C4 Therapeutics

Corporate Presentation

November 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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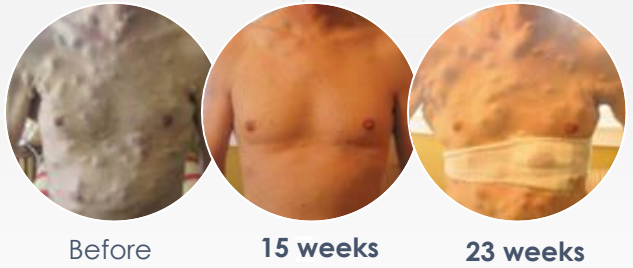
Targeted Protein Degradation Has the Potential to Transform Treatment of Disease

<15%

Of Human Proteome Addressable by Small Molecule Inhibitors

Substantial opportunity to develop treatments for targets previously considered undruggable



Adapted from Wagle et al, J Clin Oncol, 2011

Cancers become resistant to standard therapies and treatment options are then limited

$63B

2018 Global Revenue

Oncology small molecule therapies generate significant revenue despite known limitations

Targeted Protein Degradation Has Potential to Drug the Remaining ~85% of the Human Proteome and Overcome Resistance to Existing Inhibitor Medicines

Sources: Hopkins, A., Groom, C. The druggable genome. Nat Rev Drug Discov 1, 727–730 (2002). https://doi.org/10.1038/nrd892; "A view on drug resistance in cancer" Nature | Vol 575 | 14 November 2019; Fact.MR: https://www.factmr.com/report/3747/oncology-small-molecule-drugs-market

C4 Therapeutics

C4T is Well Positioned to Develop Targeted Protein Degradation Medicines to Transform Patient Care

*as of 9/30/21

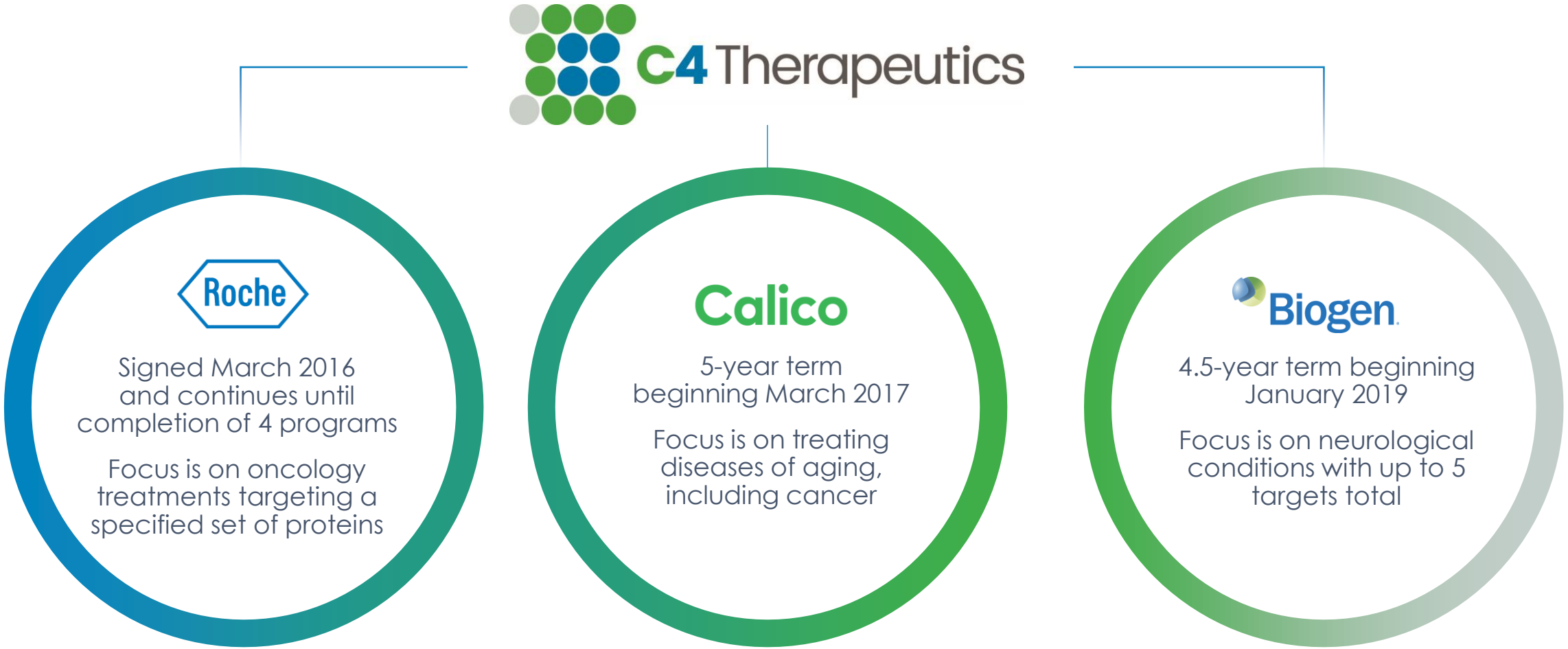
C4 Therapeutics

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 V600X (CFT1946)	Drug-Resistant BRAF mutant Tumors				C4 Therapeutics
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

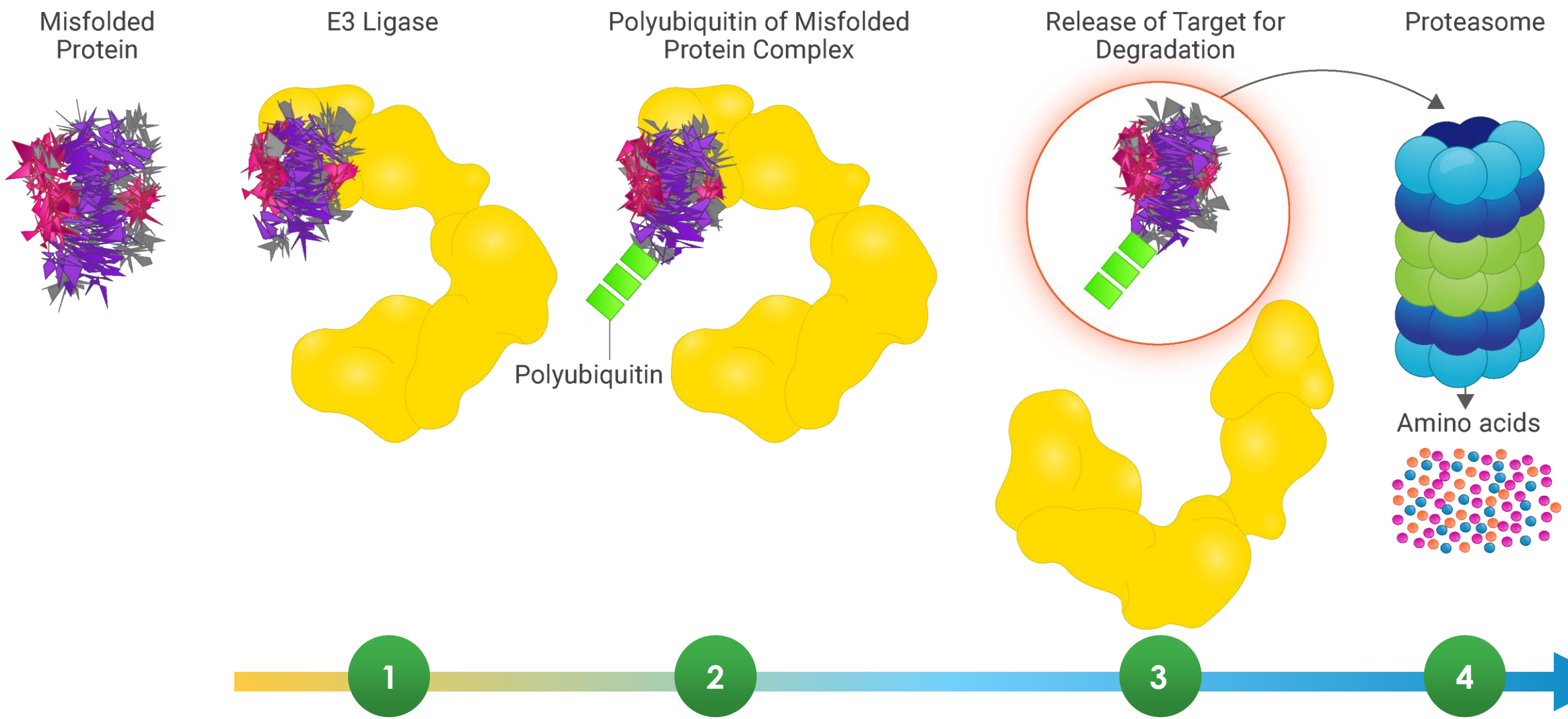
Three Strategic Target Platform Collaborations Expand Platform Potential



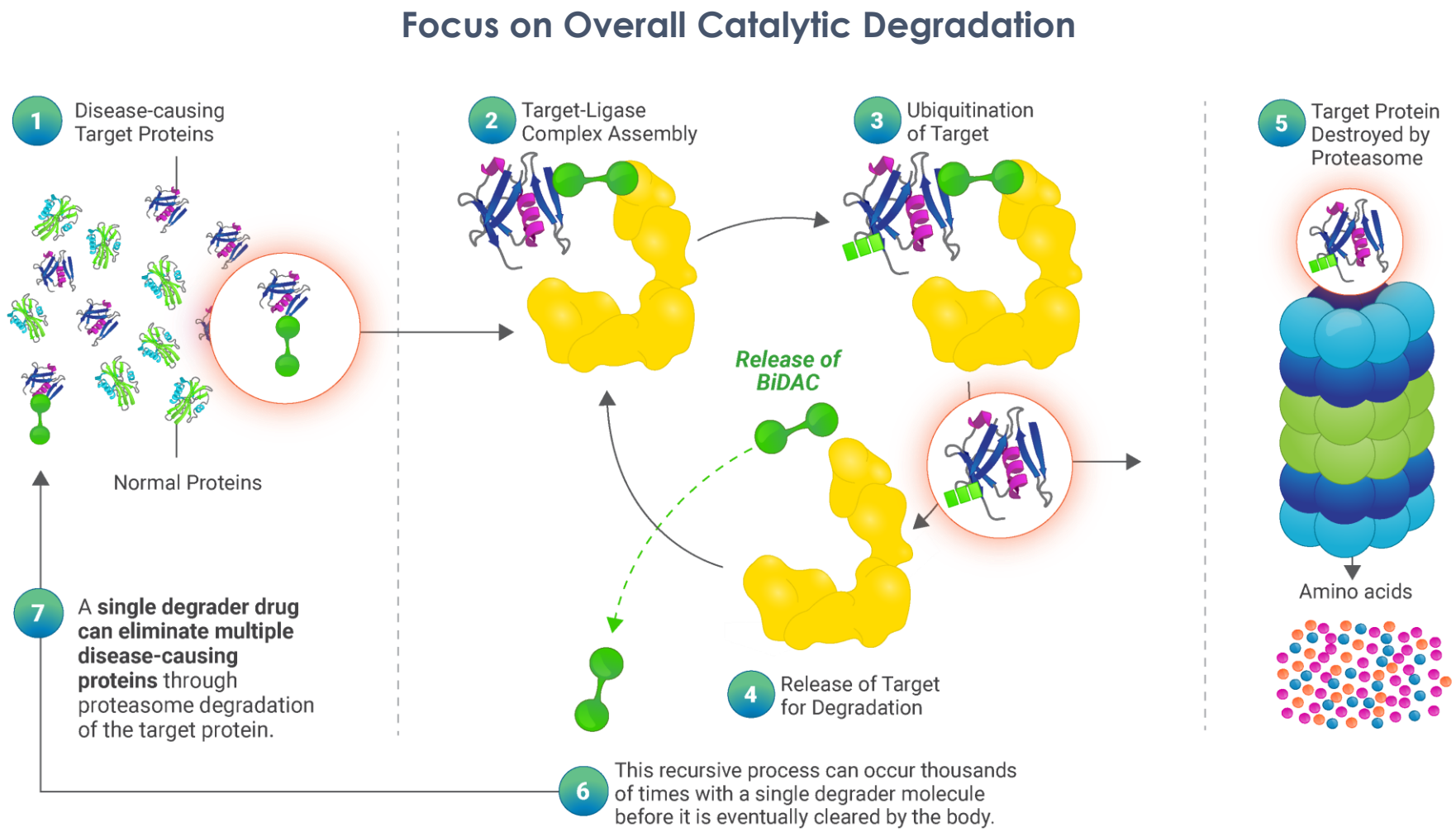
2021 Milestones Support Progress Toward Goal of Four Clinical-Stage Programs by Year-End 2022

	2021	2022
IKZF1/3 (CFT7455)	✓ Phase 1/2 Initiation ✓ Orphan Drug Designation	❑ Phase 1 Safety & Efficacy ❑ Proof of Mechanism
BRD9 (CFT8634)	❑ IND Submission	❑ Phase 1 Initiation
EGFR (CFT8919)	✓ IND Enabling Activities	❑ IND Submission ❑ Phase 1 Initiation
BRAF (CFT1946)	✓ Development Candidate ✓ IND Enabling Activities	❑ IND Submission ❑ Phase 1 Initiation
RET	❑ Lead Optimization	

The Human Body Has A Natural Process to Destroy Unwanted Proteins

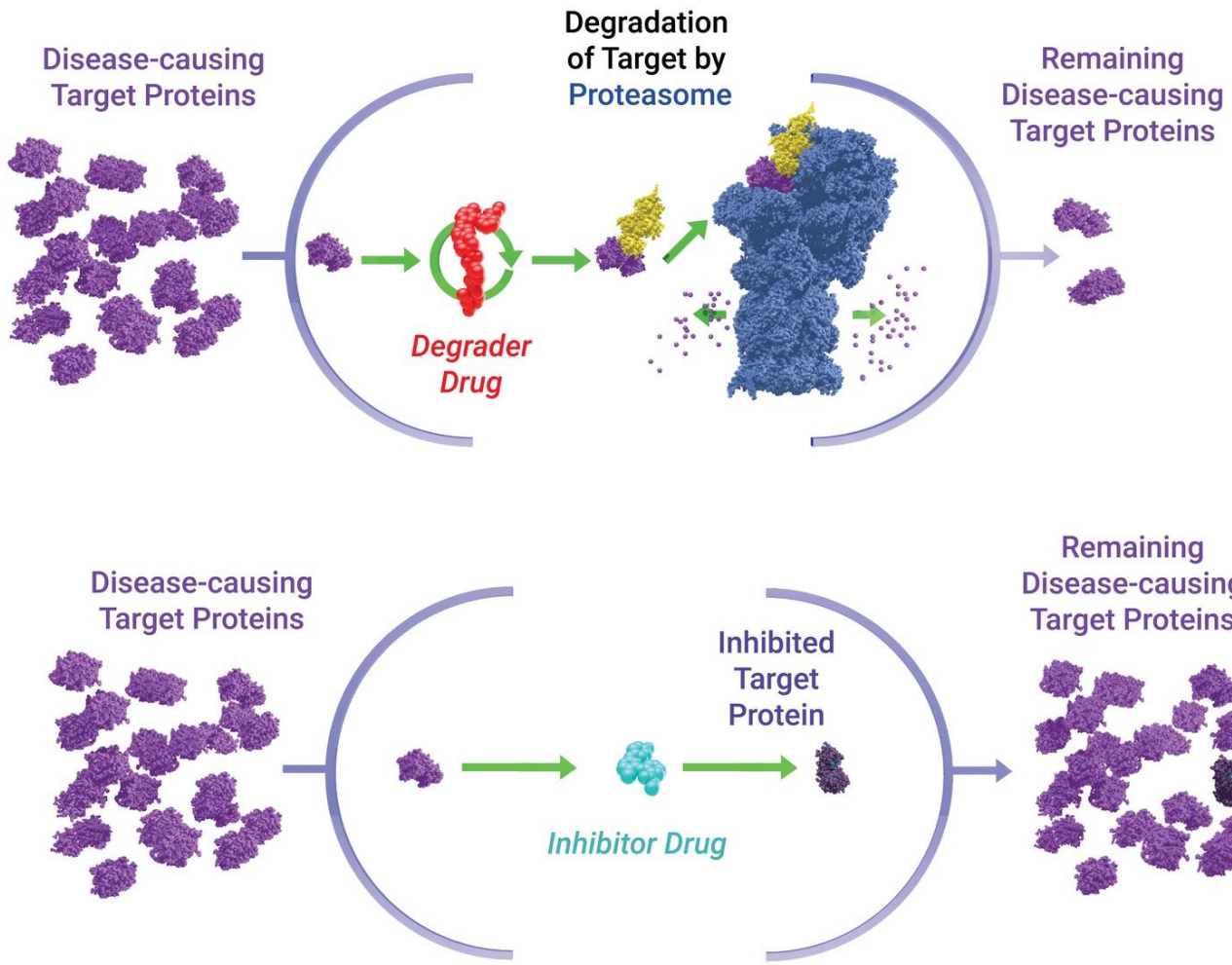


Targeted Protein Degradation Leverages the Body's Natural Process to Destroy Disease-Causing Proteins



Targeted Protein Degradation Offers Fundamental Advantages Over Protein Inhibition

1. **Improved Potency**
2. **Fast Response**
3. **High Selectivity**
4. **Expansive Target Landscape**



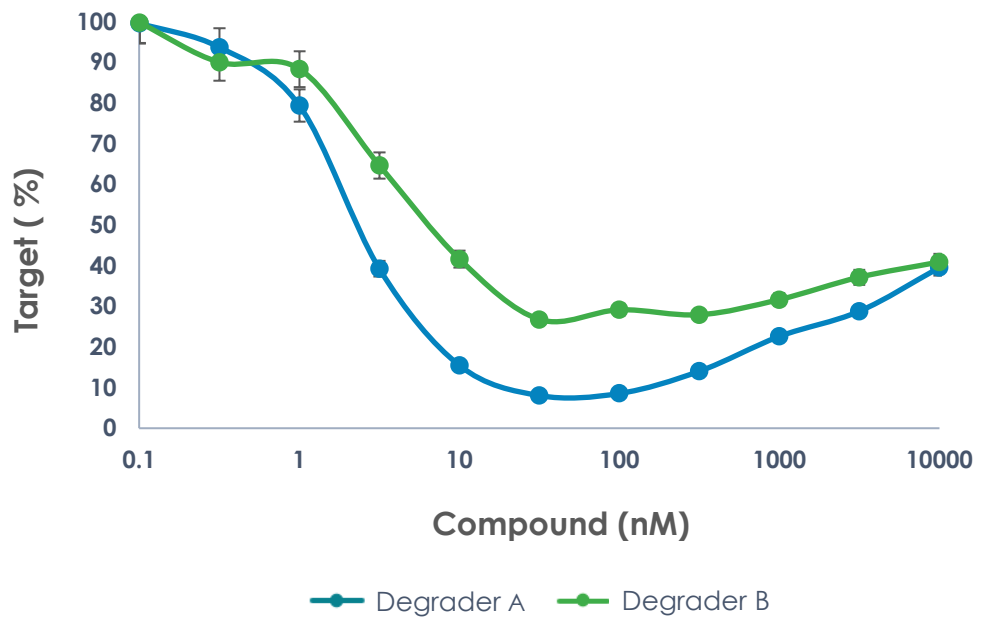
TORPEDO (Target ORiented ProtEin Degrader Optimizer) Platform

Our TORPEDO Platform Has Potential to Efficiently Design Highly Potent Targeted Protein Degrader Medicines

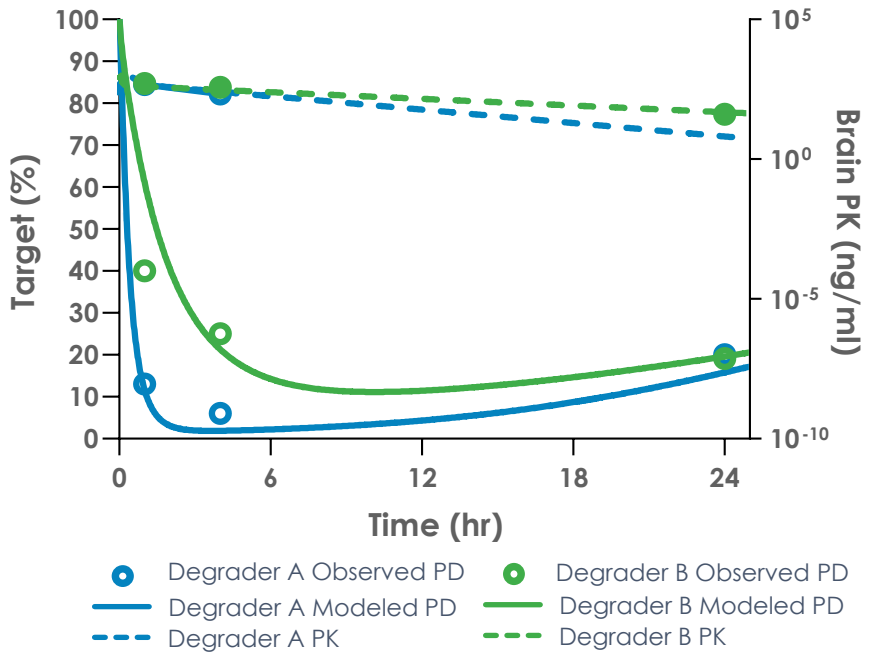
Elements	Benefits
Focus on Catalytic Efficiency	Optimization of overall degradation process results in maximal efficacy
Ability to Design, Analyze & Predict Degrader Performance	Rapid delivery of potent drug candidates through informed and efficient drug discovery
Investment in Cereblon as E3 Ligase	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

Enhanced Catalytic Activity Drives Efficacy

Improved Catalytic Activity of Degrader A…



…Drives Significant Improvement in Target Knockdown



Source: C4T data on file

C4 Therapeutics

TORPEDO Platform: Robust Drug Discovery Process Enabling Higher Confidence in *In Vivo* Efficacy

Design

Computational method incorporates experimental data to identify top models

Atomic-level degrader design utilized to improve selectivity and potency

Analyze

Cellular degradation data fitted using an enzymology framework

Key parameters describe intrinsic degradation activity

Predict

Universal modeling framework merges degradation activity with degrader exposure

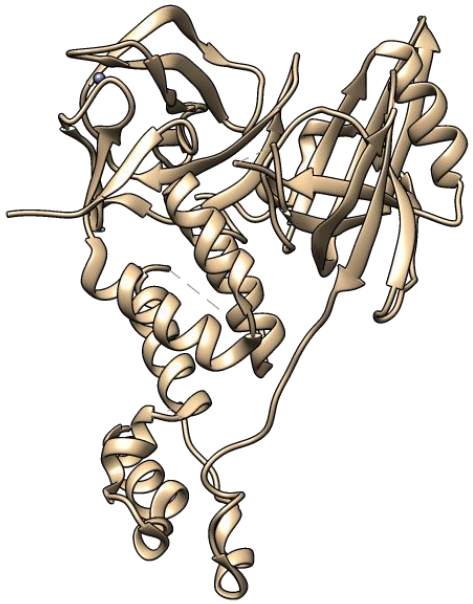
Robust predictions of depth and duration of *in vivo* target degradation at any dose

Rapid Delivery of Potent Drug Candidates Through Informed and Efficient Drug Discovery

C4 Therapeutics

TORPEDO is Based on a Deep Focus on Cereblon, Providing the Largest Target Selection Opportunity

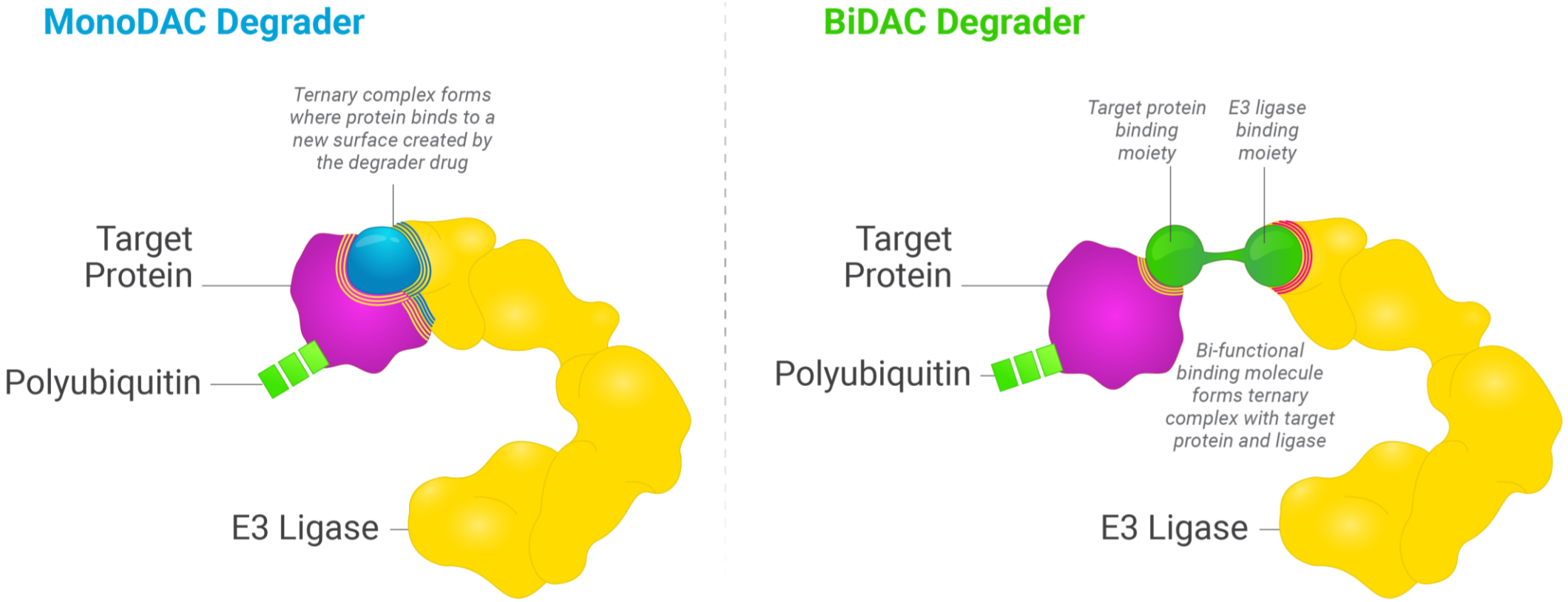
Cereblon E3 Ligase



- Cereblon, harnessed by IMiDs, is the only clinically validated ligase for targeted protein degradation
- Cereblon is expressed in all tissues and in all cellular compartments
- Investment in rich toolkit of intellectual property with more than 15 structurally distinct Cereblon binders
- C4T's binders enable drug discovery with enhanced oral bioavailability, solubility, permeability & stability

Programs Benefit from Desirable Properties of C4T's Cereblon Binders

TORPEDO Platform Offers Flexibility to Design MonoDAC and BiDAC Degraders



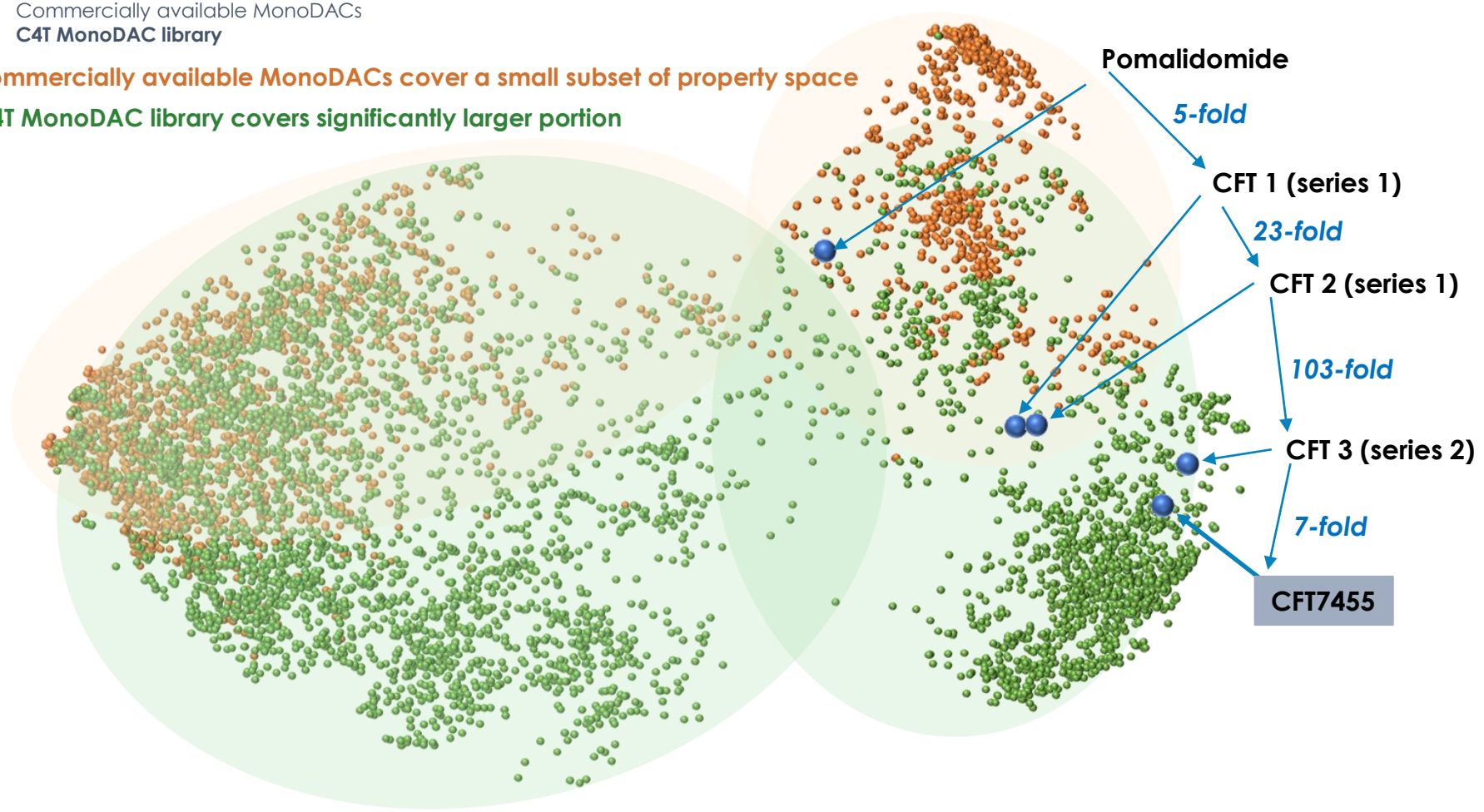
Flexibility to Address Different Targets with Tailored Approach

C4T MonoDAC Library: Expanding the Cereblon Toolbox

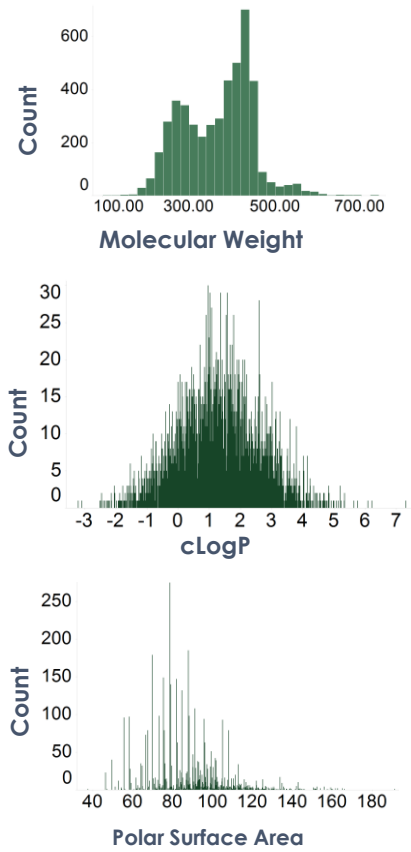
Commercially available MonoDACs
C4T MonoDAC library

Commercially available MonoDACs cover a small subset of property space

C4T MonoDAC library covers significantly larger portion



Drug-like property space



>4,000 membered library constructed from >200 unique scaffolds to maximize MonoDAC structural diversity and cereblon surface remodeling

C4 Therapeutics

IKZF1/3
CFT7455

IKZF1/3: Maximal Catalytic Activity Leads to Improved Efficacy

Strong Rationale for Degrader Approach

- Multiple myeloma (MM) and Non-Hodgkin's lymphomas (NHLs) are dependent on IKZF1/3
- Existing IKZF1/3 degraders have limited potency

Clear Unmet Need

- Patients progress on approved IMiD therapies
- Approved IMiDs have limited activity in NHLs

Defined Patient Populations

- MM: ~32K cases/year; median 5-year overall survival (OS): 53.9%
- NHL: ~77K cases/year
- PTCL: ~4% of all NHLs; median 5-year OS: 20-32%
- MCL: ~7% of all NHLs; median OS: 4-5 years

Compelling Development Opportunity

- Potential for accelerated approval in select indications
- Opportunity to expand into earlier lines of MM therapy

Sources: NIH SEER Database 2020, Primary Literature Consensus

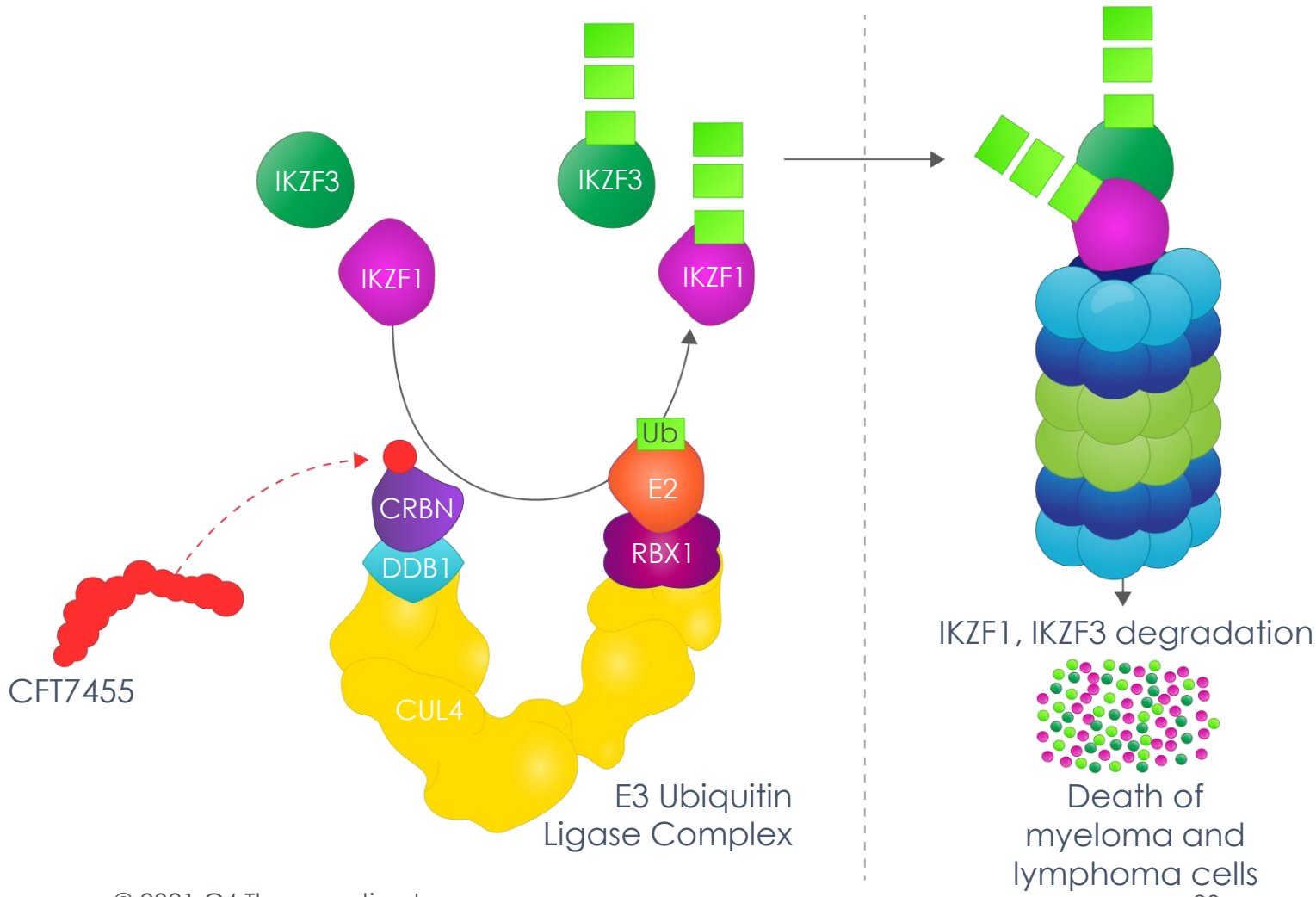
Patient figures represent estimated U.S. annual incidence
PTCL = peripheral T-cell lymphoma; MCL = mantle cell lymphoma

C4 Therapeutics

CFT7455: Potent Small Molecule IKZF1/3 Degrader Optimized for Catalytic & Pharmacologic Properties

Goal: Develop an IKZF1/3 Monofunctional Degradation Activating Compound (MonoDAC) with these properties:

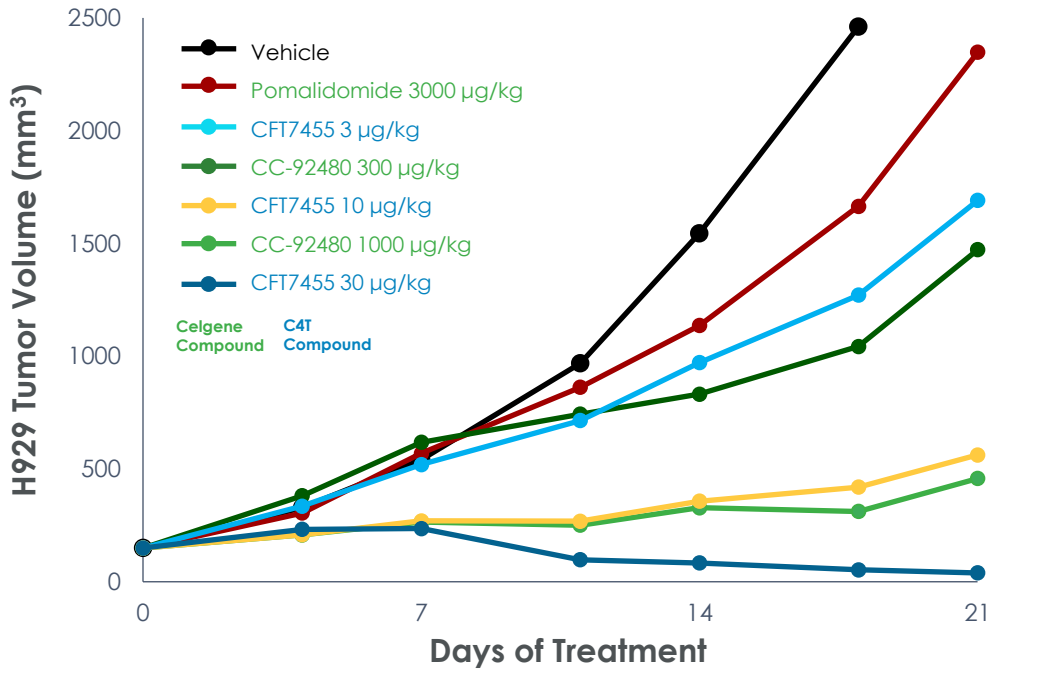
- Class-leading catalytic activity to enable potent, rapid, and deep target degradation
- High binding affinity to overcome IMiD resistance
- Selective to reduce off-target liabilities
- Optimized pharmacologic profile to enable sustained IKZF1/3 degradation



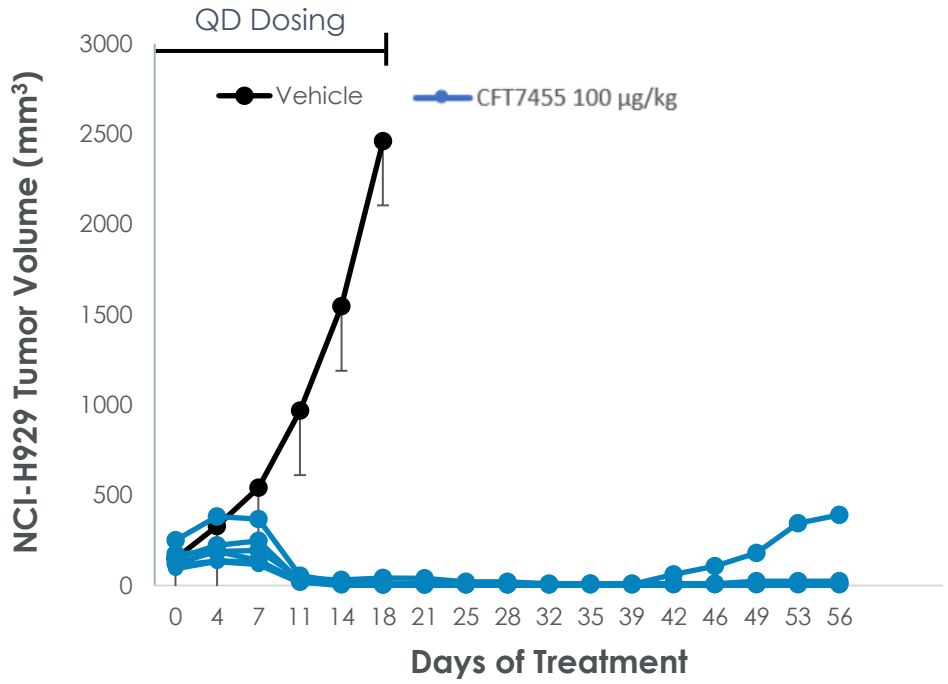
C4 Therapeutics

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

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



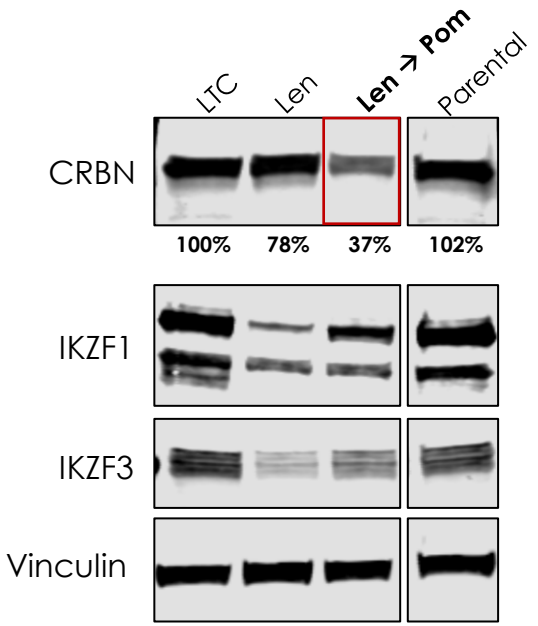
CFT7455 *In Vivo* Efficacy Durable After End of Dosing Period



Source: C4T data on file

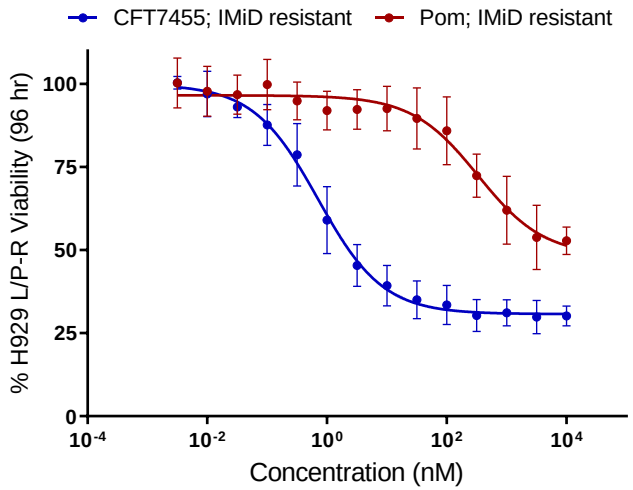
CFT7455 Demonstrates Tumor Regression in Multiple Myeloma Xenograft Insensitive to Pomalidomide

Reduction in CRBN Expression with Chronic IMiD Dosing

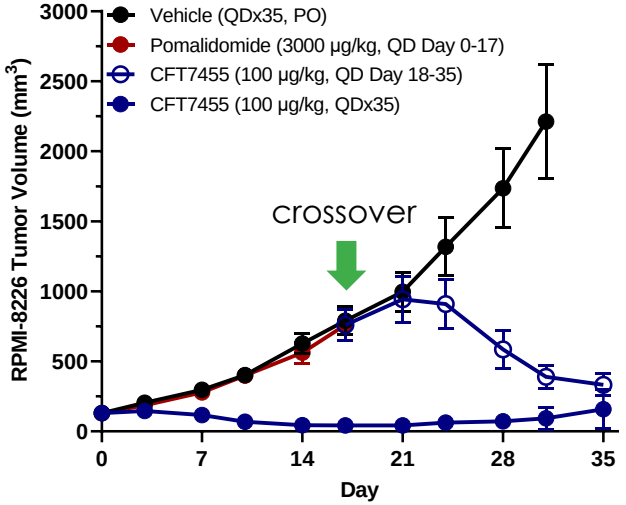


LTC = long term culture in DMSO
Parental = Original, naive H929 cells

CFT7455 Retains Activity in Len- & Pom-Resistant MM Cells



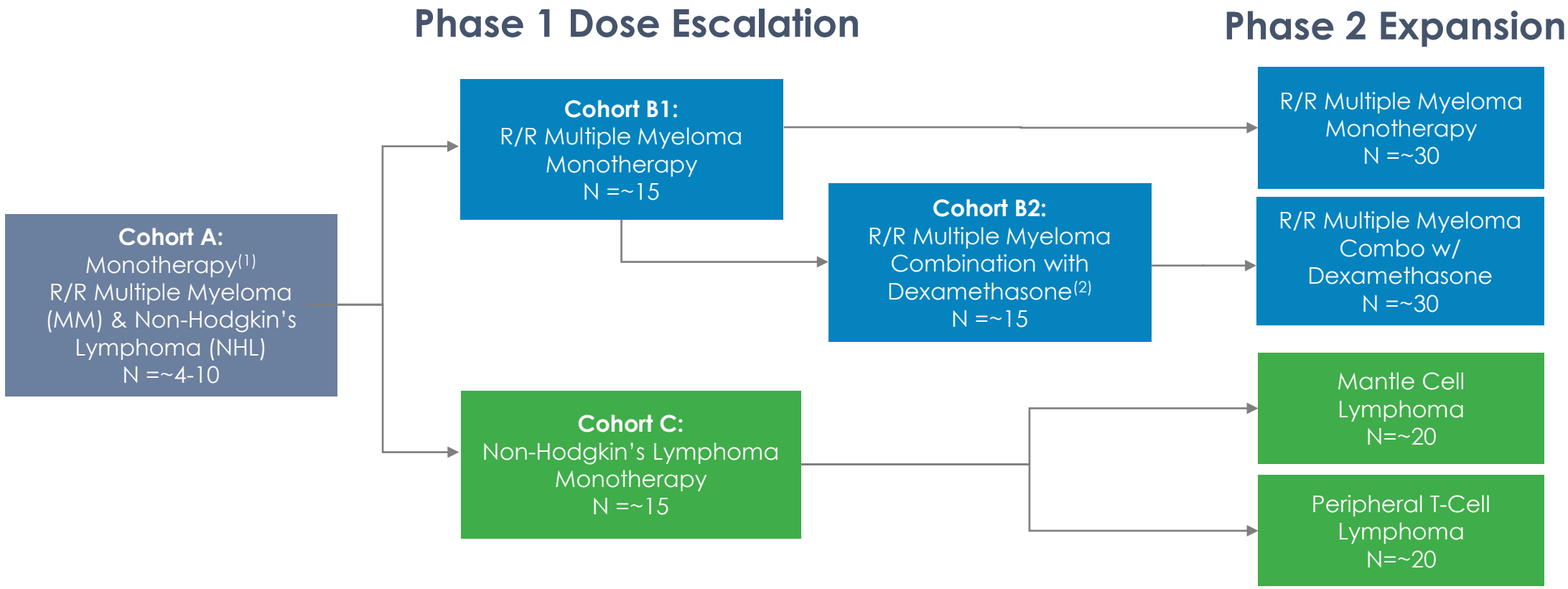
CFT7455 Promotes Regression in Tumors Insensitive to Pomalidomide



Len, lenalidomide; L/P-R, Len/Pom-Resistant

Source: AACR 2021, C4T data on file

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



First Clinical Data Expected in 2022

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

C4 Therapeutics

BRD9
CFT8634

BRD9: Drugging the Undruggable with a Degrader Approach

Strong Rationale for Degrader Approach

- Synovial sarcoma (SS) is dependent on BRD9, which is caused by the oncogenic SS18-SSX translocation
- Oncogenicity of BRD9 depends on sub-domains not addressed by traditional inhibitors

Clear Unmet Need

- Very limited benefit of treatments for metastatic or advanced SS – median survival ~18 months

Defined Patient Populations

- SS: ~900 cases/year
- ~10% of all soft tissue sarcomas

Compelling Development Opportunity

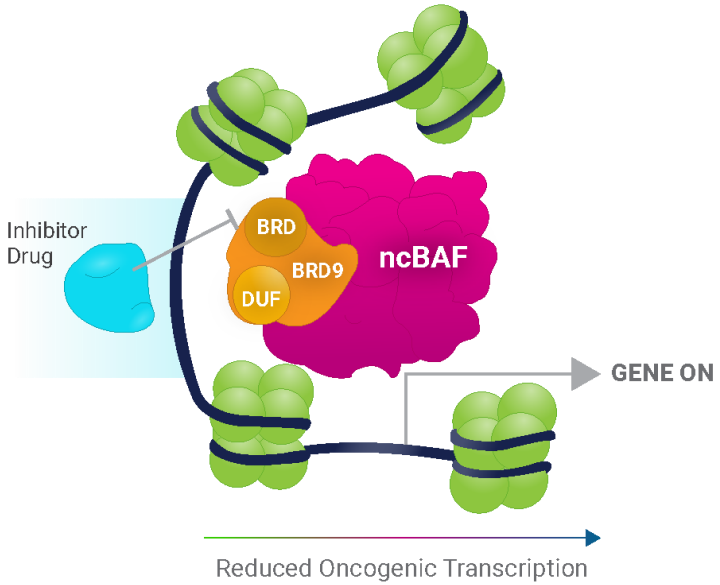
- Well defined path to registration in SS and metastatic population already under management at academic centers
- Precedent for approval with a single-arm study in second-line setting

Sources: NIH SEER Database 2020, Primary Literature Consensus

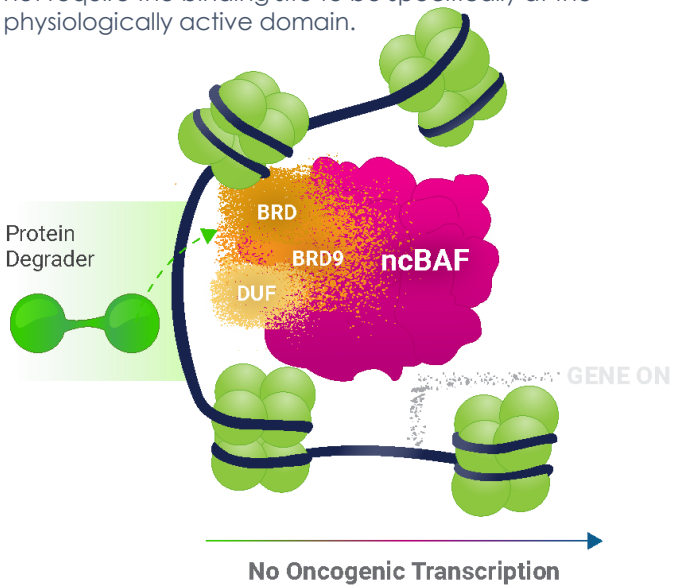
Patient figures represent estimated U.S. annual incidence

BRD9 Dependency in Synovial Sarcoma

Mechanistic Rationale



Leveraging a protein degrader approach enables us to effectively target BRD9 since our degraders do not require the binding site to be specifically at the physiologically active domain.

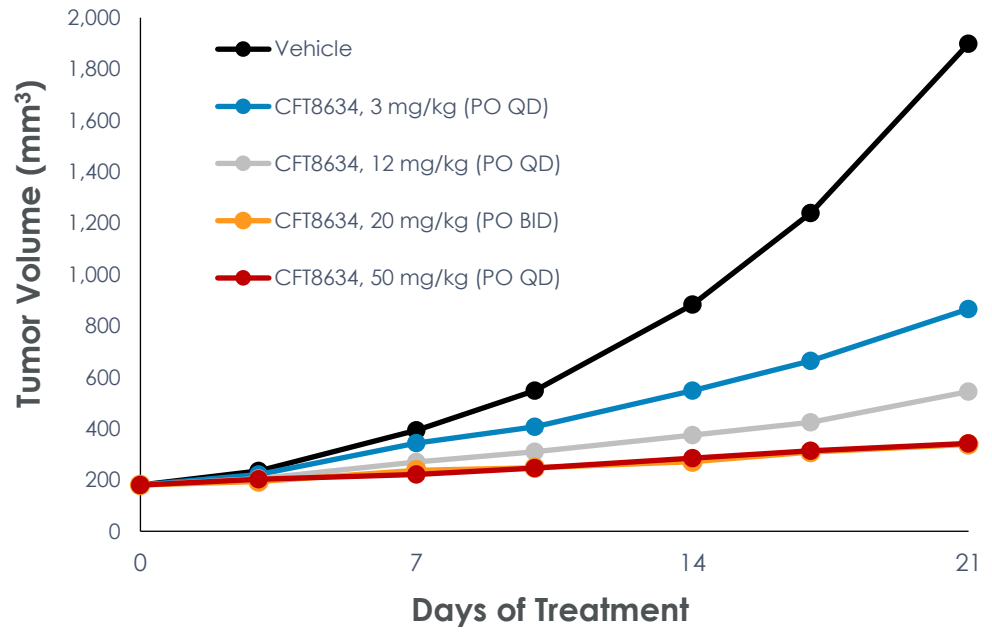


Advantages of BRD9 degradation

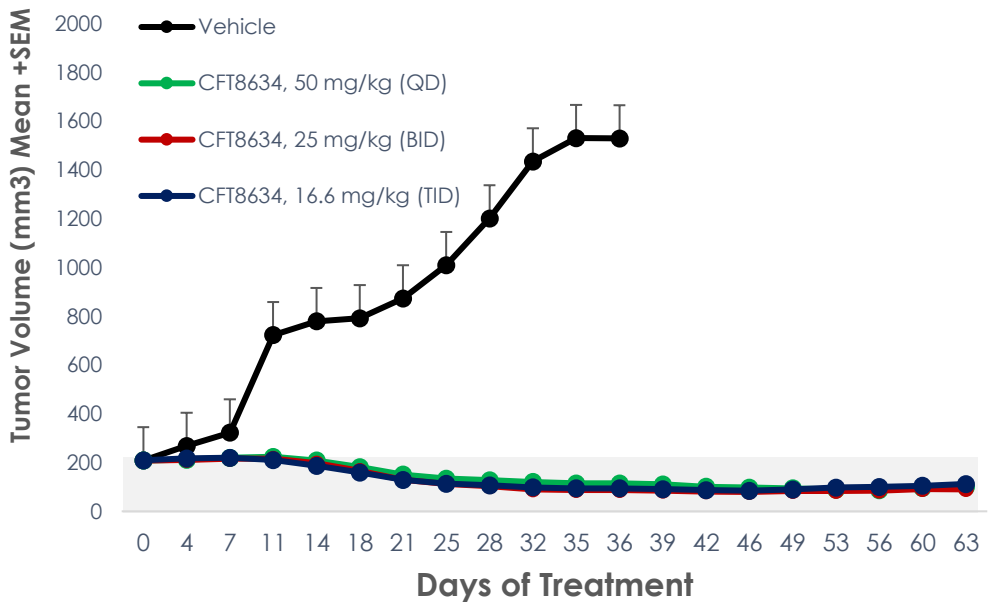
- Specifically degrades BRD9 and spares BRD4 and BRD7, avoiding potential off-target toxicities
- Oncogenicity of BRD9 depends on sub-domains not addressed by traditional inhibitors

Robust Responses of CFT8634 Seen in Preclinical Synovial Sarcoma Models

Dose Response Activity Yamato Xenograft Model

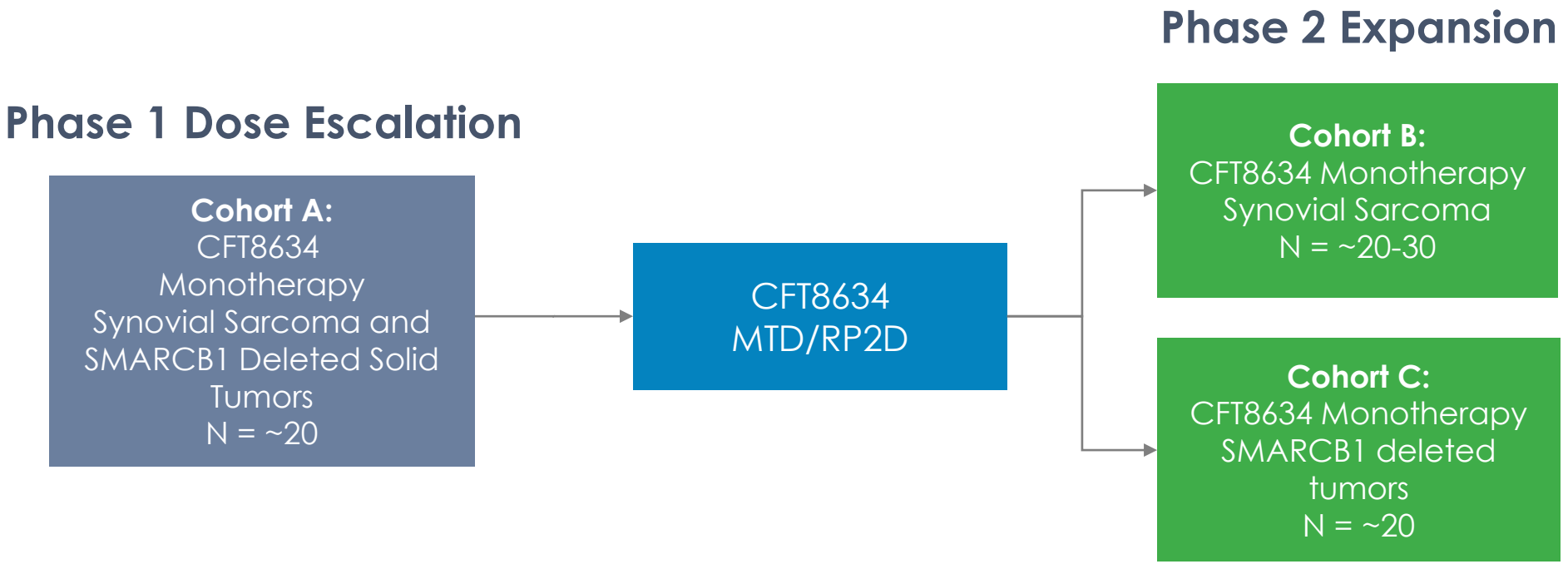


Dose Response Activity Patient Derived Xenograft Model



Source: C4T data on file

CFT8634 First-in-Human Protocol Concept Schema



IND Submission for CFT8634 Expected by End of 2021

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

C4 Therapeutics

EGFR
CFT8919

EGFR: Utilizing a Degrader Approach to Overcome Resistance to Approved EGFR Inhibitors and Address a Wider Range of Mutations

Strong Rationale for Degrader Approach

- Overcome resistance to approved EGFR inhibitors
- Ability to address wide range of EGFR resistance mutations
- Potential to effect deeper and more durable response due to advantages of degraders

Clear Unmet Need

- L858R mutation predicts less durable response to EGFR inhibitors
- Osimertinib 1st line PFS:
  - L858R: 14.4 mo
  - Ex19del: 21.4 mo
- Current therapies all bind at the same site and resistance can occur by genetic changes that block inhibitor binding

Defined Patient Populations

- NSCLC comprises ~85% of all US lung cancer cases, ~195K patients diagnosed in 2020
- EGFR is the most common receptor tyrosine kinase (RTK) driver in NSCLC
- ~25-45% of mEGFR NSCLC driven by L858R activating mutation

Compelling Development Opportunity

- Target Population: patients who have progressed on approved EGFR inhibitors and potential for frontline opportunity

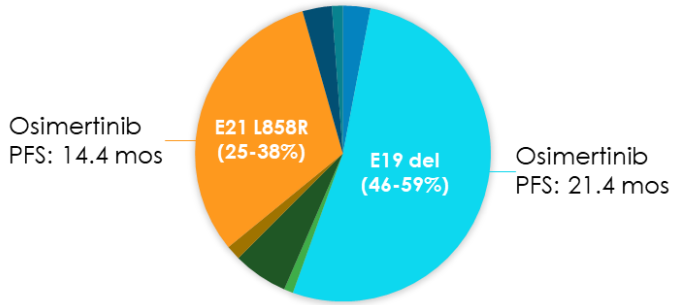
Sources: Soria, J.-C. et al. NEJM 378, 113–125 (2018), Sher, T. et al, *Mayo Clin. Proc.* 83, 355-367 (2008), NIH SEER Database 2020, Primary Literature Consensus Patient figures represent estimated U.S. annual incidence

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

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

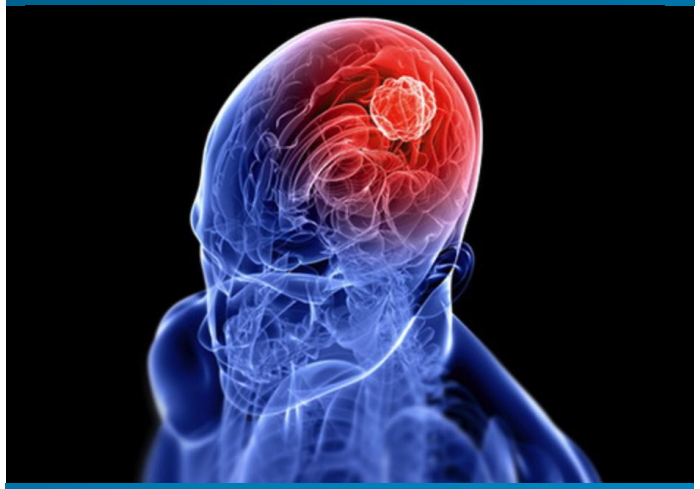
This rises to nearly 40% in Asian population

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

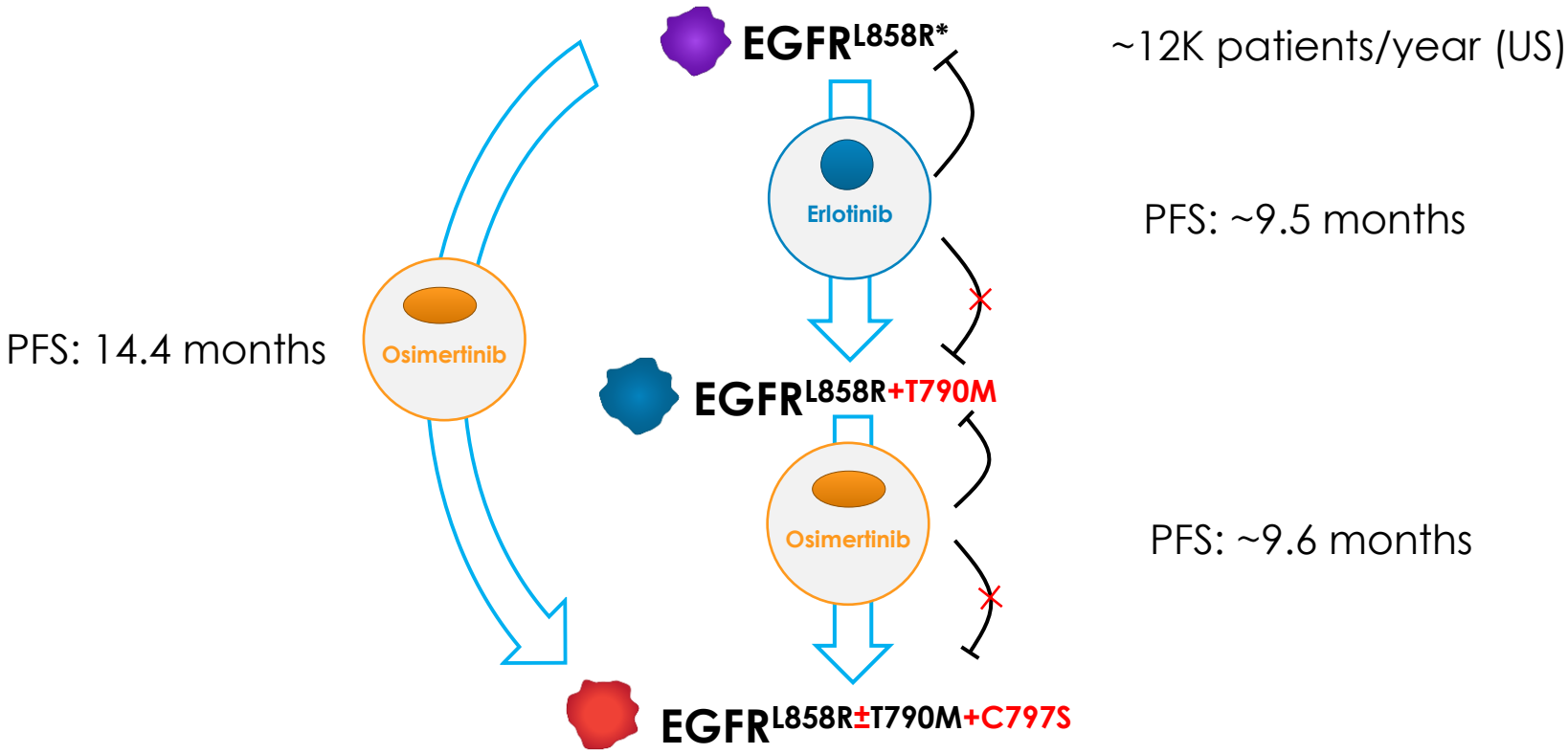


CNS activity desirable to be competitive

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)

C4 Therapeutics

Secondary Mutations in EGFR Cause Resistance to Osimertinib



~12K patients/year (US)

PFS: ~9.5 months

PFS: 14.4 months

PFS: ~9.6 months

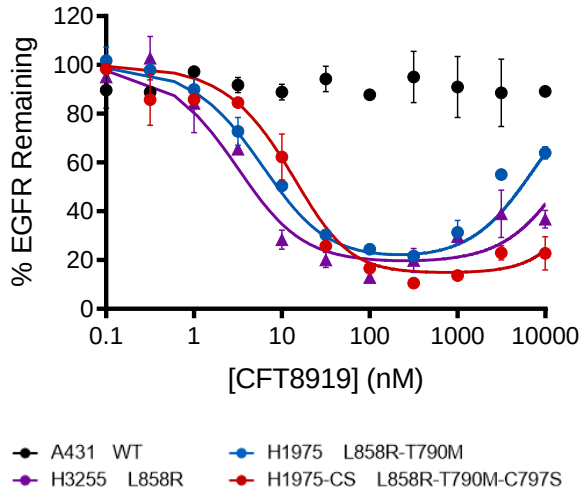
Currently No Approved Therapies Targeting EGFR C797S After Osimertinib Failure

Sources: Yang, J. C.-H. et al., J. Clin Oncol. 35, 1288-1296 (2017): Soria, J.-C. et al. NEJM 378, 113–125 (2018); Primary Literature Consensus

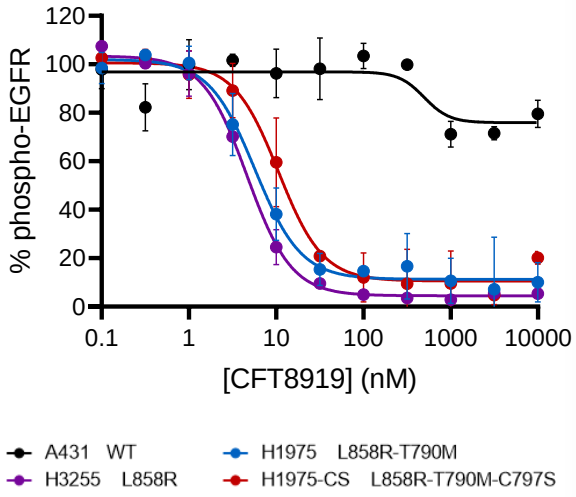
C4 Therapeutics

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

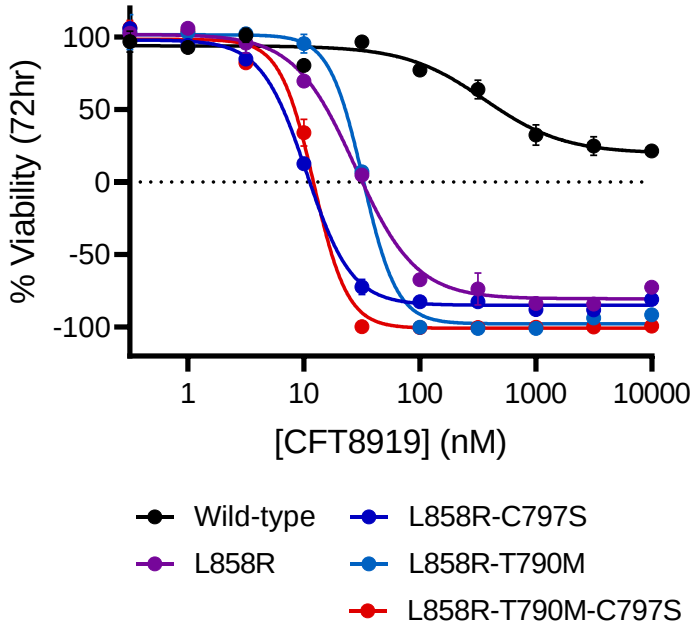
Selectivity against wild-type	Activity against resistant mutations
25 < FC	FC < 5
5 ≤ FC ≤ 25	5 ≤ FC ≤ 25
FC < 5	25 < FC

Source: Keystone 2021, C4T data on file

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

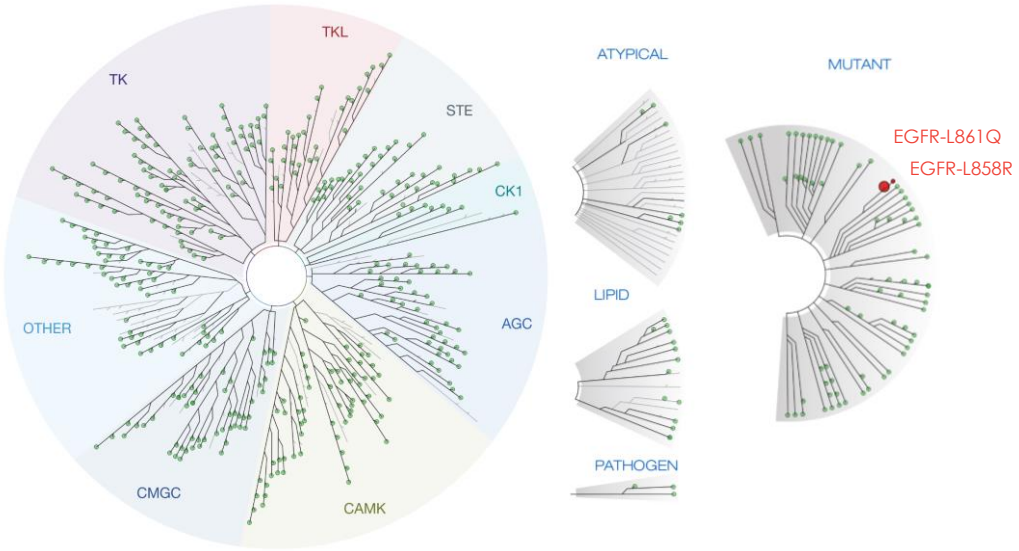
Source: Keystone 2021, C4T data on file

C4 Therapeutics

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

A

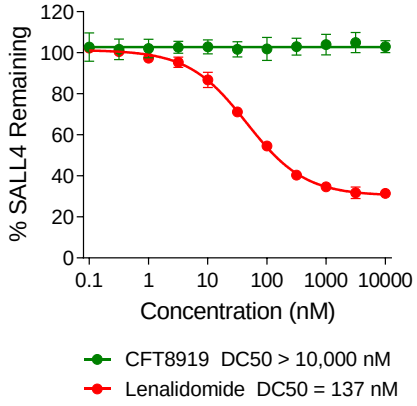
Kinome Binding Specificity



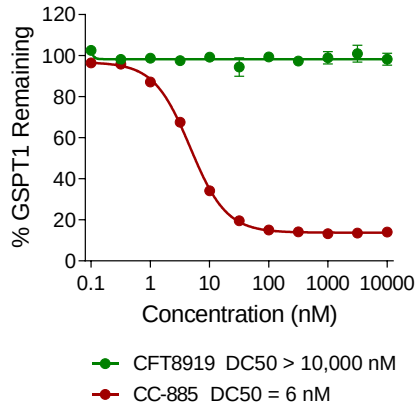
B

Evaluation Against Known Cereblon Neo-substrates

No SALL4 degradation



No GSPT1 degradation

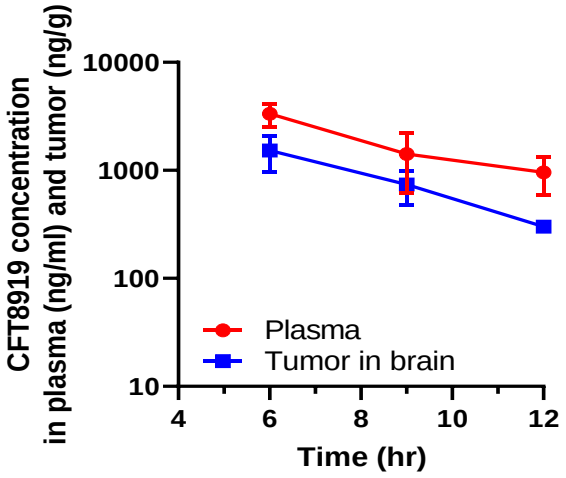


Source: Keystone 2021, C4T data on file

C4 Therapeutics

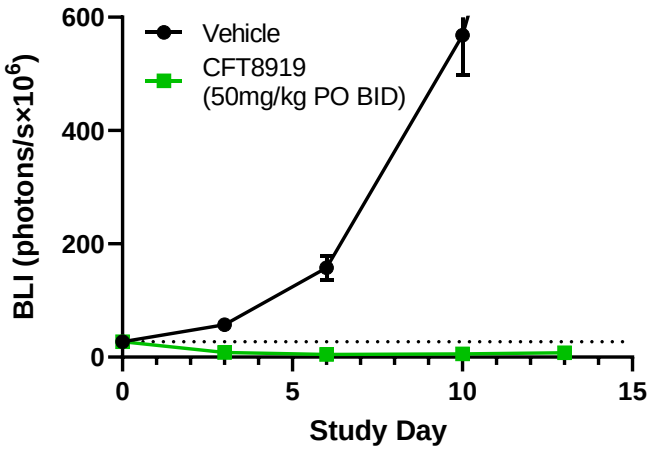
CFT8919 Demonstrates Activity in H1975-LUC (EGFR-L858R-T790M) Brain Metastasis Model

Mean Plasma & Tumor Concentration

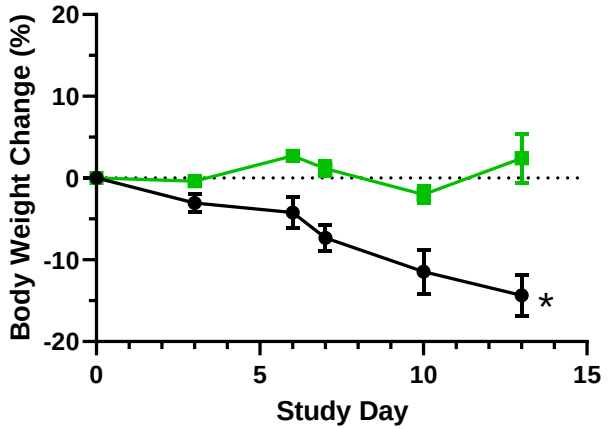


Plasma clearance $t_{1/2}$ = 3.1 hrs

In vivo Efficacy



In vivo Body Weight Change



**Body weight loss due to tumor burden*

Source: Keystone 2021, C4T data on file

BRAF
CFT1946

BRAF: Utilizing a Degrader Approach to Overcome Resistance Mutations

Strong Rationale for Degrader Approach

- Approved BRAF inhibitors cause paradoxical RAF activation, which may result in diminished efficacy
- Potential for degraders to effect deeper elimination of mutant BRAF signaling and create more durable response

Clear Unmet Need

- BRAF mutations occur in ~15% of all cancers
- ~70% - 90% of BRAF mutations are V600X
- Resistance to three approved BRAF inhibitors emerges through multiple paths, resulting in a median PFS of <15 months

Defined Patient Populations

- >70K annual incidence across melanoma, NSCLC, colorectal cancer (CRC) and other malignancies
- 50% of late-stage melanoma
- 1-2% of NSCLC
- 10-20% of CRC
- 50% of papillary thyroid cancer
- 100% of hairy cell leukemia
- >50% of Langerhans cell histiocytosis (LCH)

Compelling Development Opportunity

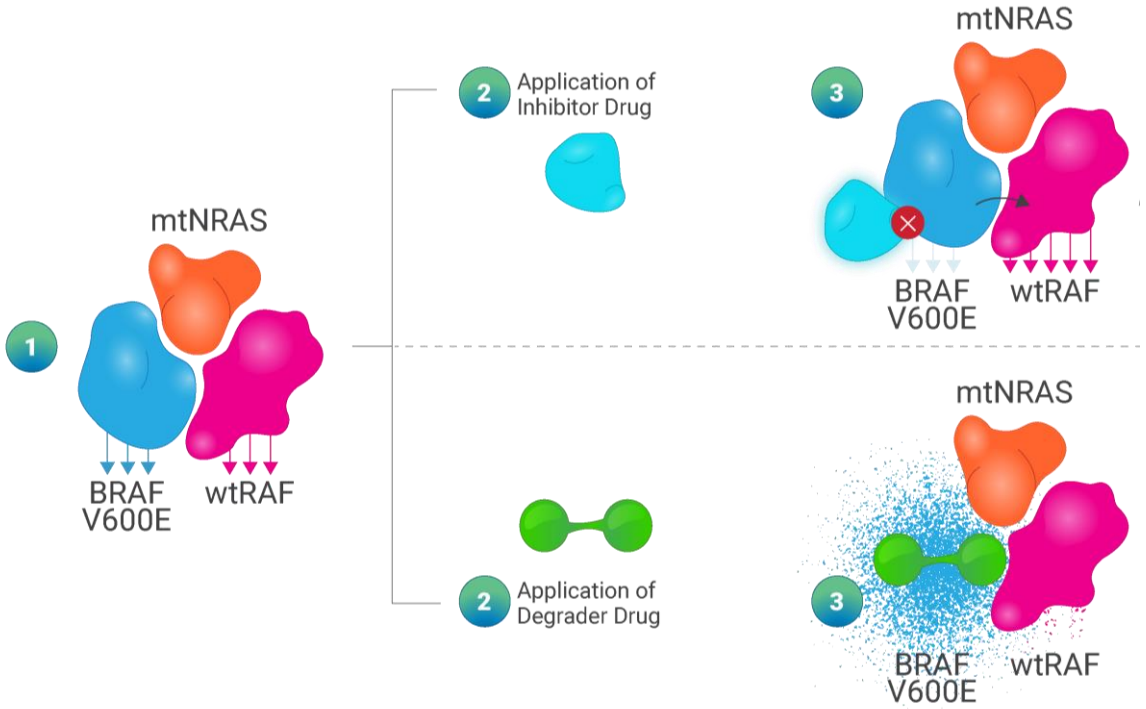
- Large patient population defined by failure of available BRAF inhibitors
- Target Population: V600X mutant melanoma, NSCLC and CRC after BRAF inhibitor containing regimens

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

Patient figures represent estimated U.S. annual incidence

BRAF Degrader to Overcome Limitations of Approved BRAF Inhibitors

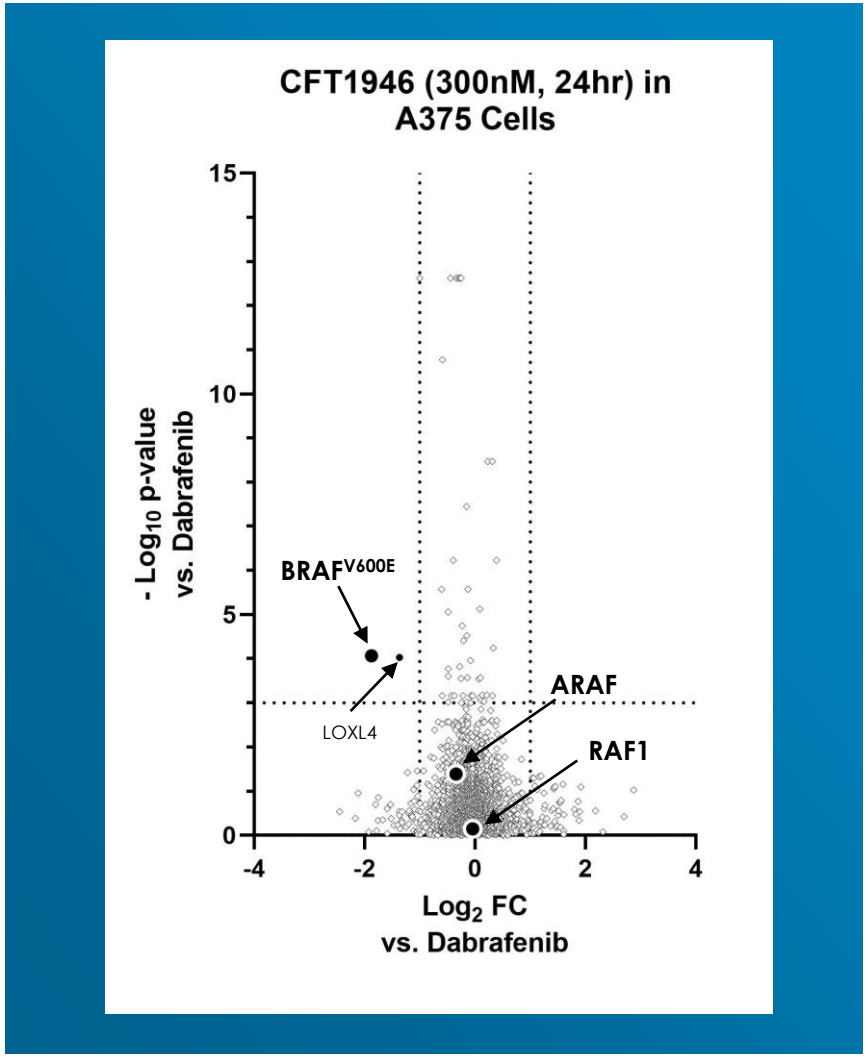
Mechanistic Rationale

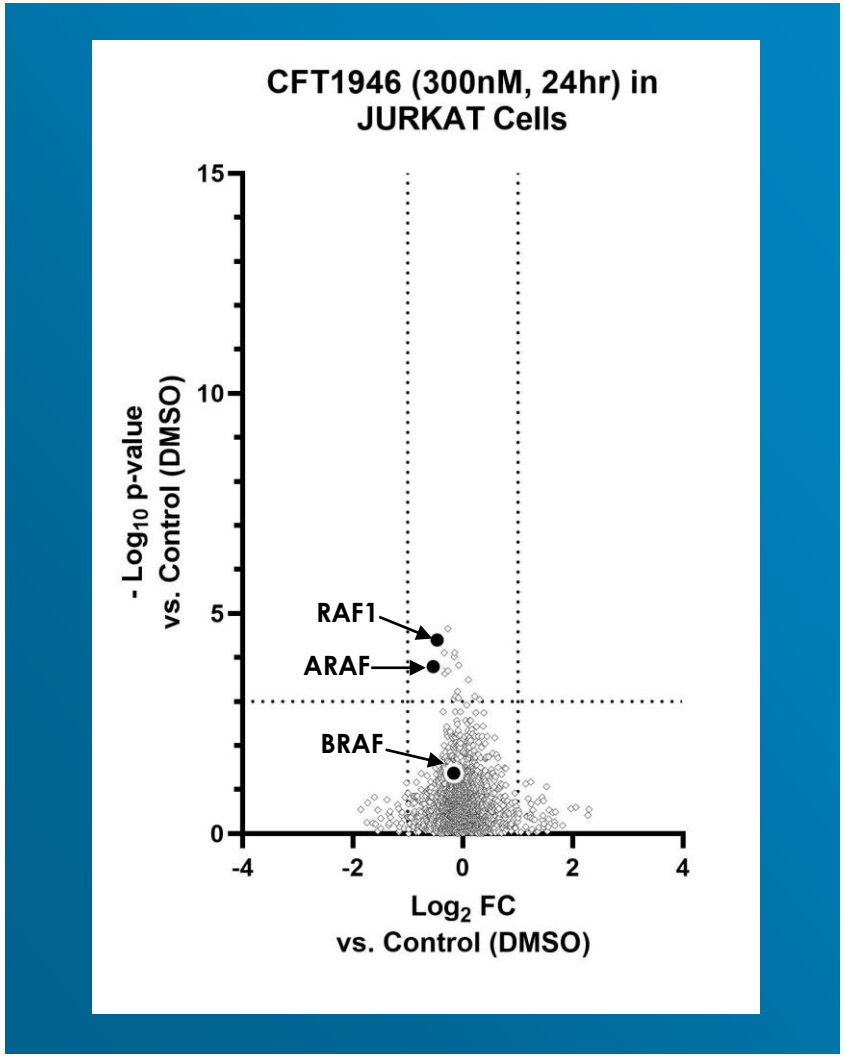


Advantages of BRAF V600E Degradation

- 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

CFT1946 is Highly Selective for BRAF V600E Degradation and Spares Wildtype BRAF



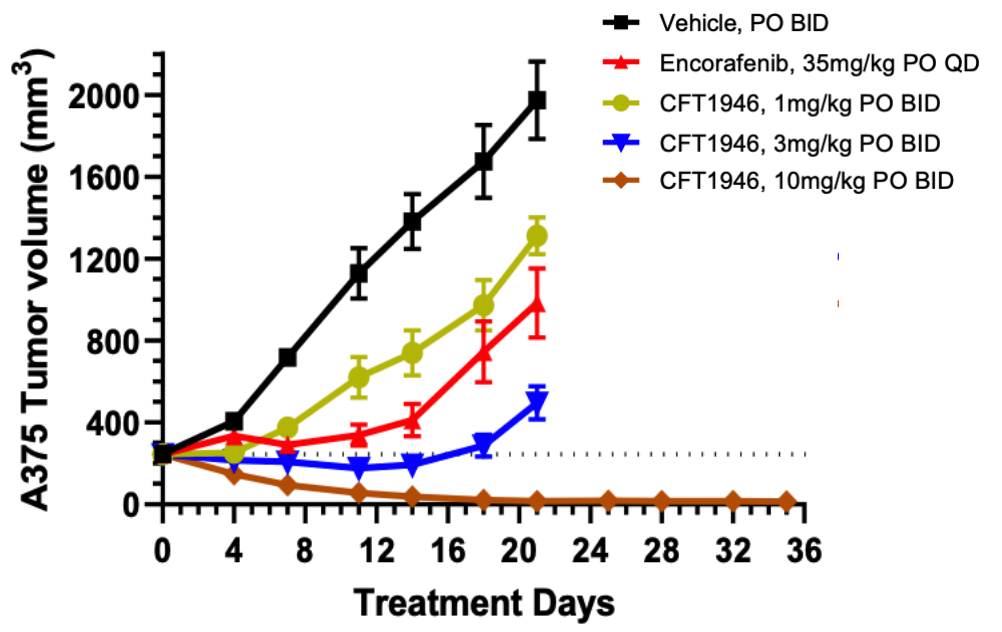


Source: C4T data on file

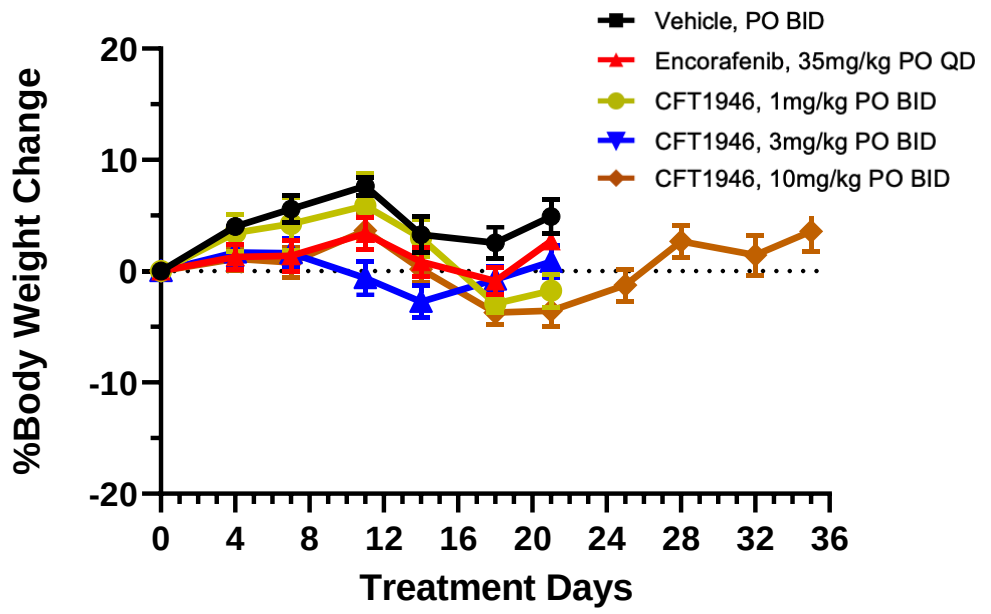
C4 Therapeutics

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

CFT1946 Shows More Durable Efficacy Than Encorafenib



CFT1946 is Well Tolerated

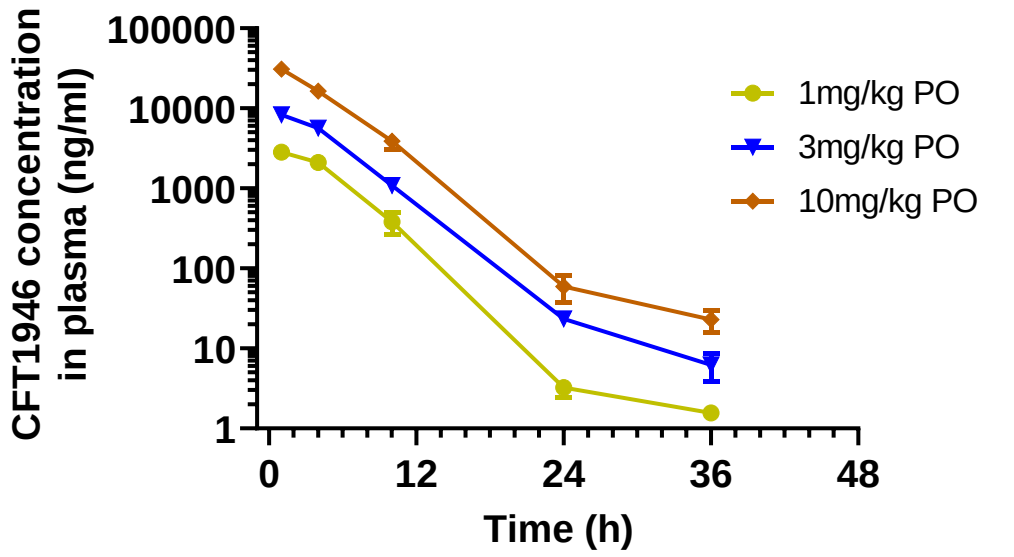


Source: C4T data on file

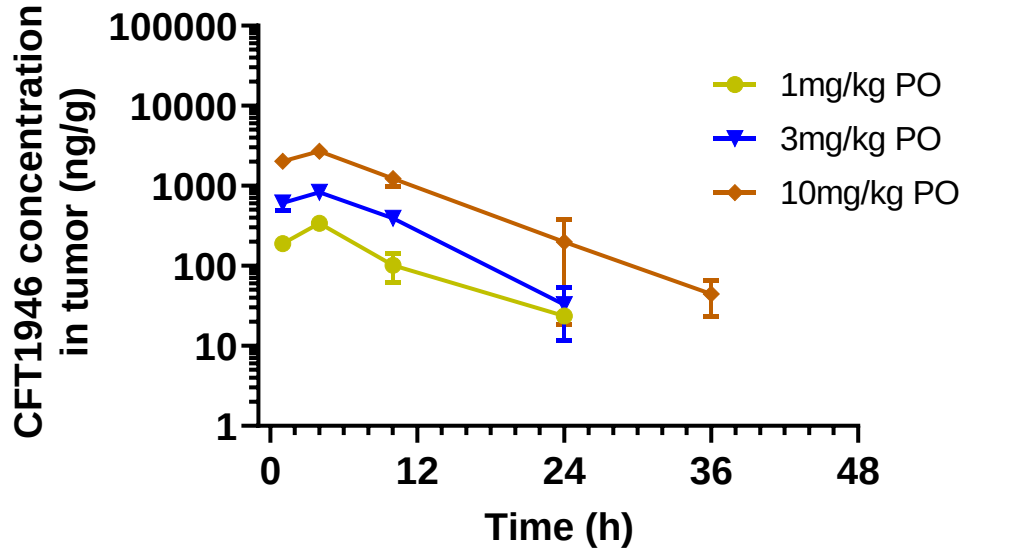
C4 Therapeutics

CFT1946 Has Excellent Pharmacokinetic Properties in Both Plasma and A375 Tumor Xenografts

Plasma PK



Tumor PK



Source: C4T data on file

RET

RET Degradation: Opportunity to Overcome Resistance Mutations

Strong Rationale for Degrader Approach

- RET is a receptor tyrosine kinase (RTK) that plays a role in normal development but can cause cancer when mutated
- Resistance develops to approved RET inhibitors due to mechanisms including new RET mutations, which make inhibitors inactive

Clear Unmet Need

- No effective targeted therapy after failure of approved first-line RET inhibitors

Defined Patient Populations

- ~10K annual incidence of RET-driven disease across lung, thyroid, and other cancers
- 1-2% of NSCLC
- 60% of sporadic medullary thyroid cancer

Compelling Development Opportunity

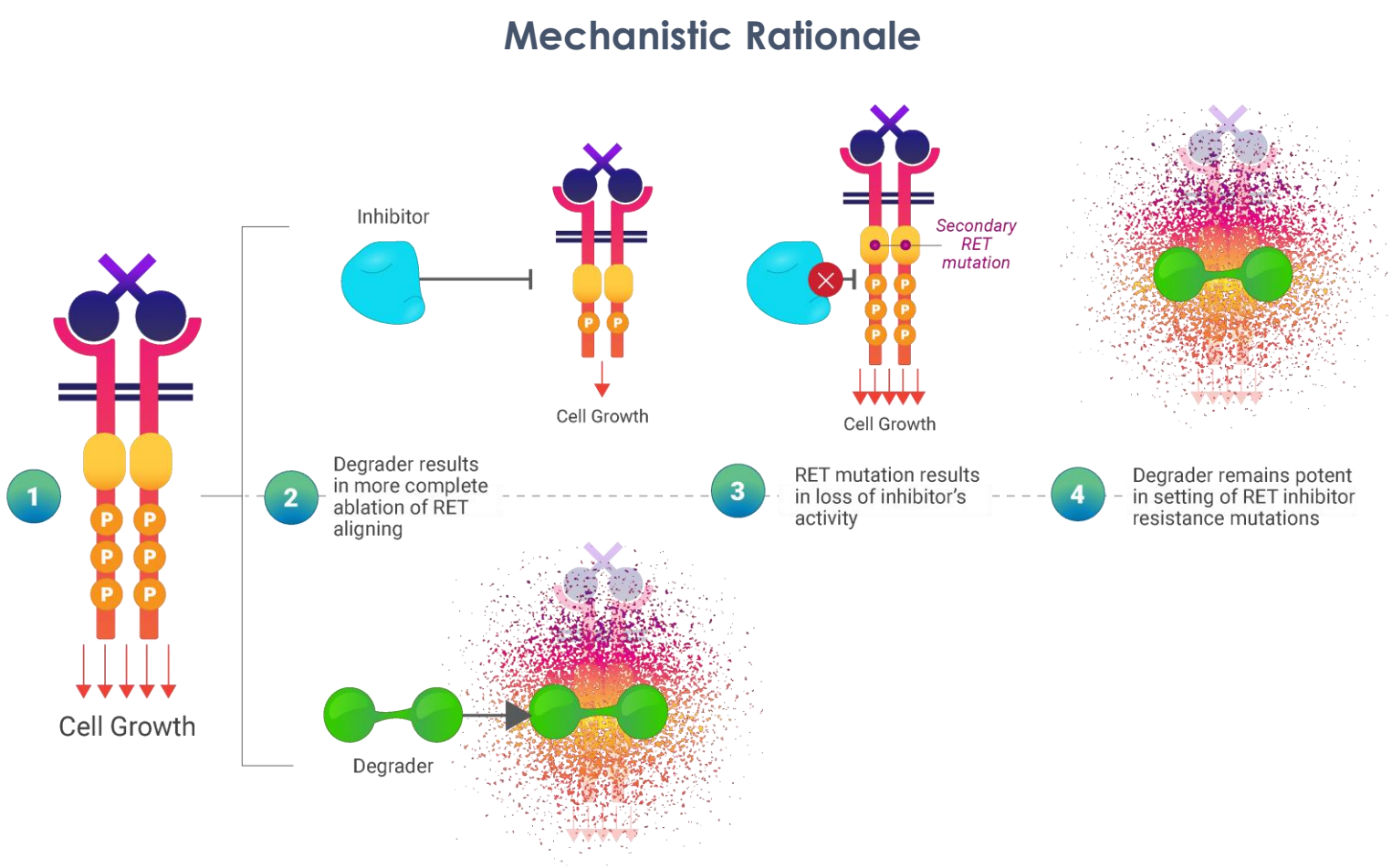
- Well defined registration path in existing, genetically defined patient population with no effective treatment option after RET tyrosine kinase inhibition (TKI)
- Target Population: second line RET-altered cancers; potential for front-line opportunity

Sources: NIH SEER Database, https://pubmed.ncbi.nlm.nih.gov/29284153/, Primary Literature Consensus

Patient figures represent estimated U.S. annual incidence

C4 Therapeutics

RET Degradation May Have Improved Activity Compared to Best-In-Class RET Inhibitors



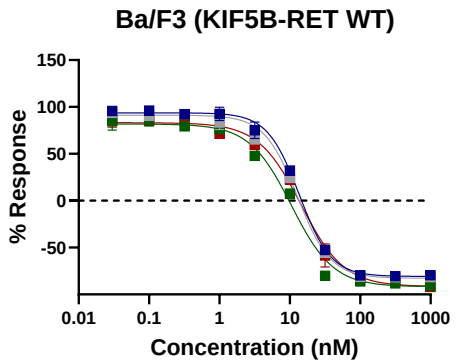
Advantages of RET Degradation

- RET degrader is active against key secondary mutations that cause resistance, including both the gatekeeper and solvent front mutations
- Against RET without secondary mutation, as in the front-line setting, degradation may offer deeper and more durable response than inhibition

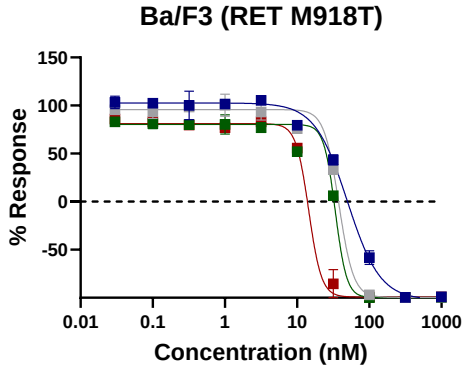
RET Degrader Has an Excellent Cell Growth Inhibition Profile In RET Fusions and Common Resistance Mutations

Drug Naïve, Driver Translocation/Mutation

KIF5B-RET Fusion

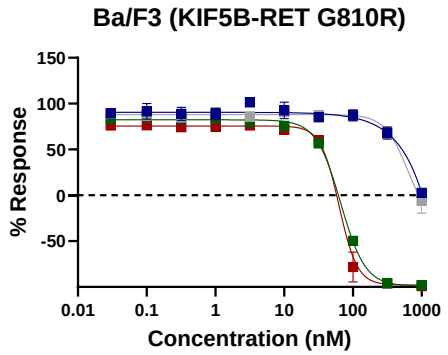


Activating Mutation

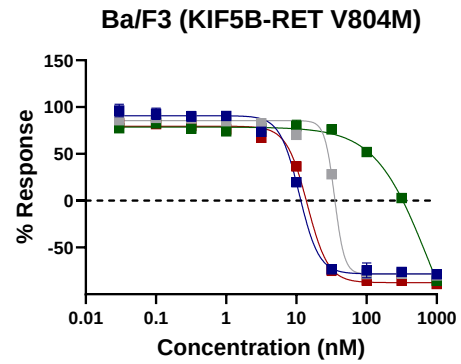


RET Inhibitor Acquired-Resistance Mutants

Solvent Front Mutation



Gatekeeper Mutation



Pralsetinib Selpercatinib 2nd Gen RET TKI CFT RET Degrader

Continue Lead Optimization Activities in 2021

Source: C4T data on file

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

	2021	2022
IKZF1/3 (CFT7455)	✓ Phase 1/2 Initiation ✓ Orphan Drug Designation	❑ Phase 1 Safety & Efficacy ❑ Proof of Mechanism
BRD9 (CFT8634)	❑ IND Submission	❑ Phase 1 Initiation
EGFR (CFT8919)	✓ IND Enabling Activities	❑ IND Submission ❑ Phase 1 Initiation
BRAF (CFT1946)	✓ Development Candidate ✓ IND Enabling Activities	❑ IND Submission ❑ Phase 1 Initiation
RET	❑ Lead Optimization	

Thank You