C4 Therapeutics

CFT8919 Pre-Clinical Data Investor Call

June 7, 2021

Forward-looking Statements and Intellectual Property

Forward-looking Statements

The following presentation contains forward-looking statements. All statements other than statements of historical fact are forward-looking statements, which are often indicated by terms such as "anticipate," "believe," "could," "estimate," "expect," "goal," "intend," "look forward to," "may," "plan," "potential," "predict," "project," "should," "will," "would" and similar expressions. These forward-looking statements include, but are not limited to, statements regarding the therapeutic potential of C4 Therapeutics, Inc.'s technology and products. These forward-looking statements are not promises or guarantees and involve substantial risks and uncertainties. Among the factors that could cause actual results to differ materially from those described or projected herein include uncertainties associated generally with research and development, clinical trials and related regulatory reviews and approvals, as well as the fact that the product candidates that we are developing or may develop may not demonstrate success in clinical trials. Prospective investors are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date hereof. C4 Therapeutics, Inc. undertakes no obligation to update or revise the information contained in this presentation, whether as a result of new information, future events or circumstances or otherwise.

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Today's Agenda

Topic	Participants
Introductions	Kendra Adams, SVP Communications & Investor Relations
Opening Remarks	Andrew Hirsch, President and CEO
CFT8919 Pre-clinical Data Overview	Adam Crystal, M.D., Ph.D., CMO
Q&A Session	Andrew Hirsch, Adam Crystal and Stew Fisher, CSO

What You Will Hear Today

- CFT8919 is an orally bioavailable, selective, allosteric degrader of EGFR L858R
- Active *in vitro* and *in vivo* in models with secondary EGFR mutations
- Demonstrates intracranial activity indicating potential to prevent or treat brain metastases in patients with EGFR L858R-driven tumors
- 25-45% of mutant EGFR NSCLC is driven by L858R activating mutation; these patients are not adequately addressed with current EGFR therapies
- Pre-clinical data suggests CFT8919 has path to registration in EGFR patients who develop resistance to osimertinib

Sources: Li, K et al. *Oncol Rep* 37, 1347–1358 (2017);Jin Y. et al. Scientific Reports 6:31636 (2016); Soria, J.-C. et al. NEJM 378, 113–125 (2018)

TORPEDO Platform Has Delivered a Robust Degrader Pipeline; Four Clinical Programs Expected by End of 2022

Target	Indication(s)	Discovery	Preclinical	Clinical	Ownership
IKZF1/3 (CFT7455)	Multiple Myeloma & Lymphoma				C4 Therapeutics
BRD9 (CFT8634)	Synovial Sarcoma & SMARCB1 Deleted Tumors				C4 Therapeutics
EGFR (CFT8919)	Drug-Resistant EGFR+ NSCLC				C4 Therapeutics
BRAF V600E	Drug-Resistant BRAF mutant Tumors				C4 Therapeutics Roche
RET	Drug-Resistant RET-Altered Tumors				C4 Therapeutics
Transcriptional Control	Undisclosed Solid Tumors				C4 Therapeutics
Cancer Signaling	Undisclosed Cancers				C4 Therapeutics
Transcriptional Control	Undisclosed Liquid Tumors				C4 Therapeutics
Cancer Signaling	Undisclosed Solid Tumors				C4 Therapeutics

Nine Additional Undisclosed Collaborator Programs in Discovery

Updated 2021 Milestones Continue to Support Progress Toward Goal of Four Clinical-Stage Programs by Year-End 2022

	2021	2022
IKZF1/3 (CFT7455)	❑ Phase 1/2 Initiation	❑ Phase 1 Top-line Safety & Efficacy ❑ Proof of Mechanism
BRD9 (CFT8634)	❑ IND Submission	❑ Phase 1 Initiation
EGFR (CFT8919)	❑ IND Enabling Studies	❑ IND Submission ❑ Phase 1 Initiation
BRAF	❑ IND Enabling Studies	❑ IND Submission ❑ Phase 1 Initiation
RET	❑ Lead Optimization	

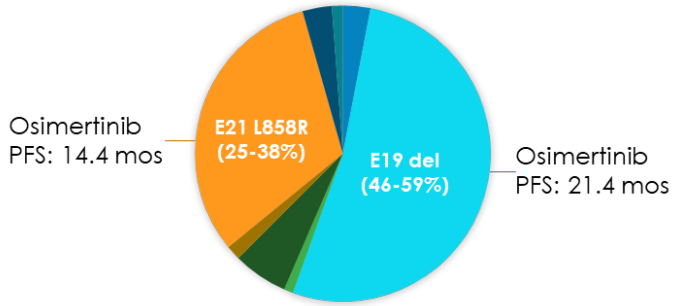
Preclinical Evaluation of CFT8919 as a Mutant Selective Degrader of EGFR with L858R Activating Mutations for the Treatment of Non-Small Cell Lung Cancer

Mutations in EGFR Drive Oncogenesis and Resistance in Non-Small Cell Lung Cancer

10-15% of Non-Small Cell Lung Cancer has Mutant EGFR

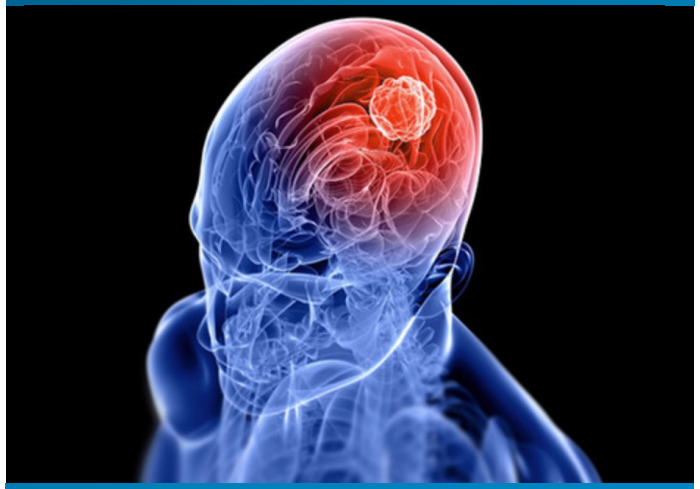
This rises to nearly 40% in Asian population

25-45% of Mutant EGFR NSCLC is Driven by L858R Activating Mutation



Patients with L858R have inferior clinical outcome

30-40% of Mutant EGFR NSCLC Patients will Develop Brain Metastases



CNS activity desirable to be competitive

Sources: Zhang, Y.-L. et al. *Oncotarget* 7, 78985–78993 (2016); Li, K et al. *Oncol Rep* 37, 1347–1358 (2017); Shin, D.-Y. et al. *J Thorac* Oncol 9, 195–199 (2014); Rangachari, D. et al. Lung Cancer 88, 108-111 (2015); Jin Y. et al. Scientific Reports 6:31636 (2016); Soria, J.-C. et al. NEJM 378, 113–125 (2018)

Despite Three Generations of Approved EGFR Inhibitors, L858R Patients Have Poorer Prognosis

Median PFS	L858R	Exon 19 Deletion
Osimertinib	14.4 months	21.4 months
Standard EGFR TKI	9.5 months	11.0 months

L858R mutation predicts less durable response to EGFR inhibitors

No evidence that L858R is a more aggressive disease

L858R Patients are Underserved by Current EGFR Inhibitor Therapies

Source: Soria, J.-C. *et al. New Engl J Medicine* 378, 113–125 (2018)

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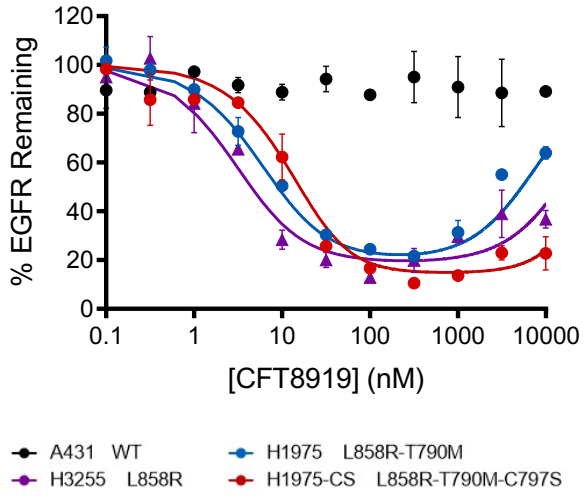
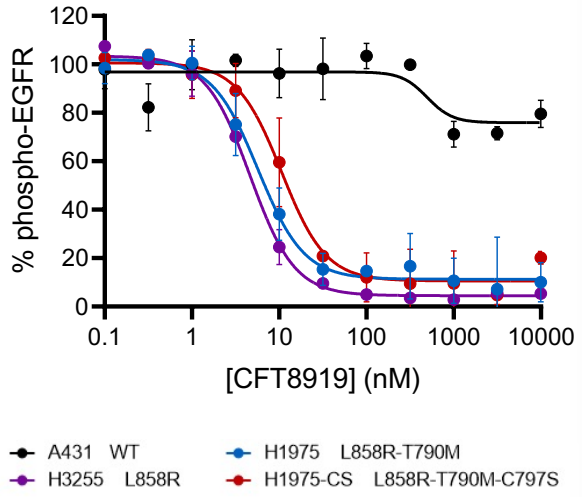
CFT8919 Selectively Targets EGFR-L858R in Human Cancer Cell Lines and is Not Impacted by EGFR T790M or C797S

A EGFR Degradation



B Phospho-EGFR Inhibition



C Degradation and Inhibition Potency

			Degradation (DC50, nM)	Inhibition (IC50, nM)		
	Cell line	EGFR genotype	CFT8919	CFT8919	Osimertinib 3rd gen	Erlotinib 1st gen
Selectivity	A431	wild-type	>10000	>10000	901	>10000
1L	H3255	L858R	5	5	32	142
2L	H1975	L858R-T790M	8	9	54	>10000
3L	H1975-CS*	L858R-T790M-C797S	14	13	2285	>10000

Color key: Potency fold change (FC) relative to L858R

Selectivity against wild-type
25 < FC
5 ≤ FC ≤ 25
FC < 5

Activity against resistant mutations
FC < 5
5 ≤ FC ≤ 25
25 < FC

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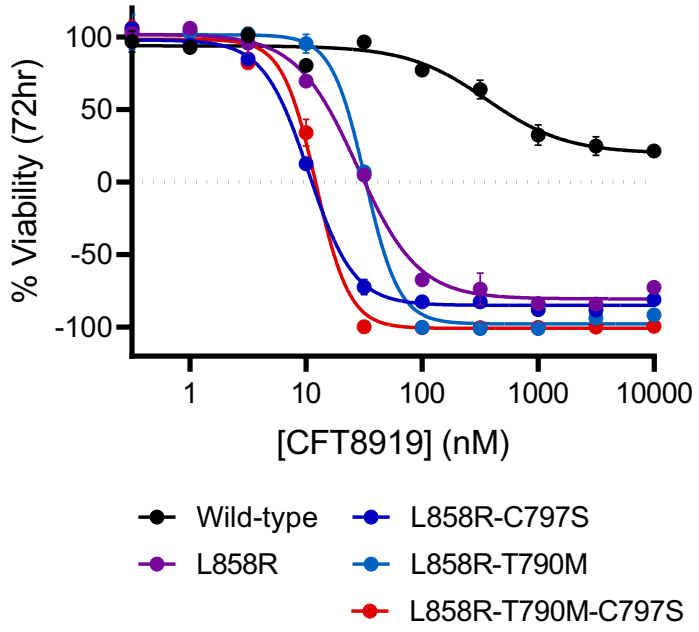
CFT8919 is Active in Ba/F3 Models Expressing Secondary Mutations Resistant to Approved EGFR Inhibitors

A

Viability of Ba/F3 Cells Expressing the Indicated EGFR Variant



B

Ba/F3 Cell Growth Inhibition Potency

	EGFR genotype	CFT8919	Osimertinib 3rd gen	Erlotinib 1st gen
Selectivity	wild-type	486	12	200
1L	L858R	16	3	8
2L	L858R-T790M	16	6	5951
2L	L858R-C797S	7	2753	not determined
2L	L858R-L718Q	23	1206	1033
2L	L858R-L792H	8	314	142
3L	L858R-T790M-C797S	8	2671	6605
3L	L858R-T790M-L718Q	36	1280	>10,000
3L	L858R-T790M-L792H	17	385	>10,000

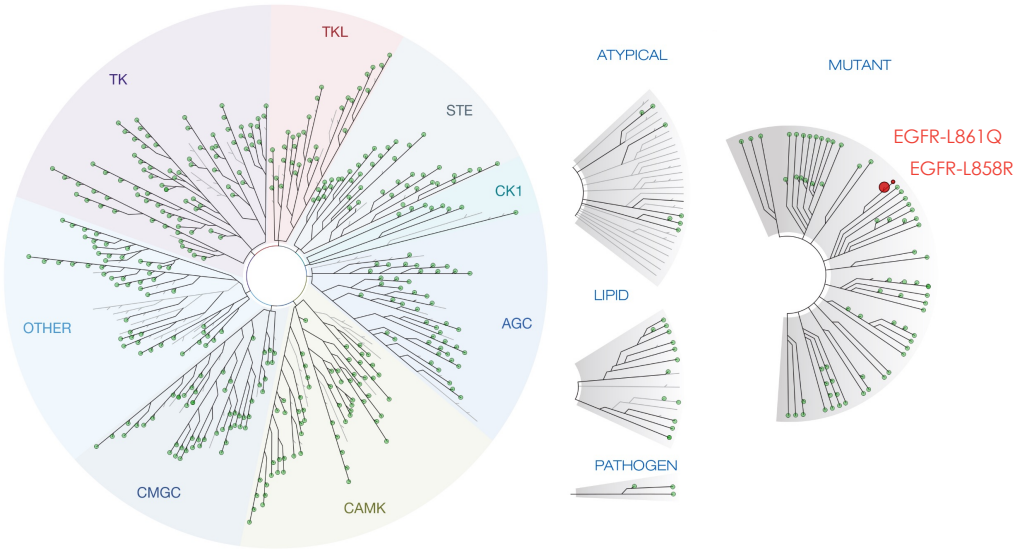
Color key: Potency fold change (FC) relative to L858R

Selectivity against wild-type	Activity against resistant mutations
25 < FC	FC < 5
5 ≤ FC ≤ 25	5 ≤ FC ≤ 25
FC < 5	25 < FC

CFT8919 is Highly Selective Against Kinase Targets and Known Cereblon Neo-Substrates

A

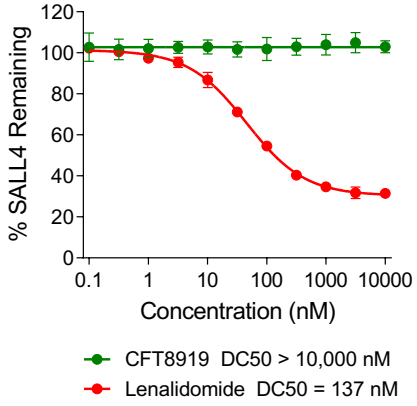
Kinome Binding Specificity



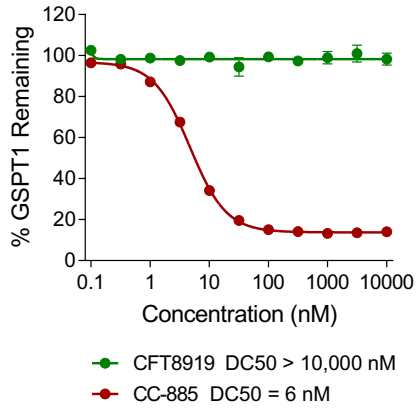
B

Evaluation Against Known CRBN Neo-substrates

No SALL4 degradation



No GSPT1 degradation



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CFT8919 Shows Excellent Proteome-Wide Selectivity

Global Proteomic Evaluation

Cell Line	EGFR Genotype	# of Proteins Detected	# of Proteins with >50% Protein Level Decrease*
A431	**Wild-type**	**9190**	**0**
H1975	**L858R-T790M**	**8853**	**2 (EGFR, CCND1+)**

*p-value < 0.001
+Likely due to the biological effect of EGFR suppression; similar change observed upon osimertinib treatment

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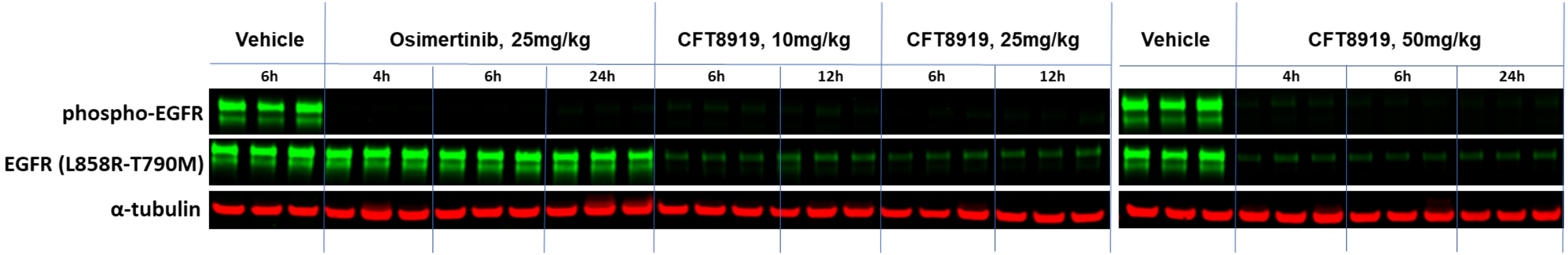
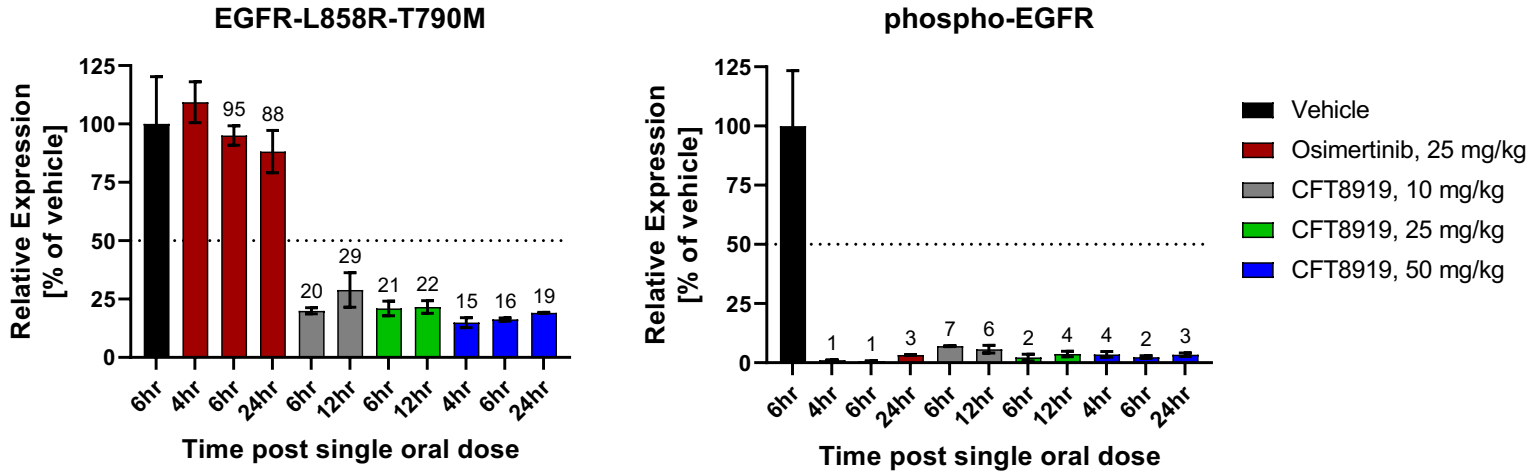
CFT8919 Degrades and Inhibits Mutant EGFR in Tumors Upon Oral Administration

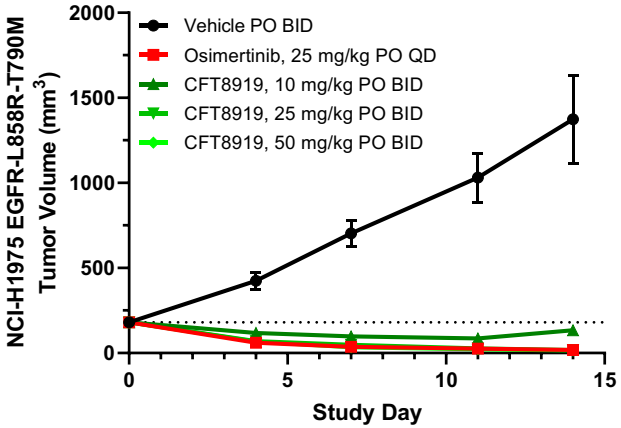
Tumor PD in H1975 EGFR-L858R-T790M xenograft model

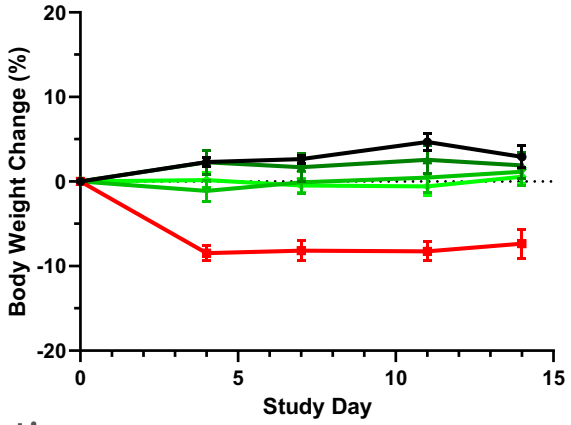




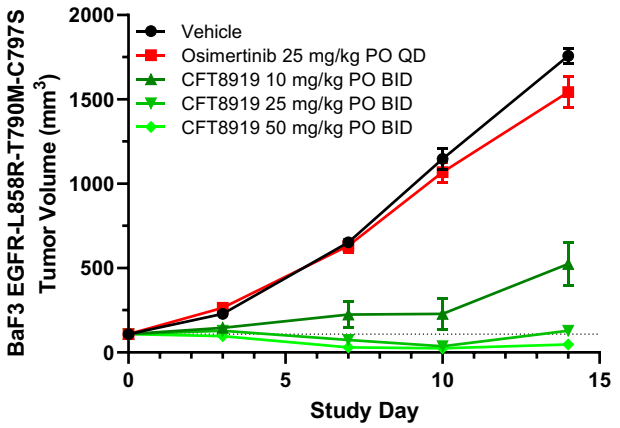
CFT8919 Induces Tumor Regression in Mouse Models Resistant to First and Third-Generation EGFR Inhibitors

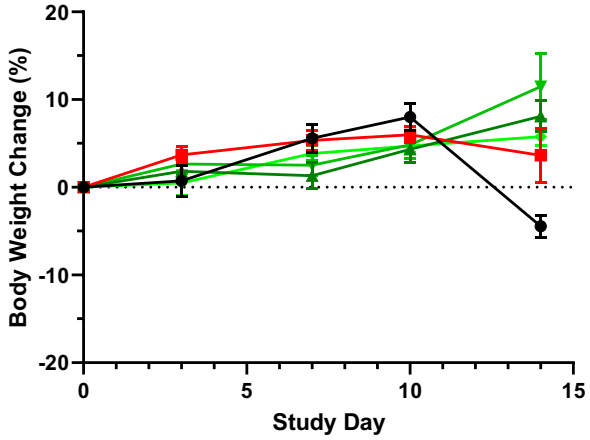
1st-Generation EGFRi Resistant H1975 (L858R-T790M) Xenograft





3rd-Generation EGFRi Resistant Ba/F3 (L858R-T790M-C797S) Allograft





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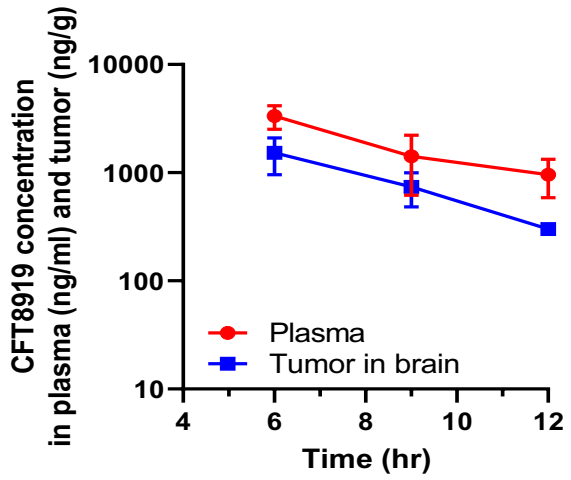
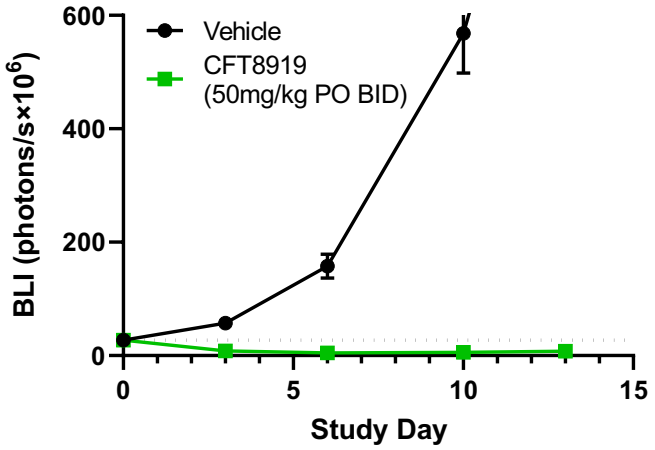
CFT8919 Demonstrates Activity in H1975-LUC (EGFR-L858R-T790M) Brain Metastasis Model

Mean Plasma & Tumor Concentration

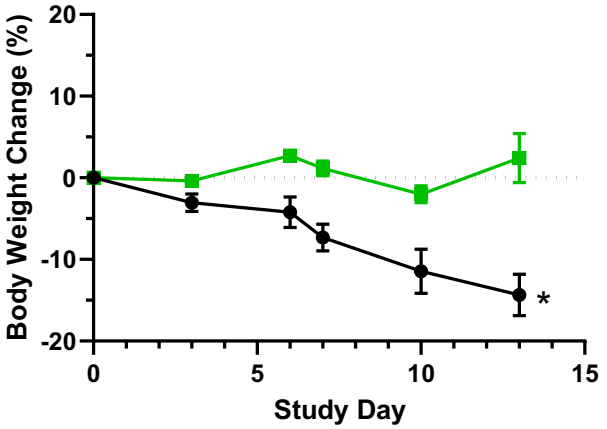


Plasma clearance $t_{1/2}$ = 3.1 hrs

In vivo Efficacy



In vivo Body Weight Change



**Body weight loss due to tumor burden*

CFT8919 is a Potent, Oral, Allosteric, Mutant-selective Degrader of EGFR L858R

- Active *in vitro* and *in vivo* in models with secondary mutations (such as T790M, C797S, T790M-C797S) that cause acquired resistance to 1st-, 2nd-, and 3rd-generation EGFR inhibitors
- Demonstrates intracranial activity indicating potential to prevent or treat brain metastases in patients with EGFR L858R-driven tumors
- Clinical evaluation is warranted in patients with EGFR L858R driven NSCLC who have progressed on prior EGFR inhibitors
- By binding to an allosteric EGFR site, CFT8919 may combine with approved EGFR inhibitors which bind to the EGFR active site
- Pre-clinical profile highlight potential for single agent activity in the front-line setting

IND Submission Expected mid-2022 with Potential Phase 1 Trial Initiation by YE 2022

Q&A Session

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Thank You