



**C4** Therapeutics

# Corporate Presentation

January 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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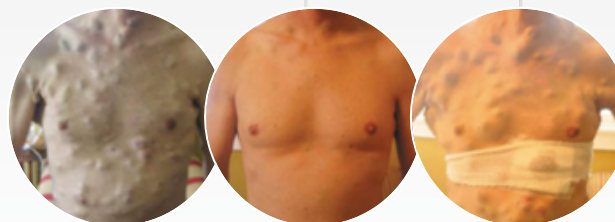
# Targeted Protein Degradation Has the Potential to Transform Treatment of Disease



<15%

Of Human Proteome  
Addressable by Small  
Molecule Inhibitors

Substantial opportunity to develop  
treatments for targets previously  
considered undruggable



Before

15 weeks

23 weeks

Adapted from Wagle et al, J Clin Oncol, 2011

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



\$63B

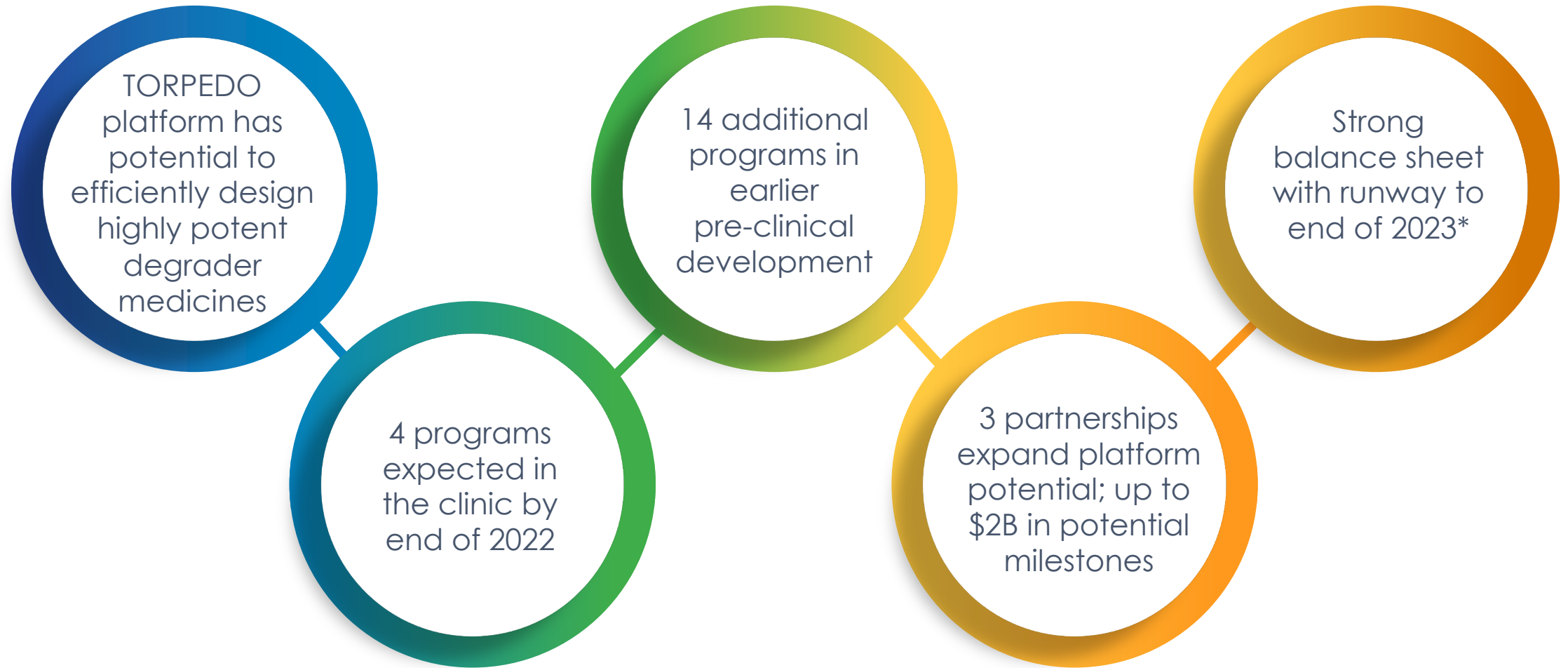
2018 Global  
Revenue

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>

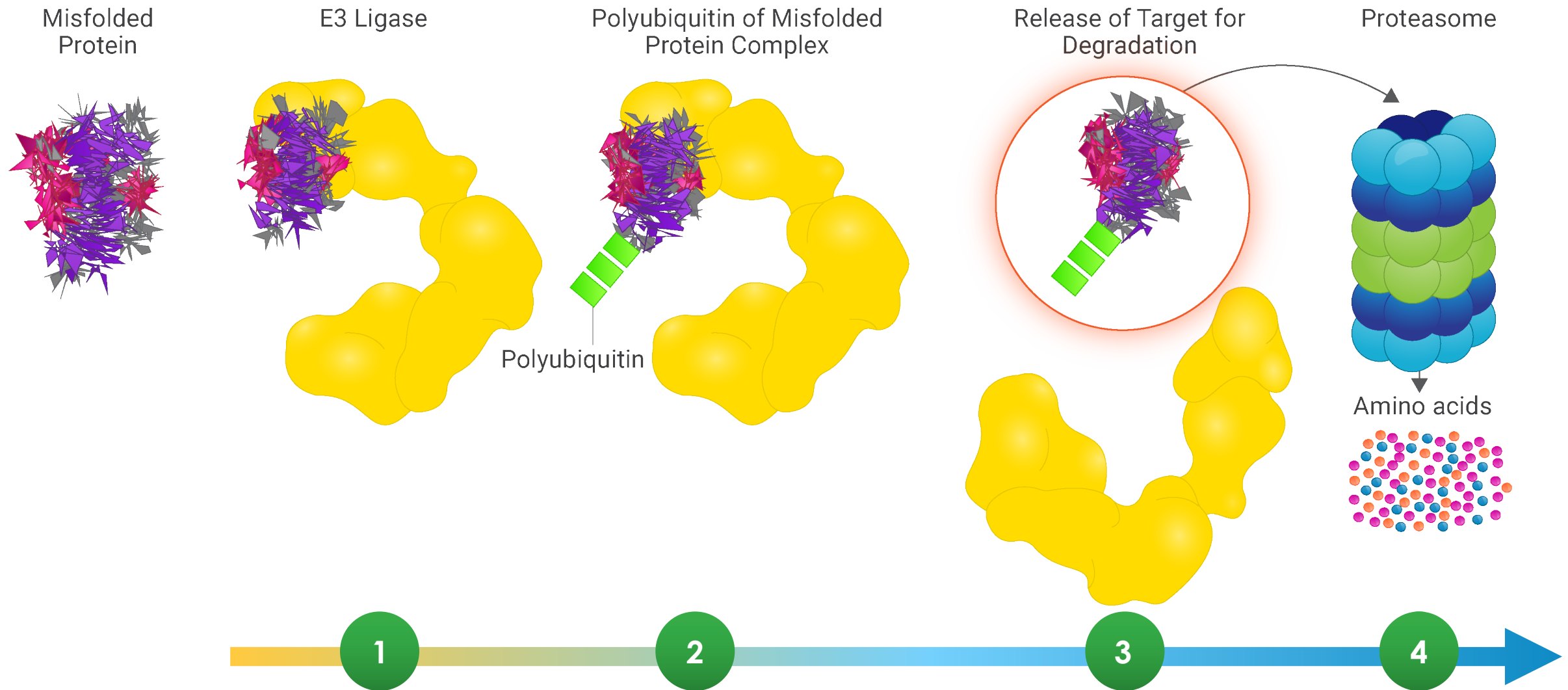
# C4T is Well Positioned to Develop Targeted Protein Degradation Medicines to Transform Patient Care



\*12/31/20 unaudited cash balance of approximately \$370M

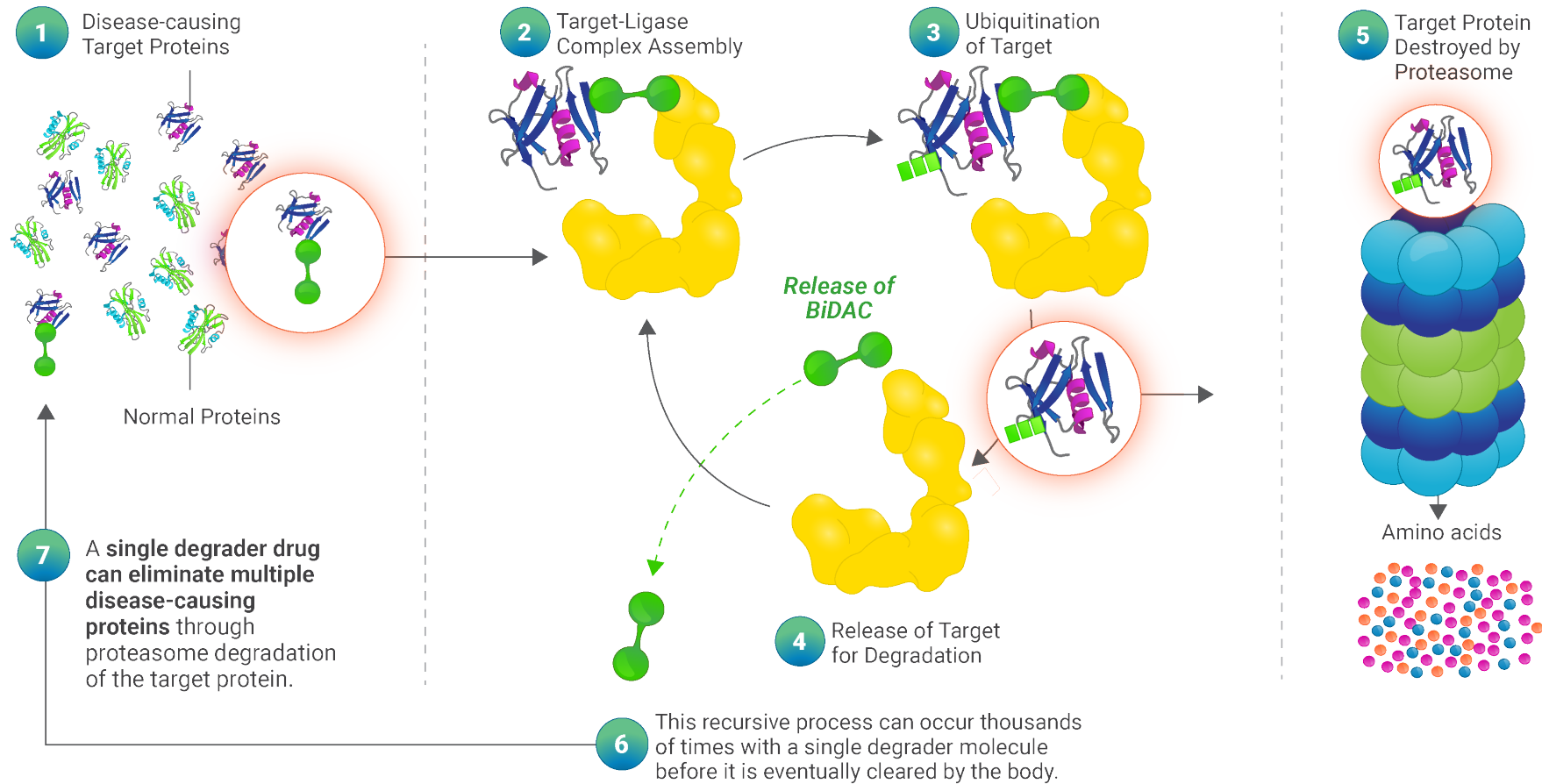


# The Human Body Has A Natural Process to Destroy Unwanted Proteins



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

## Focus on Overall Catalytic Degradation



# Targeted Protein Degradation Offers Fundamental Advantages Over Protein Inhibition

1

Improved Potency

2

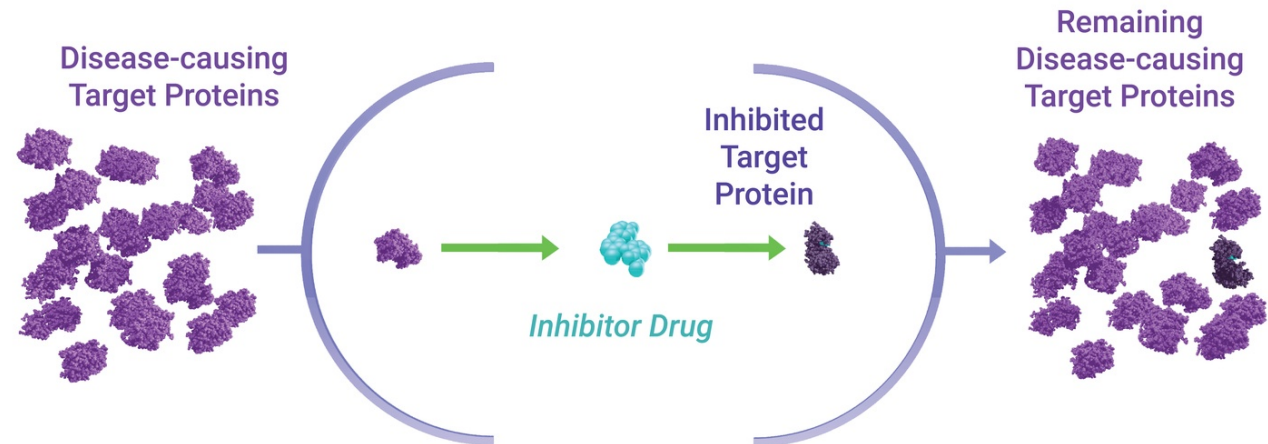
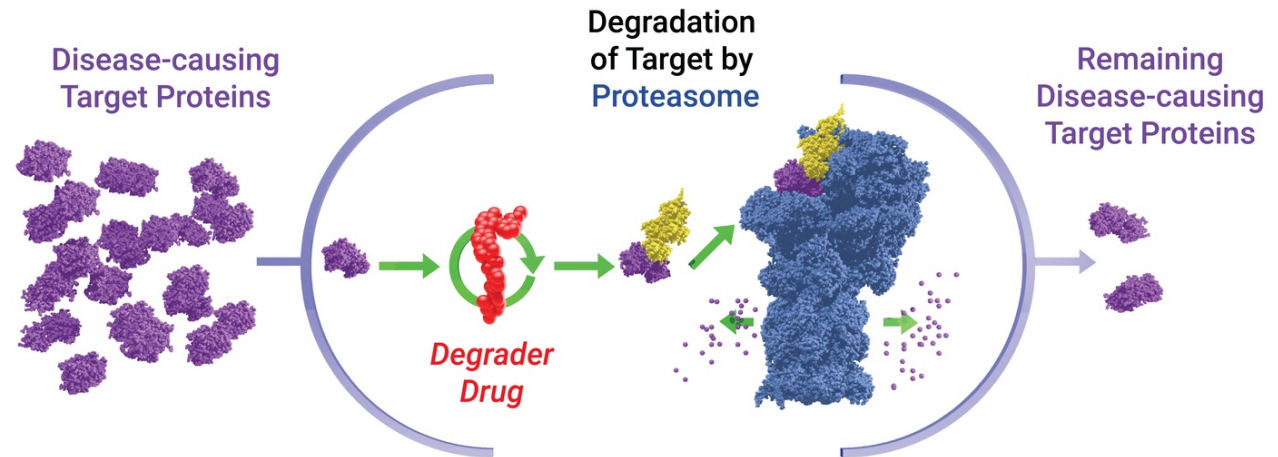
Fast Response

3

High Selectivity

4





Expansive Target Landscape



# TORPEDO (Target Oriented Protein Degrader Optimizer) Platform

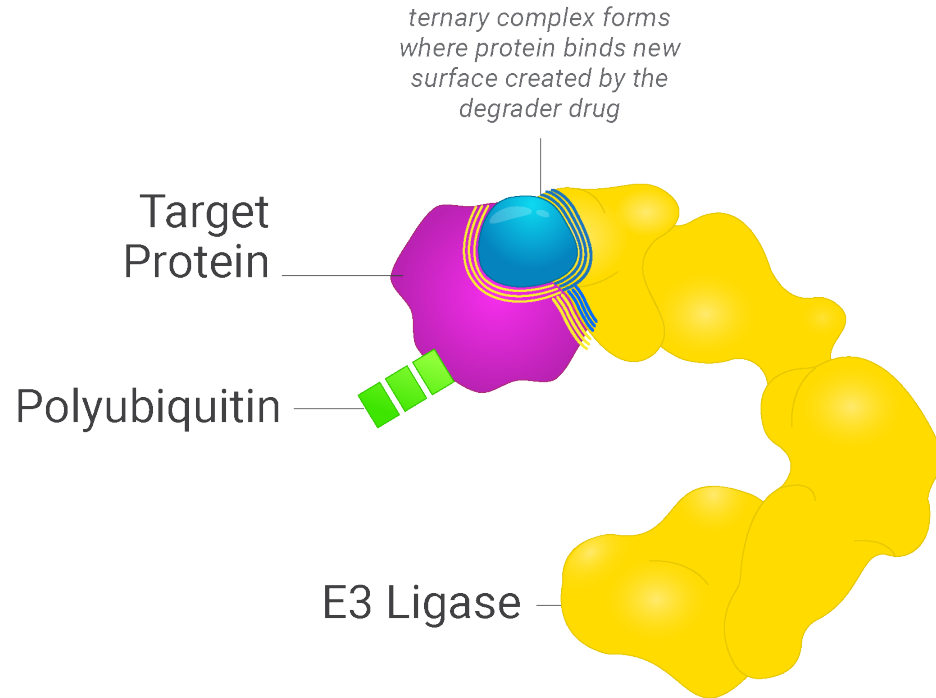


# Our TORPEDO Platform Has Potential to Efficiently Design Highly Potent Targeted Protein Degradator Medicines

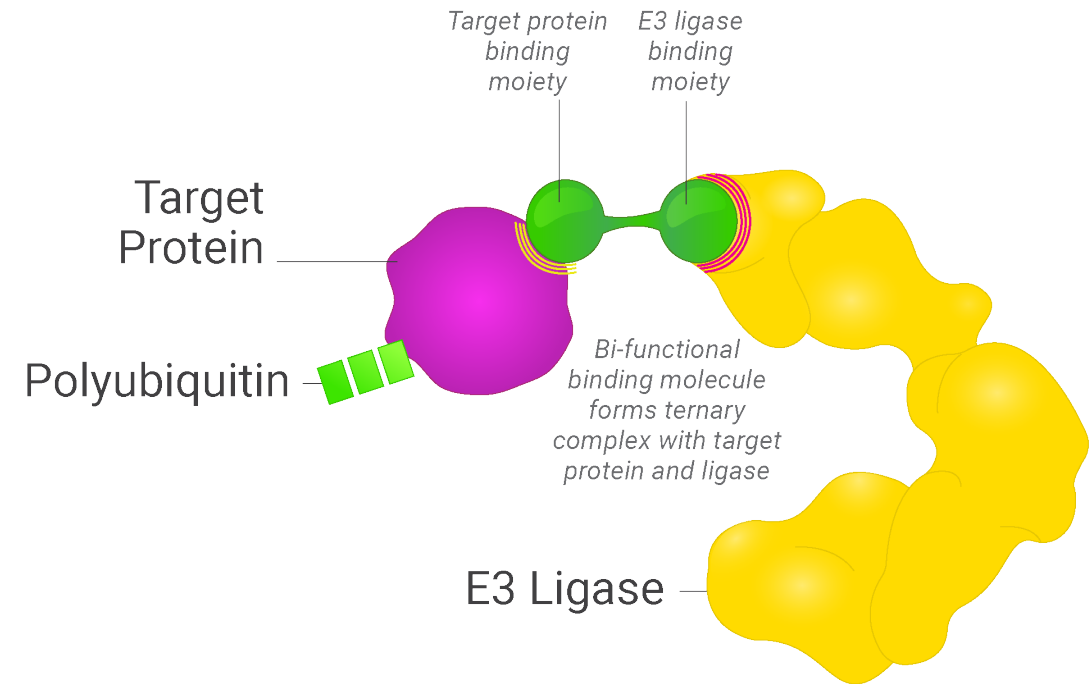
Elements	Benefits
 <b>Ability to Develop both MonoDACs &amp; BiDACs</b>	Flexibility to address different targets with tailored approach
 <b>Focus on Catalytic Efficiency</b>	Optimization of overall degradation process results in maximal efficacy
 <b>Ability to Design, Analyze &amp; Predict Degradator Performance</b>	Rapid delivery of potent drug candidates through informed and efficient drug discovery
 <b>Investment in Cereblon as E3 Ligase</b>	Cereblon is expressed in all tissues and cellular compartments, thereby providing the largest target selection opportunity

# TORPEDO Platform Offers Flexibility to Design MonoDACs and BiDACs

## MonoDAC



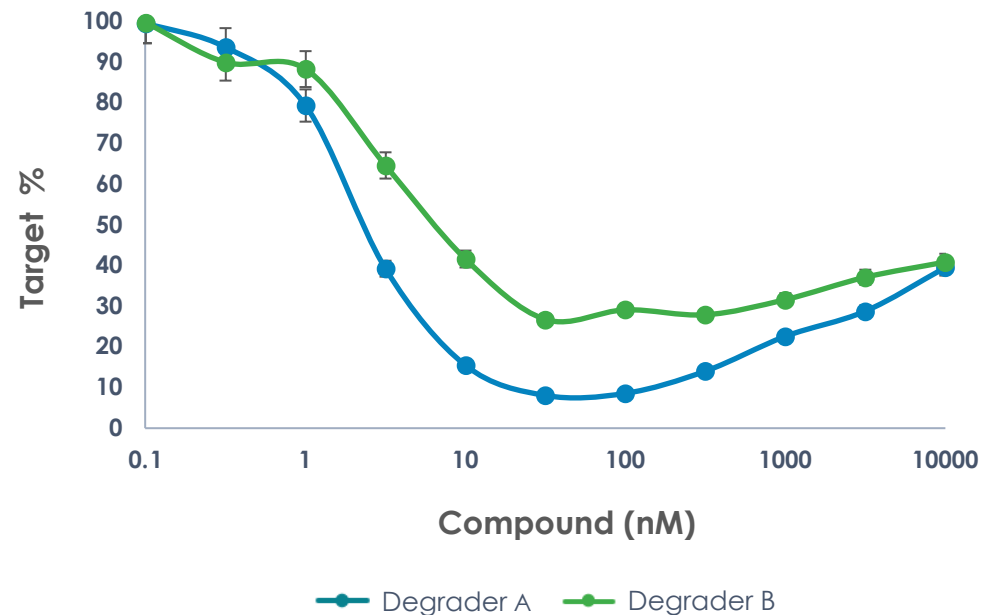
## BiDAC



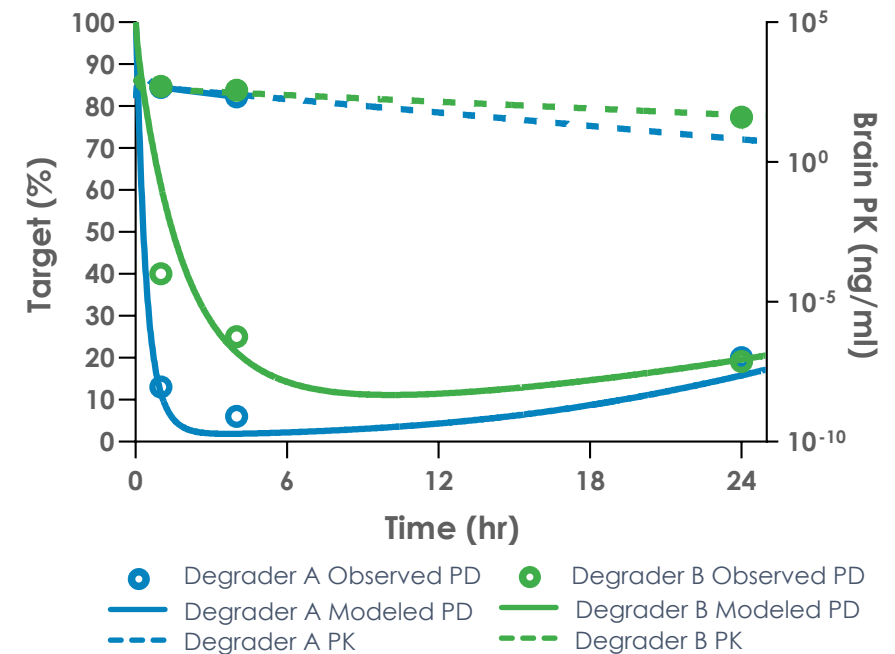
Flexibility to Address Different Targets with Tailored Approach

# Enhanced Catalytic Activity Drives Efficacy

## Improved Catalytic Activity of Degrader A...



## ...Drives Significant Improvement in Target Knockdown



Source: C4T data on file

# 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



# 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 14 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 Has Delivered a Robust Degradader Pipeline; Four Clinical Programs Expected by End of 2022

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

9 Additional Undisclosed Collaborator Programs in Discovery

# Three Strategic Target Platform Collaborations Expand Platform Potential



Signed March 2016  
and continues until  
completion of 6 programs

Focus is on oncology  
treatments targeting a  
specified set of proteins

**Calico**

5-year term  
beginning March 2017

Focus is on treating  
diseases of aging,  
including cancer



4.5-year term beginning  
January 2019

Focus is on neurological  
conditions with up to 5  
targets total

IKZF1/3  
CFT7455



# IKZF1/3: Maximal Catalytic Activity Leads to Improved Efficacy

## Strong Rationale for Degradator 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

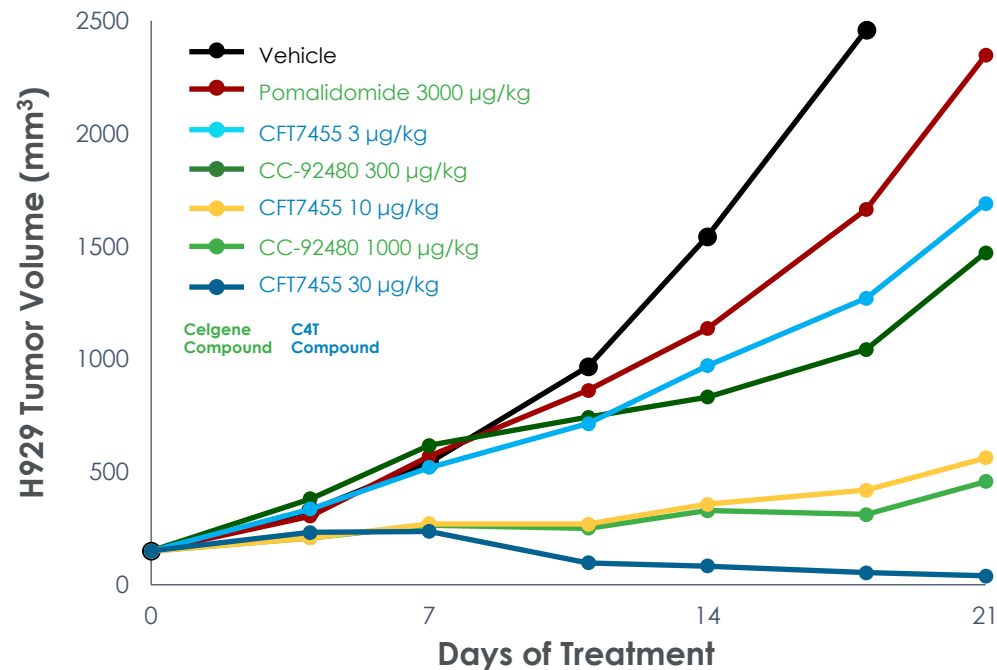
- Potential for accelerated approval in select indications
- Opportunity to expand into earlier lines of MM therapy

Source: NIH SEER Database, Primary Literature Consensus

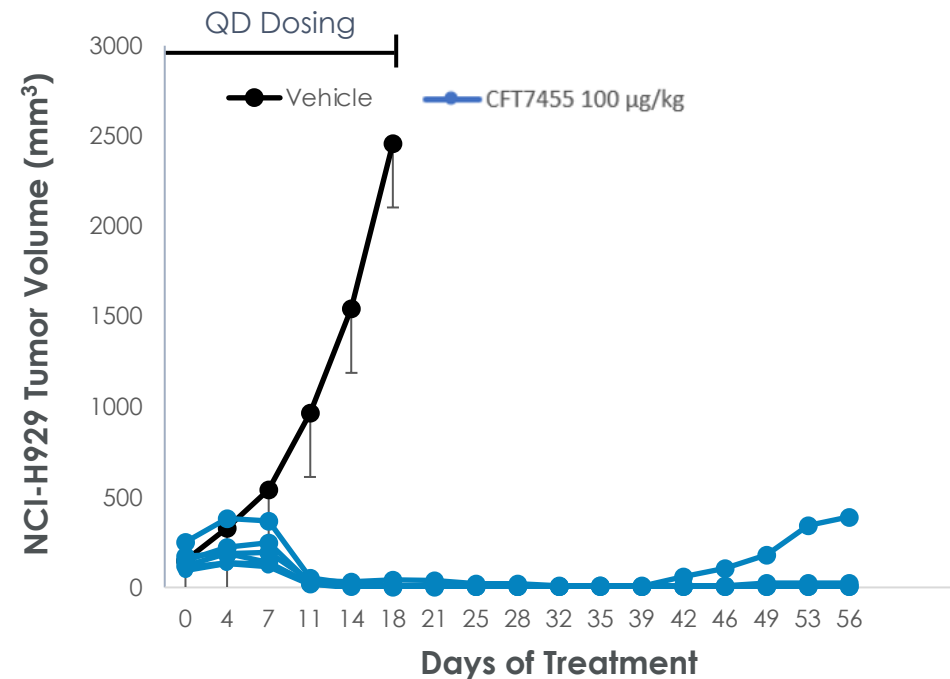
Patient figures represent estimated U.S. annual incidence  
PTCL = peripheral T-cell lymphoma; MCL = mantle cell lymphoma

# 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



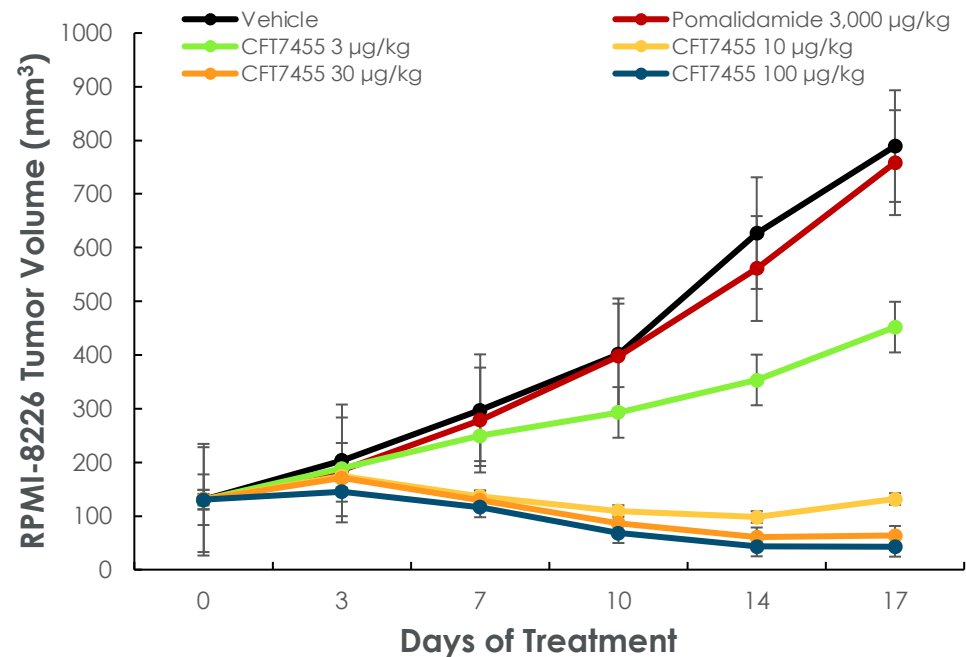
## CFT7455 *In Vivo* Efficacy Durable After End of Dosing Period



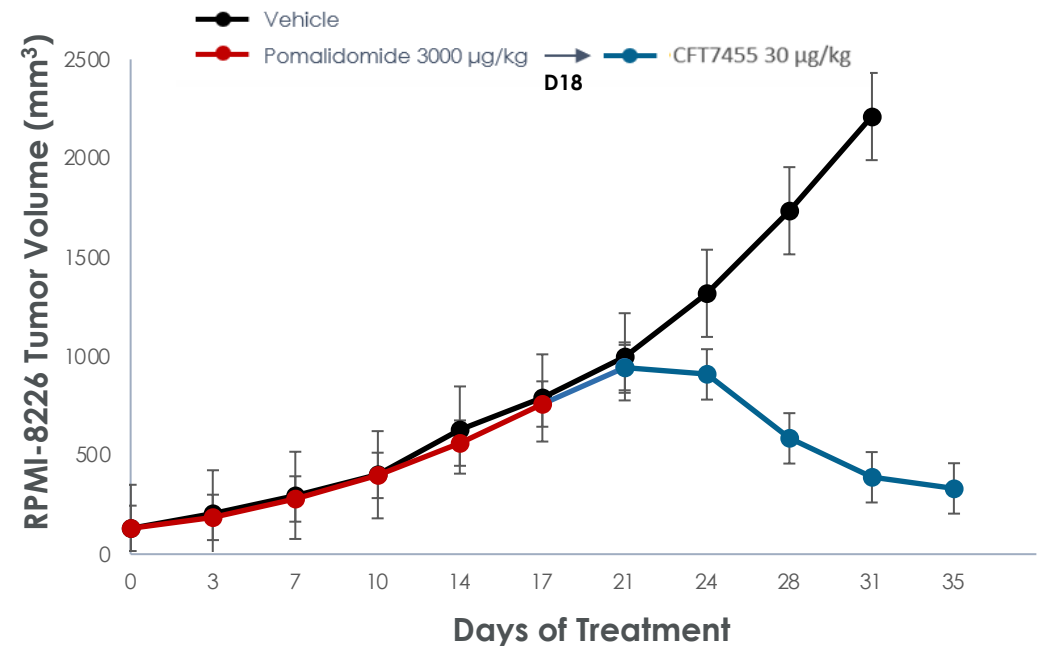
Source: C4T data on file

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

## CFT7455 Active in RPMI-8226, Relative to Pomalidomide

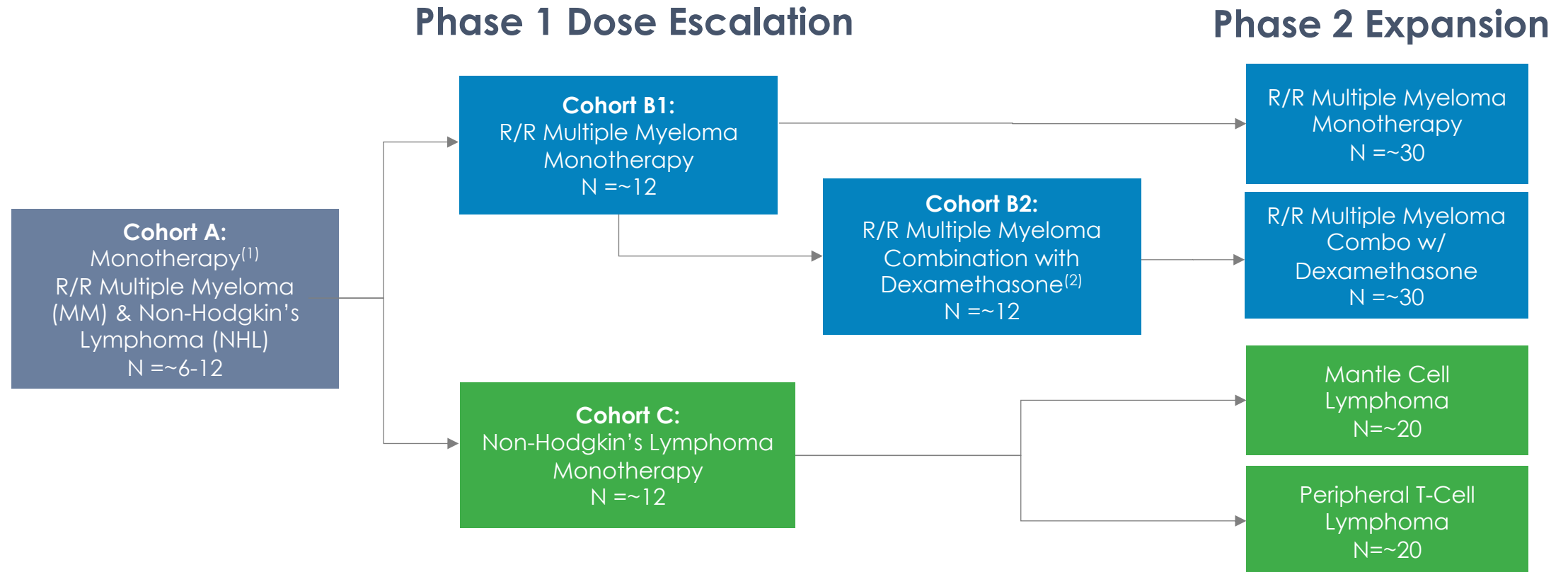


## CFT7455 Active in RPMI-8226 After Tumor Progression on Pomalidomide Treatment



Source: C4T data on file

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



IND Clearance Achieved; Trial Expected to Initiate in 1H 2021

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



BRD9  
CFT8634

# BRD9: Drugging the Undruggable with a Degradar Approach

## Strong Rationale for Degradar 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

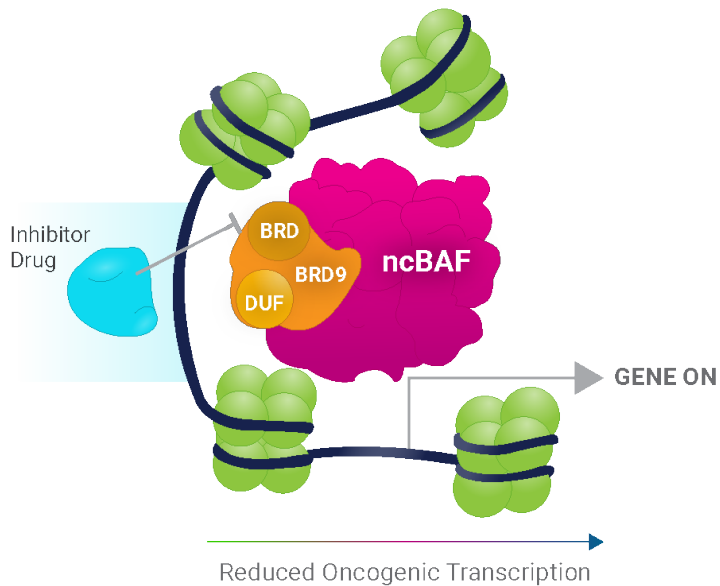
- Well defined path to registration in SS and metastatic population already under management at academic centers
- Precedent for approval with a single-arm study in second-line setting

Source: NIH SEER Database, Primary Literature Consensus

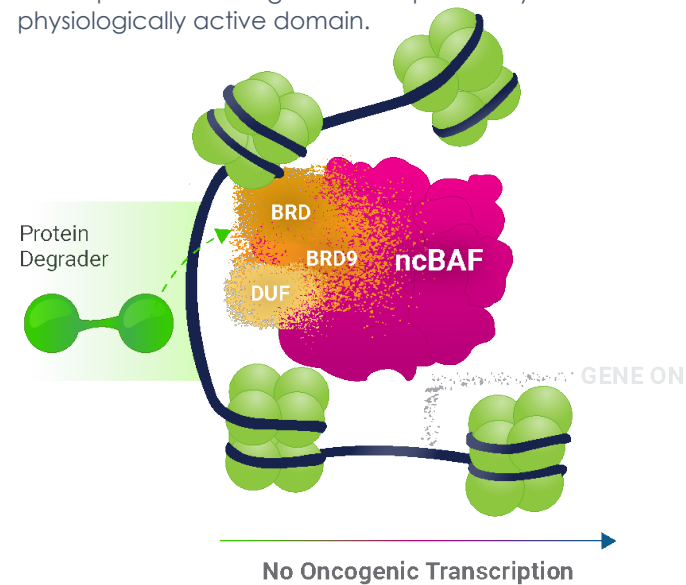
Patient figures represent estimated U.S. annual incidence

# 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.

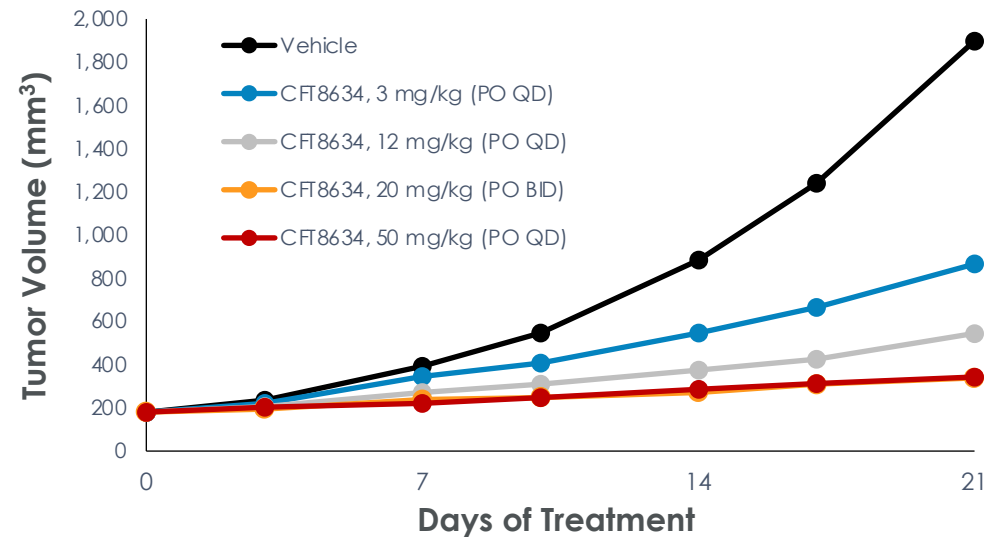


## Advantages of BRD9 degradation

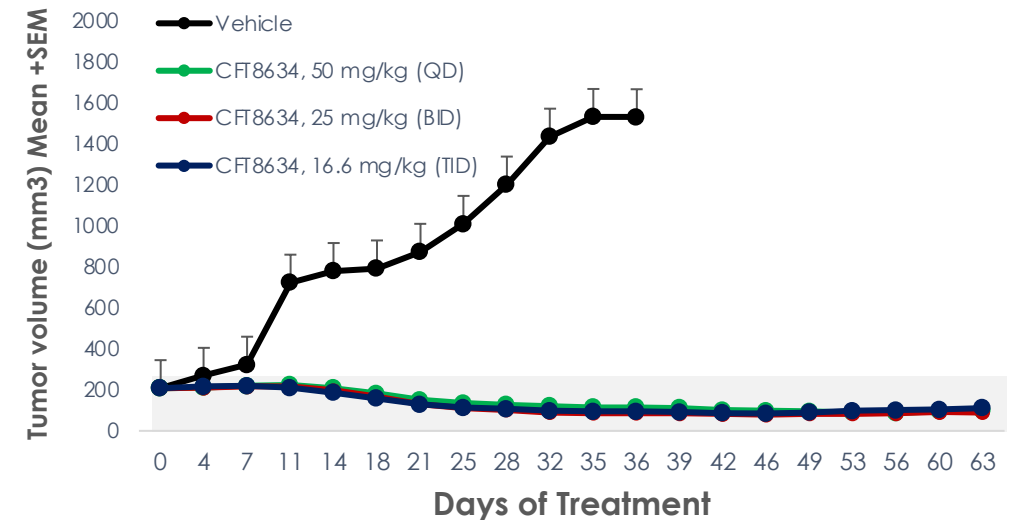
- Specifically degrades BRD9 and spares BRD4 and BRD7, avoiding potential off-target toxicities
- Oncogenicity of BRD9 depends on sub-domains not addressed by traditional inhibitors

# Robust Responses of CFT8634 Seen in Preclinical Synovial Sarcoma Models

## Dose Response Activity Yamato Xenograft Model



## Dose Response Activity Patient Derived Xenograft Model



IND Submission for CFT8634 Expected in 2H 2021

Source: C4T data on file

BRAF

# BRAF: Utilizing a Degradar Approach to Overcome Resistance Mutations

## Strong Rationale for Degradar 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

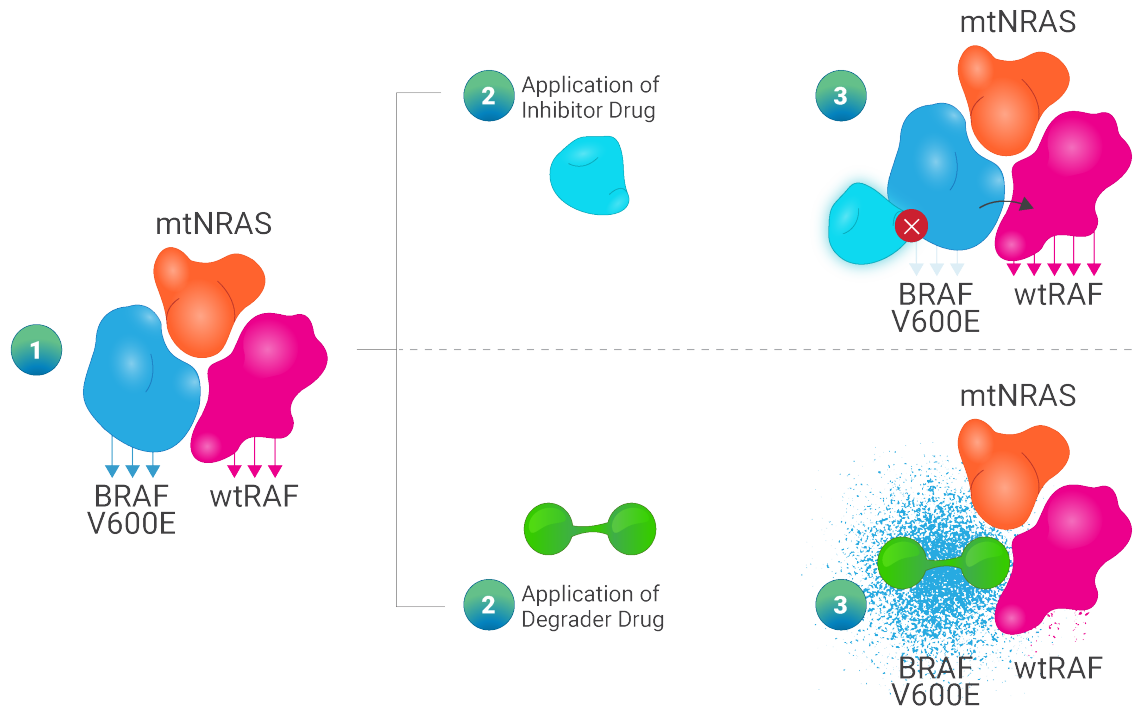
Patient figures represent estimated U.S. annual incidence  
BRAF program is partnered with Roche



# BRAF Degraders to Overcome Limitations of Approved BRAF Inhibitors

## Mechanistic Rationale

Inhibitor causes paradoxical activation of wildtype RAF



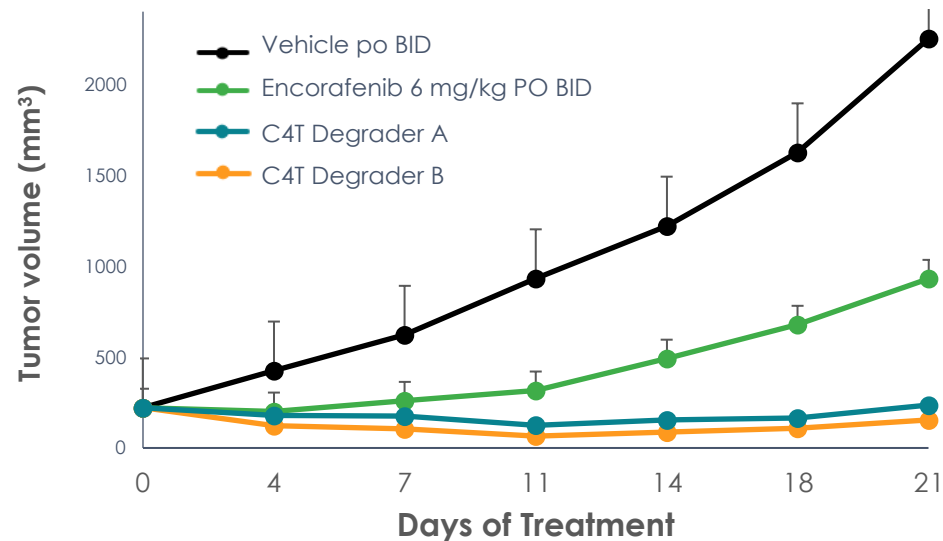
Degrader prevents dimer formation and avoids paradoxical activation

## Advantages of BRAF V600E Degradation

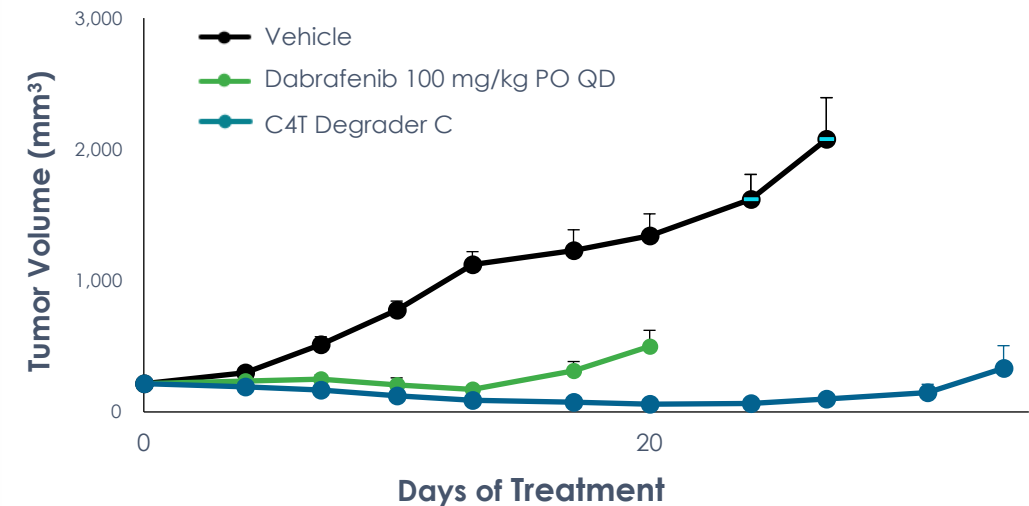
- Specifically target mutant BRAF over wildtype BRAF
- Prevent mutant BRAF incorporation into RAF dimers
- Avoid paradoxical activation and associated failure of therapy due to resistance mechanisms dependent on BRAF inhibitor mediated paradoxical activation

# BRAF Degraders Show Superior Efficacy Compared to Approved BRAF Inhibitors

## C4T BRAF Degraders Show More Durable Efficacy Than Encorafenib



## C4T BRAF Degraders Show More Durable Efficacy Than Dabrafenib



IND Enabling Studies Planned for 2021

Source: C4T data on file

RET

# RET Degradation: Opportunity to Overcome Resistance Mutations

## Strong Rationale for Degradation 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

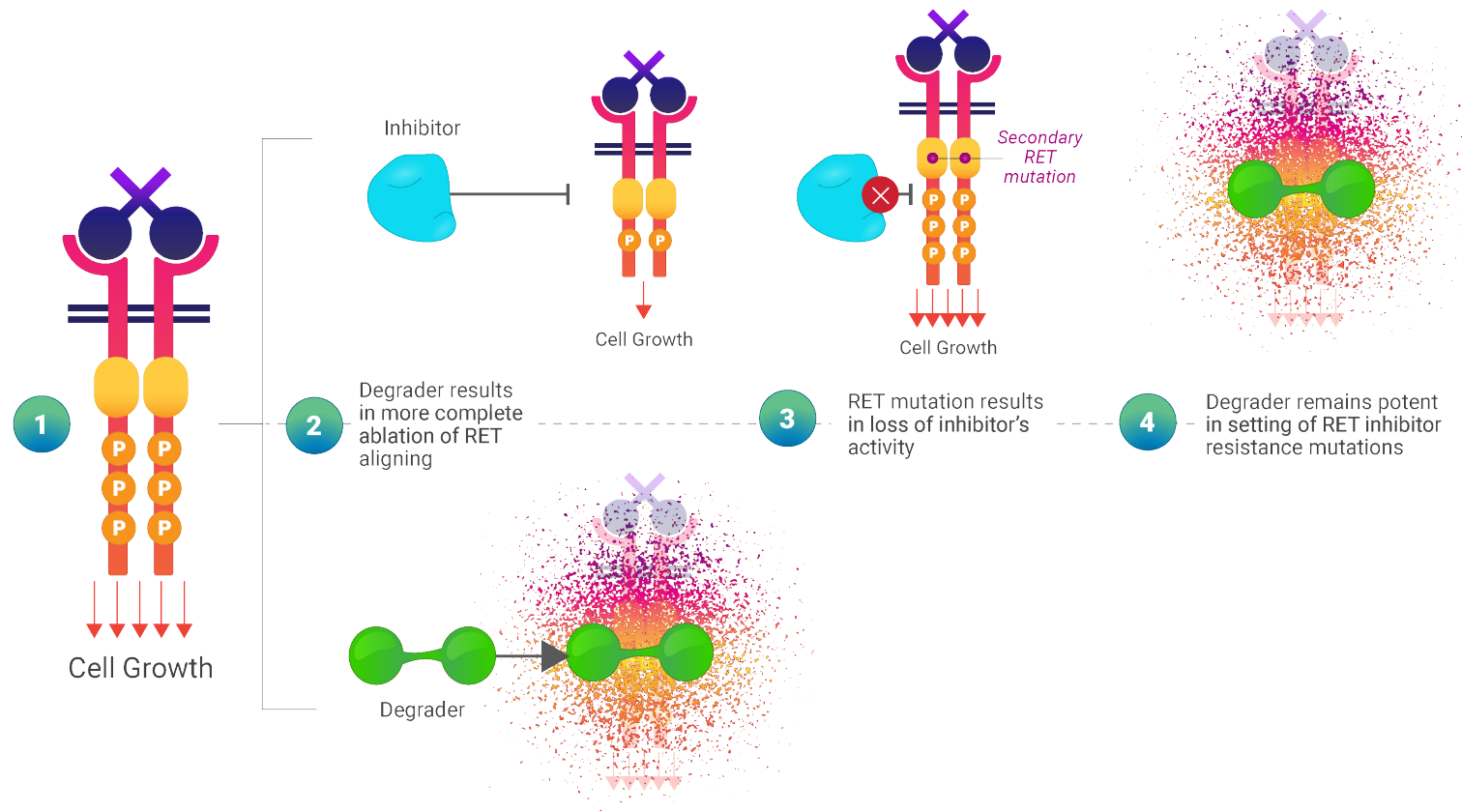
- Well defined registration path in existing, genetically defined patient population with no effective treatment option after RET tyrosine kinase inhibition (TKI)
- Target Population: second line RET-altered cancers; potential for front-line opportunity

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

Patient figures represent estimated U.S. annual incidence

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

## Mechanistic Rationale



## Advantages of RET Degradation

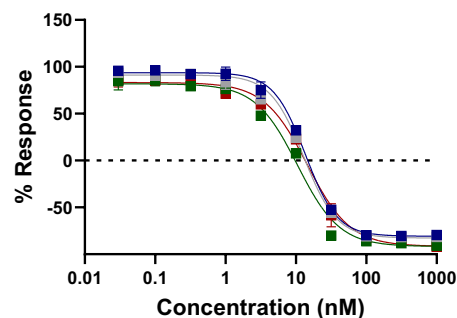
- RET degrader is active against key secondary mutations that cause resistance, including both the gatekeeper and solvent front mutations
- Against RET without secondary mutation, as in the front-line setting, degradation may offer deeper and more durable response than inhibition

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

## Drug Naïve, Driver Translocation/Mutation

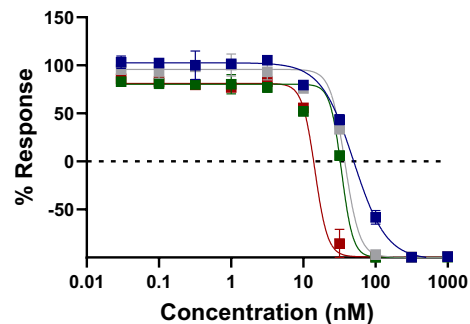
### KIF5B-RET Fusion

#### Ba/F3 (KIF5B-RET WT)



### Activating Mutation

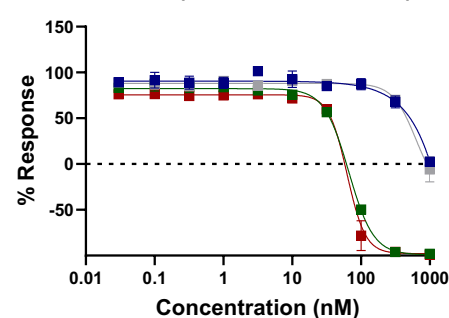
#### Ba/F3 (RET M918T)



## RET Inhibitor Acquired-Resistance Mutants

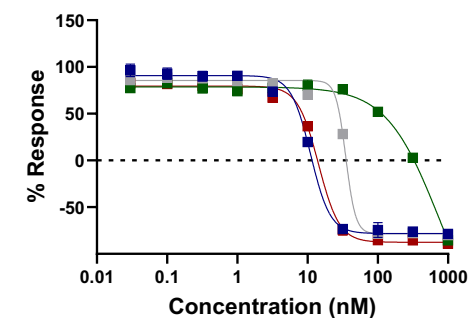
### Solvent Front Mutation

#### Ba/F3 (KIF5B-RET G810R)



### Gatekeeper Mutation

#### Ba/F3 (KIF5B-RET V804M)



■ Pralsetinib   ■ Selpercatinib   ■ 2<sup>nd</sup> Gen RET TKI   ■ CFT RET Degradar

IND Enabling Studies Planned for 2021

Source: C4T data on file



# Lead Programs Offer Compelling Opportunities to Address Unmet Need in Multiple Patient Populations

**IKZF1/3  
CFT7455**

**NON-  
HODGKIN's  
LYMPHOMA** **77K**  
cases/year

**32K** **MULTIPLE  
MYELOMA**  
cases/year

5-year survival  
**52%**

**BRD9  
CFT8634**

**SYNOVIAL  
SARCOMA**  
**900**  
cases/year

MEDIAN PFS OF 1L  
CHEMOTHERAPY

**6.3**  
months

**BRAF  
BiDAC**

**>70K**  
cases/year

**MELANOMA, NSCLC,  
CRC AND OTHER  
MALIGNANCIES**

PFS across approved  
BRAF inhibitors

**<15**  
months

**RET  
BiDAC**

**1-2%**  
of NSCLC

median **PFS**

**~16.5**  
months  
(selpercatinib)

**60%**  
of sporadic  
medullary  
thyroid  
cancer

Sources: National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Database

MM survival: [https://seer.cancer.gov/archive/csr/1975\\_2015/browse\\_csr.php?sectionSEL=18&pageSEL=sect\\_18\\_table.08.html#table2](https://seer.cancer.gov/archive/csr/1975_2015/browse_csr.php?sectionSEL=18&pageSEL=sect_18_table.08.html#table2). SS PFS: M. Vlentier et al. European Journal of Cancer 58 (2016) 62e72; BRAF

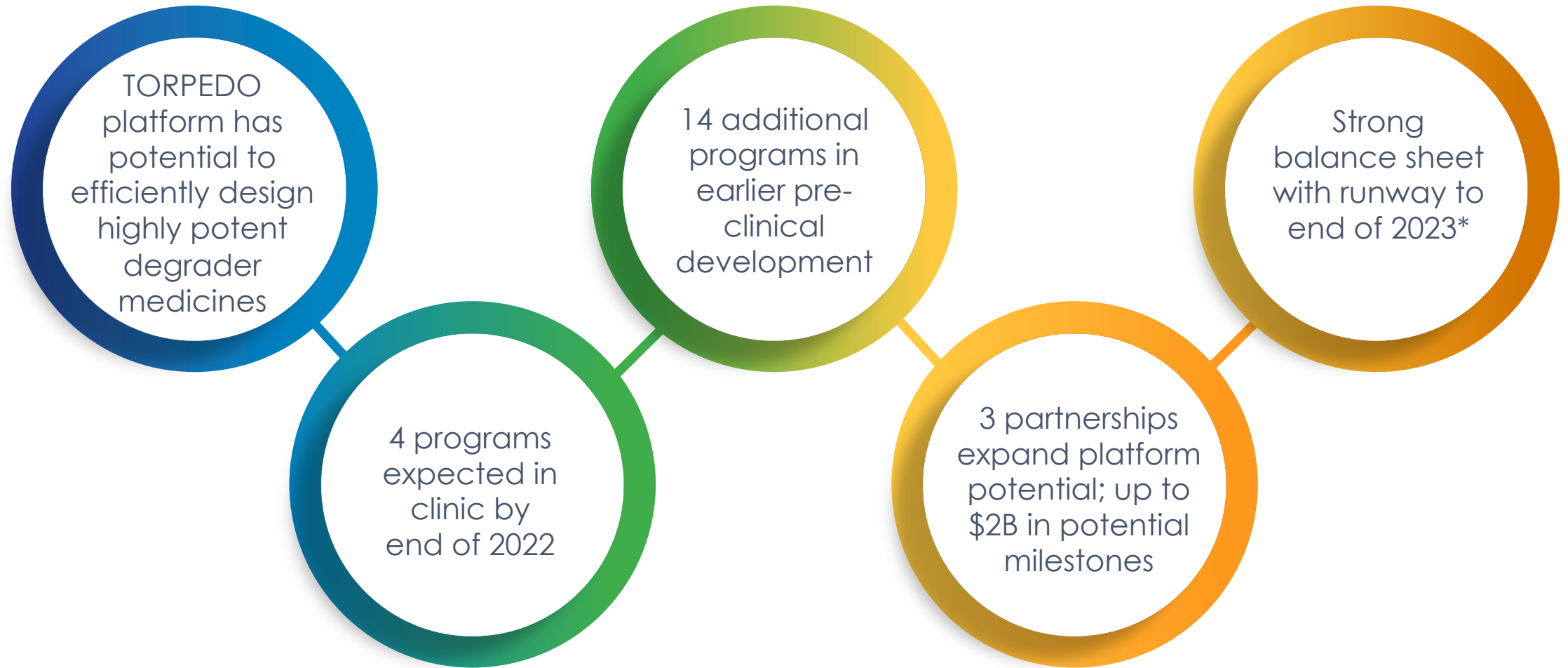
PFS: Cell Press Review, Trends in Cancer, September 2020, Vol. 6, No. 9; RET PFS: NJEM 383;9 nejm.org 8/27/20

Patient figures represent estimated U.S. annual incidence

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



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



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# C4 Therapeutics

## Thank You

