C4 Therapeutics

Discovery of CFT8919 as an oral, CNS-active, mutant-selective allosteric degrader of EGFR L858R for the treatment of EGFR inhibitor-resistant non-small cell lung cancer

October 27, 2021

4th Annual TPD (Targeted Protein Degradation) Summit

Eunice Park on behalf of the C4T Team

Forward-looking Statements and Intellectual Property

Forward-looking Statements

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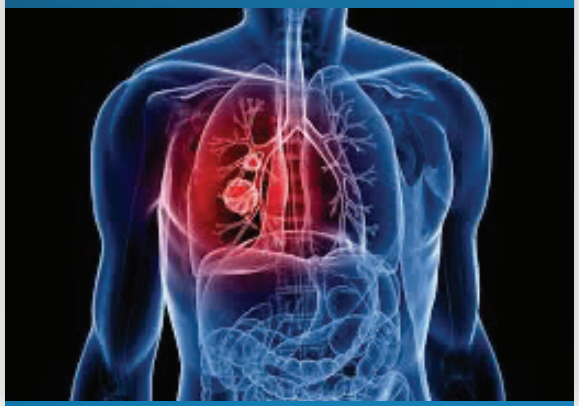
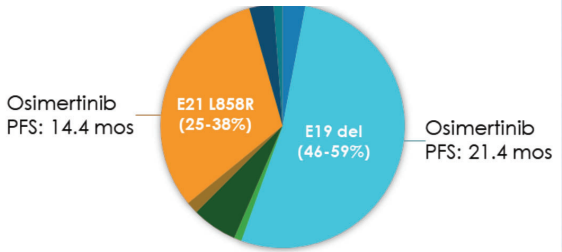
Mutations in EGFR Drive Oncogenesis in Non-Small Cell Lung Cancer

10-15% of Non-Small Cell Lung cancer has mutant EGFR



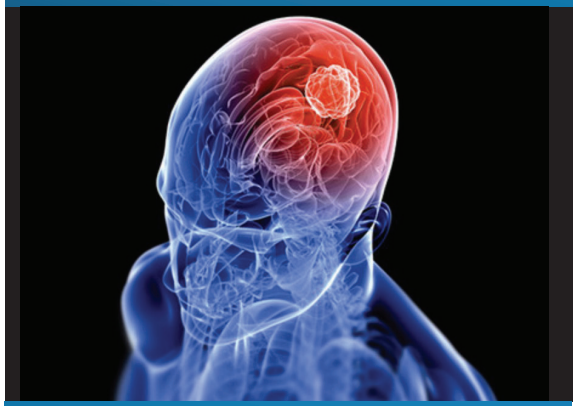
This rises to nearly 40% in Asian population

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

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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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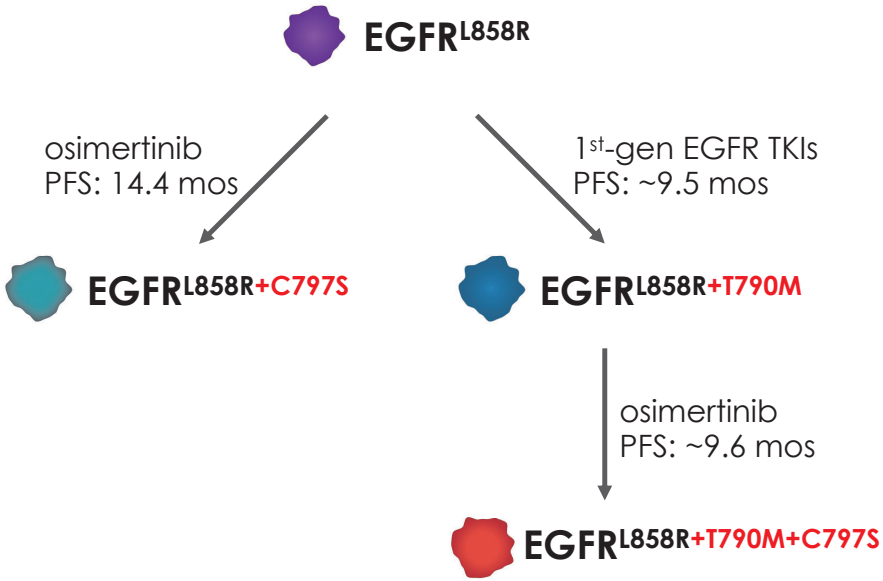
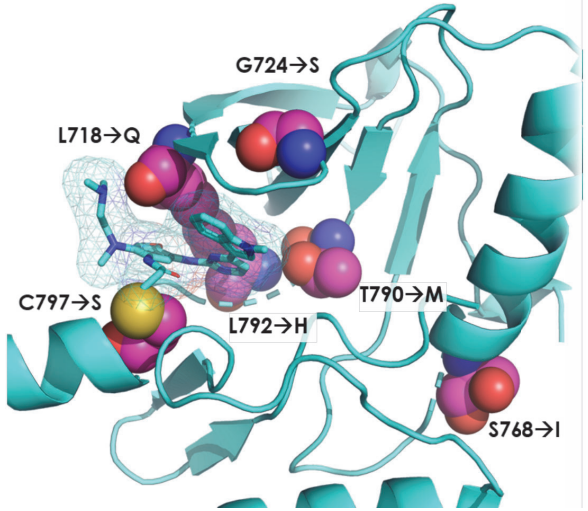
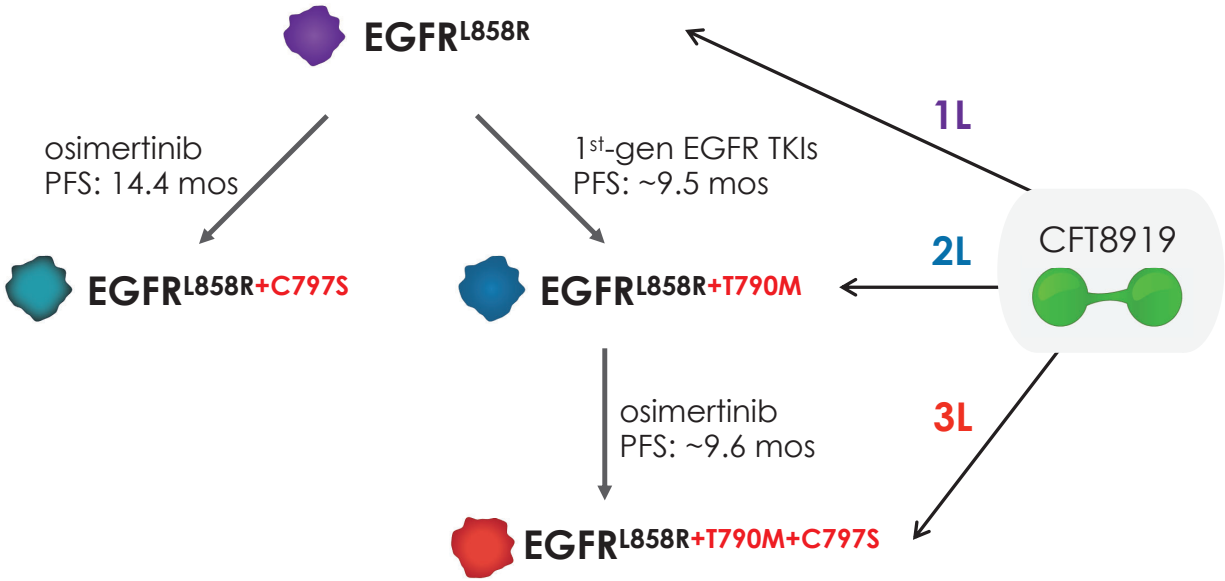
Significant Unmet Need for Patients Who Progress After Current EGFR Inhibitor Therapies



Resistance mutations occur around the ATP binding site



CFT8919 is an Oral, CNS-Active, Allosteric Degrader to Overcome Resistance to Approved EGFR Inhibitors

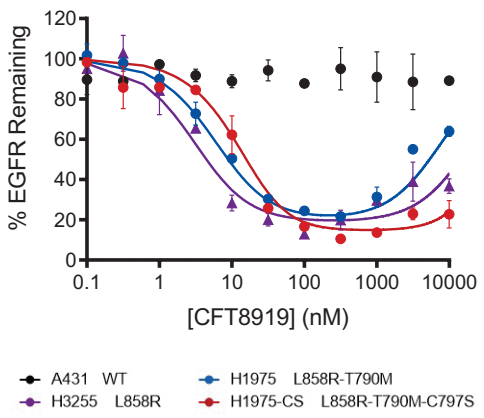


CFT8919 Compelling Profile

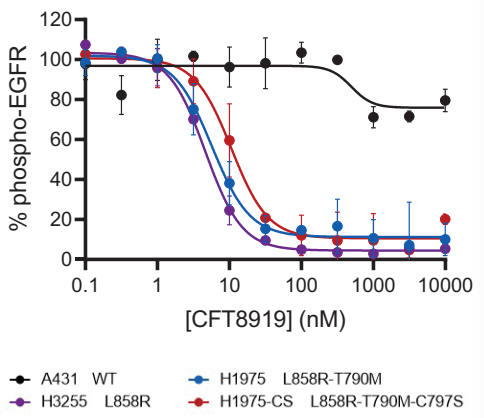
- Orally bioavailable, selective, allosteric degrader of EGFR L858R
- Active *in vitro* and *in vivo* in models with secondary mutations
- Demonstrates intracranial activity
- Potential to be active as single agent in the frontline setting

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

	Cell line	EGFR genotype	Degradation (DC50, nM) CFT8919	Inhibition (IC50, nM) 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

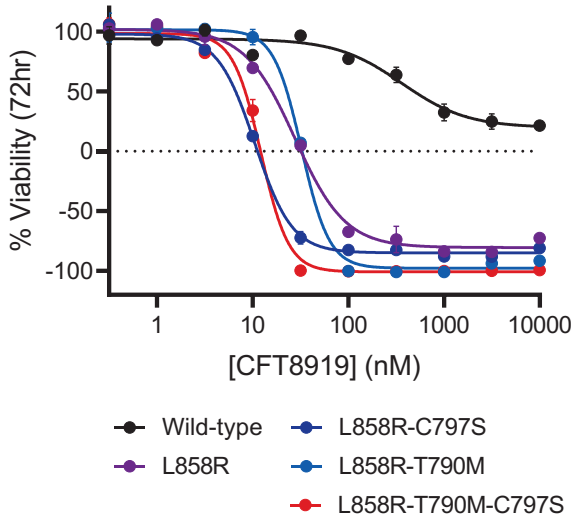
Selectivity against wild-type	Activity against resistant mutations
25 < FC	FC < 5
5 ≤ FC ≤ 25	5 ≤ FC ≤ 25
FC < 5	25 < FC

EGFR-L858R specific antibody was used to specifically detect degradation of mutant EGFR protein in EGFR mutant cell lines. Pan-EGFR antibody was used for A431 EGFR WT cell line.

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 (GI50, nM)

	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

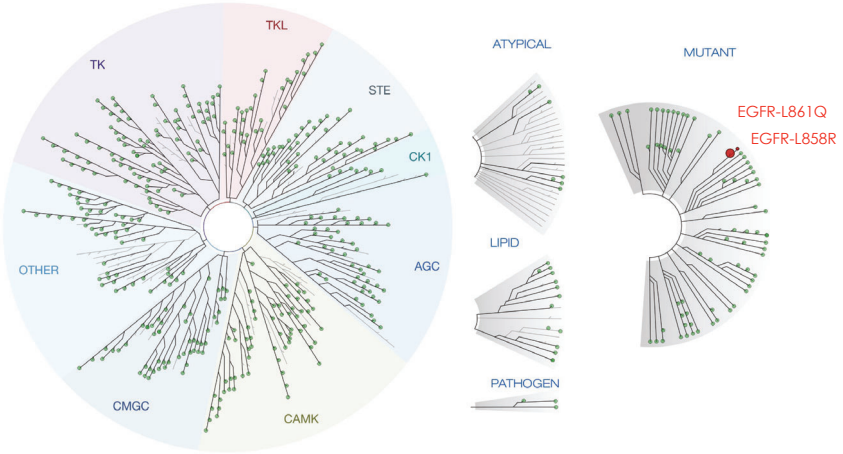
Color key: Potency fold change (FC) relative to L858R

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

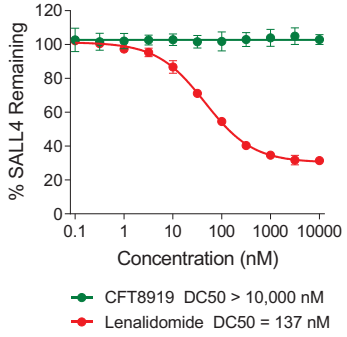
Kinome Binding Specificity



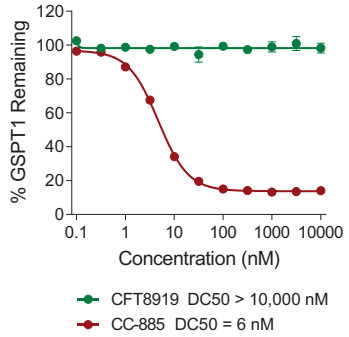
B

Evaluation Against Known CRBN Neo-substrates

No SALL4 degradation



No GSPT1 degradation



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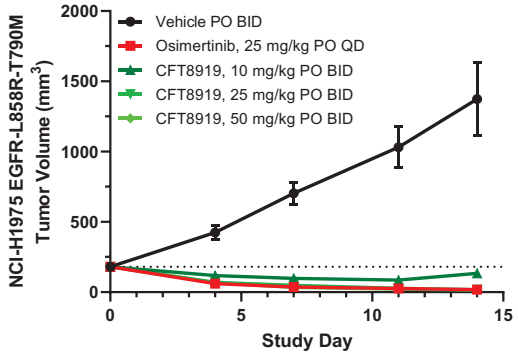
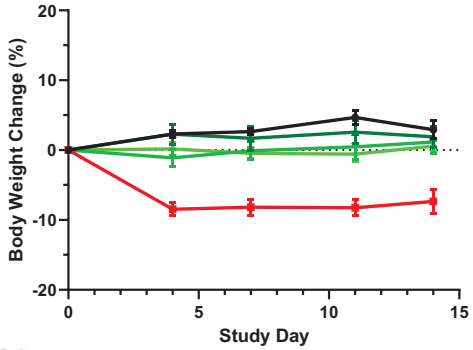
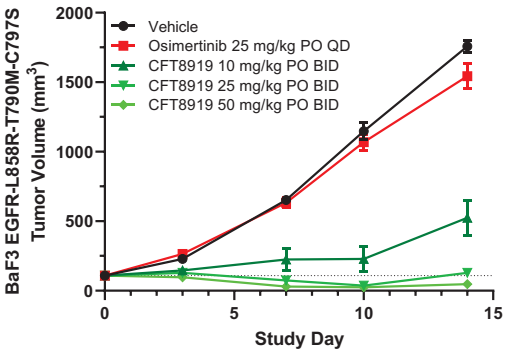
CFT8919 Induces Tumor Regression in Mouse Models Resistant to First and Third-Generation EGFR Inhibitors

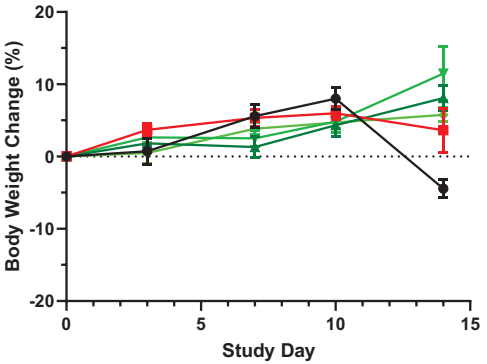
1st-generation EGFRi Resistant H1975 (L858R-T790M) Xenograft





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





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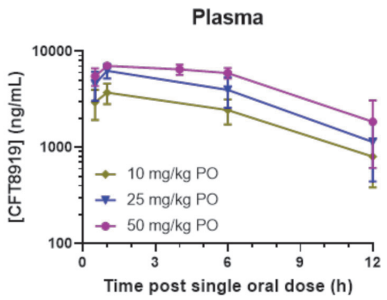
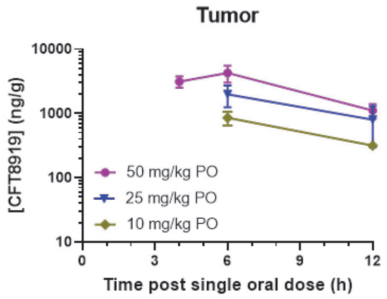
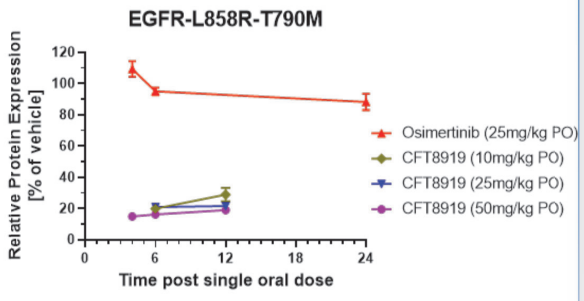
Dose Proportional Exposure Correlates with the Depth of PD and Tumor Regression Responses in H1975 EGFR L858R-T790M Xenograft Model

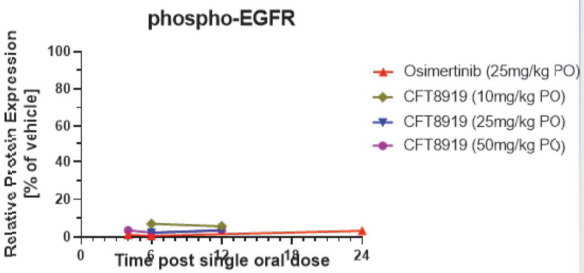
Plasma and Tumor PK



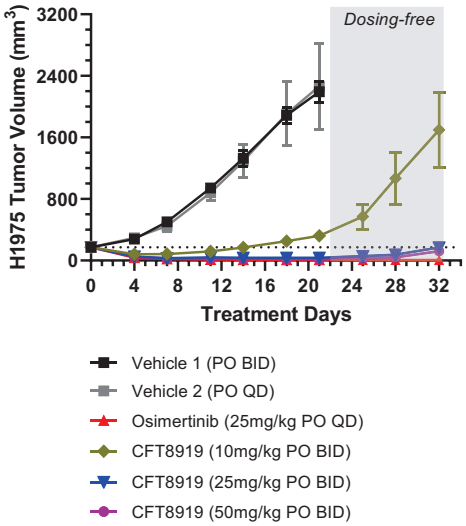


Tumor PD



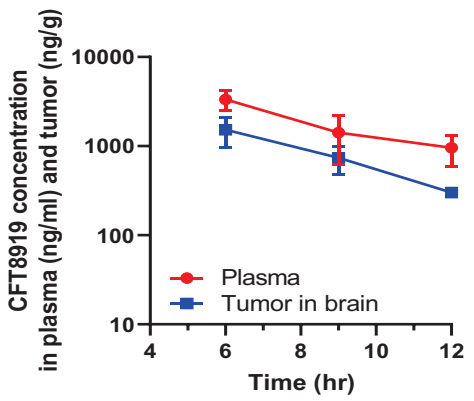


Efficacy



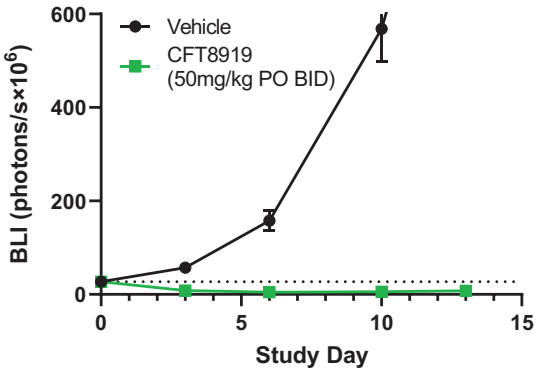
CFT8919 Demonstrates Activity in H1975-LUC (EGFR-L858R-T790M) Brain Metastasis Model (via Intracranial Implant)

Mean Plasma & Tumor Concentration

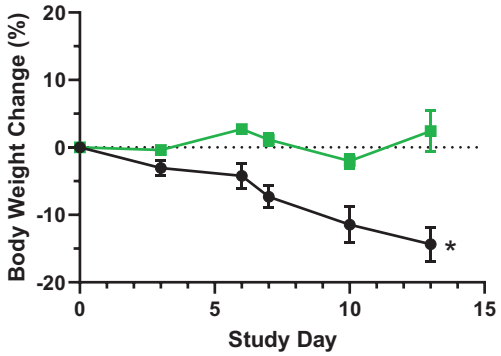


Plasma clearance $t_{1/2}$ = 3.1 hrs
50 mg/kg PO single dose

In vivo Efficacy



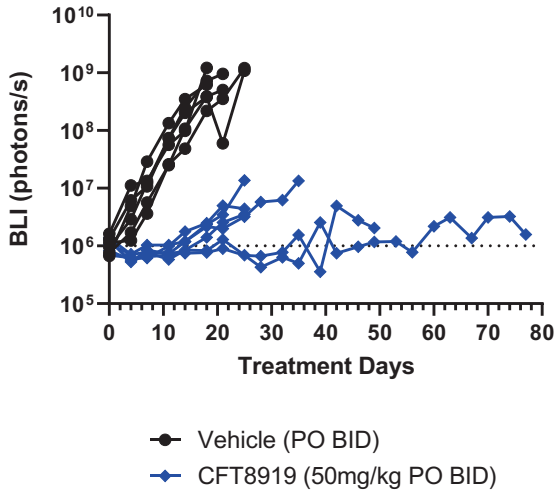
In vivo Body Weight Change



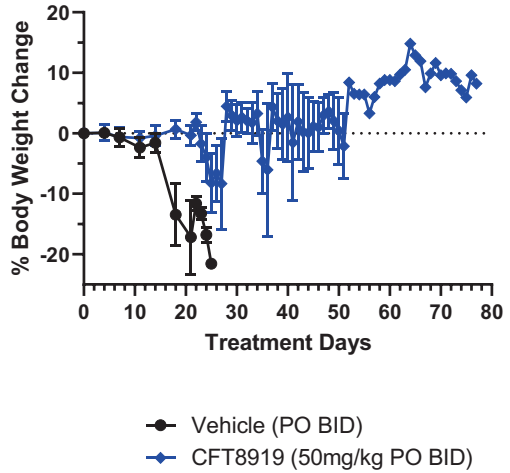
**Body weight loss due to tumor burden*

CFT8919 Demonstrates Activity in H1975-LUC (EGFR-L858R-T790M) Brain Tumor Metastasis Model (via Intracarotid Injection)

In Vivo Efficacy



In vivo Body Weight Change



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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

The C4 Therapeutics Team

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