C4 Therapeutics

# Corporate Presentation

May 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.

## Intellectual Property

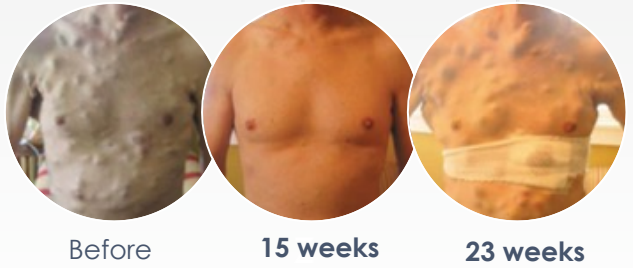
C4 Therapeutics, Inc. owns various registered and unregistered trademarks in the U.S. and internationally, including, without limitation, C4 THERAPEUTICS, our housemark logo, the name of our TORPEDO platform, and the names of our BIDAC and MONODAC degrader products. All trademarks or trade names referred to in this presentation that we do not own are the property of their respective owners. Solely for convenience, the trademarks and trade names in this prospectus are referred to without the symbols ® and ™, but those references should not be construed as any indicator that their respective owners will not assert, to the fullest extent under applicable law, their rights thereto.

# 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**

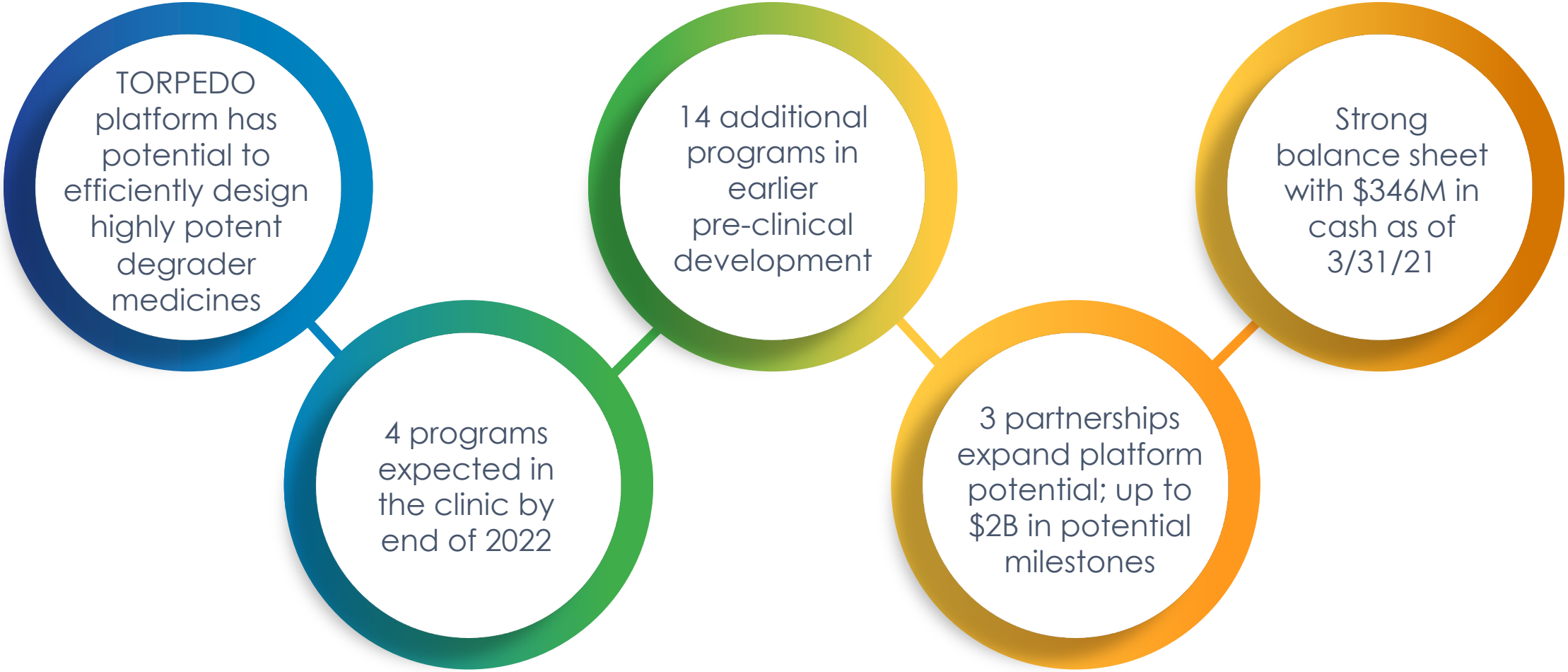
Oncology small molecule therapies generate significant revenue despite known limitations

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

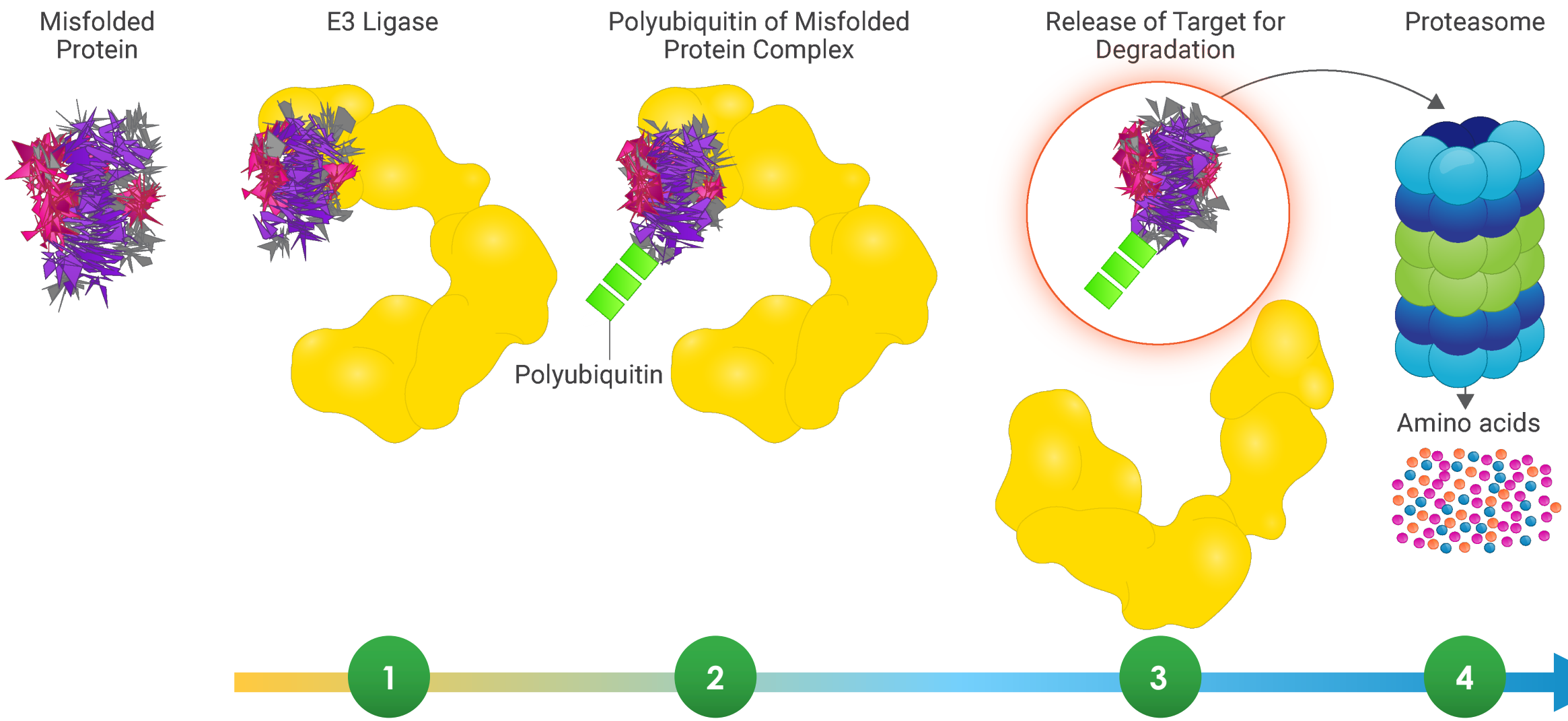
C4 Therapeutics

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

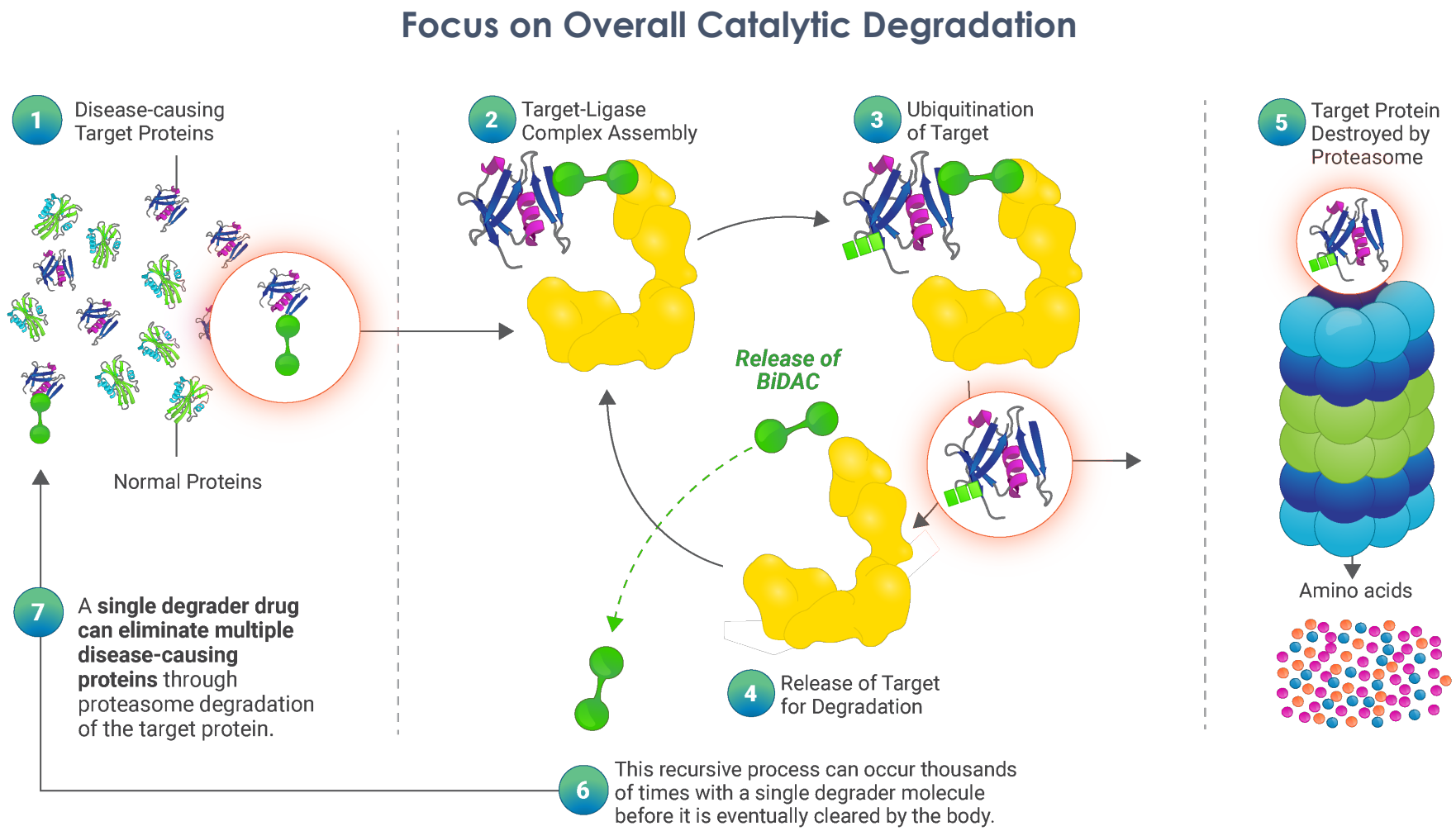



C4 Therapeutics

# The Human Body Has A Natural Process to Destroy Unwanted Proteins

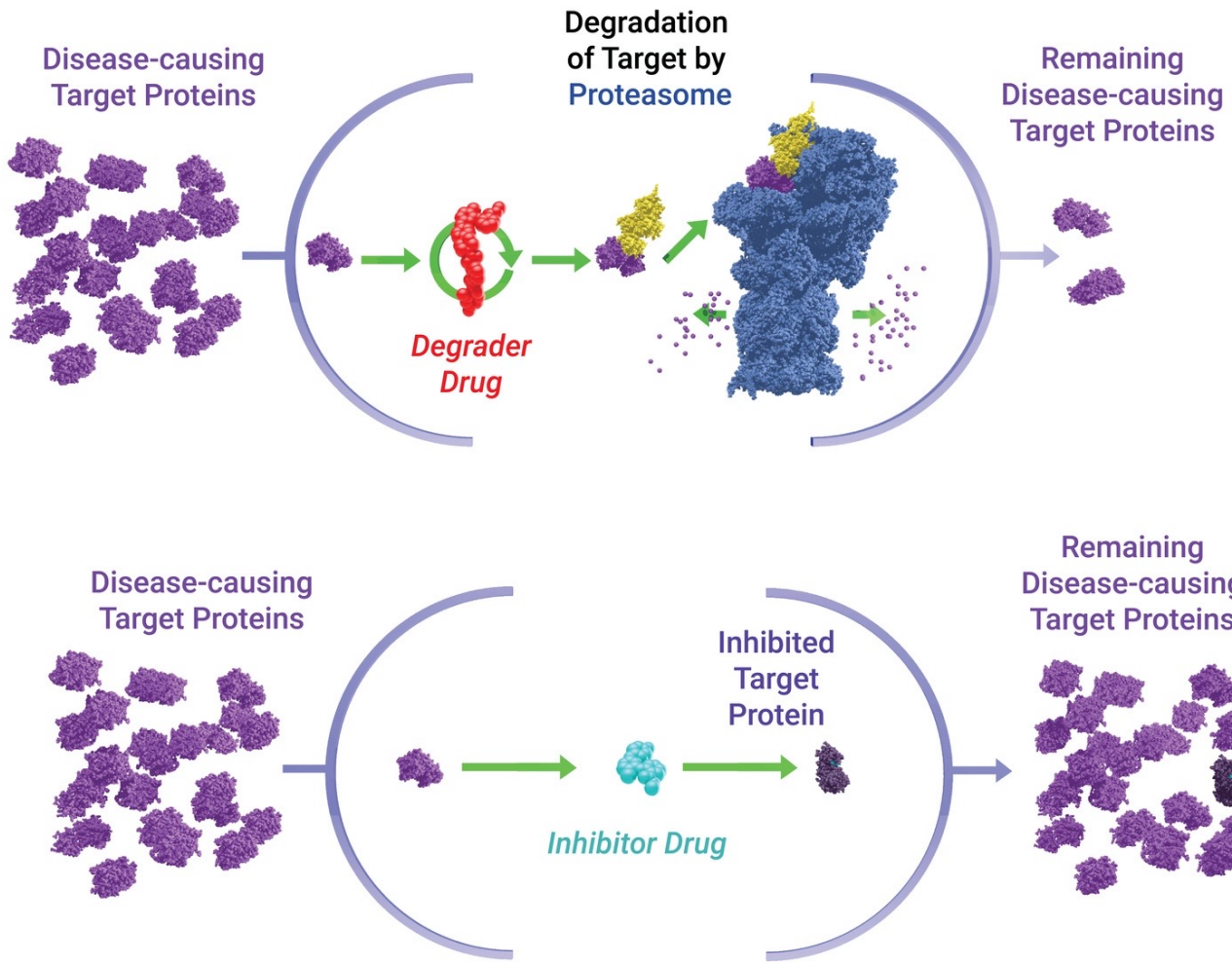


# Targeted Protein Degradation Leverages the Body's Natural Process to Destroy Disease-Causing Proteins



# Targeted Protein Degradation Offers Fundamental Advantages Over Protein Inhibition

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



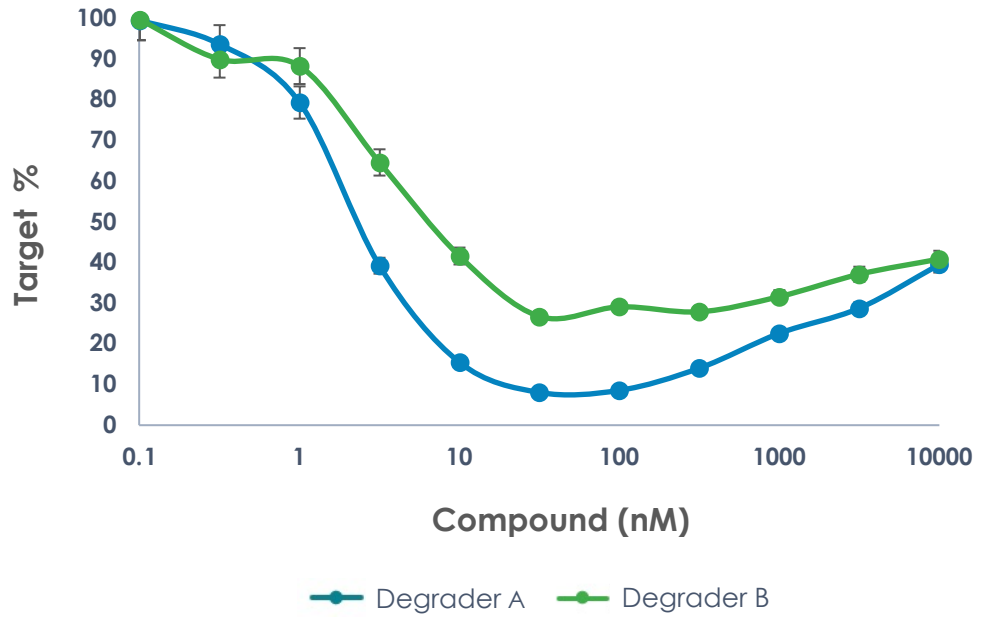
# TORPEDO (Target ORiented ProtEin Degrader Optimizer) Platform

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

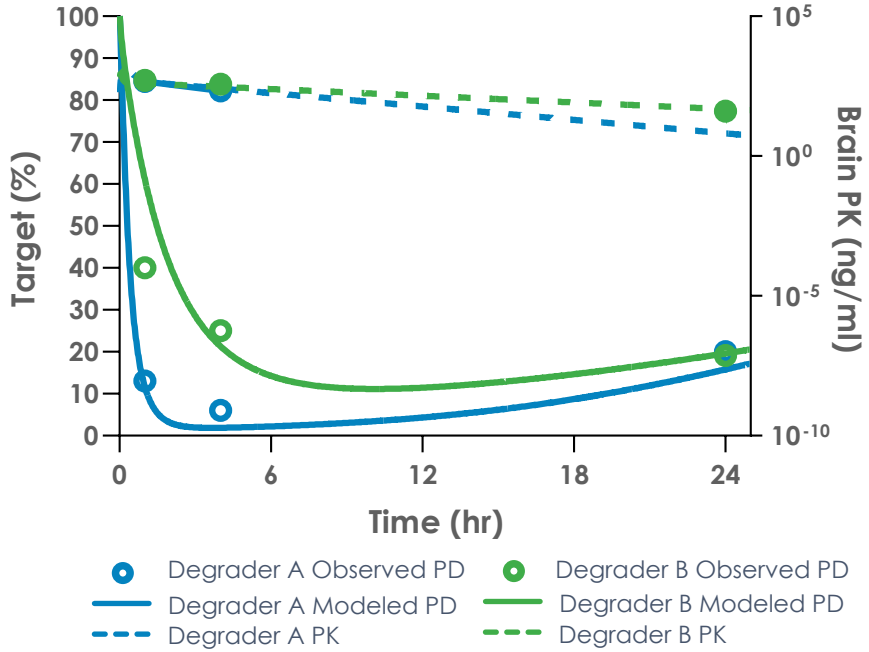
| Elements | Benefits |
| --- | --- |
| **Focus on Catalytic Efficiency** | Optimization of overall degradation process results in maximal efficacy |
| **Ability to Design, Analyze & Predict Degrader Performance** | Rapid delivery of potent drug candidates through informed and efficient drug discovery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

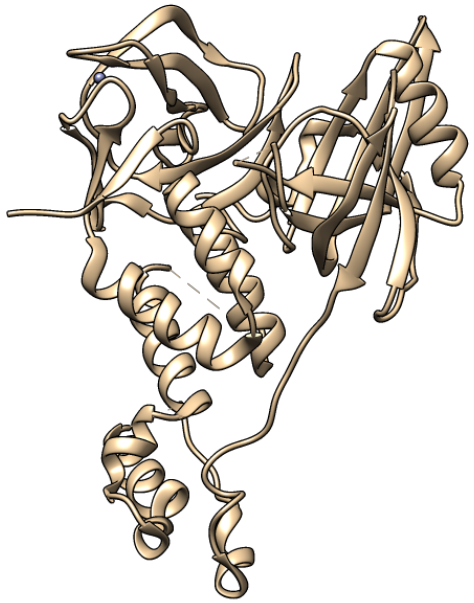
Robust predictions of depth and duration of *in vivo* target degradation at any dose

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

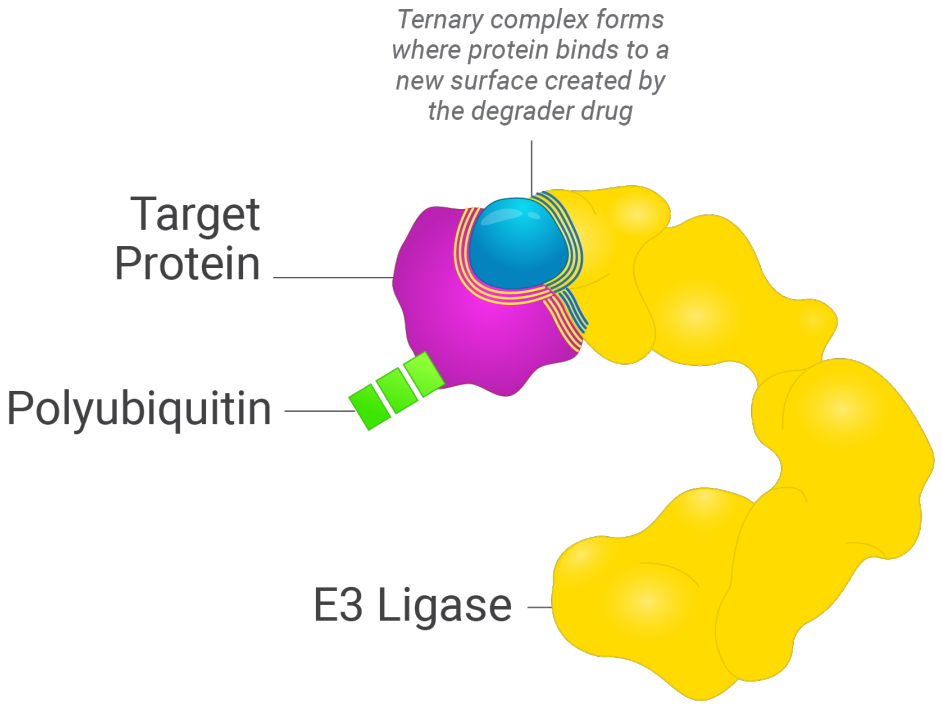


- Cereblon, harnessed by IMiDs, is the only clinically validated ligase for targeted protein degradation
- Cereblon is expressed in all tissues and in all cellular compartments
- Investment in rich toolkit of intellectual property with more than 15 structurally distinct Cereblon binders
- C4T's binders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

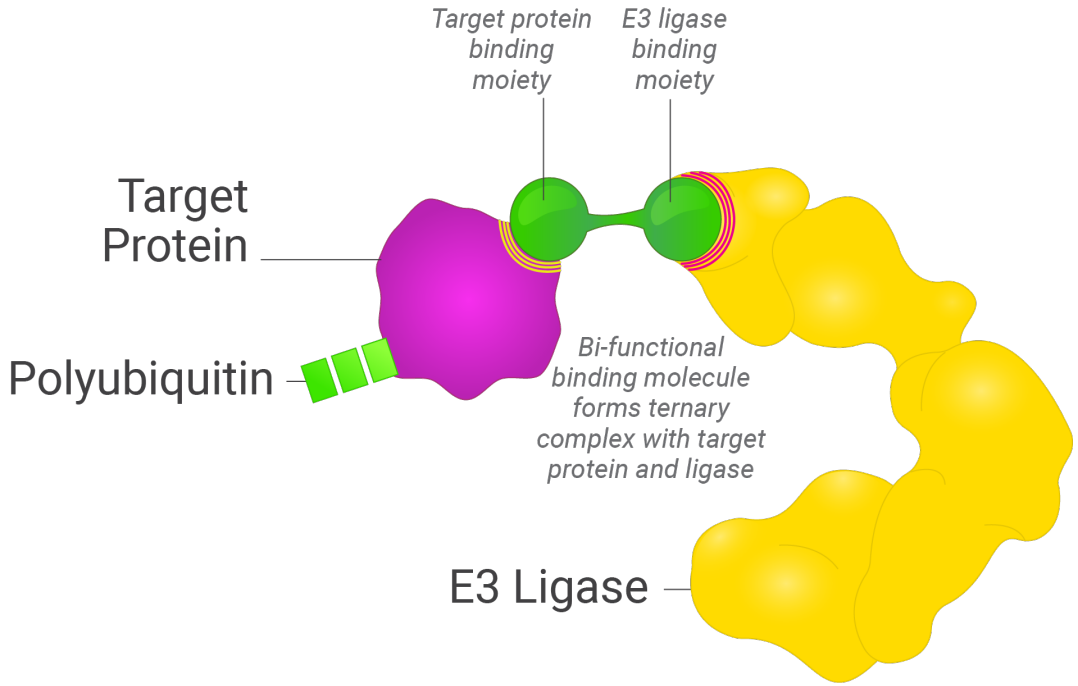
Programs Benefit from Desirable Properties of C4T's Cereblon Binders

# TORPEDO Platform Offers Flexibility to Design MonoDAC and BiDAC Degraders

## MonoDAC Degrader




## BiDAC Degrader




Flexibility to Address Different Targets with Tailored Approach

# 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

# Three Strategic Target Platform Collaborations Expand Platform Potential

# 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): 52%
- 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

Source: NIH SEER Database, Primary Literature Consensus

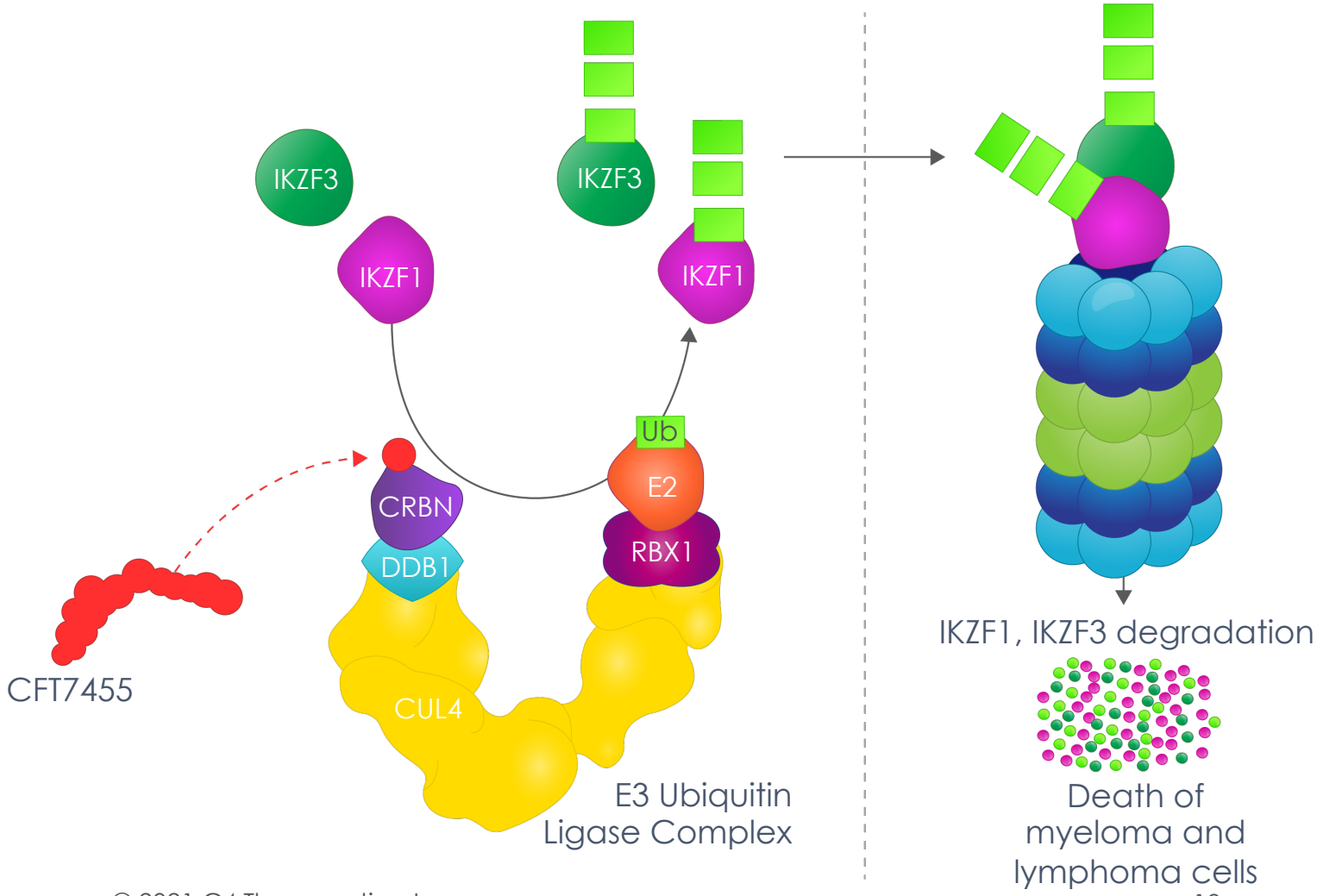
Patient figures represent estimated U.S. annual incidence
PTCL = peripheral T-cell lymphoma; MCL = mantle cell lymphoma

C4 Therapeutics

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

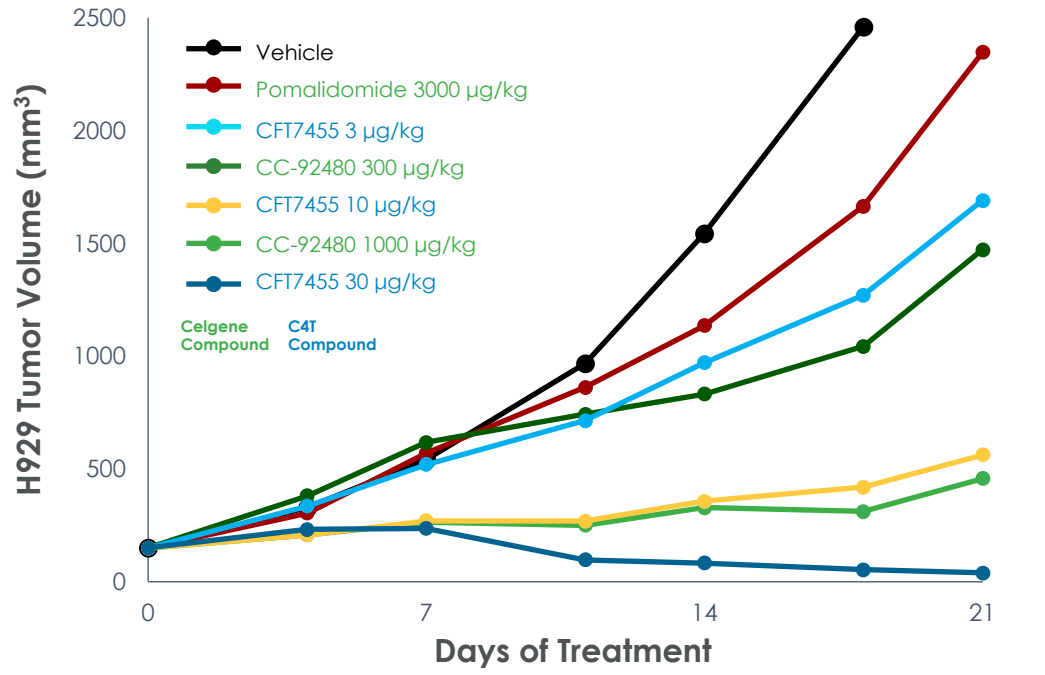
Goal: Develop an IKZF1/3 Monofunctional Degradation Activating Compound (MonoDAC) with these properties:

- 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

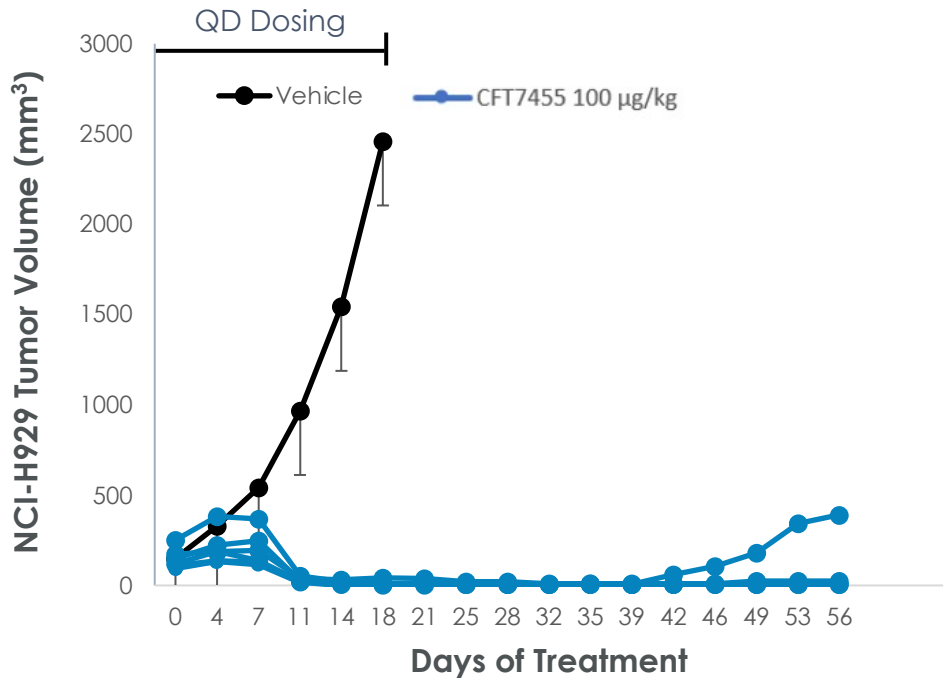


# CFT7455 Demonstrates Improved Efficacy Compared to Both Approved and Most Advanced Development-stage IKZF1/3 Degraders

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



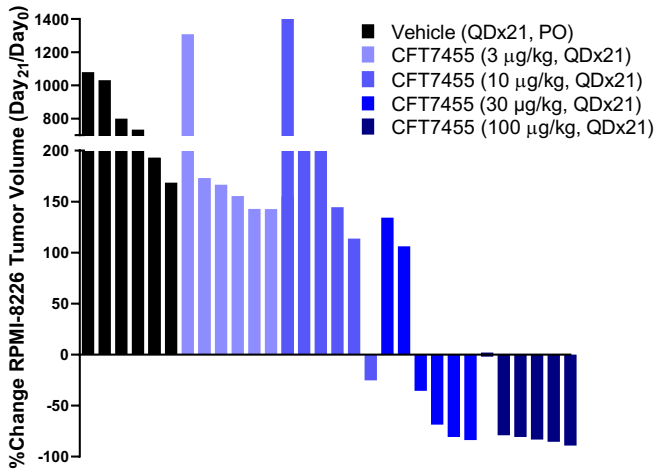

## CFT7455 *In Vivo* Efficacy Durable After End of Dosing Period



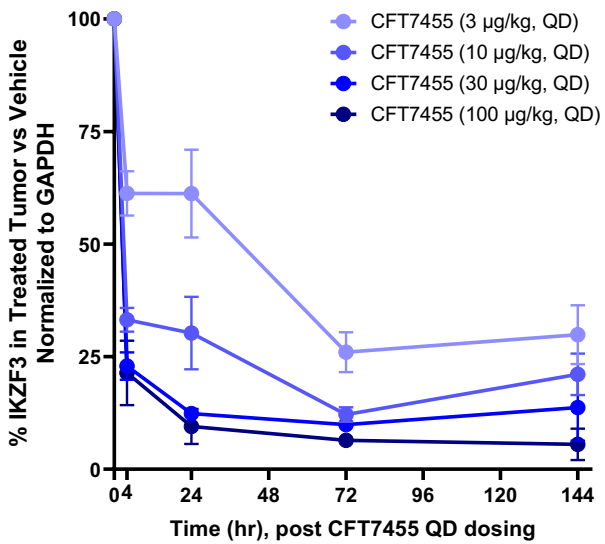

Source: C4T data on file

# Depth and Duration of IKZF3 Degradation Associated with CFT7455 Efficacy

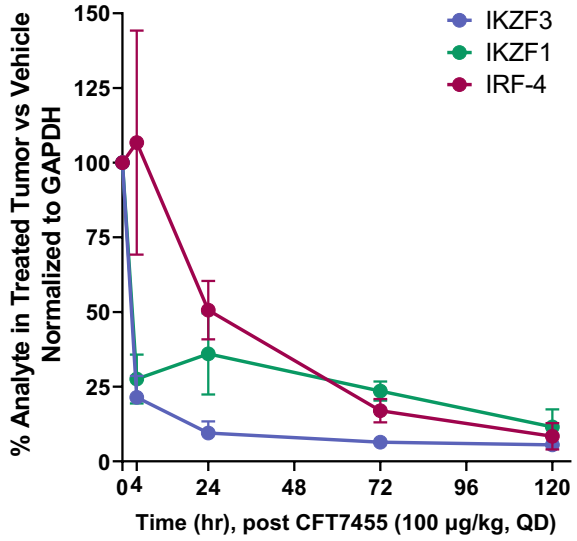
## Dose Dependent Efficacy




## Dose-Dependent IKZF3 Degradation



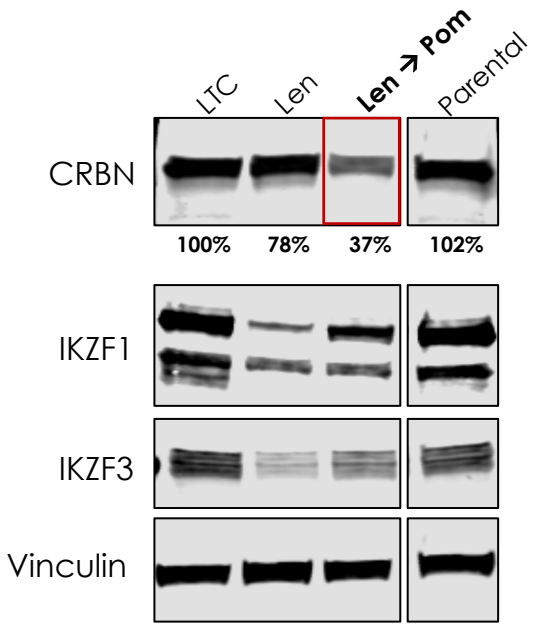

## Loss of IRF-4 via IKZF1/3 Degradation




Source: C4T data on file

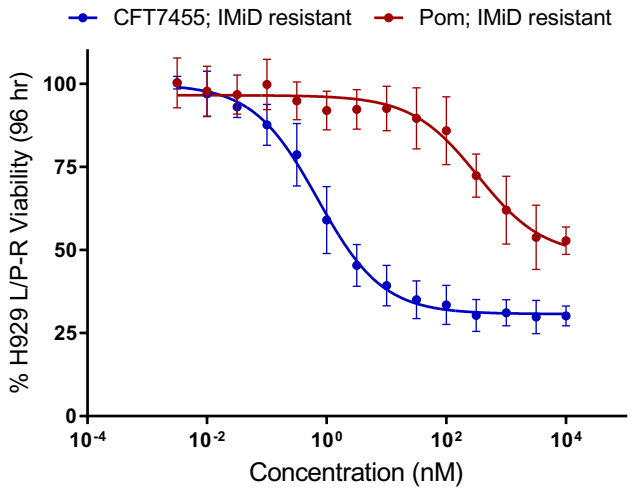
# CFT7455 Demonstrates Tumor Regression in Multiple Myeloma Xenograft Insensitive to Pomalidomide

## Reduction in CRBN Expression with Chronic IMiD Dosing

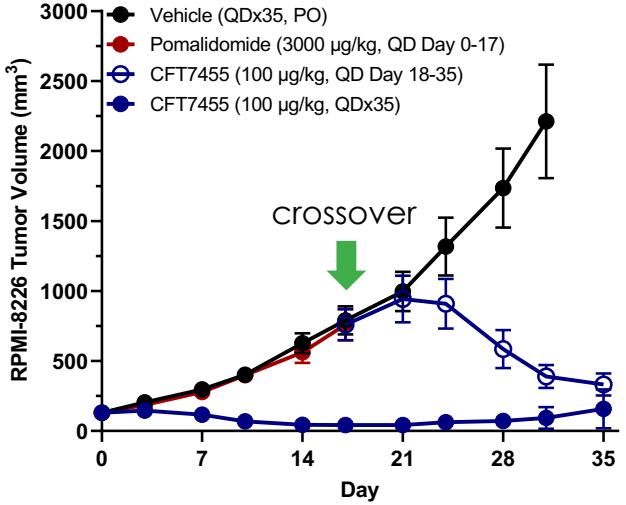



LTC = long term culture in DMSO
Parental = Original, naive H929 cells

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



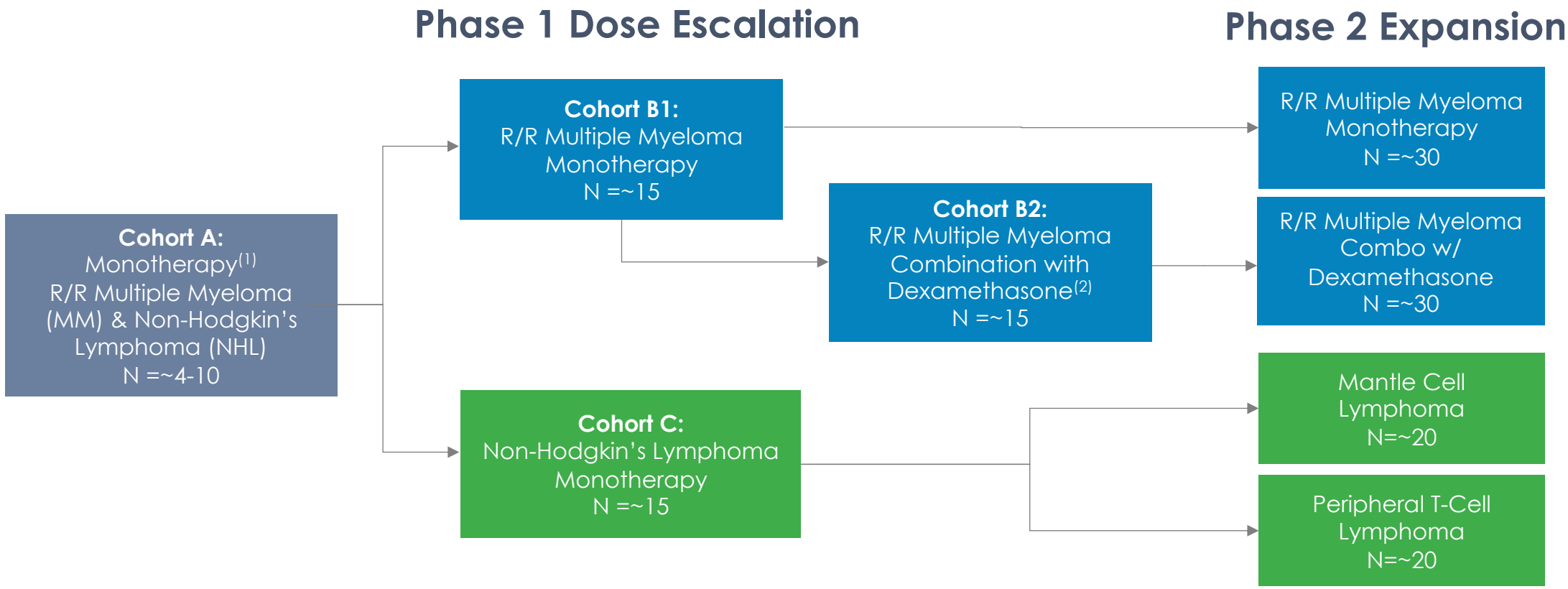

## CFT7455 Promotes Regression in Tumors Insensitive to Pomalidomide




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

Source: C4T data on file

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




Trial Open for Enrollment, 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

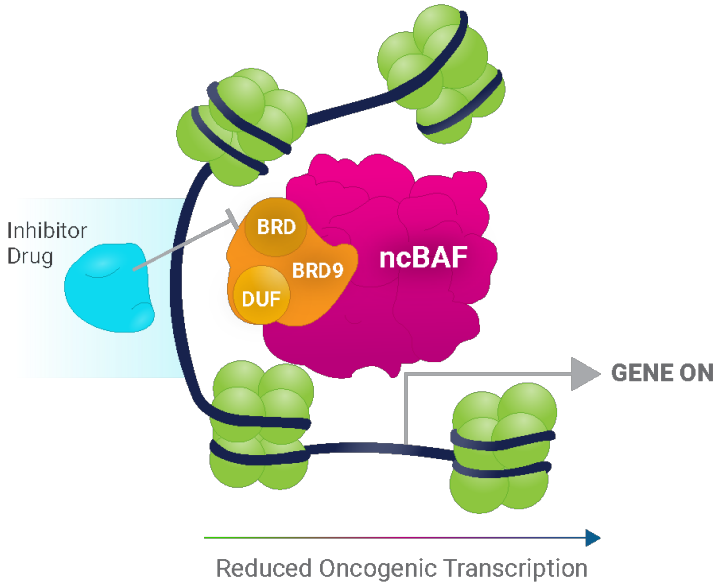
- Well defined path to registration in SS and metastatic population already under management at academic centers
- Precedent for approval with a single-arm study in second-line setting

Source: NIH SEER Database, Primary Literature Consensus

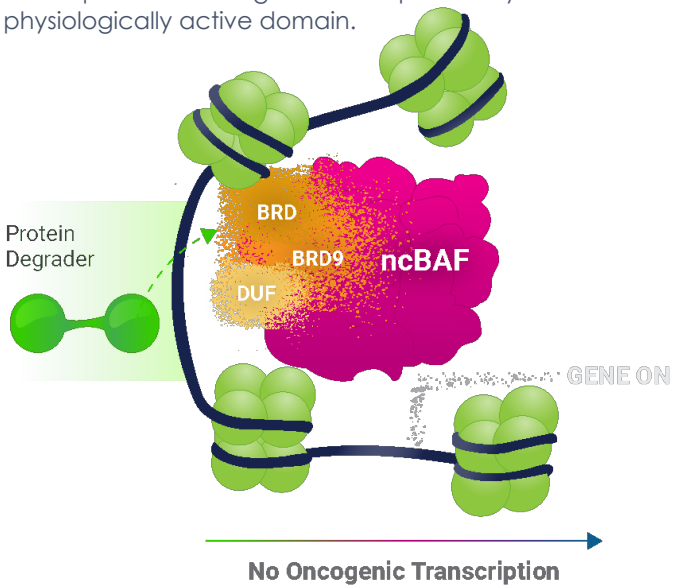
Patient figures represent estimated U.S. annual incidence

# 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.

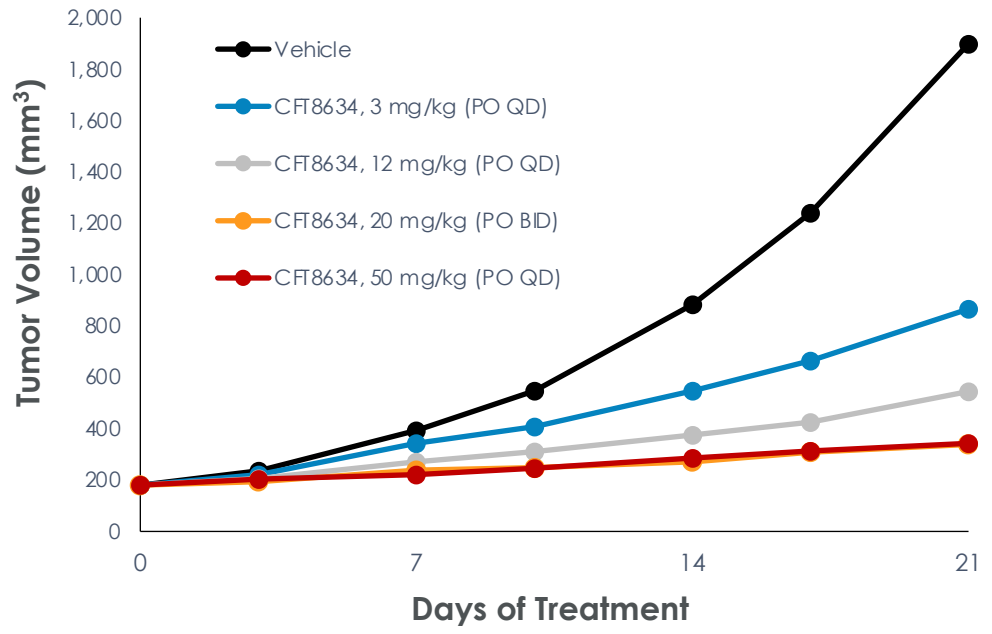



## Advantages of BRD9 degradation

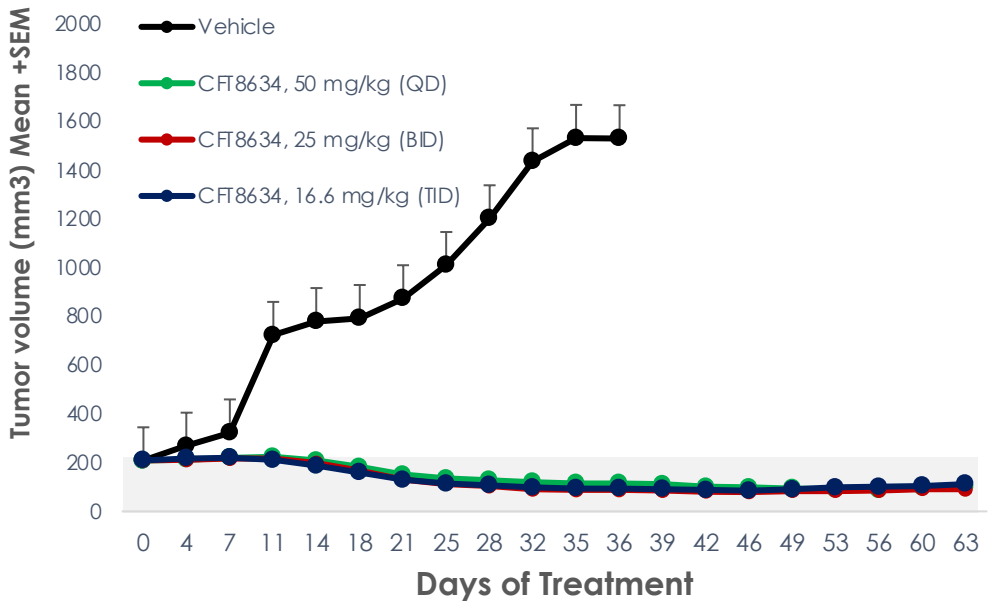
- Specifically degrades BRD9 and spares BRD4 and BRD7, avoiding potential off-target toxicities
- Oncogenicity of BRD9 depends on sub-domains not addressed by traditional inhibitors

# Robust Responses of CFT8634 Seen in Preclinical Synovial Sarcoma Models

## Dose Response Activity Yamato Xenograft Model

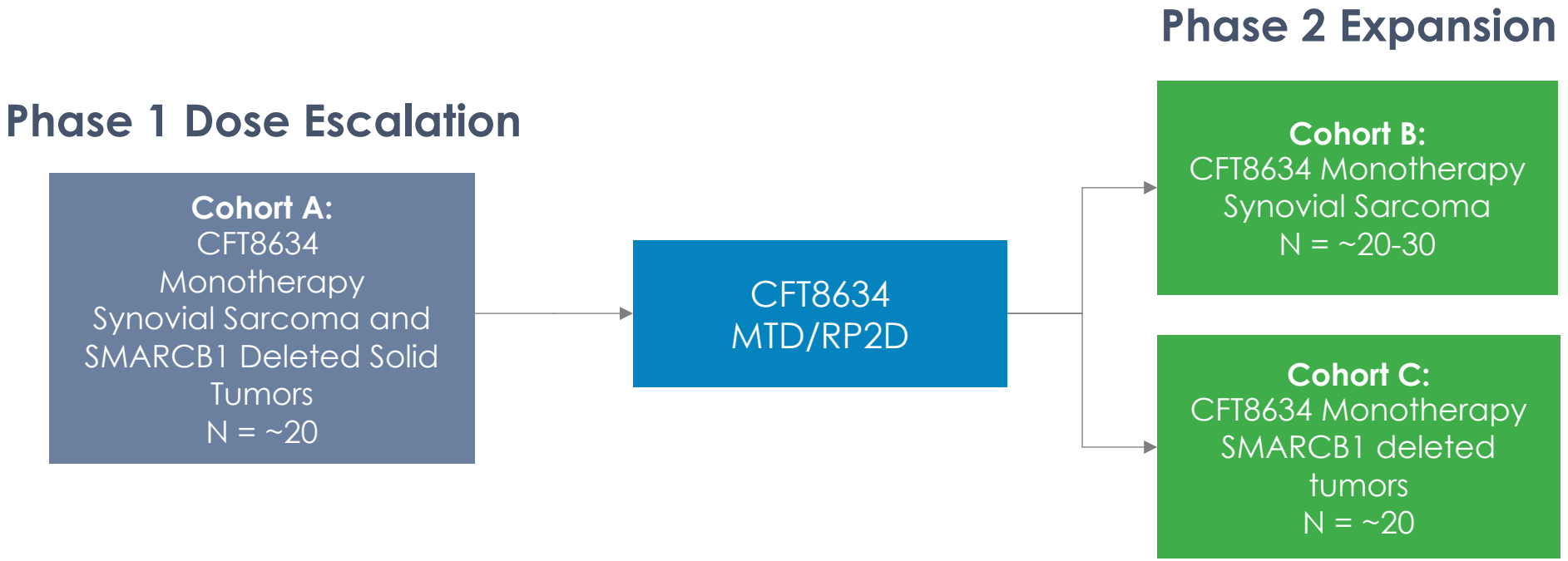



## Dose Response Activity Patient Derived Xenograft Model




Source: C4T data on file

# CFT8634 First-in-Human Protocol Concept Schema




IND Submission for CFT8634 Expected in 2H 2021

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

# 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

- Patients whose tumors harbor EGFR L858R do less well on approved 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
- 25-40% of mEGFR NSCLC driven by L858R activating mutation

## Compelling Development Opportunity

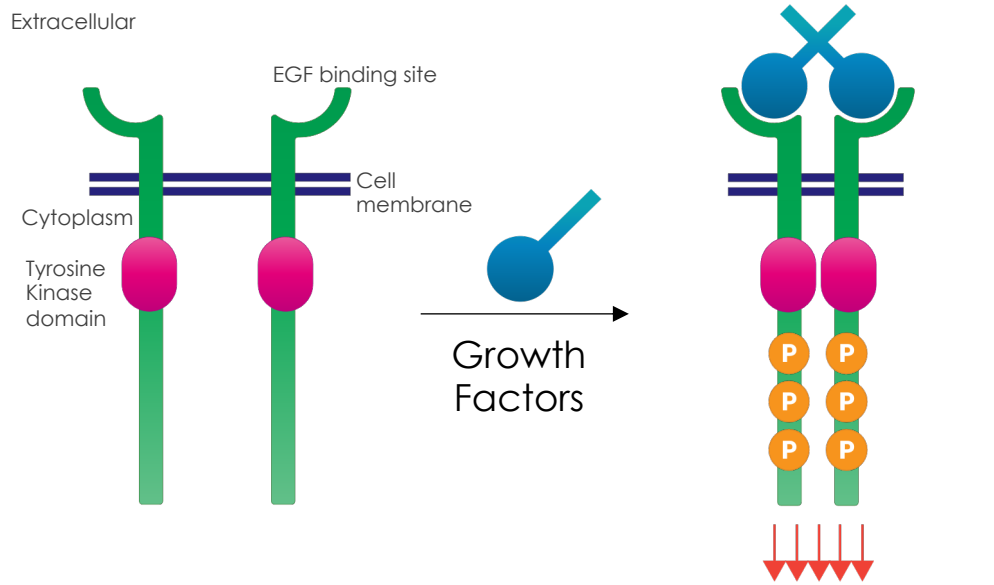
- Target Population: patients who have progressed on approved EGFR inhibitors and potential for frontline opportunity

Source: https://www.nejm.org/doi/10.1056/NEJMoa1713137, NIH SEER Database, Primary Literature Consensus

Patient figures represent estimated U.S. annual incidence

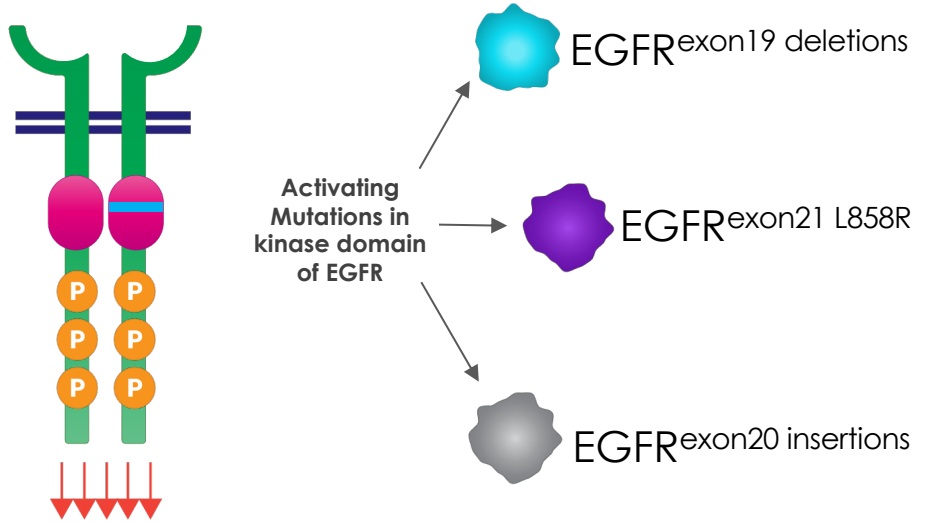
# EGFR Activating Mutations Drive NSCLC Cancer Growth

## Normal Physiology



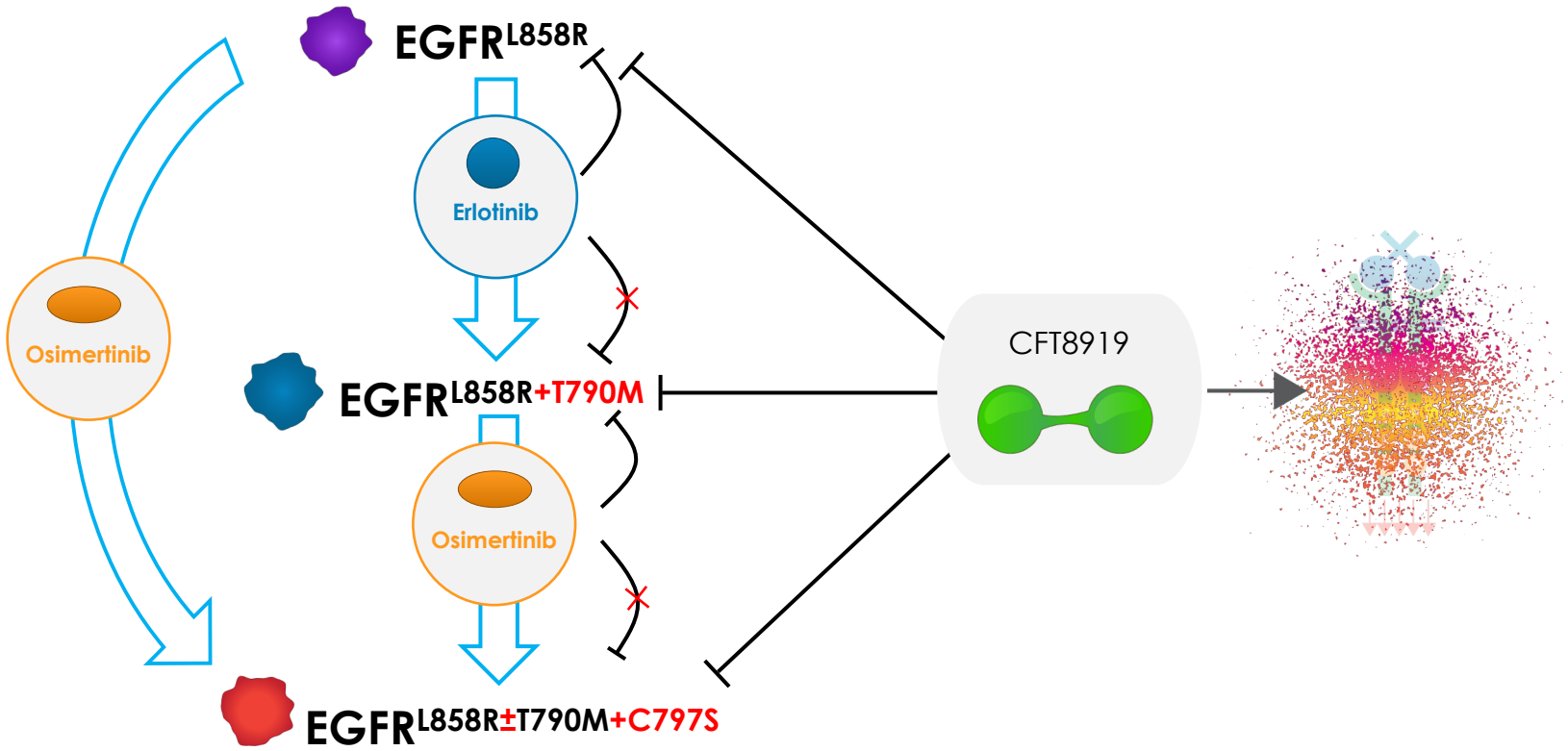

**Signaling is activated in response to extracellular growth factors**

## Mutant EGFR Tumor Cells




**Downstream signaling in absence of extracellular signal**

# CFT8919 May Overcome Resistance to Approved EGFR Inhibitors and Address a Wide Range of Acquired EGFR Resistance Mutations




## 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

IND Submission Expected mid-2022 with Potential Phase 1/2 Trial Initiation by YE 2022

Sources: Yang, J. C.-H. et al., J. Clin Oncol. 35, 1288-1296 (2017); Soria, J.-C. *et al. New Engl J Medicine* 378, 113–125 (2018)

# BRAF

# 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 V600E
- 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: V600E melanoma and/or NSCLC after failure of MEK inhibitor + BRAF inhibitor with indication specific expansion opportunities

Source: NIH SEER Database, Primary Literature Consensus

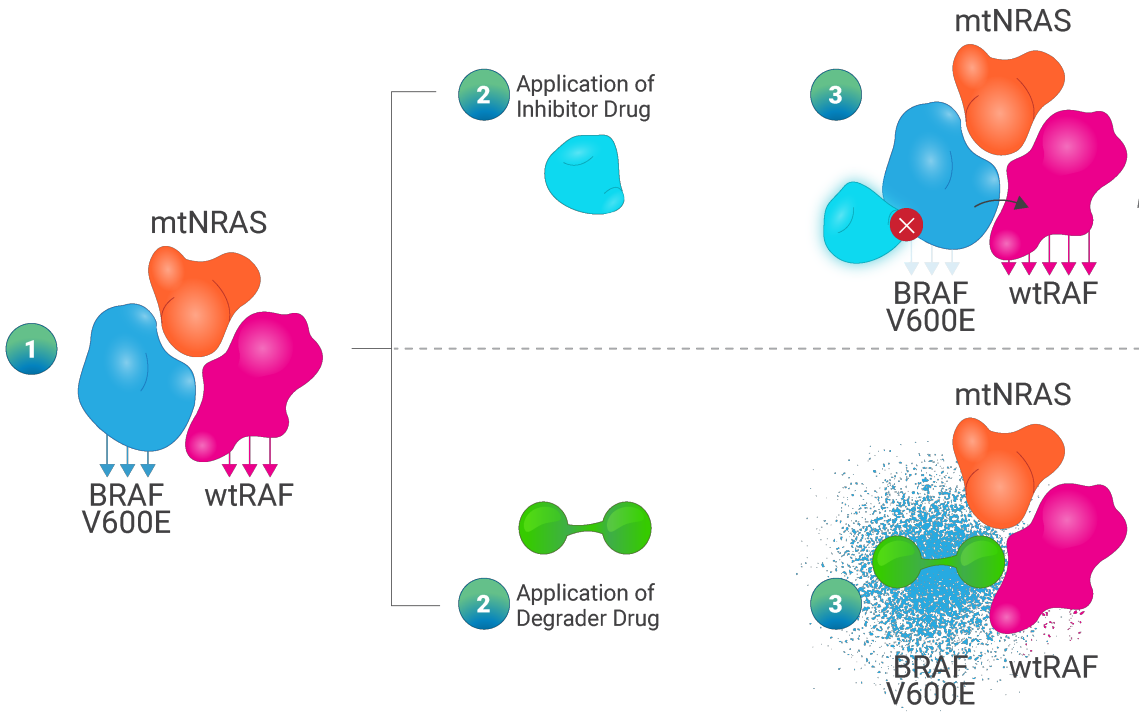
Patient figures represent estimated U.S. annual incidence

*BRAF program is partnered with Roche*

C4 Therapeutics

# BRAF Degrader to Overcome Limitations of Approved BRAF Inhibitors

## Mechanistic Rationale




Inhibitor causes paradoxical activation of wildtype RAF

Degrader prevents dimer formation and avoids paradoxical activation

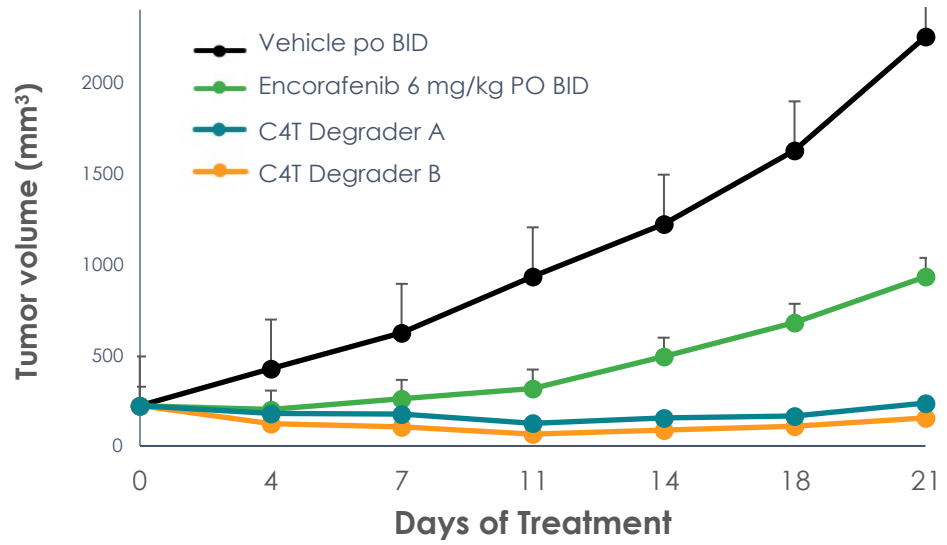
## Advantages of BRAF V600E Degradation

- 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

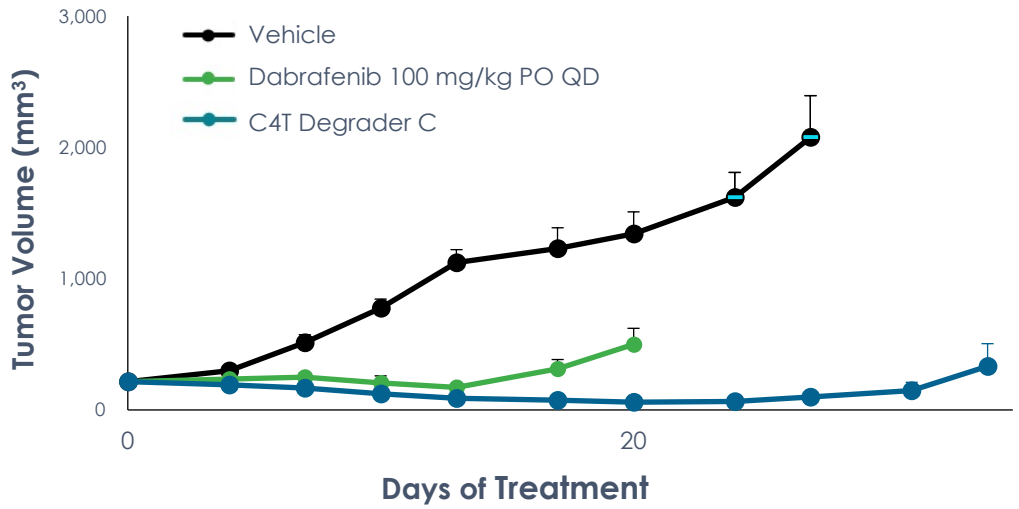
*BRAF program is partnered with Roche*

# BRAF Degraders Show Superior Efficacy Compared to Approved BRAF Inhibitors

## C4T BRAF Degrader Shows More Durable Efficacy Than Encorafenib




## C4T BRAF Degrader Shows More Durable Efficacy Than Dabrafenib




## IND Enabling Studies Planned for 2021

Source: C4T data on file

*BRAF program is partnered with Roche*

# 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

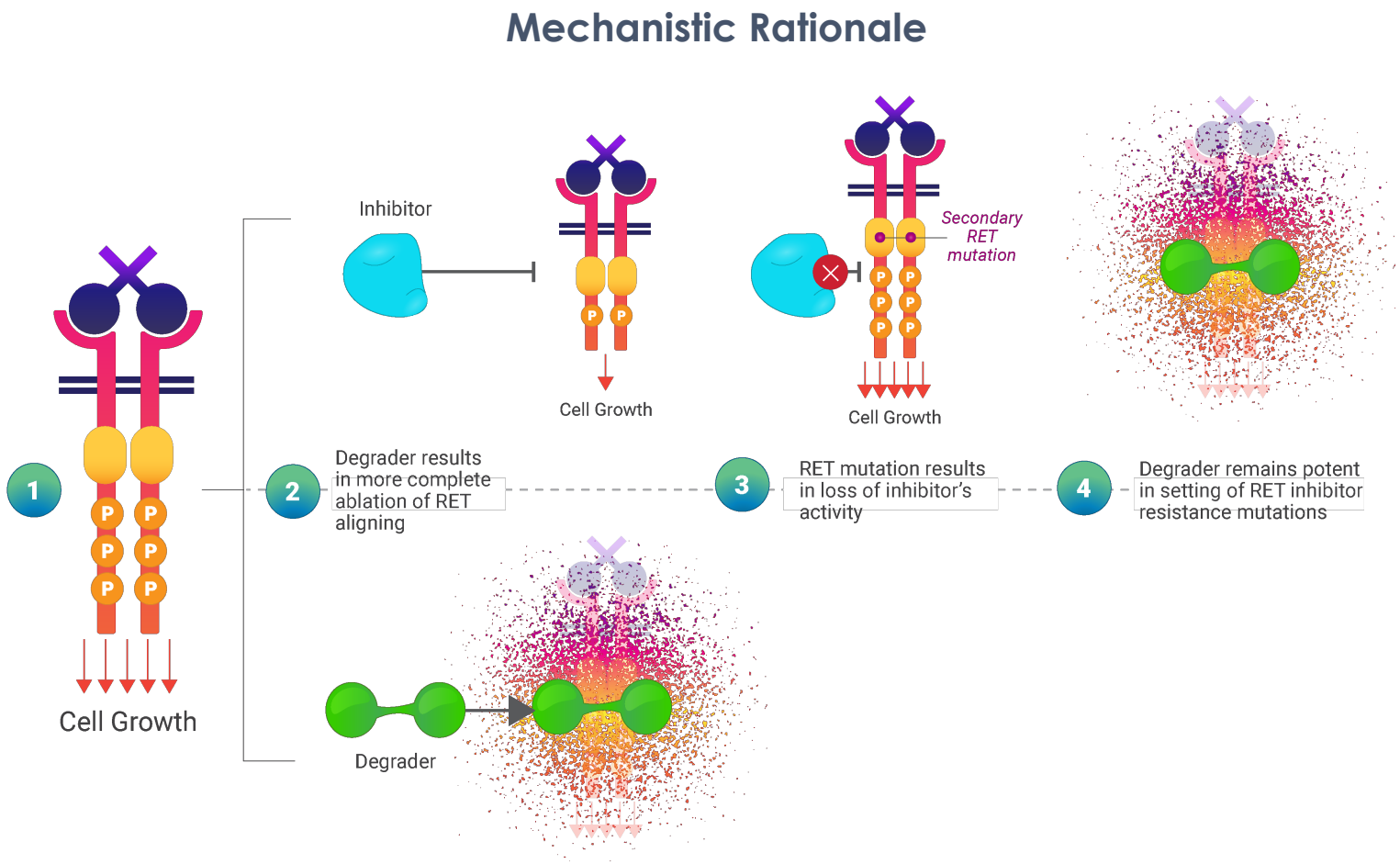
- Well defined registration path in existing, genetically defined patient population with no effective treatment option after RET tyrosine kinase inhibition (TKI)
- Target Population: second line RET-altered cancers; potential for front-line opportunity

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



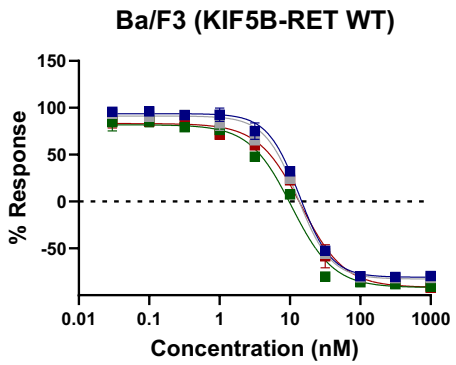

## Advantages of RET Degradation

- 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

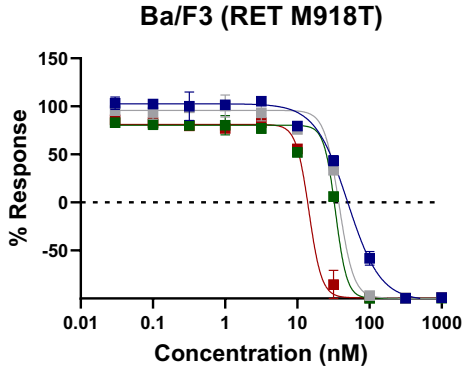
# RET Degrader Has an Excellent Cell Growth Inhibition Profile In RET Fusions and Common Resistance Mutations

## Drug Naïve, Driver Translocation/Mutation

### KIF5B-RET Fusion

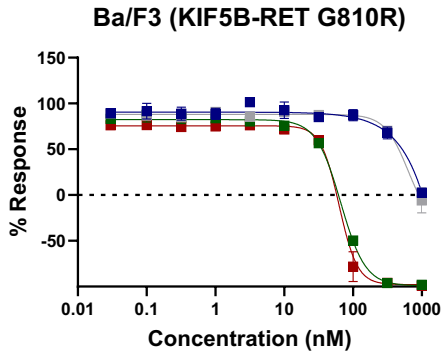



### Activating Mutation

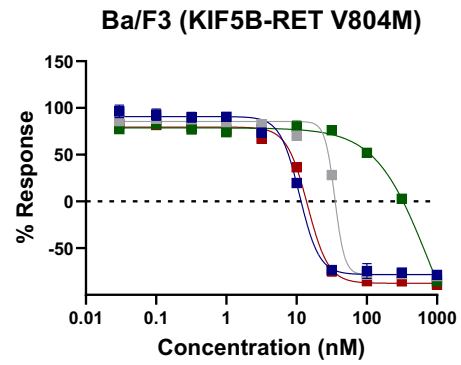



## RET Inhibitor Acquired-Resistance Mutants

### Solvent Front Mutation




### Gatekeeper Mutation




Pralsetinib  Selpercatinib  2nd Gen RET TKI  CFT RET Degrader

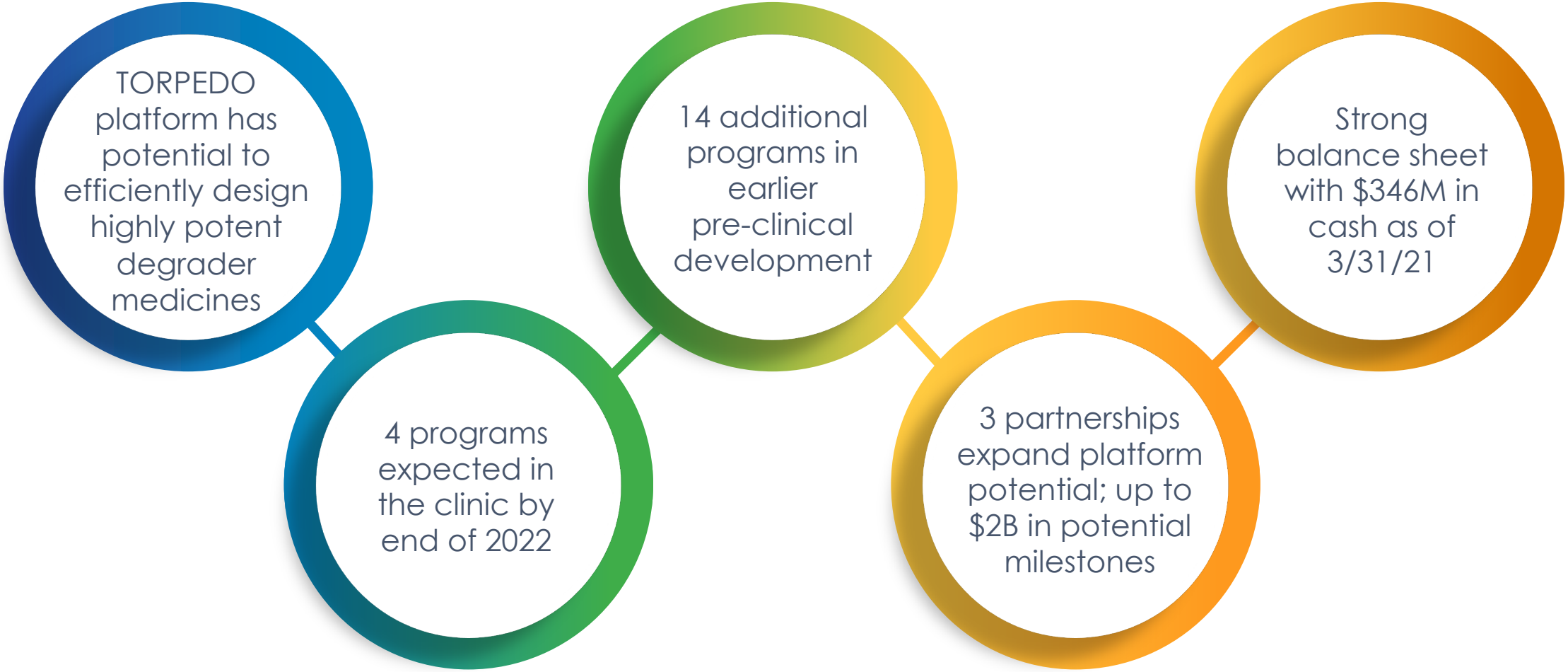
**Continue Lead Optimization Activities in 2021**

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 | ❑ Phase 1 Top-line Safety & Efficacy<br>❑ Proof of Mechanism |
| **BRD9 (CFT8634)** | ❑ IND Submission | ❑ Phase 1 Initiation |
| **EGFR (CFT8919)** | ❑ IND Enabling Studies | ❑ IND Submission<br>❑ Phase 1 Initiation |
| **BRAF** | ❑ IND Enabling Studies | ❑ IND Submission<br>❑ Phase 1 Initiation |
| **RET** | ❑ Lead Optimization | |

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




C4 Therapeutics

C4 Therapeutics

# Thank You