowledgments

Thank you to the C4T scientists & our CRO partners who made this work possible

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