BARCELONA 2024 ESMO congress

Preliminary Results from a Phase 1 Study of CFT1946, a Novel BiDAC™ Degrader in Mutant BRAF V600 Solid Tumors

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DECLARATION OF INTERESTS

Maria Vieito Villar

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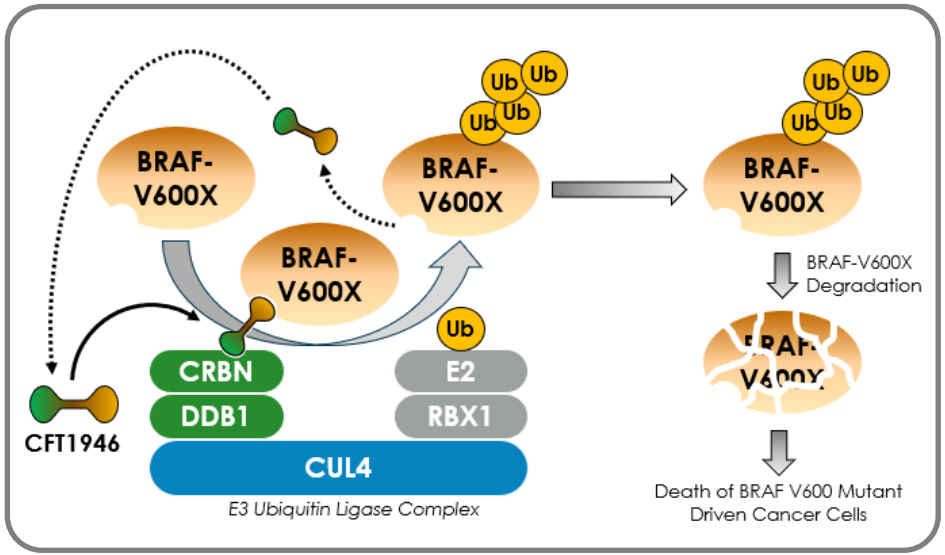
CFT1946 Targeted Degradation of BRAF V600X

Degradation of BRAF V600X with CFT1946



CFT1946 exploits cells' own proteosome machinery for targeted degradation of oncogenic BRAF V600X

Potential advantages of CFT1946, a novel, oral, BRAF V600X BiDAC™ degrader:

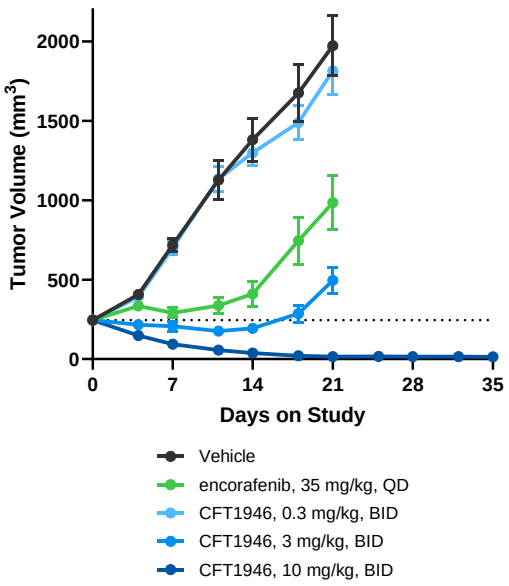
- ✓ Prevents BRAF V600 mutant **mono/heterodimer formation**[1]
- ✓ **Avoids paradoxical activation** seen with approved inhibitors[1]
- ✓ **Addresses MAPK pathway alterations** resulting from BRAF inhibitor resistance (e.g., BRAF splice variants, BRAF amplification)[1]
- ✓ **Specifically targets BRAF V600X mutations**, which includes BRAF V600 mutations beyond BRAF V600E
- ✓ Spares wild-type BRAF[1], likely **avoiding AEs associated with inhibition of wild-type BRAF**
- ✓ Enables deep elimination of mutant BRAF signaling to **create potential durable responses** through degrader molecule recycling and catalytic effect

[1]Kreger B et al. Abstract 1658, AACR 2024
Adverse event (AE); BRAF inhibitor (BRAFi); Mitogen-activated protein kinase (MAPK)

CFT1946 Shows Activity Alone and in Combination in Pre-Clinical Models Describing Tumor Types Driven by BRAF V600X

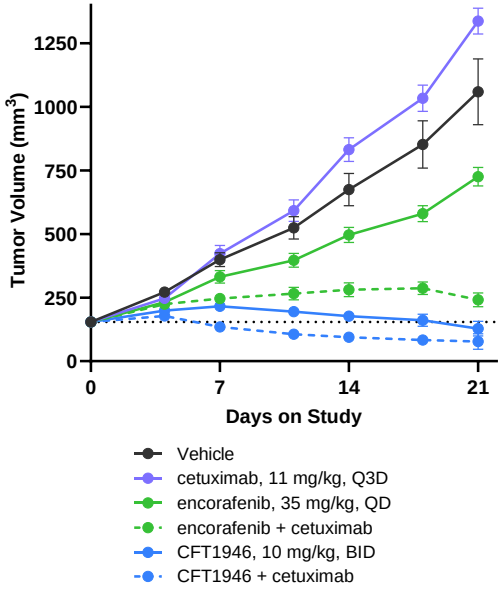
MELANOMA

A375, BRAF V600E (CDX)



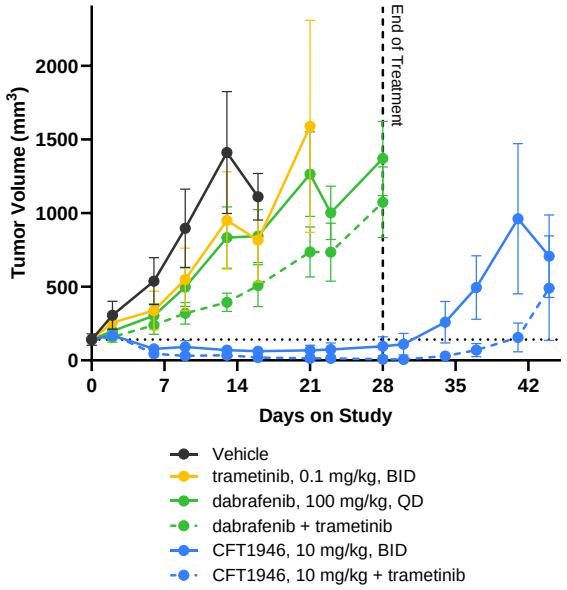
CRC

HT-29, BRAF V600E (CDX)



NSCLC

BRAF V600E (PDX)



[1] Kreger B et al. Abstract 1658, AACR 2024

Twice daily (BID); Cell line-derived xenograft (CDX); Colorectal cancer (CRC); Non-small cell lung cancer (NSCLC); Patient-derived xenograft (PDX); Once daily (QD)

CFT1946-1101: Study Design and Study Status

Phase 1 trial in BRAF V600 Mutant Solid Tumors

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KEY INCLUSION CRITERIA[1]

- BRAF V600 mutant measurable solid tumors with ≥1 prior line of SoC therapy for unresectable locally advanced or metastatic disease
- Melanoma patients must have received prior BRAFi therapy
- CRC, ATC, NSCLC or other non-CNS solid tumors: prior BRAFi therapy unless not available per SoC
- No CNS involvement (primary tumor or metastatic disease), except if clinically stable

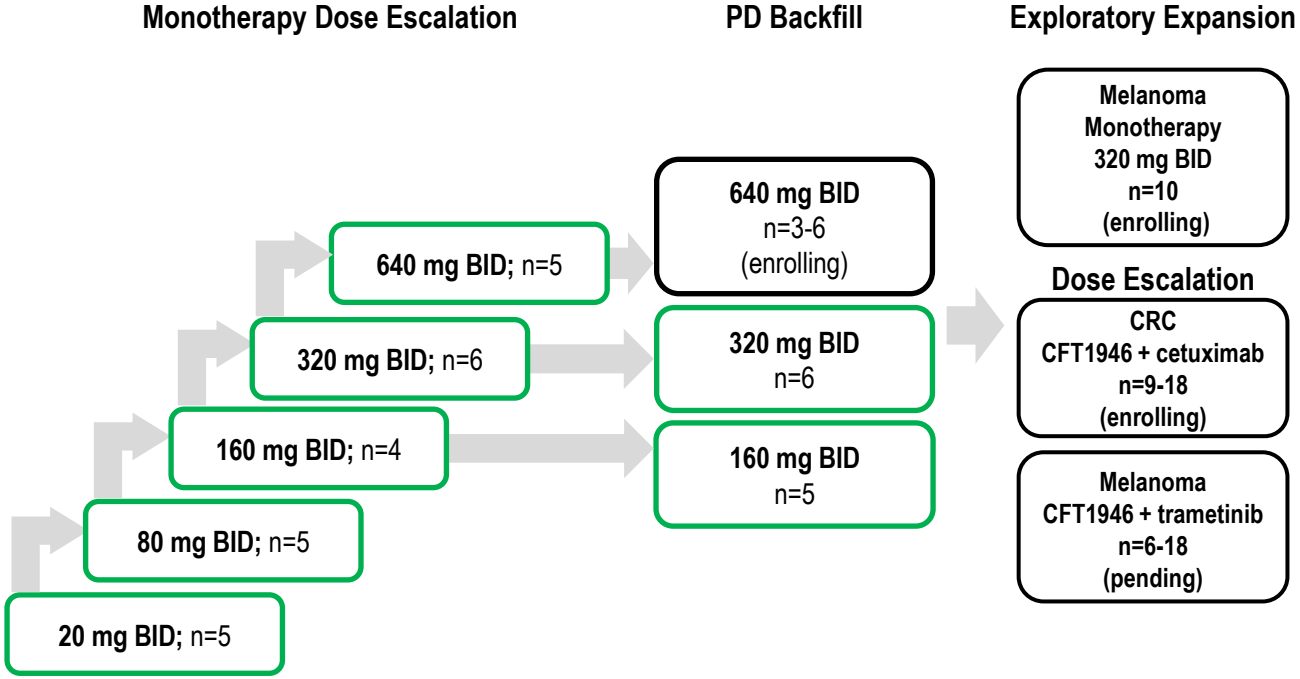
Study Endpoints

PRIMARY

- Safety and tolerability
- Determine RP2D

SECONDARY

- Estimate anti-tumor activity
- Assess PK and PD



[1]EU CT No: 2022-501618-70, NCT05668585

Anaplastic thyroid cancer (ATC); Twice daily (BID); BRAF inhibitor (BRAFi); Central nervous system (CNS); Colorectal cancer (CRC); Non-small cell lung cancer (NSCLC); Pharmacodynamics (PD); Pharmacokinetics (PK); Recommended phase 2 dose (RP2D); Standard of care (SoC). Cohorts with green outline are included in the 19 July 2024 data cut off.

CFT1946-1101: Baseline Characteristics and Disease History

BRAFi-Pretreated Population with Advanced or Metastatic BRAF V600 Mutant Solid Tumors

Baseline Characteristics	Patients Dosed (N = 36)
Age, years	
Mean	54
Median (range)	55 (25-77)
Sex, n (%)	
Male	19 (53%)
Female	17 (47%)
ECOG PS	
0	18 (50%)
1	18 (50%)
Race, n (%)	
White	33 (92%)
Asian	1 (3%)
Not Reported	2 (6%)
Ethnicity, n (%)	
Not Hispanic or Latino	29 (81%)
Not reported	6 (17%)
Unknown	1 (3%)

Disease History	Patients Dosed (N = 36)
Solid Tumor Type, n (%)	
Melanoma	14 (39%)
CRC	14 (39%)
NSCLC	2 (6%)
Other*	6 (17%)
BRAF mutation status at diagnosis, n (%)	
V600E	33 (92%)
V600K	2 (6%)
V600R	1 (3%)
Disease stage at study entry, n (%)	
III	2 (6%)
IV	32 (89%)
Unknown	2 (6%)
Median prior lines of therapy, n (range)	3 (2-7)
Prior BRAFi therapy, n (%)	35 (97%)
Prior Cancer Surgeries, n (%)	24 (67%)
Prior Immunotherapy, n (%)	22 (61%)
Prior Radiotherapy, n (%)	17 (47%)

EU CT No: 2022-501618-70, NCT05668585

BRAF inhibitor (BRAFi); Colorectal cancer (CRC); Eastern cooperative oncology group performance status (ECOG PS); Non-small cell lung cancer (NSCLC). Percentages may not add up to 100% due to rounding. *Other tumor types include cholangiocarcinoma, pancreatic carcinoma, papillary thyroid carcinoma, and small intestine cancer.

Data cut off 19 Jul 2024

CFT1946 Phase 1 Monotherapy Safety

CFT1946 Monotherapy is Well Tolerated with No DLTs Observed

	20 mg BID (N = 5)	80 mg BID (N = 5)	160 mg BID (N = 9)	320 mg BID (N = 12)	640 mg BID (N = 5)	Total (N = 36)
Subjects with Any TEAEs, n (%)	4 (80)	4 (80)	7 (78)	11 (92)	5 (100)	31 (86)
Grade ≥ 3 TEAEs, n (%)	3 (60)	2 (40)	3 (33)	3 (25)	3 (60)	14 (39)
TEAEs related to CFT1946, n (%)	0	1 (20)	3 (33)	9 (75)	3 (60)	16 (44)
Grade ≥ 3 TEAEs related to CFT1946, n (%)	0	0	0	0	1 (20)*	1 (3)
Any TESAEs, n (%)	1 (20)	3 (60)	1 (11)	2 (17)	2 (40)	9 (25)
TESAEs related to CFT1946, n (%)	0	0	0	0	0	0
TEAEs leading to CFT1946 Discontinuation, n (%)	1 (20)	1 (20)	1 (11)	0	0	3 (8)
TEAEs leading to CFT1946 Interruption, n (%)	1 (20)	2 (40)	2 (22)	2 (17)	2 (40)	9 (25)
TEAEs leading to CFT1946 Reduction, n (%)	0	0	1 (11)	0	0	1 (3)
TEAEs leading to Death, n (%)	0	1 (20)#	0	0	0	1 (3)
TRAEs leading to CFT1946 discontinuation, interruption, reduction or death, n (%)	0	0	0	0	0	0
Subjects with DLTs, n (%)	0	0	0	0	0	0

Dose limiting toxicities (DLT); Treatment-emergent adverse event (TEAE); Treatment-related adverse event (TRAE); Treatment-emergent serious adverse event (TRSAE)
*Grade 3 hypertension, possibly related to CFT1946 with no dose change; #cerebrovascular accident leading to death - not related to CFT1946

CFT1946 Phase 1 Monotherapy Safety

Majority of TEAEs Observed were Mild to Moderate

Summary of TEAEs ≥ 10% of 36 subjects treated with CFT1946

Preferred Term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Total (N=36)
Subjects with any TEAEs	3 (8)	14 (39)	11 (31)	2 (6)	1 (3)#	31 (86)
Anemia	1 (3)	4 (11)	2 (6)	0	0	7 (19)
Abdominal Pain	4 (11)	1 (3)	2 (6)	0	0	7 (19)
Peripheral edema	5 (14)	1 (3)	0	0	0	6 (17)
Pyrexia	4 (11)	2 (6)	0	0	0	6 (17)
Fatigue	1 (3)	4 (11)	0	0	0	5 (14)
Lipase increased	3 (8)	2 (6)	0	0	0	5 (14)
Back pain	1 (3)	2 (6)	1 (3)	0	0	4 (11)
Hypophosphatemia	1 (3)	3 (8)	0	0	0	4 (11)
Constipation	1(3)	2 (6)	0	0	0	4 (11)*

CTCAE v5.0 grading criteria; *Grade missing for 1 subject with TEAE; #Subject had fatal cerebrovascular accident not related to CFT1946
Data cut off 19 Jul 2024

Dose-limiting toxicities (DLT); Treatment-emergent adverse event (TEAE); Serious adverse event (SAE); Treatment-related adverse event (TRAE)

- No DLTs
- No treatment-related SAEs
- No treatment interruptions or discontinuations due to TRAE
- No Grade ≥ 3 treatment-related cutaneous AEs
- No new primary malignancies

Initial CFT1946 PK/PD Data Supports Proof of Mechanism

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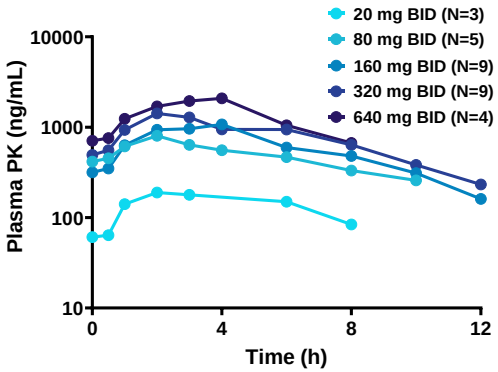
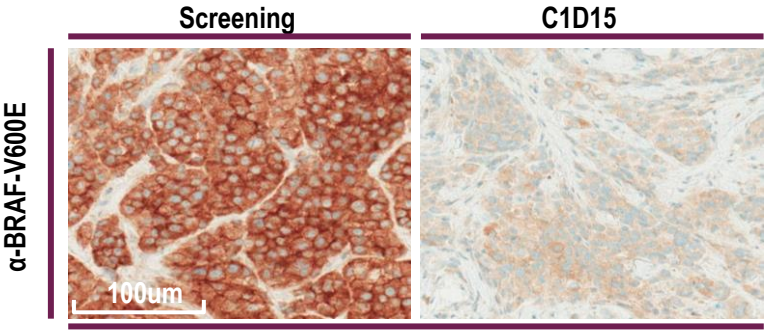
CFT1946 C1D15 Pharmacokinetics

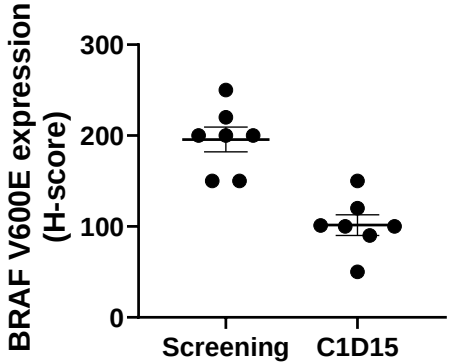


BRAF V600E Degradation at 320 mg (Paired Biopsy)



Immunohistochemistry (IHC) on paired biopsy of a melanoma patient dosed at 320 mg

CFT1946 BRAF V600E Degradation by IHC



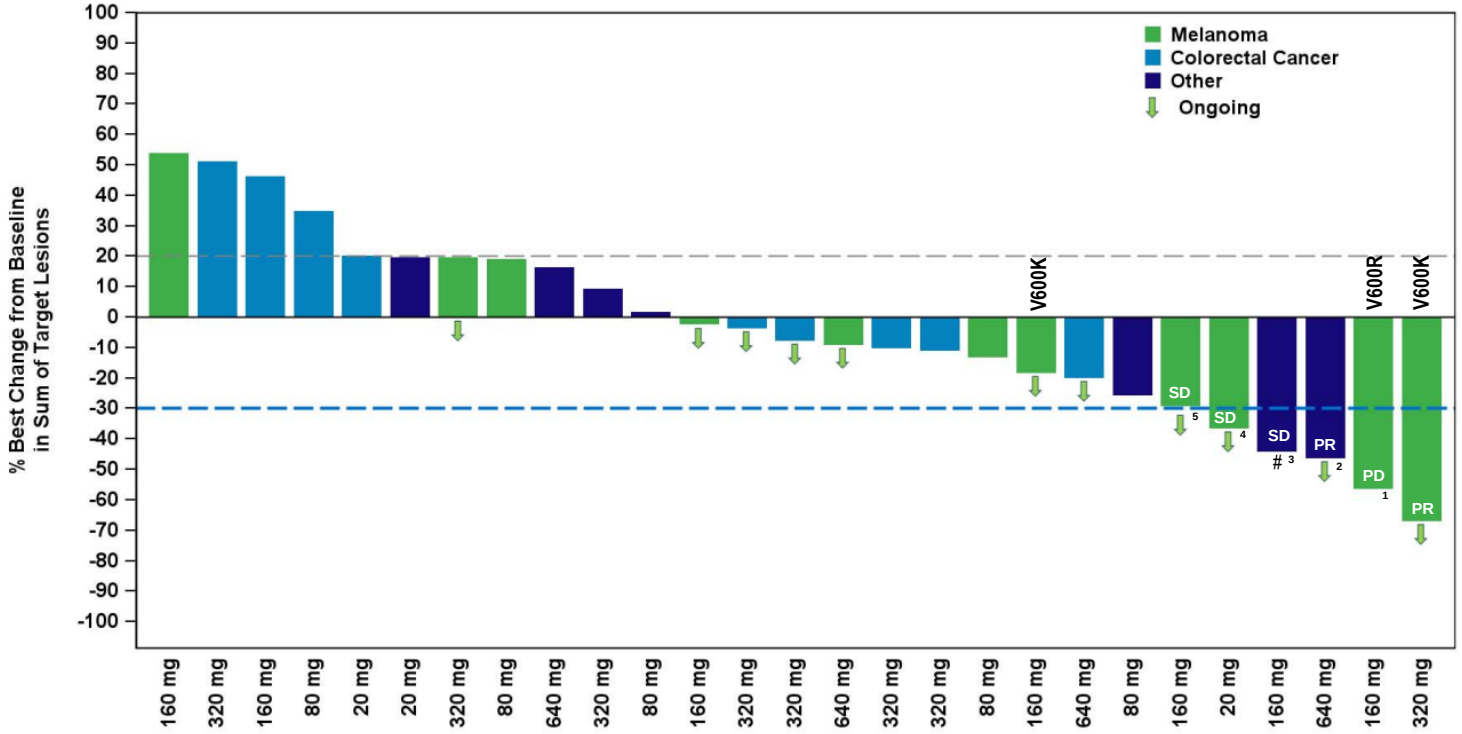
BRAF V600E degradation determined by H-score in paired biopsies at different dose levels (n=1, 80 mg; n=3, 160 mg; n=3, 320 mg)

- CFT1946 exhibited dose-dependent bioavailability
- Proof of mechanism supported by BRAF V600E degradation as measured by change in H-score of paired biopsies from different tumor types

Cycle 1 Day 15(C1D15)

CFT1946 Phase 1 Monotherapy Anti-Tumor Activity

Early Evidence of Anti-Tumor Activity by RECIST 1.1



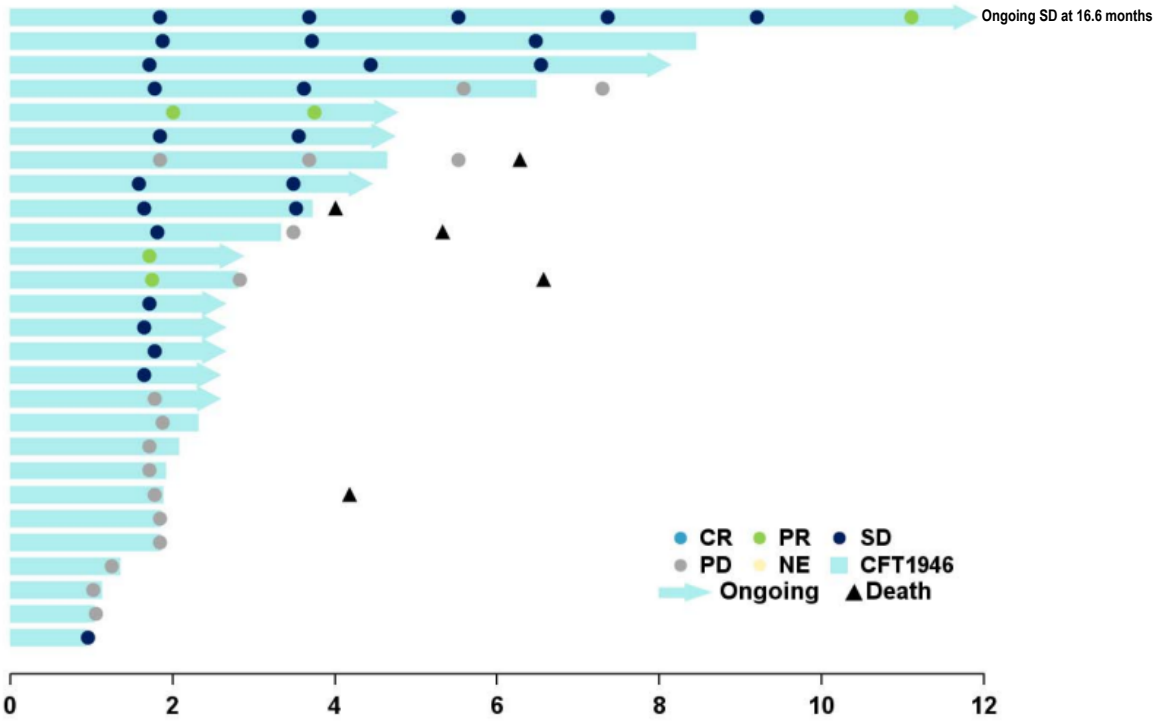
*Other tumor types include cholangiocarcinoma, non-small cell lung cancer, pancreatic carcinoma, and small intestine cancer; BRAF V600 mutation is V600E unless otherwise specified; #This subject did not receive prior BRAF inhibitor therapy, all other subjects received prior BRAF inhibitor therapy. Dotted lines represent partial response (-30%, blue line) and progressive disease (20%, gray line) per RECIST v1.1. Data cut off: 19 Jul 2024

[1] Subject on 160 mg BID had 56.2% reduction on target lesion, progression on non-target lesion and a new lesion, hence assessed as PD for overall response; [2] Subject on 640 mg BID had PR confirmed after data cut off; [3] Subject on 160 mg BID had PD following first PR (-43.9%), hence assessed as SD for overall response; [4] Subject on 20 mg BID had unconfirmed PR, hence assessed as SD for overall response; [5] Subject on 160 mg BID had -29% reduction on target lesion, hence assessed as SD

CFT1946 Phase 1 Monotherapy Anti-Tumor Activity

Early Evidence of Anti-Tumor Activity

First Dose (mg)	Cancer Type	BOR of BRAFi #	Latest Prior Therapy	Prior Lines
20	M	CR	BRAF	2
80	N	N/A	Chemo	3
160	M	PR	BRAF	4
80	M	N/A	BRAF	2
320	M	SD	BRAF	4
160	M	CR	BRAF	4
160	M	PD	I/O	5
160	M	SD	BRAF	3
80	N	SD	I/O	2
320	C	PD	I/O	7
640 *	O	PR	Chemo	4
160	O	N/A	Chemo	2
640	M	PD	BRAF	2
640	C	SD	BRAF	2
320	C	SD	Chemo	3
320	C	SD	BRAF	7
320	M	PR	BRAF	2
80	M	CR	BRAF	2
320	C	PR	Chemo	4
160	M	CR	BRAF	3
320	O	SD	Chemo	4
20	C	SD	Chemo	7
160	C	SD	Chemo	2
20	O	PD	Chemo	6
80	C	PD	BRAF	3
320	C	SD	BRAF	2
640	O	PR	Chemo	4



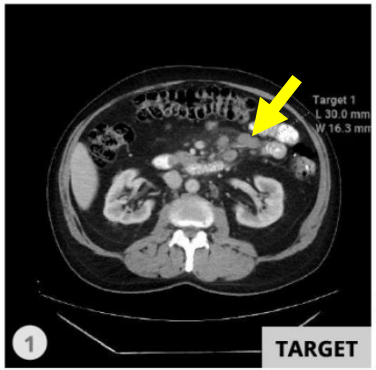
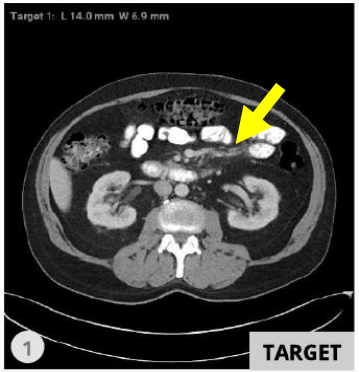
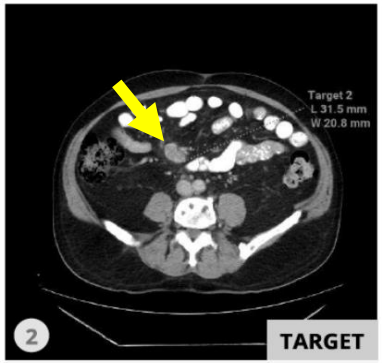
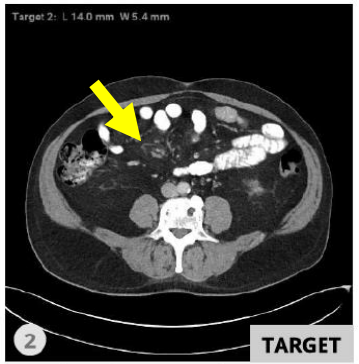
*Subject had confirmed PR after data cut off, Other tumor types include cholangiocarcinoma, non-small cell lung cancer, pancreatic carcinoma, and small intestine cancer; #As reported by sites per medical records and N/A indicates data not available; Data cut off: 19 Jul 2024; Best overall response (BOR); Colorectal cancer (C); Complete response (CR); Melanoma (M); Non-small cell lung cancer (N); Not evaluable (NE); Other (O); Progressive disease (PD); Partial response (PR); Stable disease (SD)

Case Study: Patient with BRAF V600K Melanoma

Early Evidence of Anti-Tumor Activity

- 72-year-old male with BRAF V600K Stage IV Melanoma
- Initial diagnosis Stage II in 2019
- Prior surgery and four lines of anti-neoplastic therapy:
  - Surgery: Wide local excision right posterior auricular melanoma (2019)
  - 1L: Pembrolizumab Apr 2020-July 2020: PD
  - 2L: Nivolumab and ipilimumab Aug 2020-Oct 2020: PD
  - 3L: Dabrafenib and trametinib Nov 2020-Sep 2021: SD
  - 4L: Pembrolizumab Sep 2021-Jan 2024
    Dabrafenib and trametinib Sep 2021-Nov 2023:SD
- Enrolled in CFT1946 320 mg BID cohort in Feb 2024
- Change in target lesions:
  - at Cycle 3: 64% decrease from baseline
  - at Cycle 5: 67% decrease from baseline
- Overall Response per RECIST 1.1:
  - at Cycle 3: PR
  - at Cycle 5: PR
- CFT1946 treatment ongoing in Cycle 7

Twice daily (BID); Progressive disease (PD); Partial response (PR); Stable disease (SD)

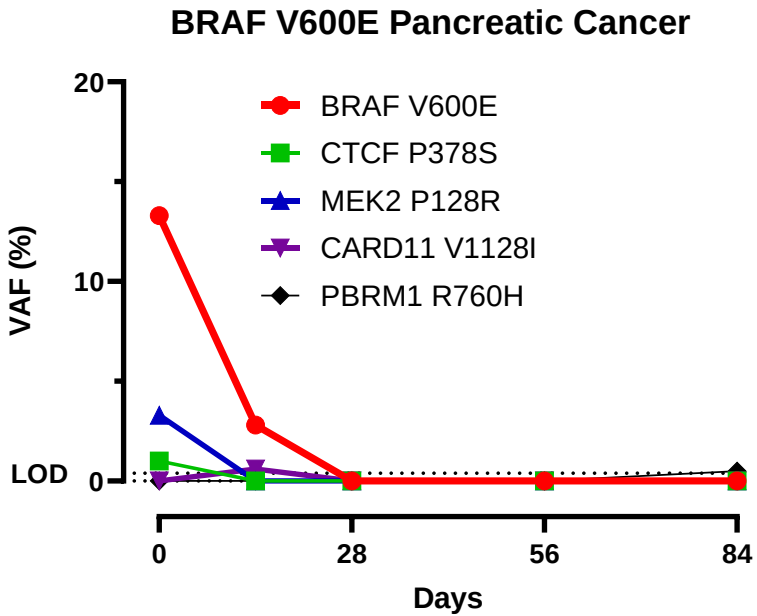
Baseline	Cycle 5 (67%↓)
	
Lymph Node Mesenteric 16.3 x 30.0 mm (S:7, I:31)	**Lymph Node Mesenteric** 6.9 x 14.0 mm (S:1, I:34)
	
Lymph Node Mesenteric 20.8 x 31.5 mm (S:7, I:43)	**Lymph Node Mesenteric** 5.4 x 14.0 mm (S:1, I:44)

Case Study: Patient with BRAF V600E Pancreatic Cancer

Early Evidence of Anti-Tumor Activity

- 63-year-old male BRAF V600E Pancreatic carcinoma (w/ two liver metastases)
- Initial diagnosis Stage IV in 2021
- Four lines of prior anti-neoplastic therapy:
  - 1L: FOLFOX Jun 2021-Oct 2022: PR
    Capecitabine (maintenance) Dec 2021- Oct 2022
  - 2L: Dabrafenib and trametinib Nov 2022-Oct 2023: PR
  - 3L: FOLFIRI Nov 2023-Feb 2024: PR
  - 4L: Abraxane and gemcitabine Mar 2024-Apr 2024: PD
- Enrolled in CFT1946 640 mg BID cohort in Apr 2024
- Change in target lesion:
  - at Cycle 3: 46% decrease from baseline in SoD
    40% and 49% reduction in liver metastases
  - at Cycle 5: 55% decrease from baseline in SoD*
- Overall Response per RECIST 1.1:
  - at Cycle 3: PR
  - at Cycle 5: PR*
- CFT1946 treatment ongoing in Cycle 5

Decrease in BRAF V600E allele fraction measured in ctDNA using WES



*Occurred after Data cutoff of 19 Jul 2024

Twice daily (BID); Limit of detection (LOD), Progressive disease (PD); Partial response (PR); Circulating tumor DNA (ctDNA); Sum of diameters (SoD); Whole exome sequencing (WES)

Conclusions

Encouraging Results from Ongoing CFT1946 Phase 1 Monotherapy Study

- **Single agent CFT1946 has a well-tolerated safety profile**
  - Only one Grade ≥3 treatment-related adverse event
  - No drug interruptions, reductions, or discontinuations due to treatment-related adverse events
  - No Grade ≥3 wild-type adverse events common to BRAFi

- **CFT1946 has demonstrated preliminary proof of mechanism**
  - Increased drug exposure observed with dose escalation
  - Degradation of BRAF V600E protein observed in all post-treatment biopsies

- **Evidence of anti-tumor activity observed in patients treated with CFT1946 who progressed on BRAFi**
  - 8/11 patients with melanoma demonstrated tumor reduction by RECIST 1.1 criteria
  - Activity seen in patients with BRAF V600E/K/R mutations

- **These data support the continued development of CFT1946 as a novel approach to treat BRAF V600X solid tumors**
  - Currently enrolling CRC patients in dose escalation safety cohorts in combination with cetuximab
  - Currently enrolling melanoma patients in monotherapy exploratory expansion

BRAF inhibitor (BRAFi); Colorectal cancer (CRC)

Acknowledgments

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- All authors contributed to and approved the presentation
- For questions, please reach out: clinicaltrials@c4therapeutics.com