C4 Therapeutics

Delivering on the Promise of Targeted Protein Degradation

Cowen 42nd Annual Health Care Conference

March 9, 2022

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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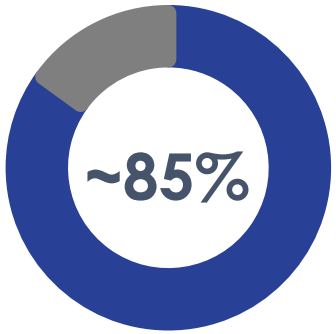
Targeted Protein Degradation Has the Potential to Transform Treatment of Disease



TPD Has an Expansive Target Landscape

85% of proteins are currently undruggable or poorly drugged

TPD Offers a Powerful Modality

Benefits of genetic knockdown with a small molecule approach

C4T's TORPEDO platform creates therapeutic candidates that have the potential to improve patient care

- Overcome Resistance
- Drug Undruggable Targets
- Improve Treatment Options

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Source: Hopkins, A., Groom, C. The druggable genome. Nat Rev Drug Discov 1, 727–730 (2002).

Our TORPEDO Platform Efficiently Designs Potent Targeted Protein Degrader Medicines

Elements	Benefits
Focus on Catalytic Efficiency	Optimization of overall degradation process results in maximal efficacy
Ability to Design, Analyze & Predict Degrader Performance	Rapid delivery of potent drug candidates through informed and efficient drug discovery
Investment in Cereblon as E3 Ligase	Cereblon is expressed in all tissues and cellular compartments, thereby providing the largest target selection opportunity
Ability to Develop Both MonoDAC & BiDAC Degraders	Flexibility to address different targets with tailored approach

C4T is Well Positioned to Deliver on the Promise of Targeted Protein Degradation to Transform Patient Care

Leading in TPD Science

World-class medicinal chemistry coupled with fundamental enzymology approach

Validated Platform

TORPEDO platform enables efficient optimization of MonoDAC and BiDAC degraders

Oncology-Focused Clinical Pipeline

Transform patient care by targeting undrugged or poorly drugged targets

Strong Foundation to Support Growth

Capabilities across discovery and clinical coupled with experience in strategic partnerships and strong balance sheet

*Cash, cash equivalents, and marketable securities were $451.5M as of 12/31/21

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Initial Programs Designed to Establish TORPEDO Platform for Validated Targets With Persistent Unmet Medical Need

Selective Target Criteria

- Strong rationale for a degrader approach
- Genetics are a clear driver of disease
- Clinically validated or de-risked targets
- Clear clinical development path
- Need for improved therapies to positively impact patient outcomes

Advancing High-Potential Programs through the Clinic

- CFT7455 – targeting IKZF1/3
- CFT8634 – targeting BRD9
- CFT1946 – targeting BRAF V600X
- CFT8919 – targeting EGFR L858R

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Unlocking Potential of TPD Science by Developing the Next Wave of Oncology Programs

Leverage Experience to Tackle Higher-risk Novel Targets that Drive Value

- Difficult-to-drug targets not adequately addressable by existing modalities
- Potential to transform patient care
- Pursuing both MonoDAC and BiDAC degraders

C4T Has the Potential to Deliver:

- First-in-class molecules
- Therapies across oncology and other therapeutic areas driven by existing collaborations
- Degraders with high patient impact

Robust Pipeline of Degrader Medicines Pursuing Meaningful Targets

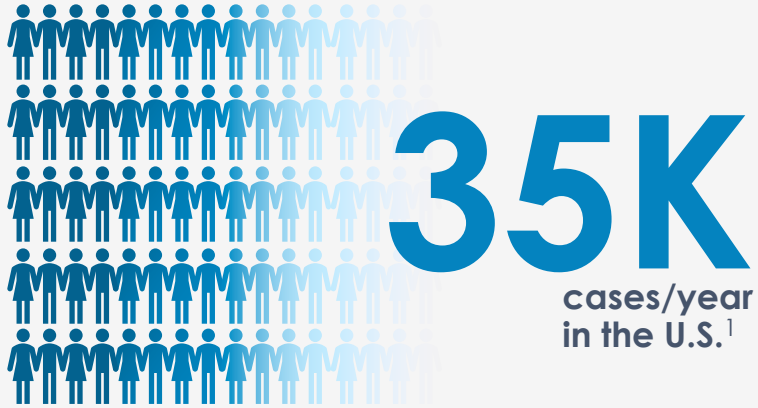
Program	Target	Indication	Discovery	Preclinical	Phase 1	Phase 2/3	Next Milestone	Rights
CFT7455	**IKZF1/3**	Multiple Myeloma & Lymphoma			Enrolling		Clinical data from Cohort A Ph1 trial at AACR	C4T
CFT8634	**BRD9**	Synovial Sarcoma & SMARCB1-null Solid Tumors					Initiate Ph1 trial in 1H22	C4T
CFT1946	**BRAF V600X**	Melanoma, CRC & NSCLC					Submit IND application and initiate Ph1 trial in 2H22	C4T
CFT8919	**EGFR L858R**	NSCLC					Complete IND-enabling activities by YE22	C4T
Earlier-Stage Undisclosed Programs (includes RET)		Various Cancers						C4T
Undisclosed Collaboration Programs		Various Cancers		*4 targets*				C4T Roche
		Neurological Conditions		*5 targets*				C4T Biogen
		Diseases of Aging, including Cancer		*1 target through March 2023*				C4T Calico

CFT7455
Targeting IKZF1/3

Multiple Myeloma
& Lymphoma

Marketed IKZF1/3 Degraders Leave Room for Improvement for Multiple Myeloma Patients

Multiple Myeloma (MM)

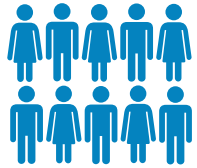


35K

cases/year in the U.S.[1]

IMiDs are suboptimal degraders, yet remain a **backbone therapy** for MM

Median time to first relapse occurs **3 – 4 years** after diagnosis[2]



R/R MM patients **not adequately addressed by currently available therapies**[3]

Significant toxicity from **chronic dexamethasone use**

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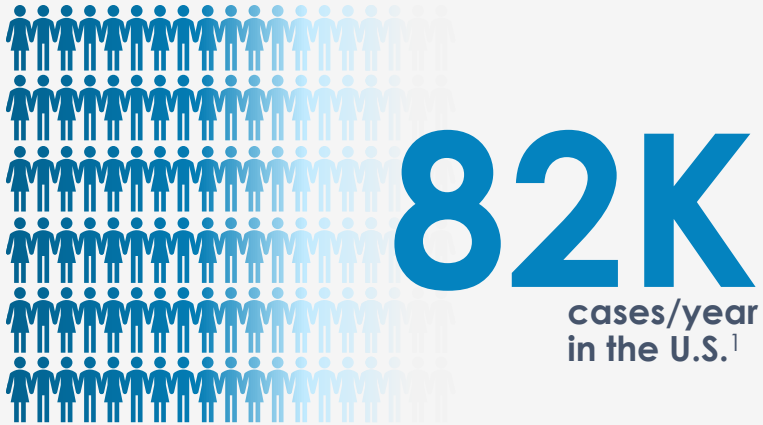
1. NIH SEER Database 2021 https://seer.cancer.gov/statfacts/html/mulmy.html
2. Rajkumar SV, Kumar S. Multiple myeloma current treatment algorithms. Blood Cancer J. 2020;10(9):94. Published 2020 Sep 28.
3. Durie 2018, Concise Review. International Myeloma Foundation

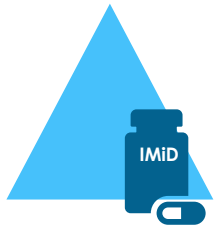
Unmet Need Remains High for Non-Hodgkin's Lymphoma Patients

Non-Hodgkin's Lymphoma (NHL)



82K
cases/year in the U.S.[1]

IKZF1/3 are **key drivers of malignancy** in NHLs



Approved IMiDs **have limited activity in NHLs**

Peripheral T-Cell Lymphoma is **4% of NHL**

years

Median Overall Survival[2]

Mantle Cell Leukemia is **7% of NHL**

years

Median Overall Survival[3]

1. NIH SEER Database 2021: https://seer.cancer.gov/statfacts/html/nhl.html
2. Stuver RN, et al. Single agents vs combination chemotherapy in relapsed and refractory peripheral T-cell lymphoma: Results from the comprehensive oncology measures for peripheral T-cell lymphoma treatment (COMPLETE) registry. Am J Hematol. 2019 Jun;94(6):641-649. doi: 10.1002/ajh.25463. Epub 2019 Apr 9. PMID: 30896890; PMCID: PMC7928240.
3. Teras LR, et al. 2016 US lymphoid malignancy statistics by World Health Organization subtypes. CA Cancer J Clin. 2016;66(6):443-459.

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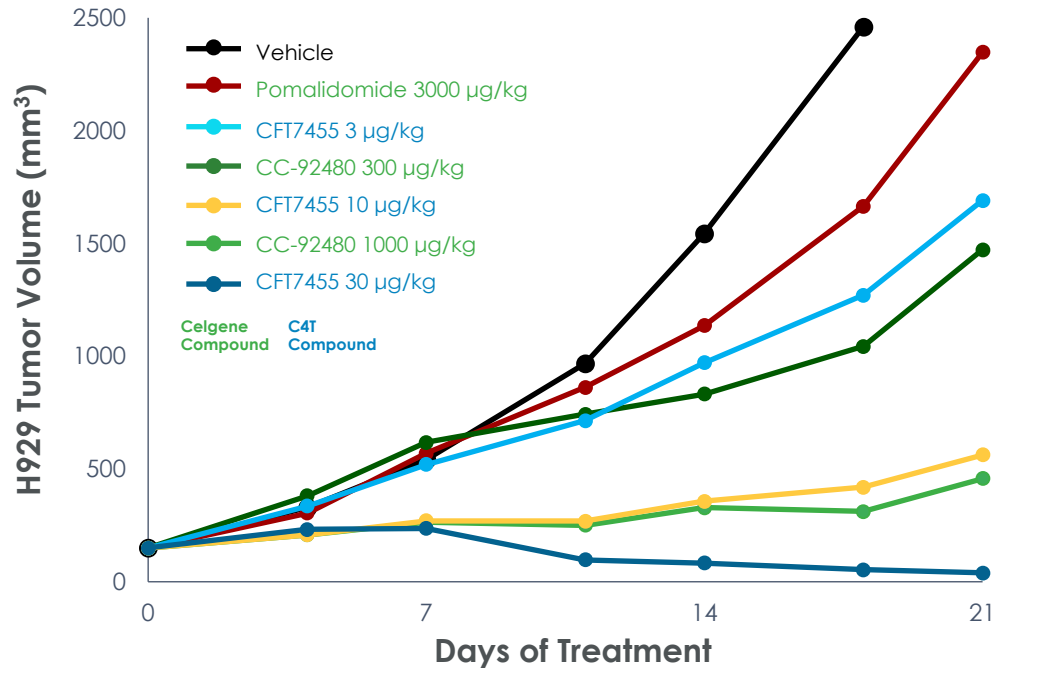
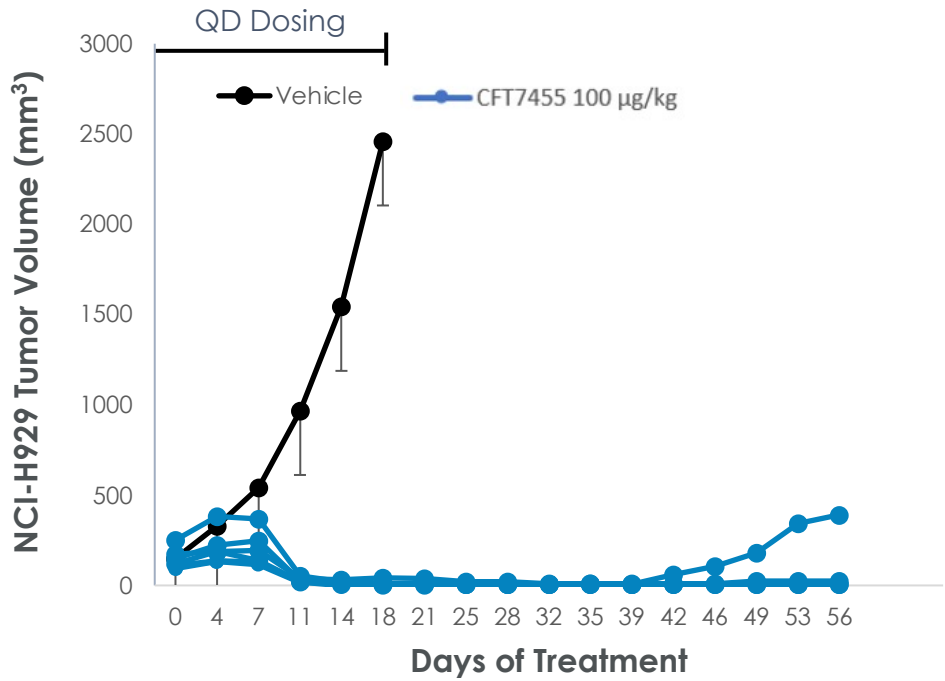
CFT7455 Demonstrates Improved Efficacy Compared to Both Approved and Most Advanced Development-Stage IKZF1/3 Degraders

CFT7455 *In Vivo* Efficacy – Near Complete Regression in MM Model

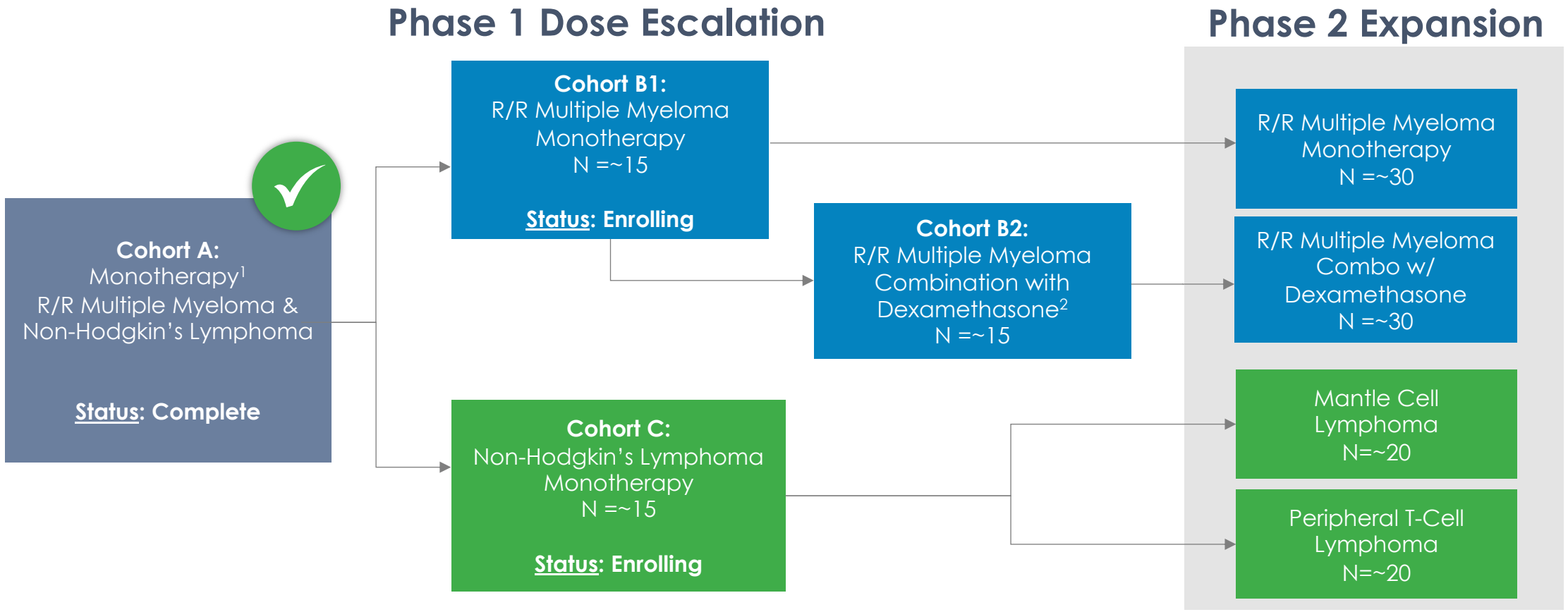


CFT7455 *In Vivo* Efficacy Durable After End of Dosing Period



Source: C4T data on file

CFT7455 Phase 1/2 Trial Design Offers Potential for Accelerated Approval across Three Indications



Cohort A Clinical Data to be Presented at AACR; Cohorts B1 & C Initiated

1. 28-day cycle / dose limiting toxicity (DLT) window
2. Combination therapy cohorts will open once the selected CFT7455 dose level has been cleared for safety

Note: 6-12 patient food effect enrichment cohort also included during escalation, not pictured in the schema

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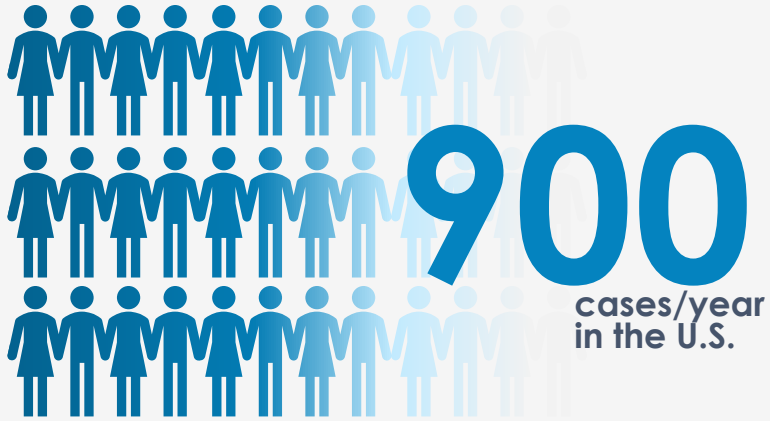
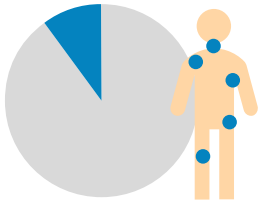
CFT8634
Targeting BRD9

Synovial Sarcoma &
SMARCB1-null Solid Tumors

Synovial Sarcoma Remains an Unmet Medical Need Due to its Undruggable Target

Synovial Sarcoma





10% of all soft tissue sarcomas are Synovial Sarcoma

All synovial sarcoma tumors harbor the **SS18-SSX fusion gene** resulting in BRD9 dependency

Current treatments have **very limited benefit** for advanced and metastatic patients

Sources: NIH SEER Database 2020, Primary Literature Consensus

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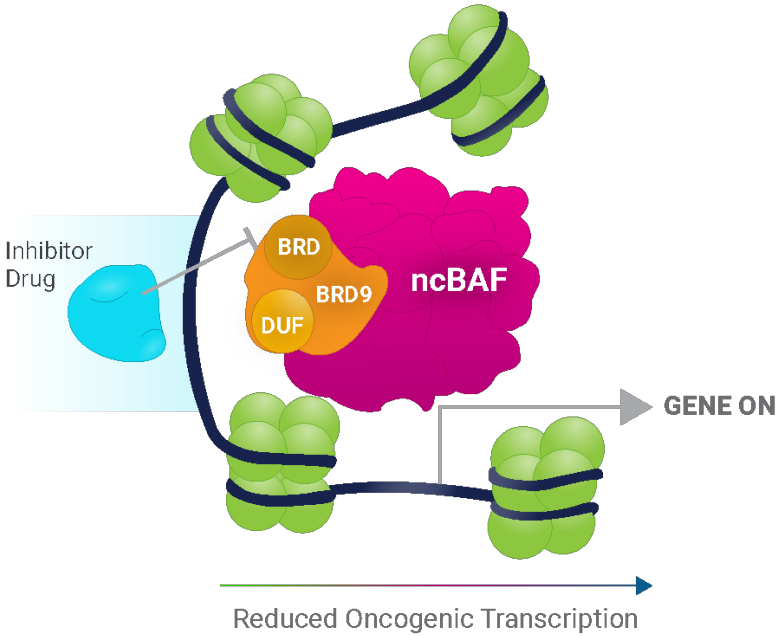
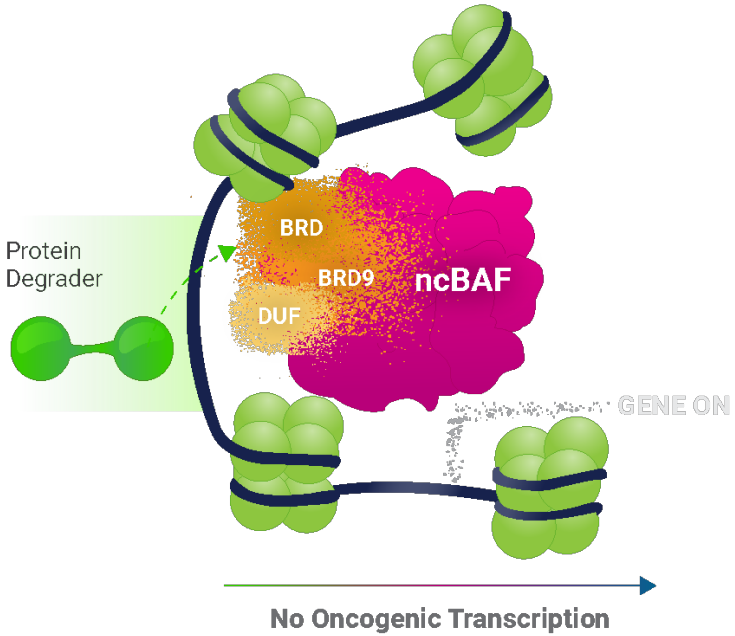
BRD9 Dependency in Synovial Sarcoma

Degrader Rationale



Protein degrader approach effectively targets BRD9 and does not require the binding site to be specifically at the physiologically active domain.



Advantages of BRD9 Degradation

- Specifically degrades BRD9 and spares BRD4 and BRD7, avoiding potential off-target toxicities
- Oncogenicity of BRD9 depends on sub-domains not addressed by traditional inhibitors

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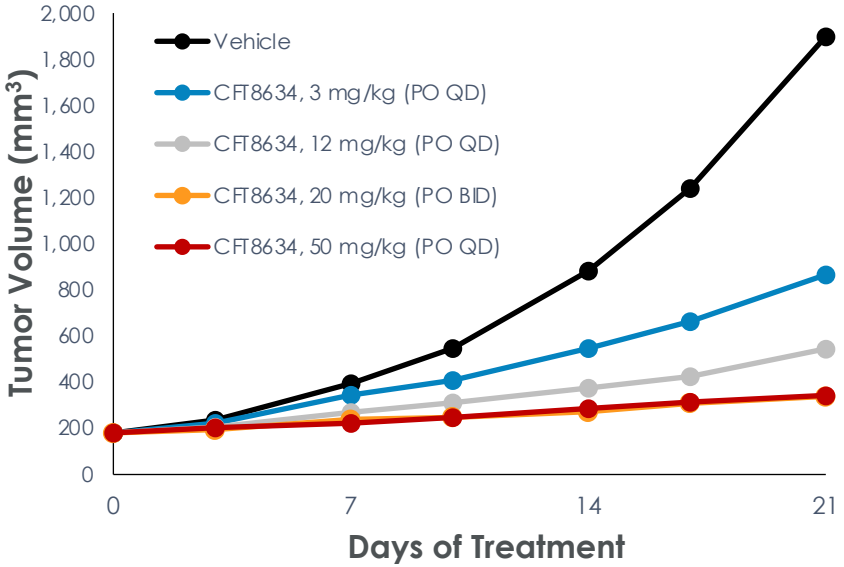
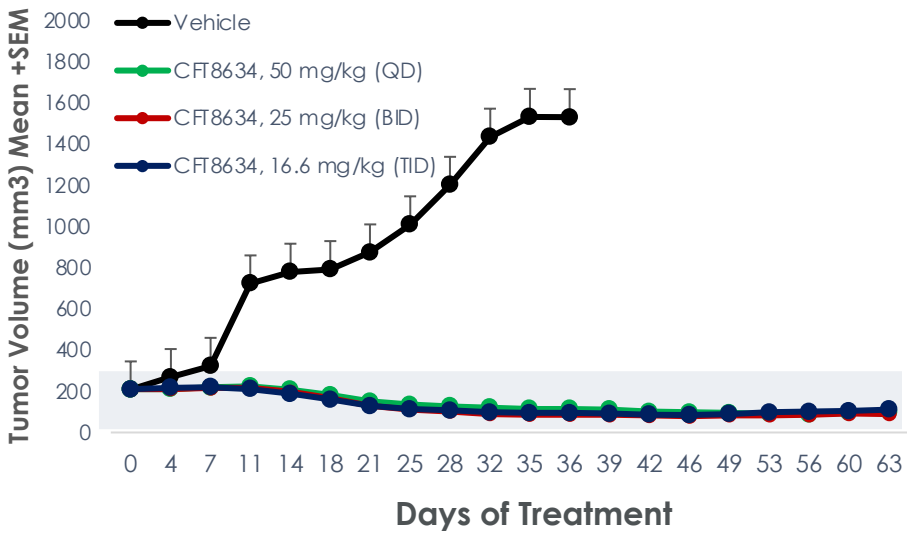
Robust Responses of CFT8634 Seen in Preclinical Synovial Sarcoma Models

Dose Response Activity Yamato Xenograft Model



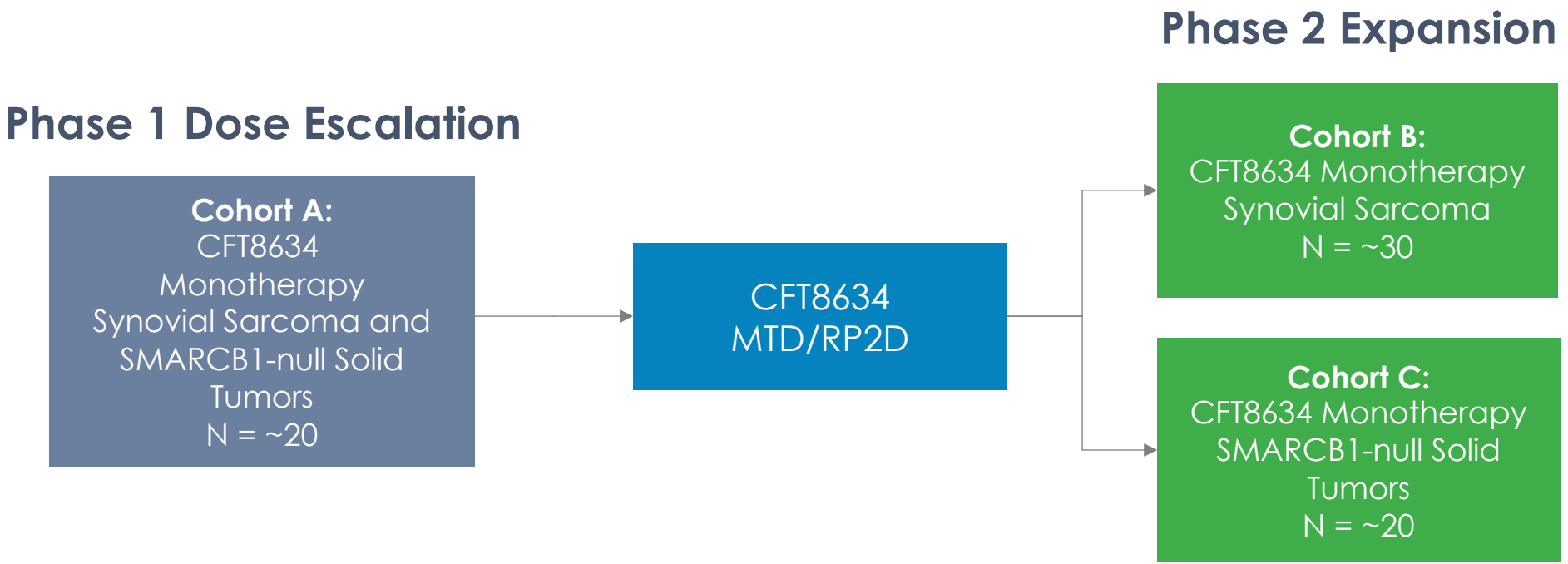
Dose Response Activity Patient Derived Xenograft Model



Pre-clinical Data to be Presented at AACR

Source: C4T data on file

CFT8634 First-in-Human Trial Design



Orphan Drug Designation Granted; Phase1/2 Trial Initiation Expected in 1H 2022

MTD = Maximum Tolerated Dose; RP2D = Recommended Phase 2 Dose

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CFT1946
Targeting BRAF V600X

Melanoma, Colorectal
& NSCLC

Multiple Tumors are Driven by BRAF Mutations; Current Treatments Often Lead to Resistance

BRAF Mutations Occur in ~15% of Cancers

>70K annual incidence

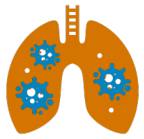
across Melanoma, Non-Small Cell Lung Cancer (NSCLC), Colorectal Cancer (CRC) and other malignancies

~70 – 90%

of BRAF mutations are V600X

Approved BRAF inhibitors cause paradoxical RAF activation, which may result in diminished efficacy

Resistance to 3 approved BRAF inhibitors emerges through multiple paths, resulting in a median PFS of <15 months



1–2% NSCLC

50% late-stage melanoma

10–20% CRC

50% Papillary thyroid

50% Langerhans cell histiocytosis

100% Hairy cell leukemia

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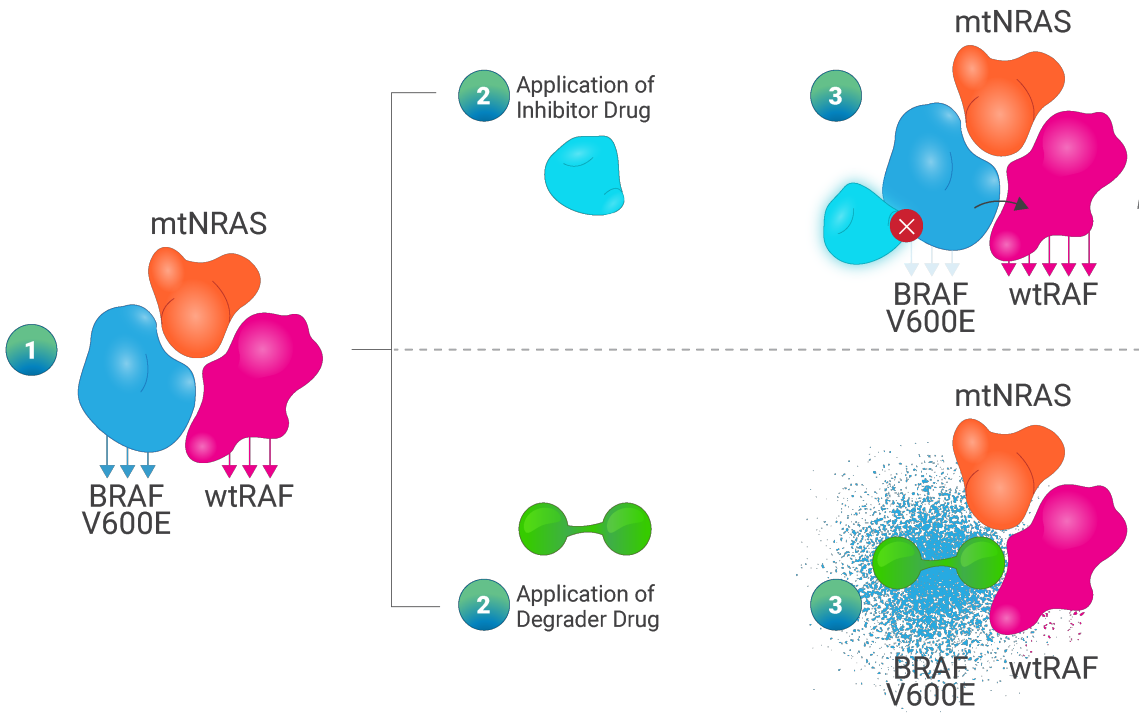
Sources: NIH SEER Database, Primary Literature Consensus. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5931274/, https://pubmed.ncbi.nlm.nih.gov/26980021/

Utilizing a Degrader Approach to Overcome Limitations of BRAF Inhibition

Degrader Rationale

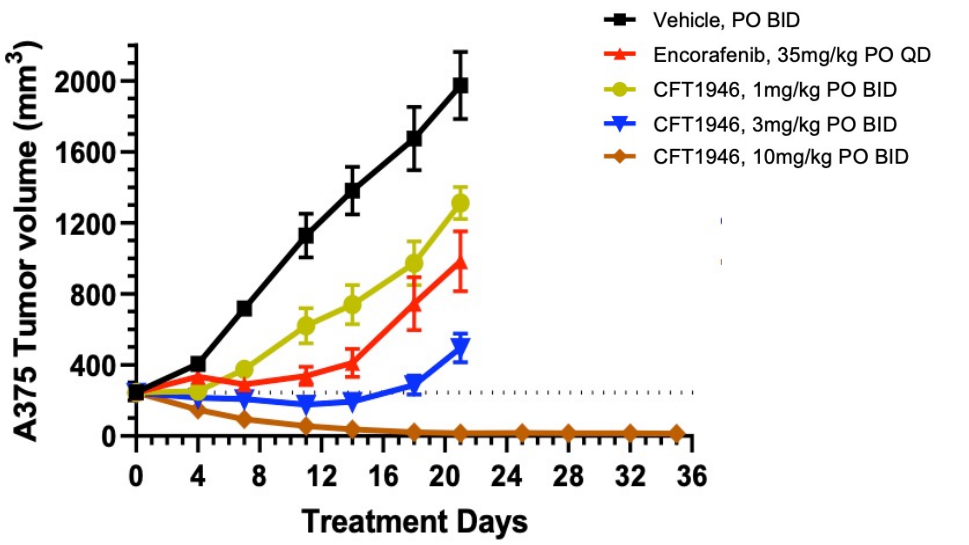


Advantages of BRAF V600E Degradation

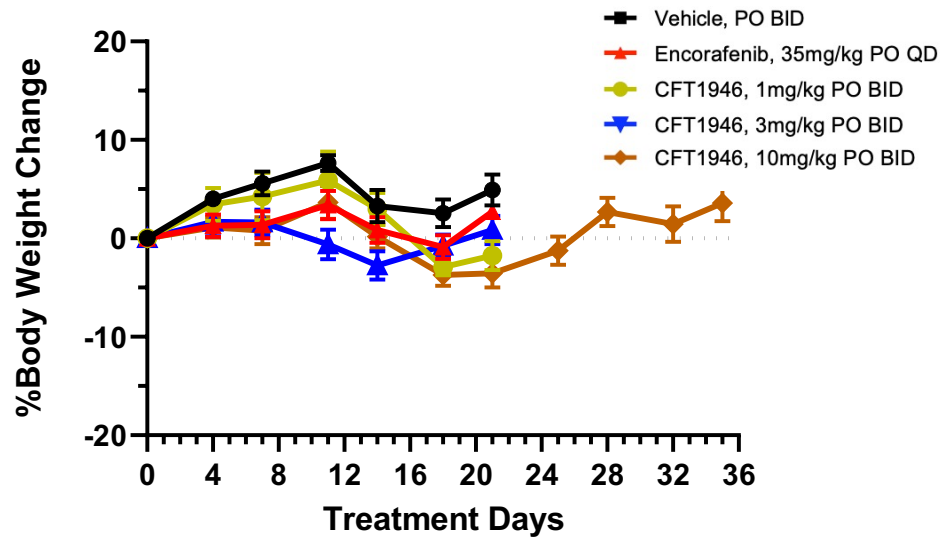
- Specifically target mutant BRAF over wildtype BRAF
- Prevent mutant BRAF incorporation into RAF dimers
- Avoid paradoxical activation and associated failure of therapy due to resistance mechanisms dependent on BRAF inhibitor mediated paradoxical activation
- Effect deeper elimination of mutant BRAF signaling and create more durable response

CFT1946 Shows Superior Efficacy Compared to Approved BRAF Inhibitor and Is Well Tolerated

CFT1946 Shows More Durable Efficacy Than Encorafenib



CFT1946 is Well Tolerated



Pre-clinical Data to be Presented at AACR; IND Submission and Phase 1 Initiation Expected in 2H 2022

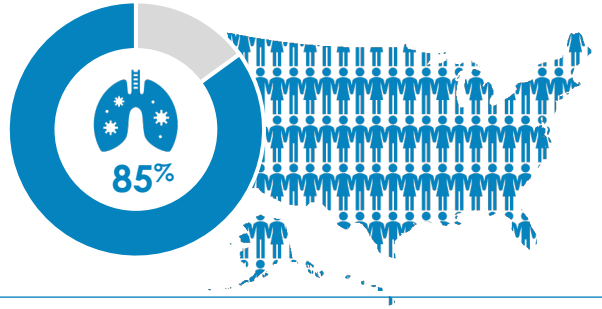
Source: C4T data on file

CFT8919
Targeting EGFR L858R

EGFR L858R
+ NSCLC

EGFR L858R Driven NSCLC Is Common and Inadequately Treated by EGFR Inhibitors

Non-Small Cell Lung Cancer (NSCLC)



2020 **195K**

US patients diagnosed

10 – 15%

of NSCLC patients have mutant EGFR (mEGFR) in the **U.S.** population

40%

of NSCLC patients have mEGFR in the **Asian** population

30 – 40%

of mEGFR NSCLC patients will develop **brain metastases**

L858R activating mutation

25–45%

mEGFR NSCLC

Osimertinib 1st line median PFS

OSI **14.4 months** (L858R)

1 years 2 years

OSI **21.4 months** (Exon 19 del)

1 years 2 years

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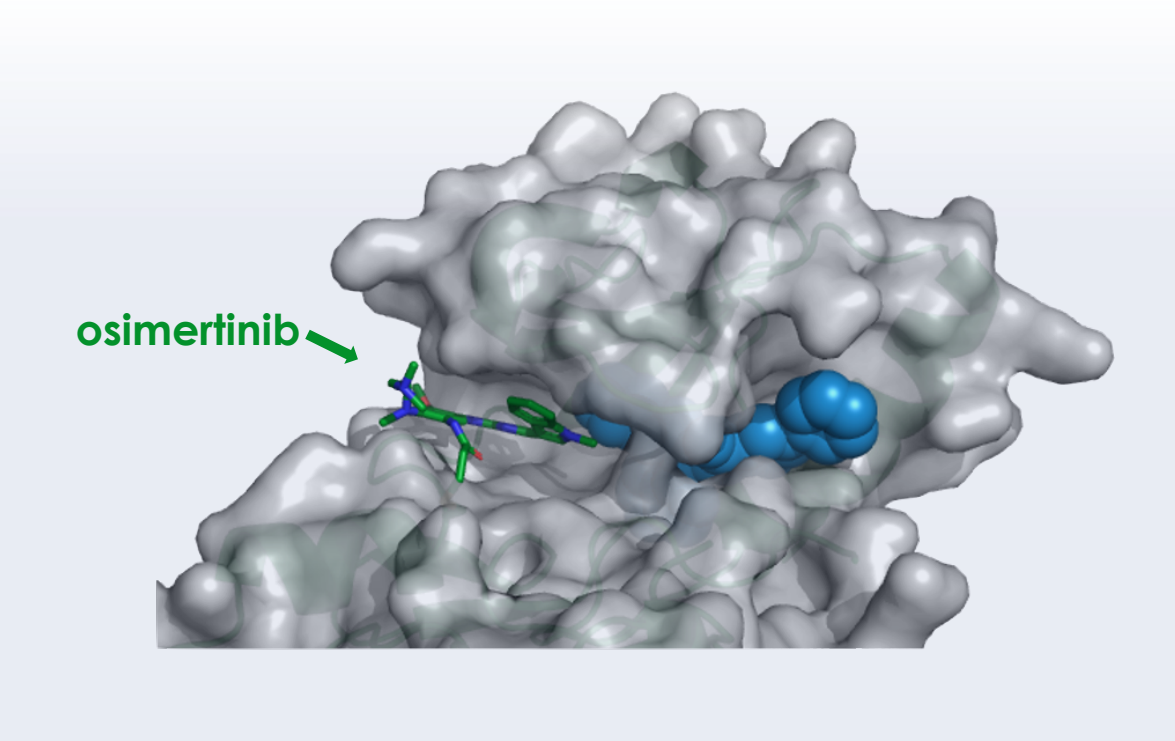
Sources:
- Zhang, Y.-L. et al. *Oncotarget* 7, 78985–78993 (2016); Li, K et al. *Oncol Rep* 37, 1347–1358 (2017); Shin, D.-Y. et al. *J Thorac* Oncol 9, 195–199 (2014); Rangachari, D. et al. Lung Cancer 88, 108-111 (2015); Jin Y. et al. Scientific Reports 6:31636 (2016); Soria, J.-C. et al. NEJM 378, 113–125 (2018)
- Soria, J.-C. et al. NEJM 378, 113–125 (2018), Sher, T. et al, *Mayo Clin. Proc.* 83, 355-367 (2008), NIH SEER Database 2020, Primary Literature Consensus

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



- CFT8919 exploits **allosteric binding site**, close to L858R activating mutation
- Allosteric binding site avoids known resistance-causing mutations in **orthosteric binding site**
- Allosteric binders do not require covalent binding through C797S and do not compete with osimertinib binding

Allosteric Binding Avoids Resistance Mutations and Wild-type Activity

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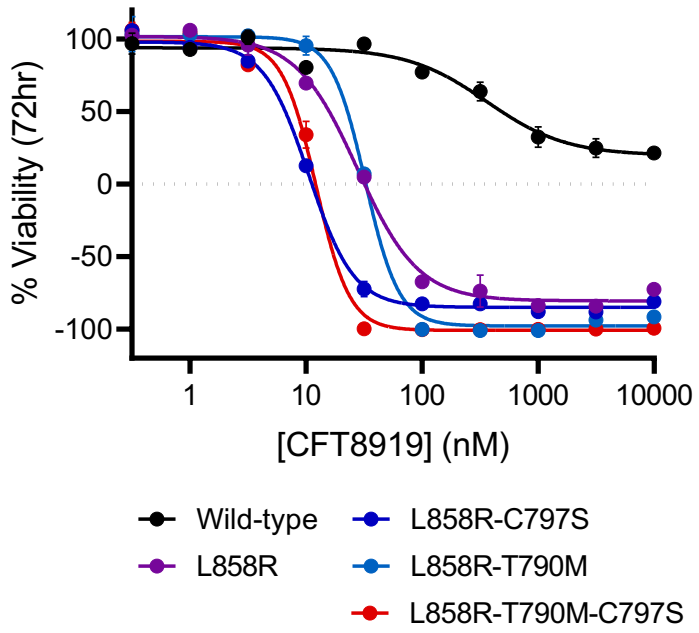
CFT8919 Is Active in Ba/F3 Models Expressing Secondary Mutations Resistant to Approved EGFR Inhibitors

Viability of Ba/F3 Cells Expressing the Indicated EGFR Variant



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

Source: Keystone 2021, C4T data on file

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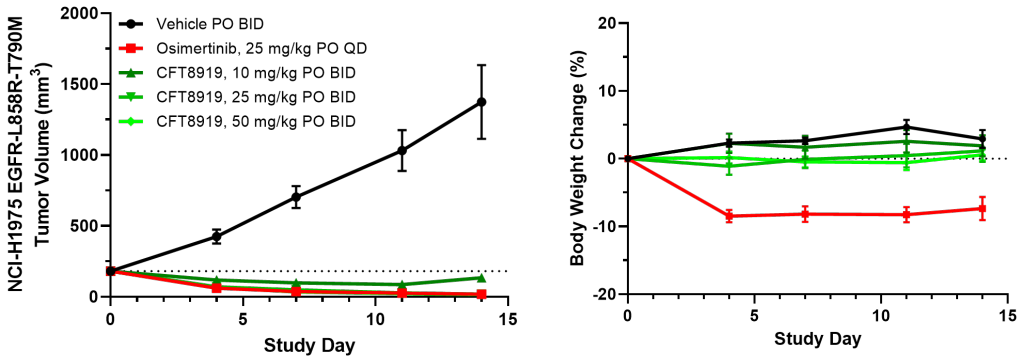
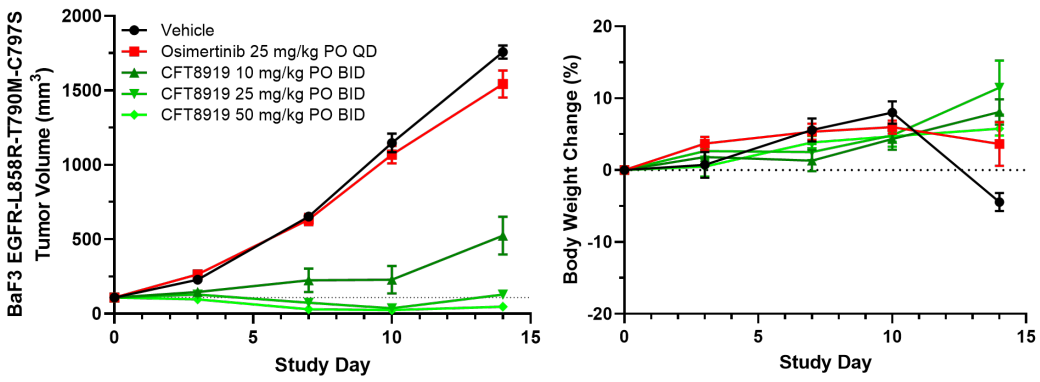
CFT8919 Induces Tumor Regression in Mouse Models Resistant to First and Third-Generation EGFR Inhibitors

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



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



Complete IND-Enabling Activities by Year-End 2022

Source: Keystone 2021, C4T data on file

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Advancing Multiple Oncology Programs to Patients

	2022 Milestones
CFT7455 (IKZF1/3)	❑ Present Cohort A Phase 1 data at AACR ❑ Present new pre-clinical data at AACR
CFT8634 (BRD9)	✓ Orphan Drug Designation ❑ Present pre-clinical data at AACR ❑ Initiate Phase 1 trial in 1H
CFT1946 (BRAF V600X)	❑ Present pre-clinical data at AACR ❑ Submit IND application in 2H ❑ Initiate Phase 1 trial in 2H
CFT8919 (EGFR L858R)	❑ Complete IND-enabling activities

AACR Presentations

Program	Session	Title
CFT7455	Time: Tuesday, April 12, 9am – 12:30 pm CT Abstract Number: CT186	"Pharmacokinetic (PK) Profile of a Novel IKZF1/3 Degrader, CFT7455, Enables Significant Potency Advantage over Other IKZF1/3 Degraders in Models of Multiple Myeloma (MM) and the Results of the Initial Treatment Cohort from a First-in-Human (FIH) Phase 1/2 Study of CFT7455 in MM"
CFT7455	New Drugs on the Horizon: Part 3 Time: Monday, April 11; 10:15 am - 11:45 am CT Abstract Number: 7922	"The Discovery and Characterization of CFT7455: A Potent and Selective Degrader of IKZF1/3 for the Treatment of Relapsed/Refractory Multiple Myeloma"
CFT8634	New Drugs on the Horizon: Part 2 Time: Sunday, April 10; 3-4:30 pm CT Abstract Number: 7756	"The Discovery and Characterization of CFT8634: A Potent and Selective Degrader of BRD9 for the Treatment of SMARCB1-Perturbed Cancers"
CFT1946	Emerging New Cancer Agents Time: Monday, April 11, 2:30 pm – 4:30 pm CT Abstract Number: 2158	"Preclinical Evaluation of CFT1946 as a Selective Degrader of Mutant BRAF for the Treatment of BRAF Driven Cancers"

Thank You