C4 Therapeutics

Preliminary Monotherapy Data from the Ongoing Phase 1 Trial of CFT1946, a BRAF V600 Mutant Degrader, for Solid Tumors

Len Reyno, MD
Chief Medical Officer

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Advancing a Broad Pipeline of Novel Degrader Medicines

Program	Target	Indications	Discovery	Preclinical	Early Phase Development	Late Phase Development	Rights
Cemsidomide	**IKZF1/3**	Multiple Myeloma & Non-Hodgkin's Lymphoma					
CFT1946	**BRAF V600 Mutant**	V600 Mutant Cancers					
CFT8919[1]	**EGFR L858R**	Non-Small Cell Lung Cancer					BETTA PHARMACEUTICALS
Discovery Stage Programs		Various Cancers					
Collaboration Programs		Autoimmune & Cancer	*2 targets*				Roche
		Cancer	*2 targets*				Merck KGaA Darmstadt, Germany
		Cancer	*1 target*				MERCK
		Autoimmune & Neurological	*2 targets*				Biogen[2]

[1]License and collaboration agreement with Betta Pharmaceuticals for development and commercialization in Greater China; [2]Delivered development candidates to Biogen in Q1 2024 and Q3 2024

CFT1946 Monotherapy Phase 1 Data Demonstrate Proof of Mechanism and Provide Early Evidence of Proof of Degrader Concept

Proof of Mechanism

- **Well tolerated** and **highly selective degrader**, results in **no Grade ≥ 3 cutaneous adverse events**, which are commonly seen with wild-type BRAF inhibition
- **Increased drug exposure** observed with dose escalation
- **Degraded BRAF V600E** protein in all available post-treatment biopsies collected to date

Proof of Degrader Concept

- Early evidence of monotherapy **anti-tumor activity** in patients who progressed after treatment with BRAF inhibitors
- Anti-tumor activity seen **across multiple BRAF V600 mutants**
- Degradation of mutant BRAF protein overcomes resistance mechanisms and results in potentially **deeper** and more **durable responses than BRAF inhibitors**

CFT1946 has the potential to **disrupt the treatment landscape** and become an **important option for patients** with **BRAF V600 mutant driven solid tumors**

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Limitations of Approved BRAF Inhibitors

- **Durable and deep responses are often not seen** in melanoma, NSCLC and CRC patients, due to **MAPK pathway resistance**

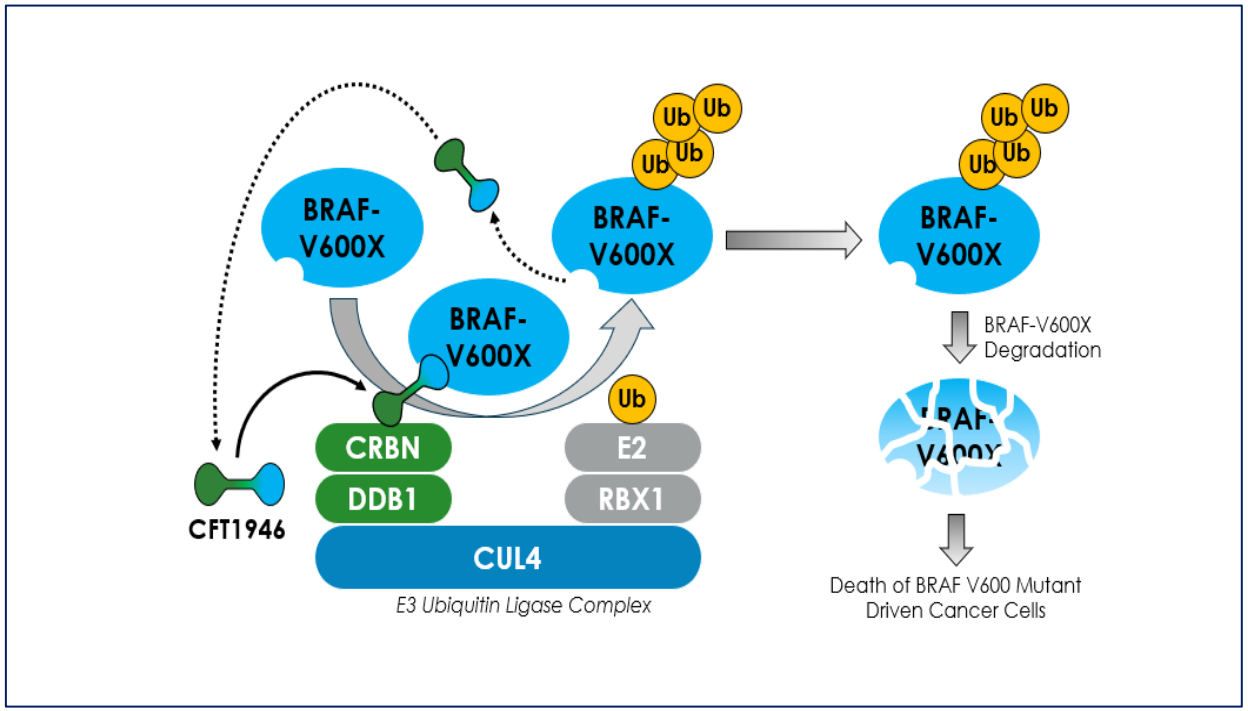
Adapted from Wagle et al, J Clin Oncol, 2011

- **Poor tolerability**, such as high-rates of cutaneous adverse events
- Often **combined with a MEK inhibitor** to **enhance both efficacy and minimize side effects resulting from paradoxical activation** by BRAF inhibitors
- **Limited approved treatment options** for BRAF V600 **patients who do not have a BRAF V600E or V600K mutation**

[1]Evaluate Pharma 2023
Colorectal cancer (CRC); Non-small cell lung cancer (NSCLC)

Mechanism of Action: CFT1946 Mediated Degradation of BRAF V600 Mutants

Degradation of BRAF V600 Mutants with CFT1946



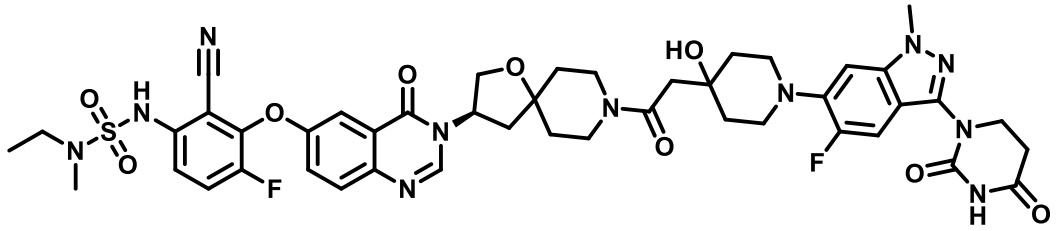
CFT1946 exploits cells' own proteosome machinery for targeted degradation of oncogenic BRAF V600 mutant

Potential Advantages of CFT1946, a Novel, Oral, BRAF V600 Mutant 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 V600 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); Mitogen-activated protein kinase (MAPK)

CFT1946 Displays A Balanced Preclinical Profile

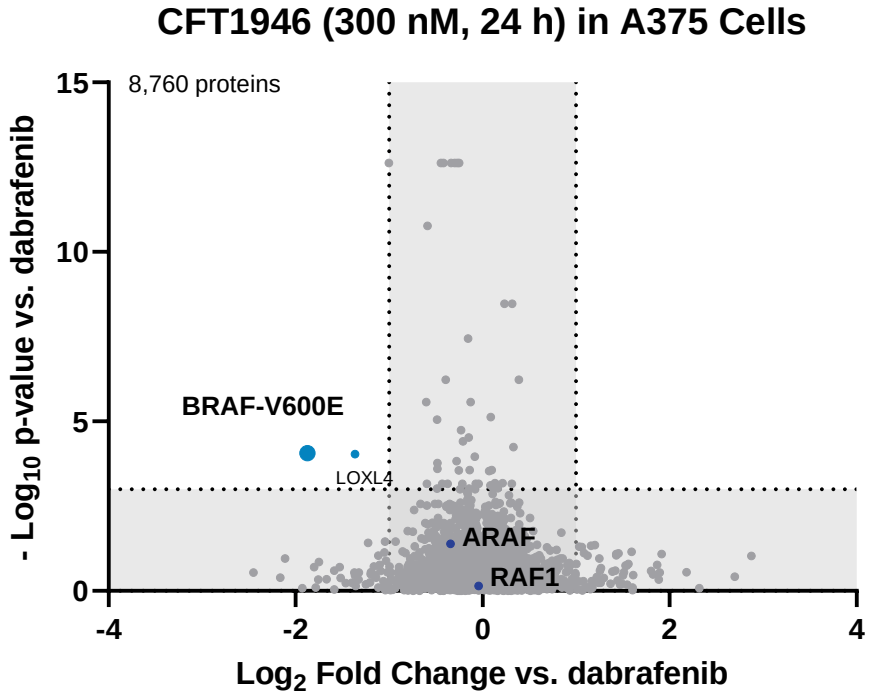


CFT1946

BRAF-V600E DC_{50} / E_{max} [24 h]	**14 nM / 26%**
A375 $NRAS^{Q61K}$ * pERK 1 h [nM]	**42**
A375 $NRAS^{Q61K}$ * GI_{50} 96 h [nM]	**150**
HepG2 GI_{50} [μM]	**>10**
CL_{obs} Mouse / Rat [mL/min/kg]	**0.8 / 0.5**
F % Mouse / Rat	**89 / 89**
Degradation Selectivity	**Exquisite for BRAF-V600E**

* An engineered disease-relevant BRAF inhibitor resistant cell line

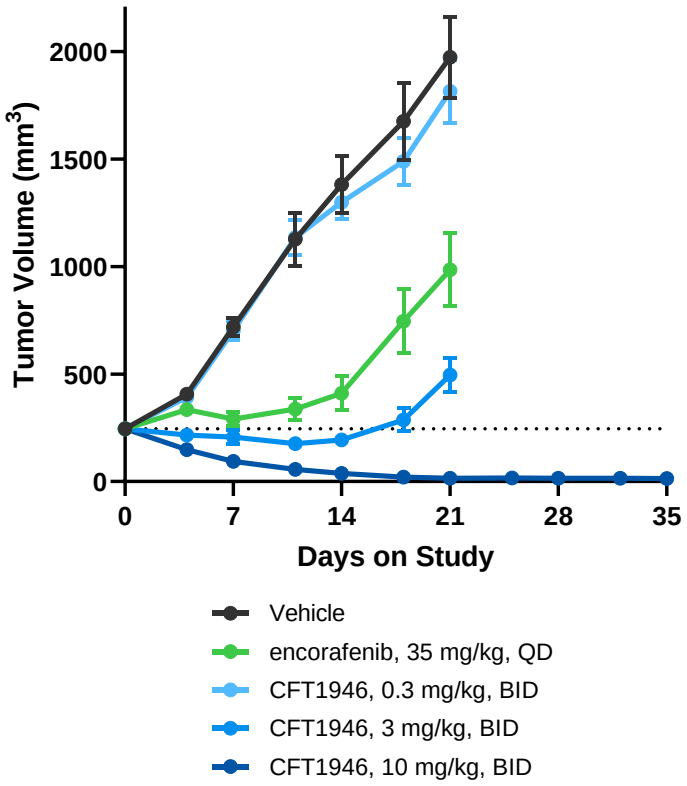
Proteome Profiling Demonstrates Selectivity of CFT1946 for BRAF-V600E



CFT1946 Shows Activity Alone and in Combination in BRAF V600X-Driven Pre-Clinical Models

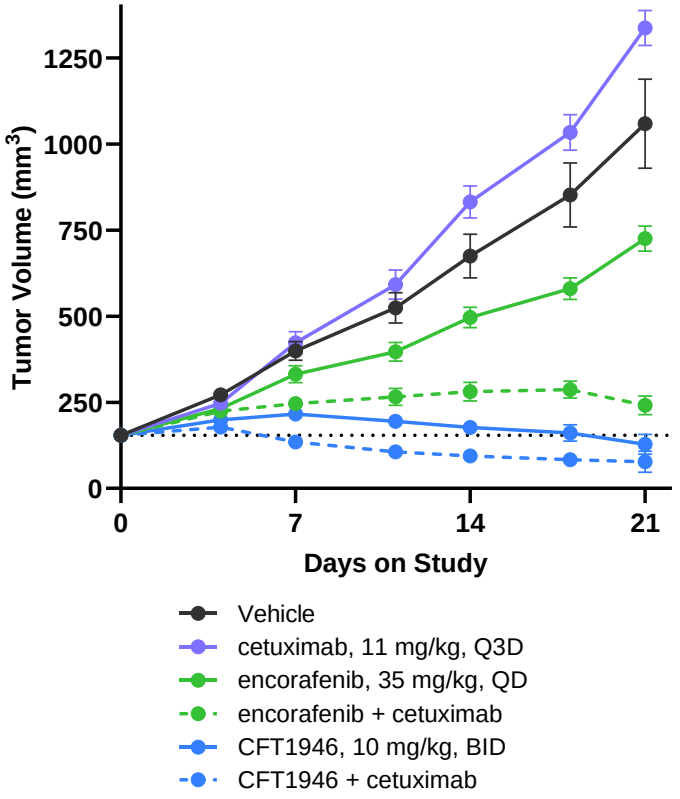
MELANOMA

A375, BRAF V600E (CDX)



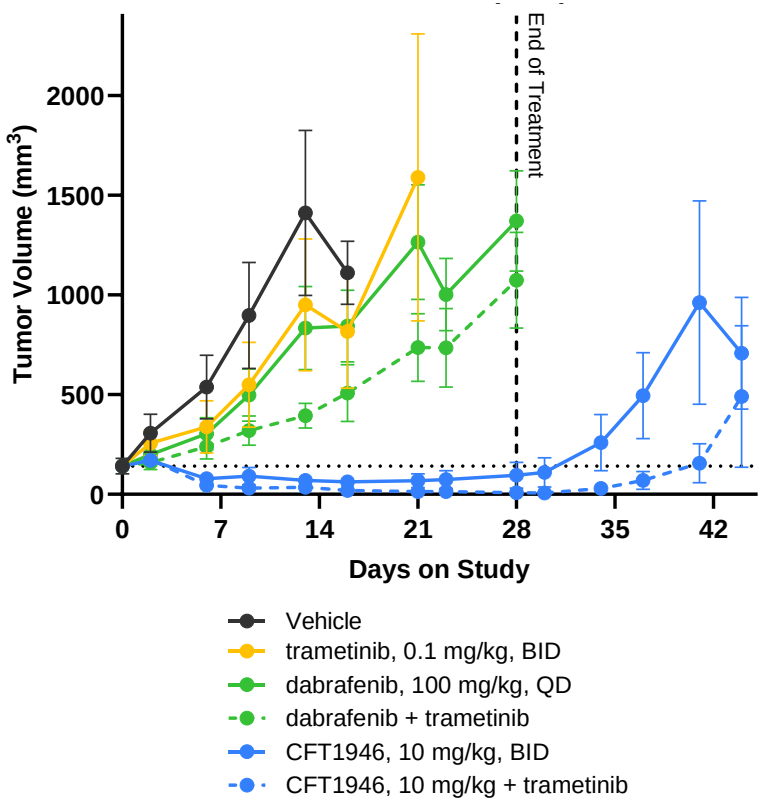
CRC

HT-29, BRAF V600E (CDX)



NSCLC

BRAF V600E (PDX)

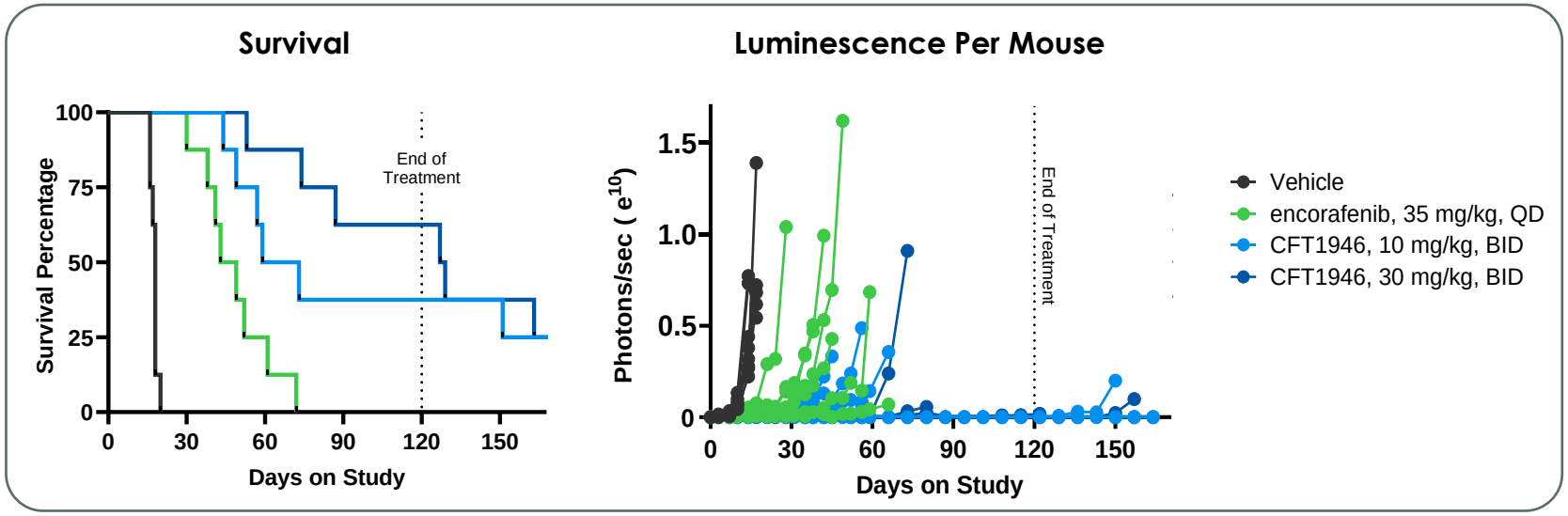


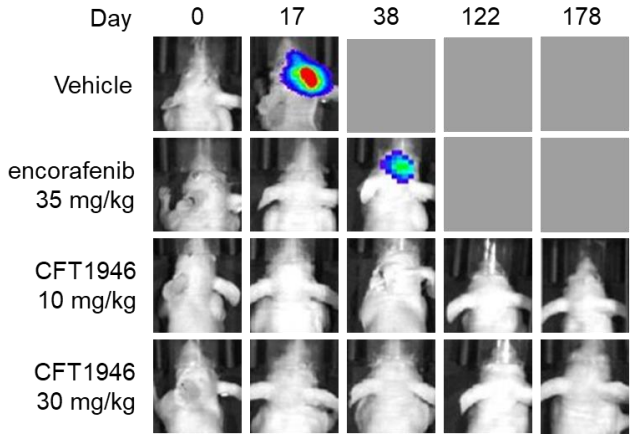
Kreger et al. 2024 AACR

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

$Kp_{U,U}$ Results Demonstrate the Ability of CFT1946 to Cross the Blood Brain Barrier and Support Activity in Preclinical Intercranial Metastatic Models

A375 BRAF V600E-Luc Intracranial Model





$Kp_{U,U}$ values for CFT1946 were experimentally measured using independent methods in two different species

The CFT1946 values of $Kp_{U,U}$ range from 0.34 – 0.88

These results demonstrate the ability of CFT1946 to cross the blood brain barrier and highlight the potential for drug delivery to CNS tumors

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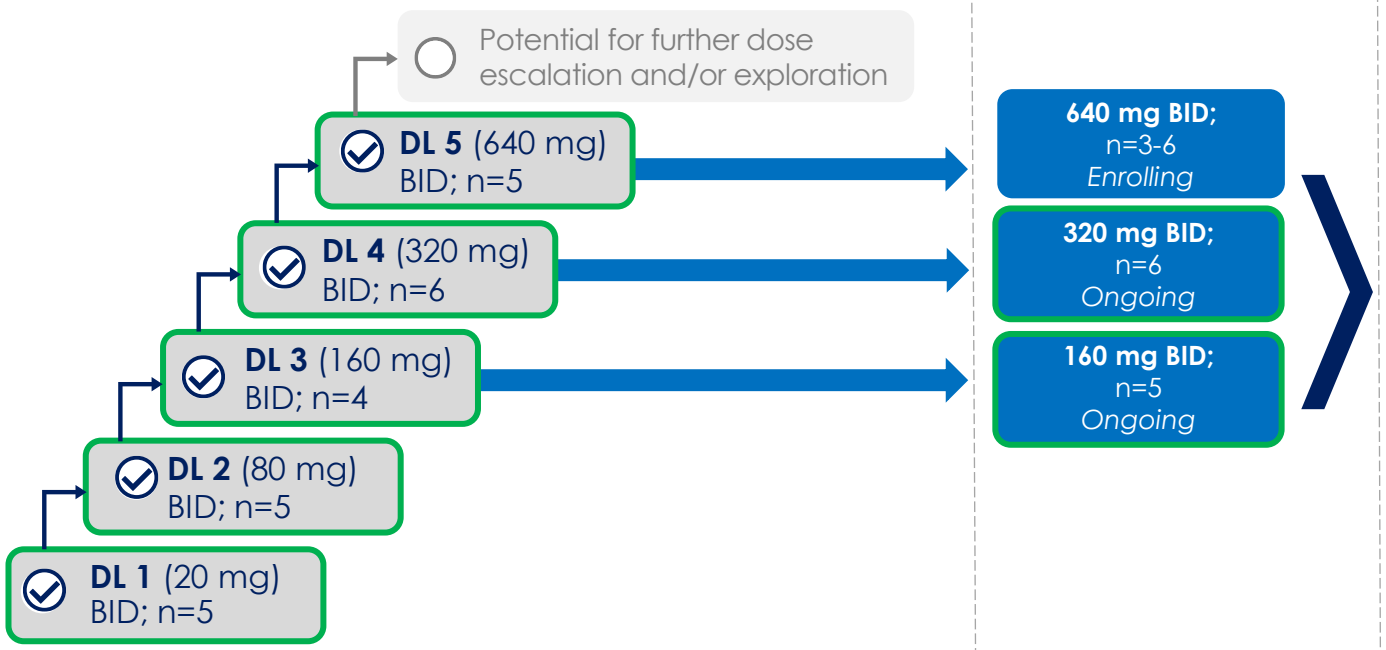
CFT1946 Phase 1/2 Dose Escalation Trial Continues to Progress Across BRAF V600 Mutant Driven Solid Tumors

KEY INCLUSION CRITERIA[1]

- Evidence of BRAF V600 mutation obtained from tumor tissue or liquid biopsy
- 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 BRAF inhibitor therapy
- CRC, ATC, NSCLC or other non-CNS solid tumors: prior BRAF inhibitor therapy unless not available per SoC
- No patient with CNS involvement (primary tumor or metastatic disease), except if clinically stable

MONOTHERAPY DOSE ESCALATION



PK, PD, ANTI-TUMOR ACTIVITY EVALUATION[2]

- **640 mg BID;** n=3-6 *Enrolling*
- **320 mg BID;** n=6 *Ongoing*
- **160 mg BID;** n=5 *Ongoing*

PRIMARY ENDPOINTS

- Safety and tolerability
- Determine RP2D/MTD

SECONDARY ENDPOINTS

- Estimate anti-tumor activity
- Assess PK and PD

Exploratory Expansion: CFT1946 monotherapy in melanoma 640 mg BID *Enrolling*

Exploratory Expansion: CFT1946 monotherapy in melanoma 320 mg BID *Ongoing*

Phase 1B: CFT1946 in combination with cetuximab in CRC 160 mg BID *Enrolling*

Phase 1B: CFT1946 in combination with trametinib for melanoma and NSCLC *Pending*

[1]NCT05668585. www.clinicaltrials.gov. Accessed 01/09/2024; [2]Evaluating additional patients for pharmacodynamic assessment pre- and post-drug exposure biopsies
Colorectal cancer (CRC); Anaplastic thyroid cancer (ATC); Non-small cell lung cancer (NSCLC); Central nervous system (CNS); Standard of care (SoC); Dose Level (DL); Twice daily (BID); Recommended Phase 2 dose (RP2D); Maximum tolerated dose (MTD); Pharmacokinetic (PK); Pharmacodynamic (PD)

All Patients Enrolled Have Advanced or Metastatic BRAF V600 Mutant Driven 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%)

*Other tumor types include cholangiocarcinoma, pancreatic carcinoma, papillary thyroid carcinoma, and small intestine cancer
Anaplastic thyroid cancer (ATC); Colorectal cancer (CRC); Eastern cooperative oncology group performance status (ECOG PS); Non-small cell lung cancer (NSCLC); BRAF inhibitor (BRAFi)
Percentages may not add up to 100% due to rounding
Source: ESMO Congress 2024; C4T data on file as of 7/19/2024

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No Discontinuations, Dose Interruptions or Reductions Due to CFT1946 Treatment-related Adverse Events

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

*Grade 3 hypertension possibly related to CFT1946 with no dose change #Adverse event of cerebrovascular accident leading to death, which was not related to CFT1946
Treatment-emergent adverse events (TEAEs); Treatment-emergent serious adverse event (TESAEs); Treatment-related adverse event (TRAE); Dose limiting toxicities (DLTs); Twice daily (BID)
Source: ESMO Congress 2024; C4T data as of 07/19/2024

Well Tolerated Monotherapy Safety Profile, Consistent with BRAF V600 Mutant Selectivity Design of CFT1946

- No DLTs
- Majority of TEAEs observed were mild to moderate
- No treatment-related SAEs
- No Grade ≥ 3 treatment-related cutaneous adverse events
- No new primary malignancies

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

Preferred Term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Total (n=36) n (%)
Patients 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)*

^A patient is only counted once with the highest severity and preferred term
#Patient had a fatal cerebrovascular accident not related to CFT1946
CTCAE v5.0 grading criteria; *Grade missing for 1 patient with TEAE

Serious adverse events (SAEs); Dose limiting toxicities (DLTs); Treatment-related adverse events (TRAES); Treatment-emergent adverse events (TEAEs)

Source: ESMO Congress 2024; C4T data as of 7/19/2024

No Grade ≥ 3 Cutaneous Adverse Events, Consistent with BRAF Mutant Selectivity Design of CFT1946

Preferred Term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Hyperkeratosis	0	0	0	0	0
Alopecia	0	0	0	0	0
PPES	0	0	0	0	0
Rash#	2 (6)	1 (3)	0	0	0
Dry skin	2 (6)	0	0	0	0
Pruritus	1 (3)	1 (3)	0	0	0
Photosensitivity reaction	1 (3)	0	0	0	0
Acne	1 (3)	0	0	0	0
Dermatitis acneiform	0	1 (3)	0	0	0
Ephelides	1 (3)	0	0	0	0

#Includes rash, rash maculopapular, and skin lesion
Palmar-plantar erythrodysesthesia syndrome (PPES)
Source: C4T data on file as of 07/19/2024

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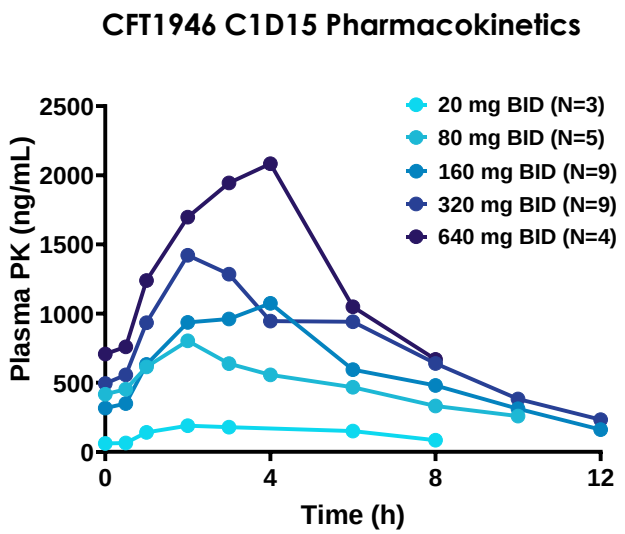
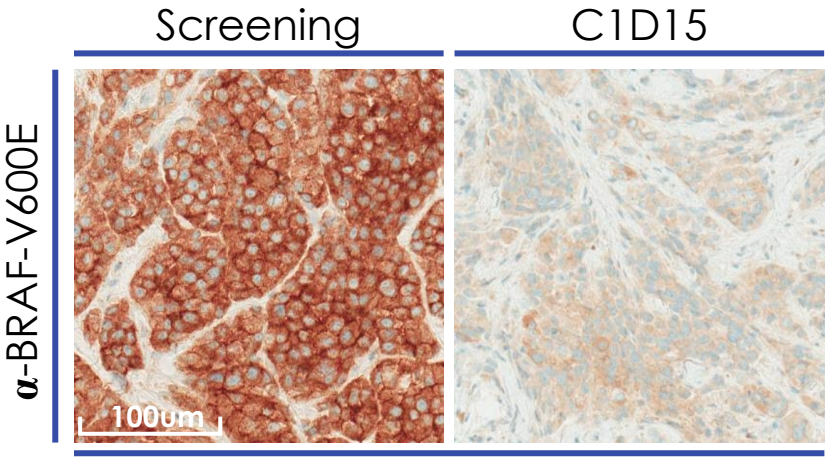
Initial CFT1946 Pharmacokinetic and Pharmacodynamic Data Support Proof of Mechanism

Exhibited dose-dependent bioavailability

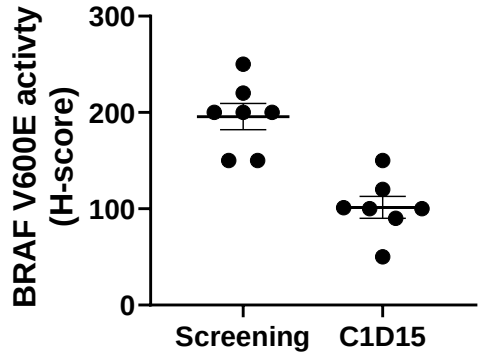


Mean plasma concentration shown for n > 2

BRAF V600E degradation determined by H-score of paired biopsies from different tumor types



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



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

H-Score Calculation:

- IHC staining is measured using BRAF VE1 (BRAF V600E) clone from Roche Laboratories
- H-scores (combining both proportion of cells and intensity of cell staining) are used as a surrogate for quantitative BRAF V600E levels

Immunohistochemistry (IHC); Twice Daily (BID, Cycle 1, Day 15 (C1D15); Pharmacokinetic (PK)
Source: ESMO Congress 2024; C4T data on file as of 7/19/2024

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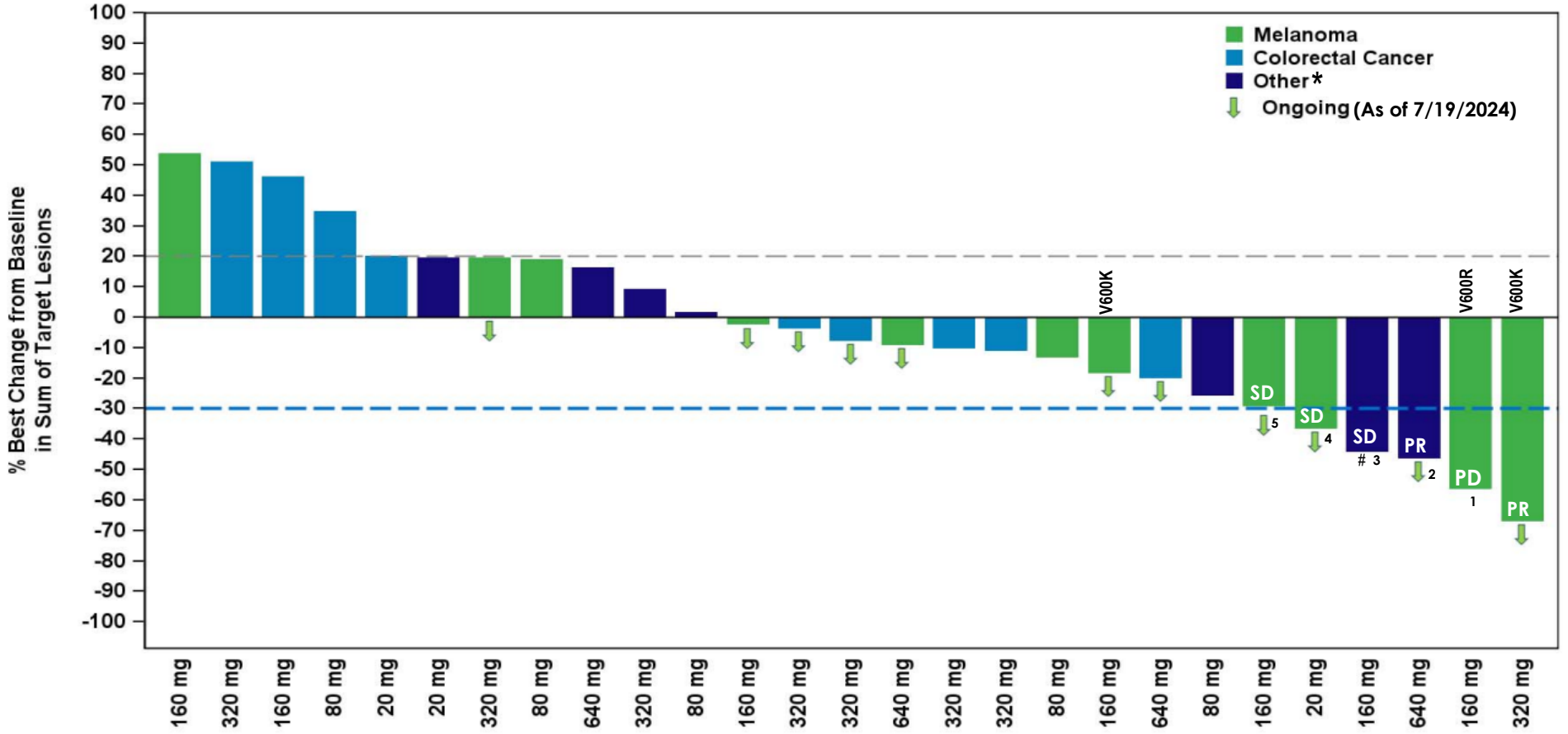
Early Signs of Anti-tumor Activity: 59% (16/27) Patients Demonstrated Target Lesion Tumor Reductions with 11 Efficacy Evaluable Patients Continuing Treatment



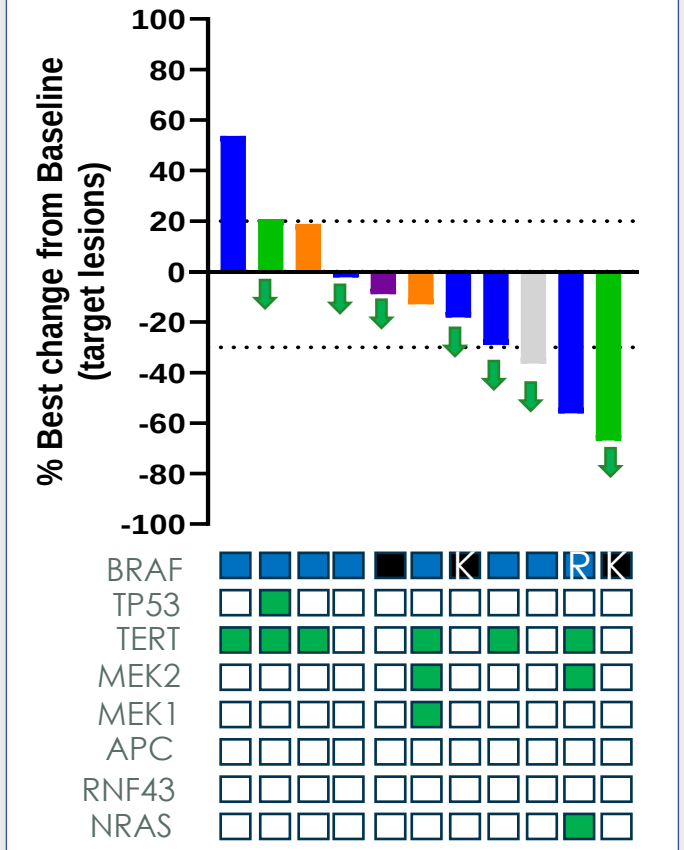
*Other tumor types include cholangiocarcinoma, non-small cell lung cancer, pancreatic carcinoma, and small intestine cancer; BRAF V600 mutation is V600E unless otherwise specified; #This patient did not receive prior BRAF inhibitor therapy, all other patients received prior BRAF inhibitor therapy. Dotted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

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

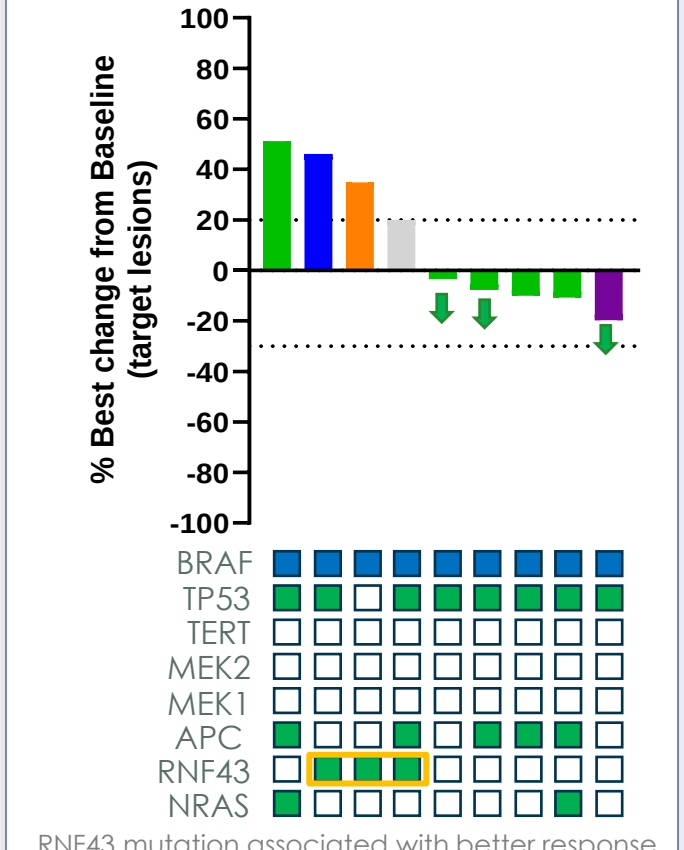
Source: ESMO Congress 2024; C4T data on file as of 7/19/2024

Tumor Reductions Observed in All V600 Mutation Types Treated with CFT1946

Melanoma

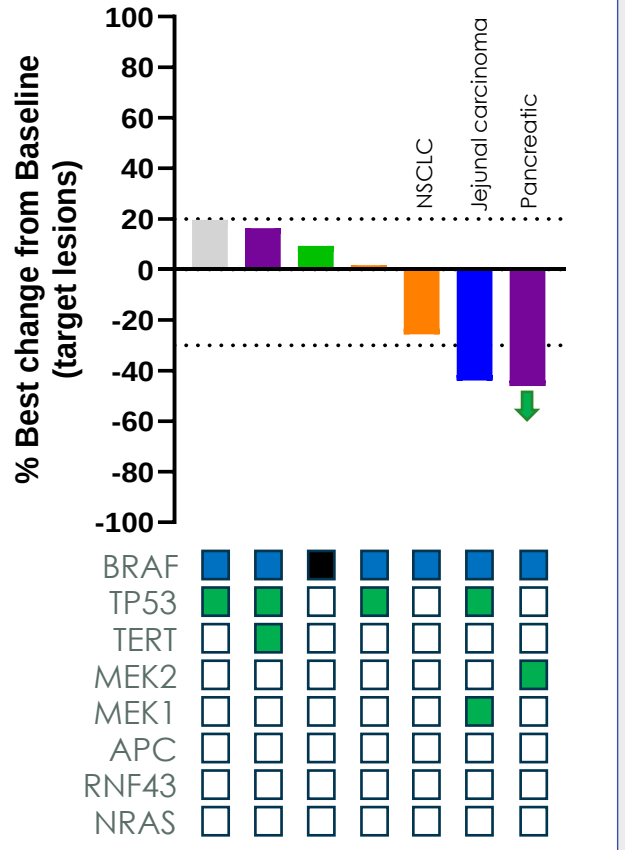


CRC



RNF43 mutation associated with better response for BRAFi when combined with cetuximab

Other Indications



Colorectal cancer (CRC); Non-small cell lung cancer (NSCLC); Circulating tumor DNA (ctDNA); BRAF inhibitor (BRAFi)
Source: C4T data on file as of 7/19/2024

- mBRAF confirmed by ctDNA
- mBRAF not confirmed by ctDNA
- Mutated gene identified
- 20 mg CFT1946
- 80 mg CFT1946
- 160 mg CFT1946
- 320 mg CFT1946
- 640 mg CFT1946
- Ongoing (as of 7/19/24)

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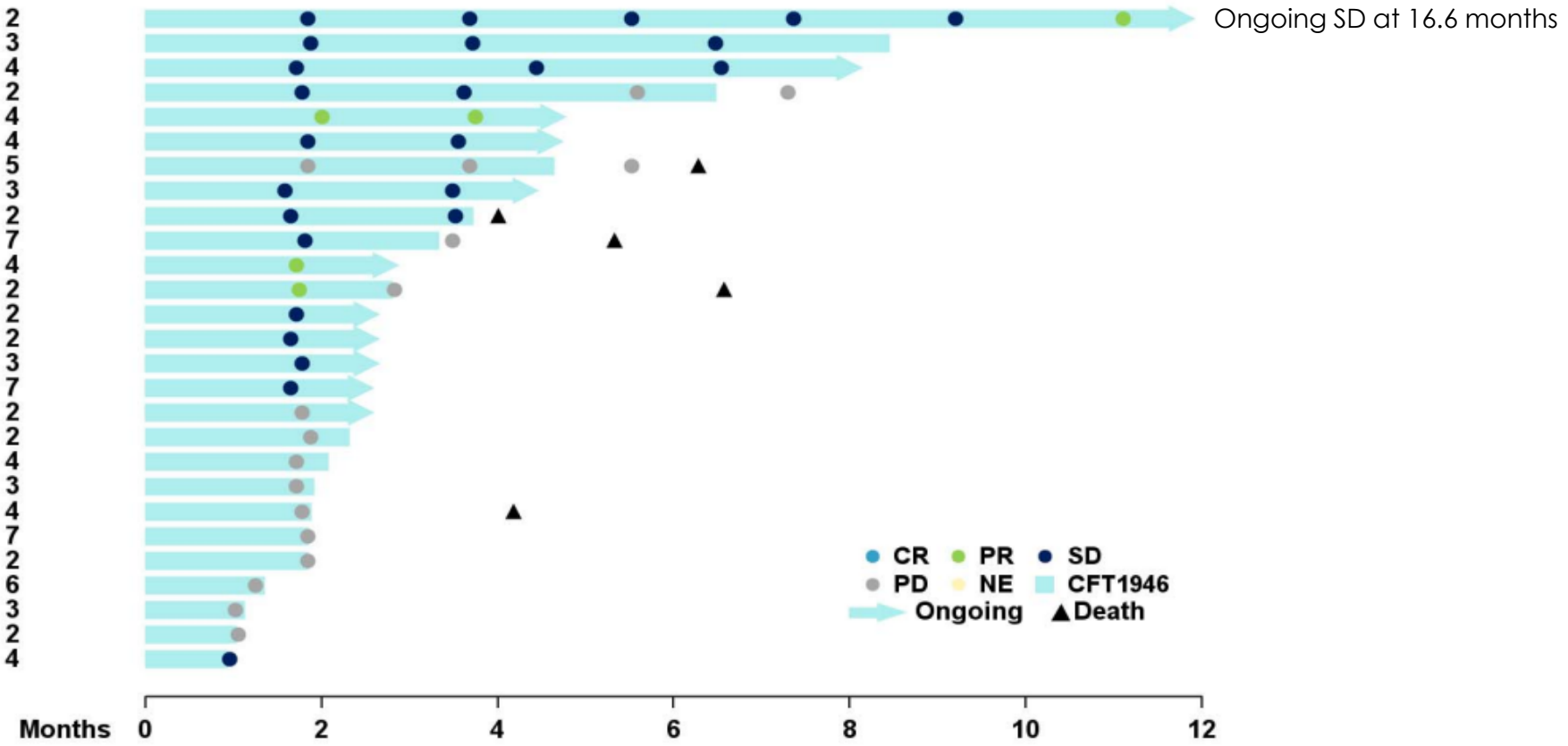
CFT1946 Treatment Duration to Date Across All Dose Levels

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



*Patient had confirmed PR after data cut off, [#]As reported by sites per medical records and N/A indicates data not available; Data cut off: 7/19/2024
Other tumor types include cholangiocarcinoma, non-small cell lung cancer, pancreatic carcinoma, and small intestine cancer;
Best overall response (BOR); BRAFi inhibitors (BRAFi) 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); Immunotherapy (I/O); Not Evaluable (NE)
Source: ESMO Congress 2024; C4T data on file as of 7/19/2024

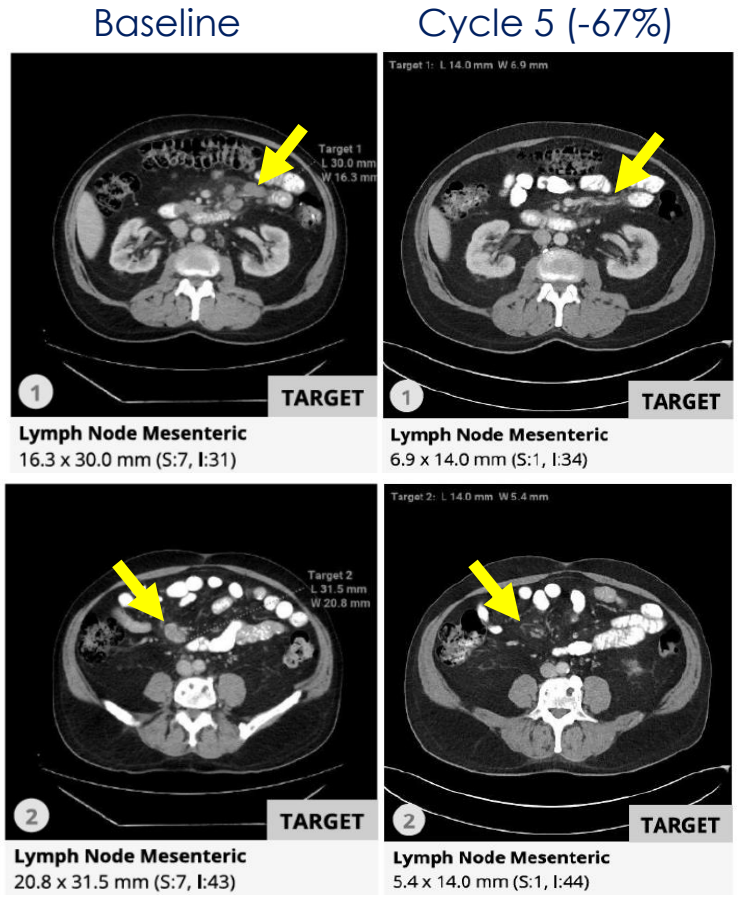
Case Study 1: Confirmed Partial Response in BRAF V600K Melanoma Patient at 320 mg

Melanoma Patient Overview:

- 72-year-old male with BRAF V600K melanoma (Stage IV) enrolled Feb 2024 into CFT1946 320 mg BID cohort
- Initial diagnosis Stage II in 2019
- Received prior surgery and four lines of anti-neoplastic therapy:

Line	Therapy
Surgery	Wide local excision right posterior auricular melanoma (2019)
1	Pembrolizumab (4/20 – 7/20) Best response: PD
2	Nivolumab and ipilimumab (8/20 – 10/20) Best response: PD
3	Dabrafenib and trametinib (11/20 – 9/21) Best response: SD
4	Pembrolizumab (9/21 – 1/24) Dabrafenib and trametinib (9/21 – 11/23) Best response: SD

- **Patient remains in response and on CFT1946 treatment**[1]



Per RECIST 1.1 criteria:

- At Cycle 3: PR (64% decrease of target lesion from baseline)
- At Cycle 5: PR (67% decrease of target lesion from baseline)

Twice daily (BID); Progressive disease (PD); Stable disease (SD); Partial response (PR)
[1]Remains on treatment as of 9/1/2024
Source: ESMO Congress 2024; C4T data on file as of 07/19/2024

C4 Therapeutics

Case Study 2: Confirmed Partial Response in BRAF V600E Pancreatic Cancer Patient with History of Liver Metastases at 640 mg

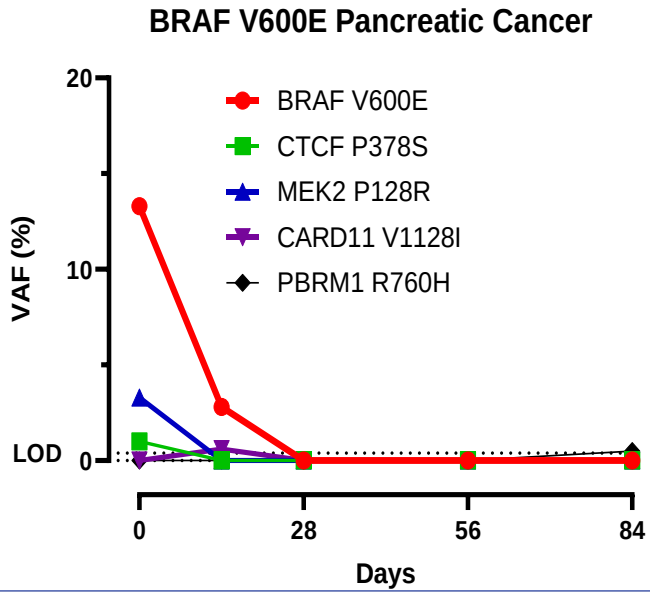
Pancreatic Cancer Patient Overview:

- 63-year-old male enrolled April 2024 into CFT1946 640 mg BID cohort
- Diagnosed with Stage IV BRAF V600E pancreatic carcinoma in 2021 with a history of liver metastases
- Received four lines of prior anti-neoplastic therapy:

Line	Therapy
1	FOLFOX (6/21 – 10/22) Best response: PR Capecitabine (maintenance) (12/21 – 10/22)
2	Dabrafenib and trametinib (11/22 – 10/23) Best response: PR
3	FOLFIRI (11/23 – 2/24) Best response: PR
4	Abraxane and gemcitabine (3/24 – 4/24) Best response: PD

- **Patient remains in response and on CFT1946 treatment**[1]

Decrease in BRAF V600E allele fraction measured in ctDNA using WES



Per RECIST 1.1 criteria:

- At Cycle 3: PR(46% decrease of target lesion from baseline in SoD)
  - 40% and 49% reduction in liver metastases
- At Cycle 5: PR* (55% decrease of target lesion from baseline in SoD)

[1]Remains on treatment as of 9/1/2024
*Occurred after data cutoff of 7/19/2024
Twice daily (BID); Partial response (PR); Progressive disease (PD); Circulating tumor DNA (ctDNA); Whole exome sequencing (WES); Variant allele frequency (VAF); Limit of detection (LOD), Sum of diameters (SoD)
Source: ESMO Congress 2024; C4T data on file as of 7/19/2024

CFT1946 Advancing as a Monotherapy and in Combination for Patients with BRAF V600 Mutant Solid Tumors

Proof of Mechanism

- **Well tolerated safety** profile in an advanced and metastatic patient population
  - **No Grade ≥ 3 cutaneous adverse events** commonly seen with wild-type BRAF inhibition
  - **No drug interruptions**, **reductions**, or **discontinuations** due to **treatment-related adverse events**
- **Dose-dependent bioavailability**
- In all post-treatment biopsies to date, **CFT1946 degrades BRAF V600E protein**

Proof of Degrader Concept

- **Monotherapy anti-tumor activity** in patients refractory to BRAF inhibitors
  - **Tumor reduction** in **16/27 patients**
  - **8/11 melanoma patients** demonstrated **tumor reduction**
- **Tumor reductions** observed in patients with **various V600 mutation types**[1]
- Intrinsic resistance in CRC patients supports CFT1946 in combination with cetuximab; CRC combination cohort ongoing

[1]Ongoing trial: data cut off as 07/19/2024
Colorectal cancer (CRC)
Source: ESMO Congress 2024; C4T data on file as of 07/19/2024

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Next Steps for CFT1946

2024

- ✓ Initiated monotherapy melanoma expansion cohort at 640 mg
- Continue dose escalation beyond 640 mg if absorption/exposure data supports
- Initiate Phase 1b portion of the trial evaluating CFT1946 in combination with trametinib for melanoma

2025

- Complete CFT1946 monotherapy dose escalation portion of ongoing Phase 1 trial and present full data in **2025**
- Data from Phase 1 expansion cohorts evaluating CFT1946 monotherapy for melanoma expected in **2025**
- Data from Phase 1b portion of the trial evaluating CFT1946 in combination with cetuximab for CRC expected in **2025**

2026

Initiate registrational trial(s) to position CFT1946 as BRAF therapy of choice

Thank you!

The C4T Team would like to thank the patients and their families for participating in this study and all the investigators and support staff who make it possible.

C4 Therapeutics