C4 Therapeutics


# Clinical Insights on Leveraging Kinetics-Based PK/PD Modeling to Drive Degrader Optimization

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7th TPD & Induced Proximity Summit

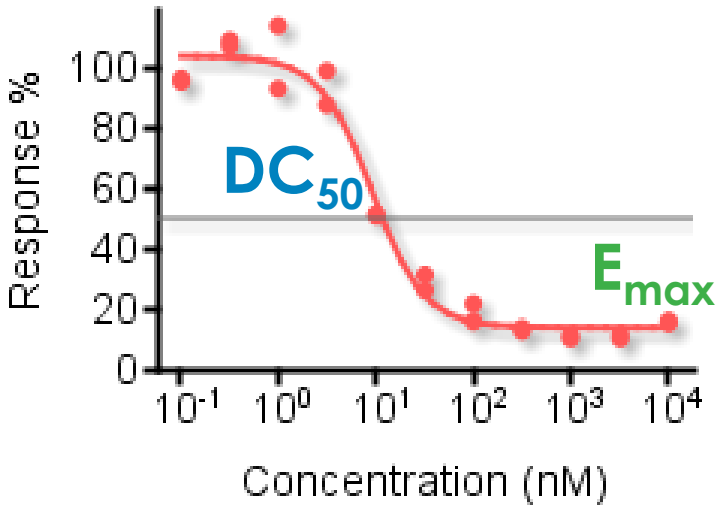
Oct 29, 2024

# Disclosure Information

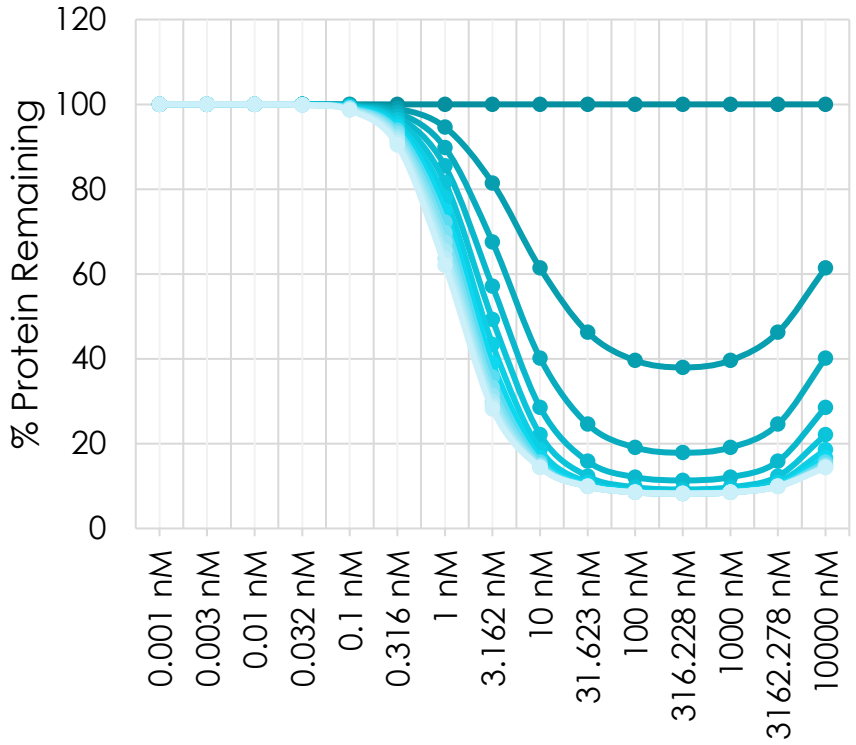
- I have the following financial relationships to disclose:
  - Stockholder in: C4 Therapeutics, Inc.
  - Employee of: C4 Therapeutics, Inc.

# Catalytic Mechanism Requires Assessment of Time Dependence

## Static Timepoint



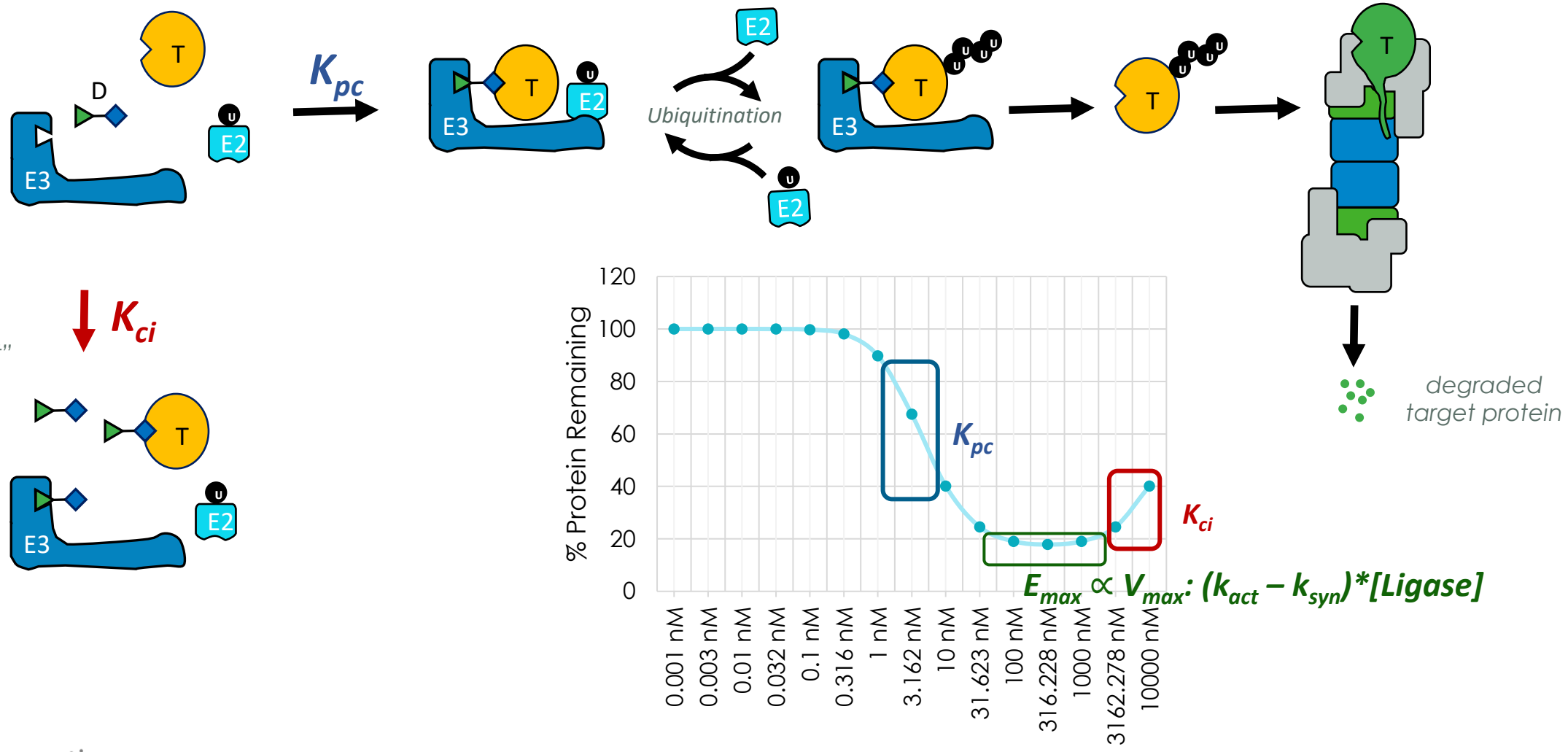

## Time course




**$DC_{50}$** – [degrader] for 50% target depletion
(≈ cellular potency)

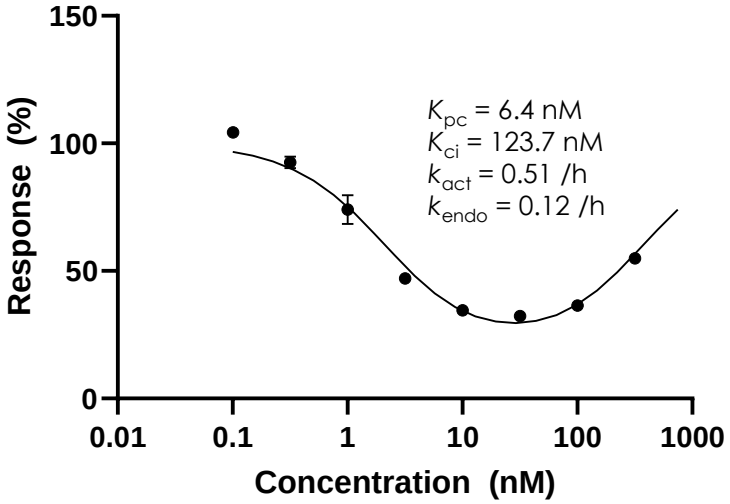
**$E_{max}$** – % remaining target @ assay timepoint
(maximal degradation ≈ degradation rate)

# Applying an Enzymology Framework Provides Quantitative Assessments of Degrader Activity



# Modeling Degrader Action Requires Tailored Equations

- Change in target concentration after degrader treatment is determined by:




endogenous synthesis; endogenous degradation; degrader-induced degradation

$$\frac{d[T]}{dt} = (100\% \times k_{endo}) - k_{endo} \times [T] - k_{deg} \times [T]$$

$$[T](t) = (100\% - E_{dss})e^{-(k_{endo}+k_{deg})t} + E_{dss}$$

$$k_{deg} = \frac{k_{act}}{1 + \frac{K_{pc}}{[D]} + \frac{[D]}{K_{ci}}} \qquad E_{dss} = \frac{100\% \times k_{endo}}{k_{endo} + k_{deg}}$$


References:

Flaxman, H., Deibler, R., Conicella, A., Ingham, O. Orsi, D., Sowa, M., Cassidy, K., Pollock, R., Fisher, S. (2023) Applications of Kinetics Modeling in Targeted Protein Degradation [Poster]. *Bioorganic Gordon Research Conference*, Andover, NH.

Segel, I. H. (1975). Enzyme kinetics : behavior and analysis of rapid equilibrium and steady state enzyme systems. Wiley.

Bartlett, D.W., Gilbert, A.M. (2021) A kinetic proofreading model for bispecific protein degraders. J Pharmacokinet Pharmacodyn 48, 149–163. https://doi.org/10.1007/s10928-020-09722-z

Haid, R.T.U. and Reichel, A. (2024), Transforming the Discovery of Targeted Protein Degraders: The Translational Power of Predictive PK/PD Modeling. Clin Pharmacol Ther, 116: 770-781. https://doi.org/10.1002/cpt.3273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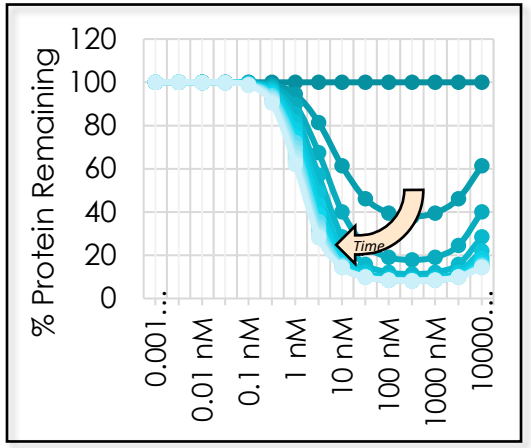
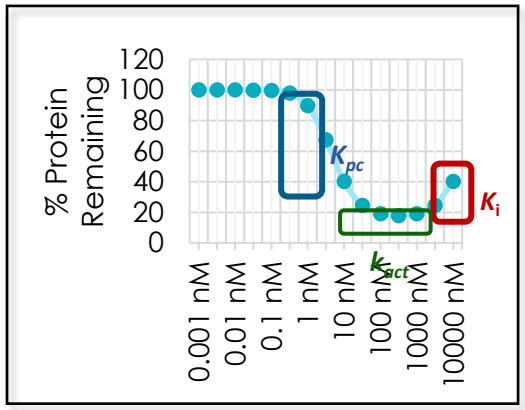
# Degrader Specific PK/PD Models Founded on Enzymology Framework

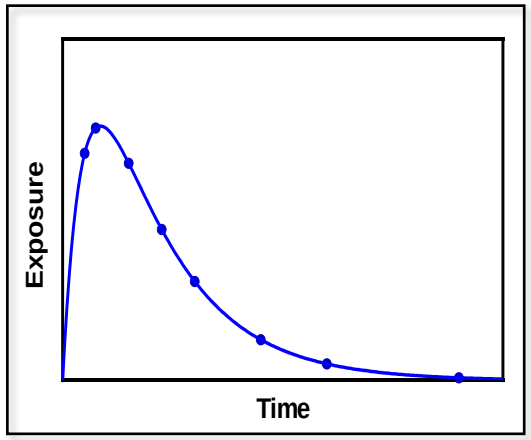
*Enzymology Framework*




**TIME DEPENDENCE**

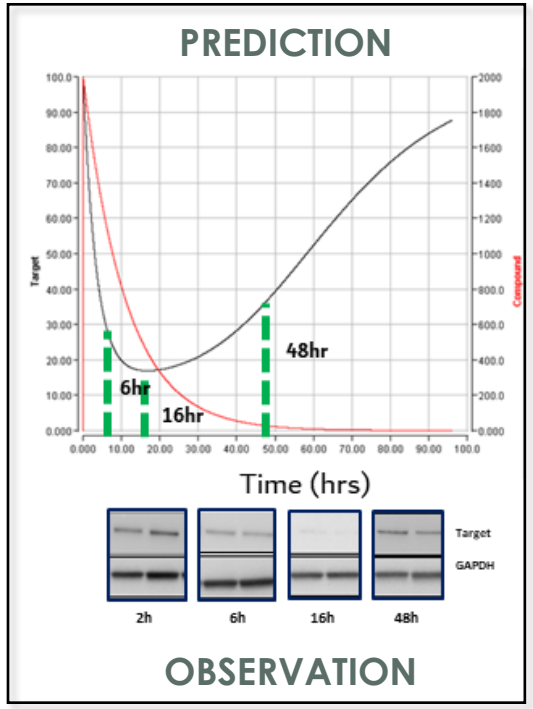



**KEY PARAMETERS**



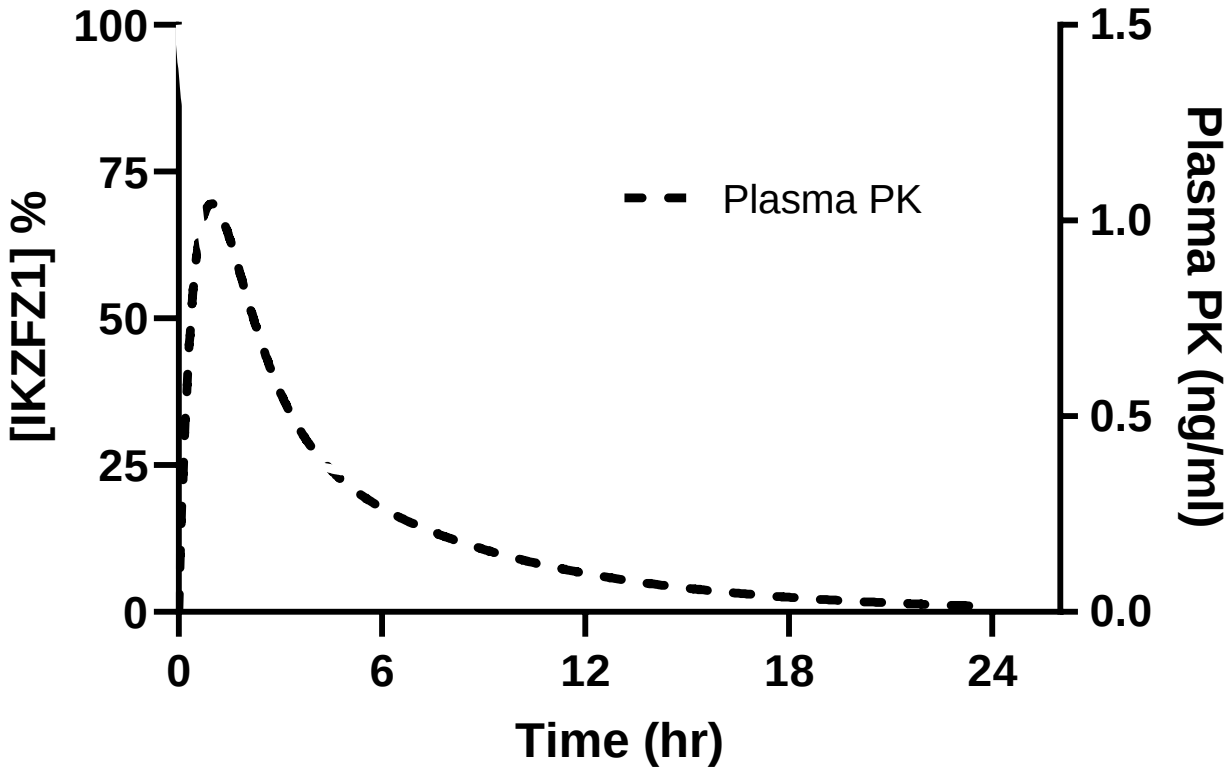

**DMPK PROPERTIES**

Kinetics-Based PK/PD Models



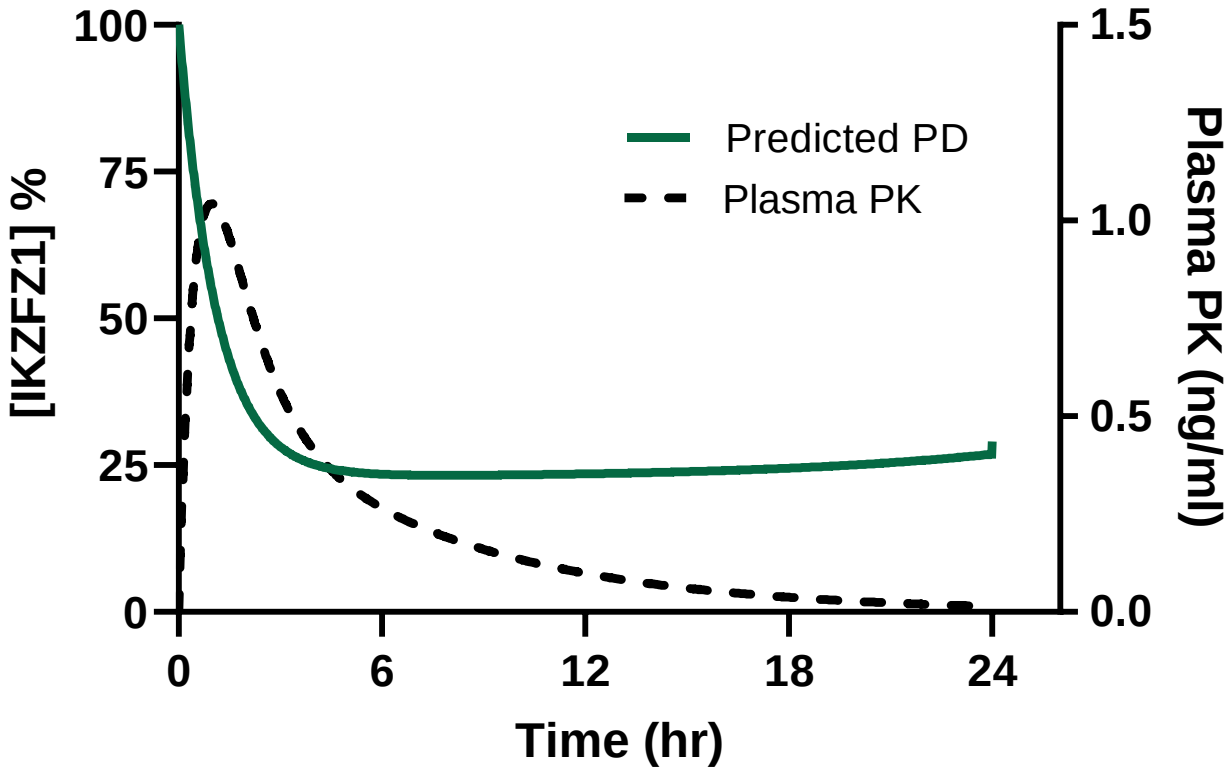

**OBSERVATION**

# Predictive PK/PD Models Drive Efficient Drug Discovery



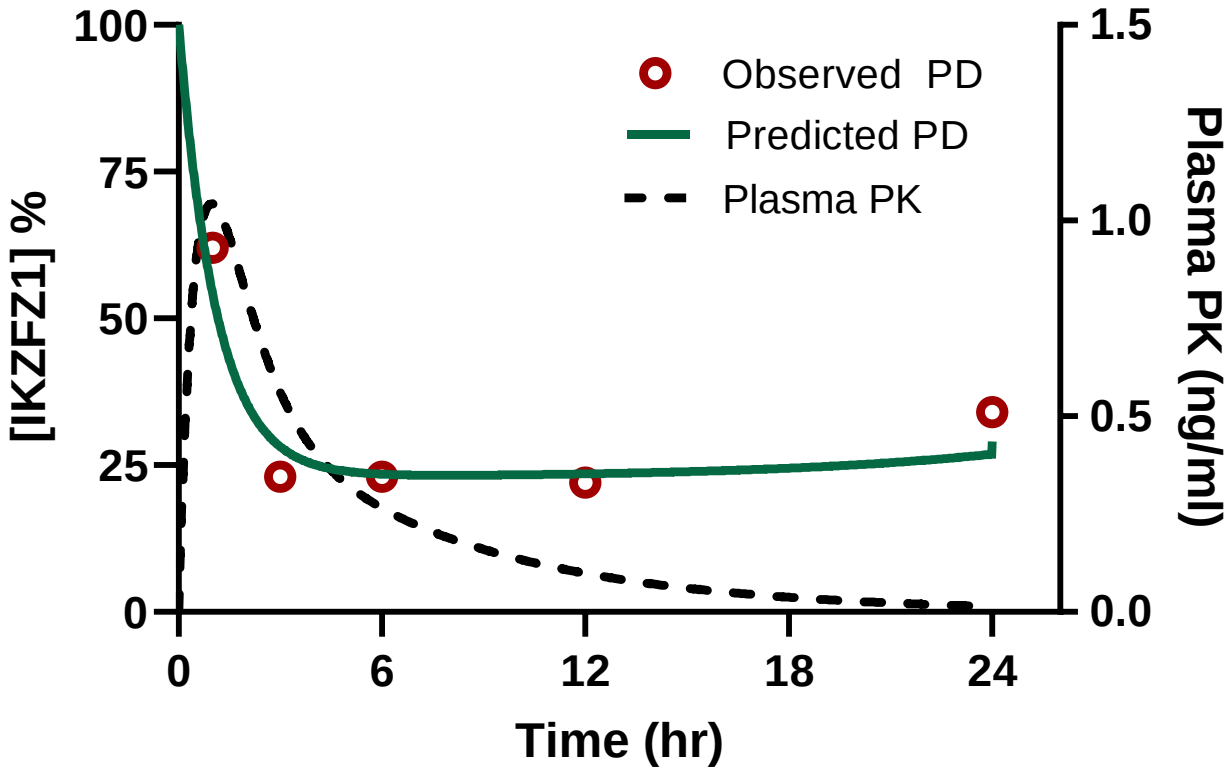

*CFT7455, 1 mg/kg dose po, KI-KJ Anaplastic Large Cell Lymphoma model*

# Predictive PK/PD Models Drive Efficient Drug Discovery




*CFT7455, 1 mg/kg dose po, KI-KJ Anaplastic Large Cell Lymphoma model*

# Predictive PK/PD Models Drive Efficient Drug Discovery

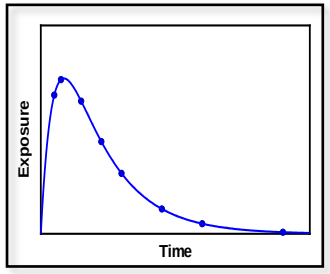



*CFT7455, 1 mg/kg dose po, KI-KJ Anaplastic Large Cell Lymphoma model*

# PK/PD Modeling is Integral to Degrader Optimization

*DMPK*

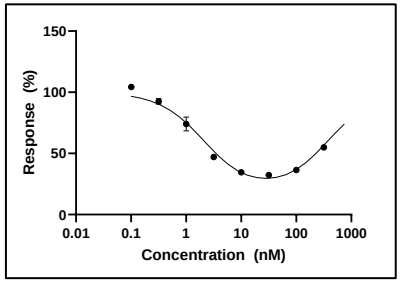
Kinetic profile selection




PK/PD Modeling Prediction

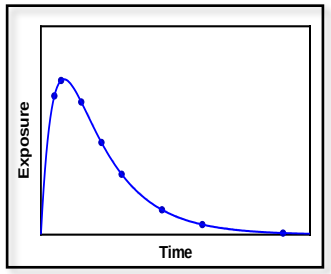
*Simulate or measure in vivo*

*Cell Pharmacology*



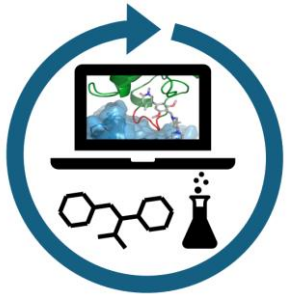

*in vitro*

*Mouse Efficacy Model*




*in vivo*

*Medicinal Chemistry*



*in silico Design*

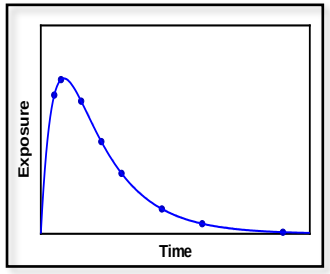
Synthesis

Identify gaps in exposure or kinetics

# PK/PD Modeling is Integral to Degrader Optimization

*DMPK*

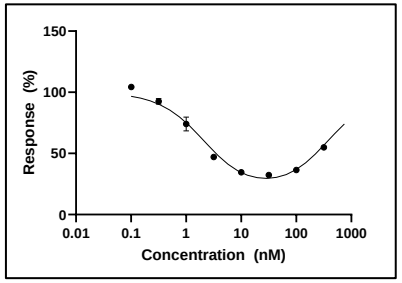
Kinetic profile selection




PKPD Modeling Prediction

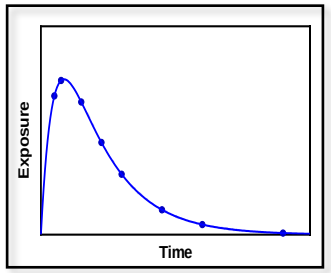
*Simulate or measure in vivo*

*Cell Pharmacology*




*in vitro*

*Mouse Efficacy Model*

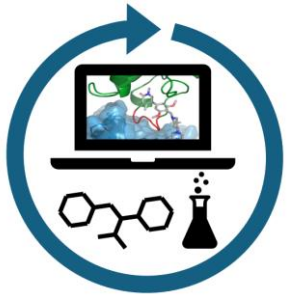



*in vivo*

*Clinical Applications?*

- Proof of Mechanism
- Optimize Dose/Schedule

*Medicinal Chemistry*



*in silico Design*

Identify gaps in exposure or kinetics

Synthesis

# Robust Pipeline of Degrader Medicines Pursuing Multiple Targets

| Program[3] | Target | Indications | Discovery | Preclinical | Early Phase Development | Late Phase Development | Rights |
|---|---|---|---|---|---|---|---|
| **Cemsidomide** | **IKZF1/3** | Multiple Myeloma & Non-Hodgkin's Lymphoma | | | | | |
| **CFT1946** | **BRAF V600 Mutant** | V600 Mutant Cancers | | | | | |
| **CFT8919[1]** | **EGFR L858R** | Non-Small Cell Lung Cancer | | | | | BETTA PHARMACEUTICALS |
| **Discovery Stage Programs** | | Various Cancers | | | | | |
| **Collaboration Programs** | | Autoimmune & Cancer | 2 targets | | | | Roche |
| | | Cancer | 2 targets | | | | Merck KGaA Darmstadt, Germany |
| | | Cancer | 1 target | | | | MERCK |
| | | Autoimmune & Neurological | 2 targets | | | | Biogen[2] |

[1]License and collaboration agreement with Betta Pharmaceuticals for development and commercialization in Greater China; [2]Delivered development candidates to Biogen in Q1 2024 and Q3 2024;
[3] CFT8634 BRD9 degrader program for synovial sarcoma and SMARCB1-null solid tumors patients was closed in Q4 2023.

# BRD9 Previously Considered an Undruggable Target Where Inhibitors Are Ineffective for Synovial Sarcoma

1. Incorporation of SS18-SSX fusion results in eviction of SMARCB1
   - cBAF complex compromised
   - Oncogenic state

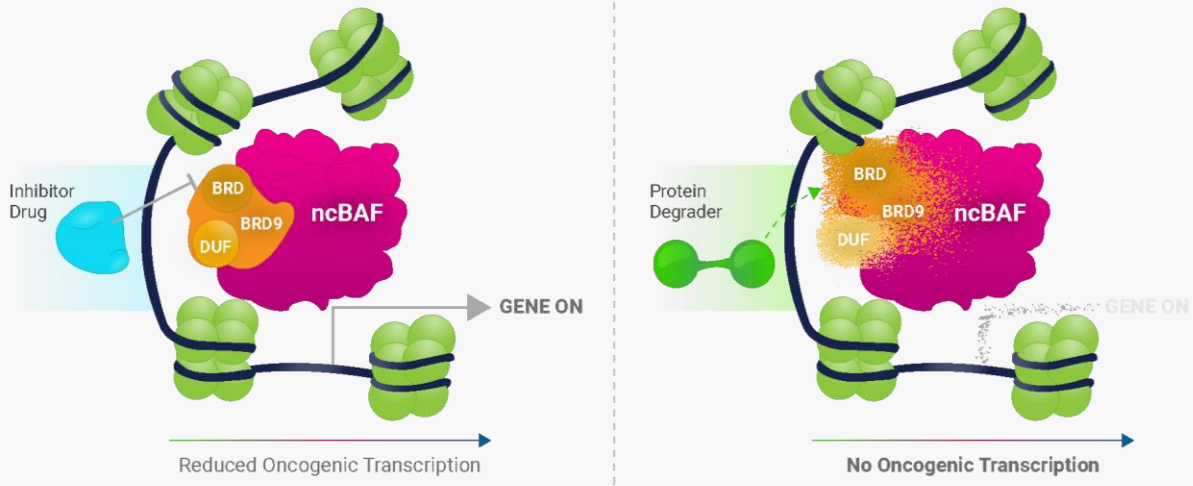
2. Inactivation of SMARCB1 leads to dependency on ncBAF complex
   - BRD9 is uniquely present in ncBAF
   - ***Synthetic lethal dependency on BRD9*** in synovial sarcoma and other SMARCB1-deficient cancers

## Key Properties of CFT8634

- Orally bioavailable
- Potent
- Selective

## Degrader Rationale

Oncogenicity of BRD9 depends on protein function not addressed by traditional inhibitors

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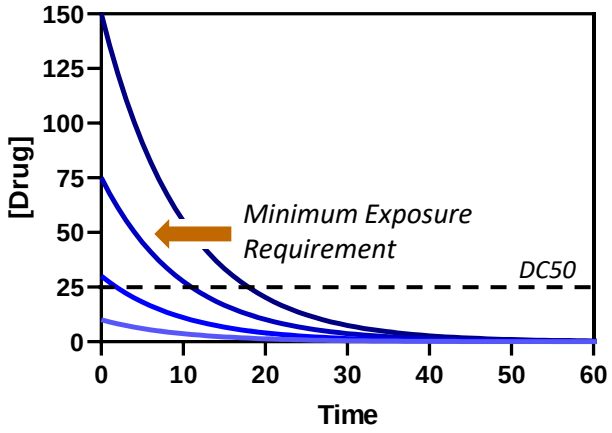
Sources:
1. Wang BC, et al. *Front Oncol.* 2021;11:76228.
2. Sleijfer S, et al. J Clin Oncol. 2009;27(19):3126-3132.

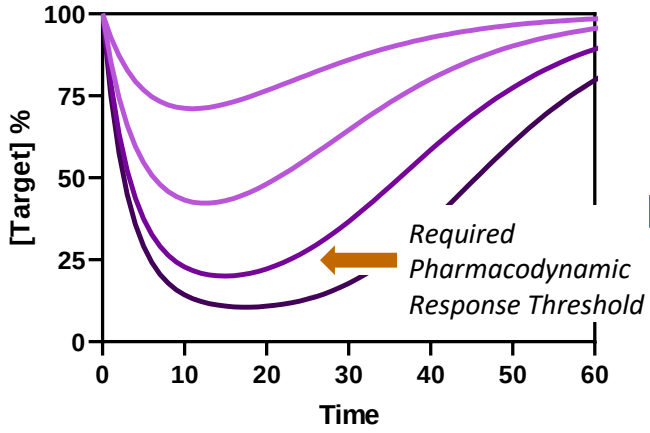
Progression Free Survival (PFS)

# Clinical PK/PD Modeling Requires Pharmacodynamic Threshold Identification

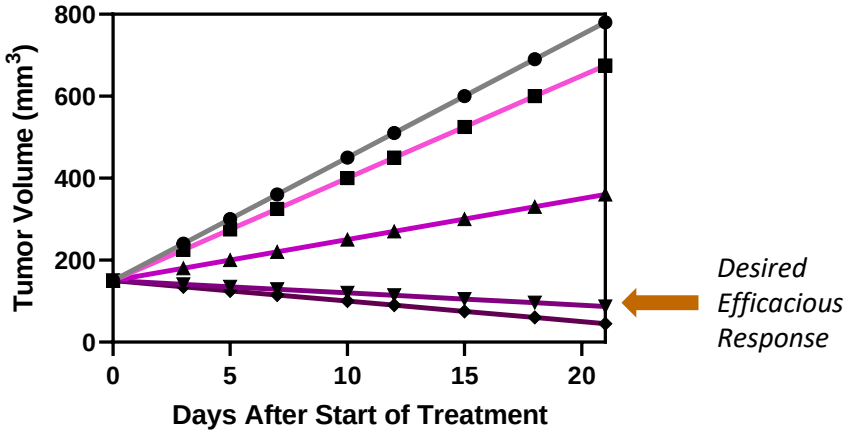
**Ascending Dose PK**




**Pharmacodynamic Response**




**Dose Response Efficacy**

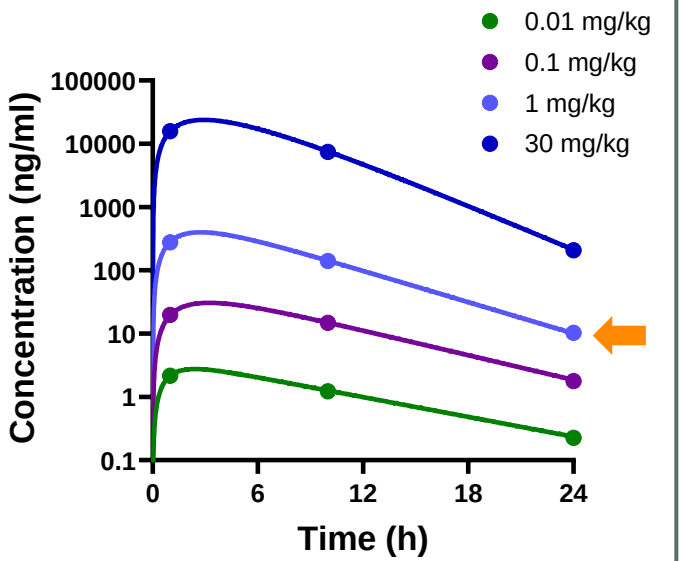



Pharmacodynamic threshold required for desired efficacious response

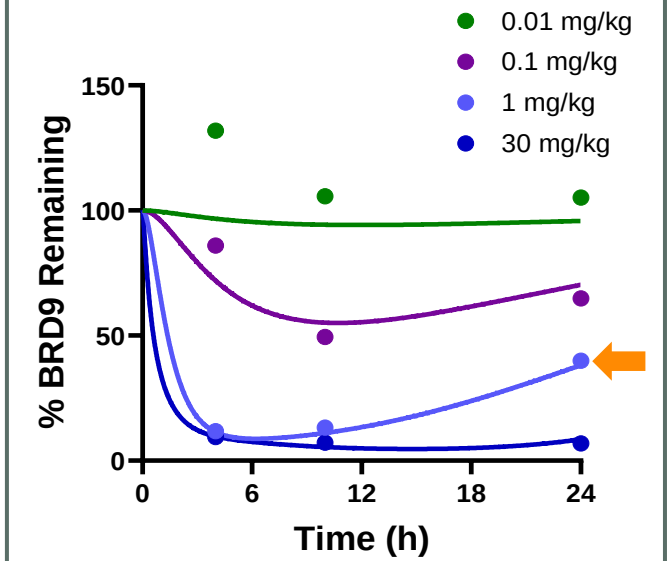
- Function of target engagement/degradation and exposure
- Dependent on target biology and tumor; not dependent on drug modality

# PK/PD Modeling of CFT8634 in a Mouse Synovial Sarcoma PDX Model

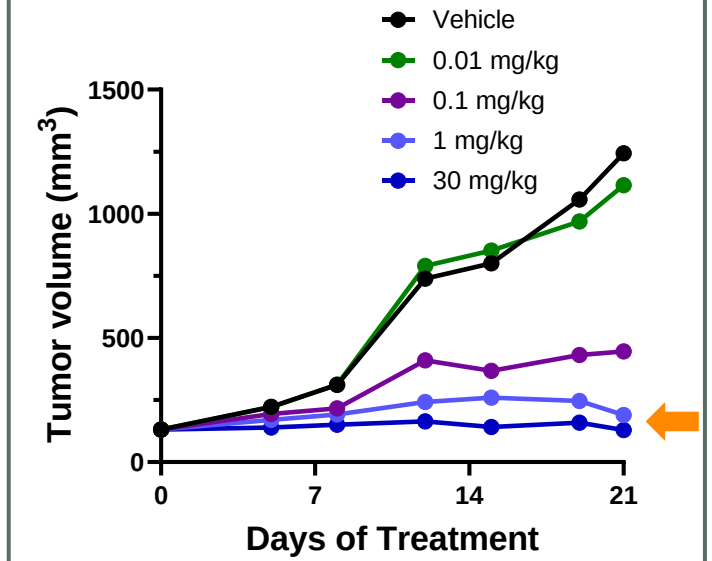
## Ascending Dose PK




## Pharmacodynamic Response




## Dose Response Efficacy



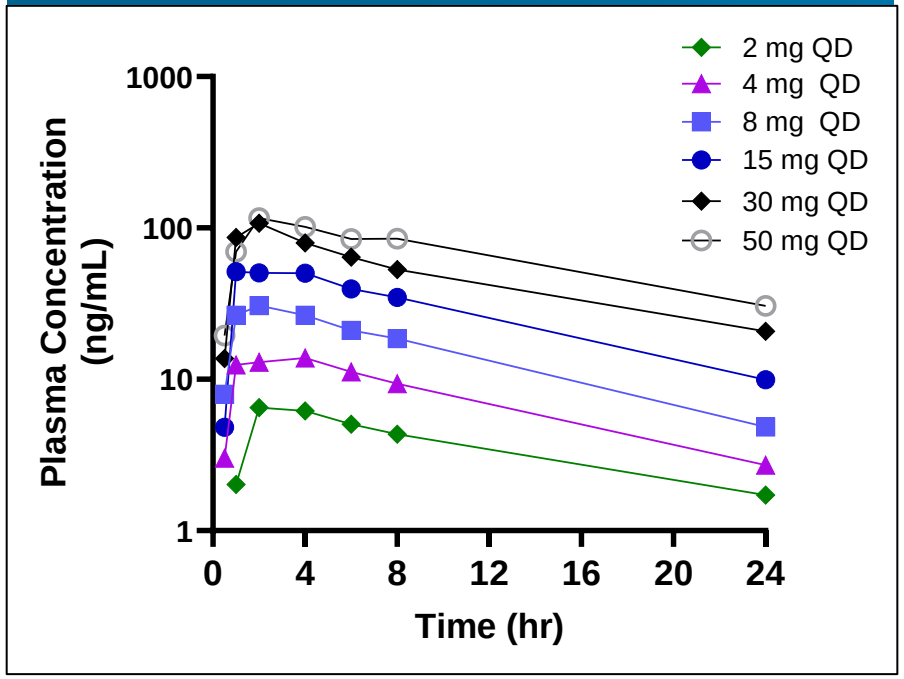

**Dose response efficacy indicates that the 1 mg/kg dose should be used to set the pharmacodynamic threshold for PK/PD modeling**



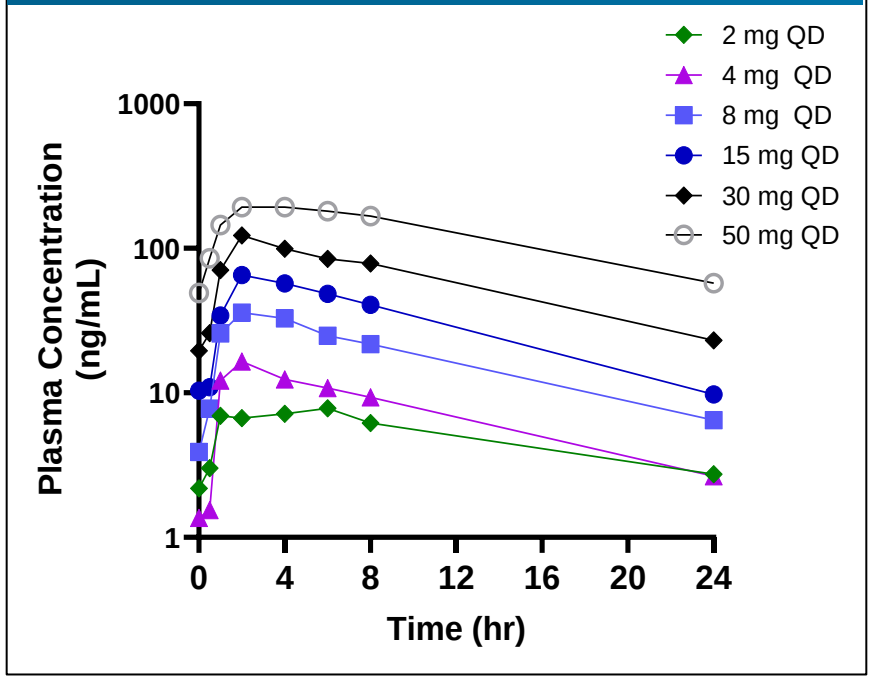
CFT8634 dosed orally
PDX Model SA13412 (Synovial Sarcoma)

# Clinical Pharmacokinetics of CFT8634 in Patients with Synovial Sarcoma and SMARCB1-null Tumors

## Human Pharmacokinetics on Day 1 (Total Drug)



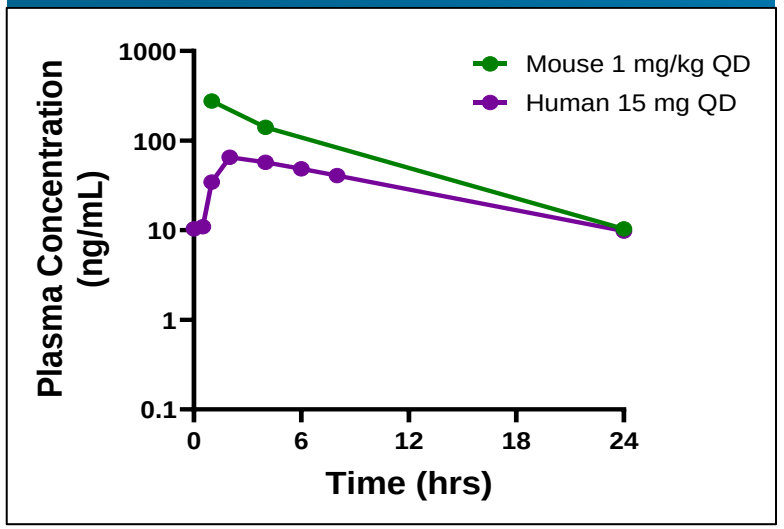

## Human Pharmacokinetics on Day 15 (Total Drug)



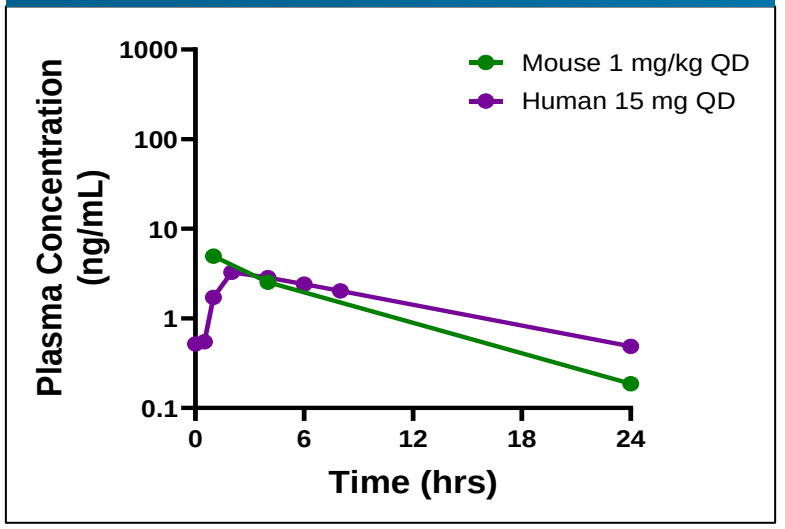

**Clinical PK is linear and dose proportional over the entire dose range minimal accumulation observed at steady state**

# Comparison of Mouse and Human Pharmacokinetic Profiles

## Total Drug Exposures




## Free Drug Exposures

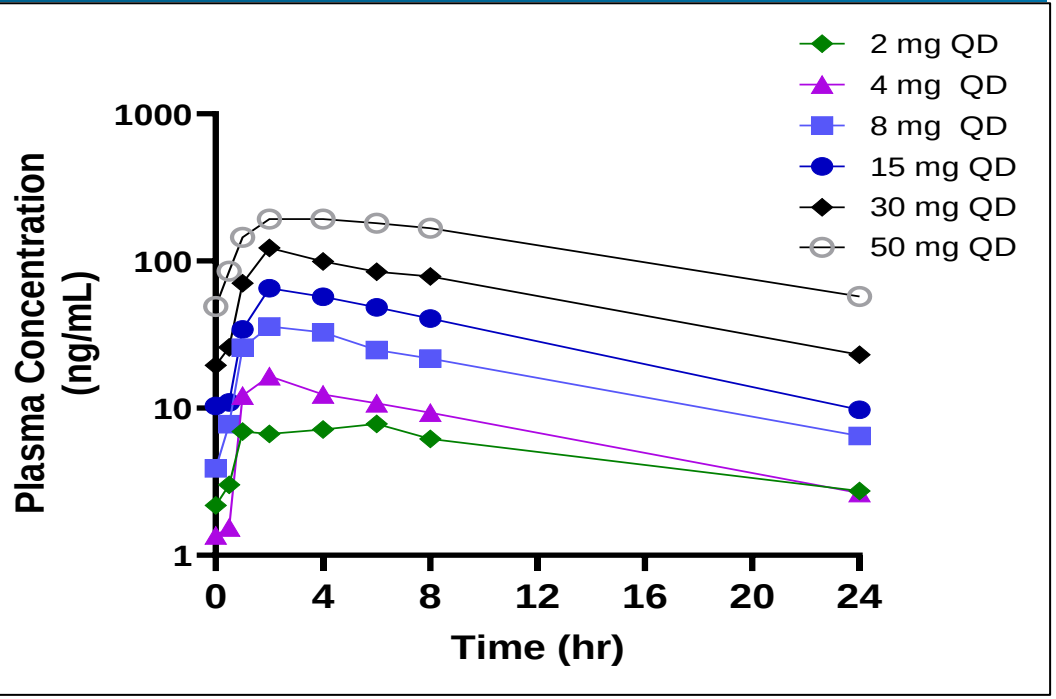



Human PPB Free Fraction: 0.05
Mouse PPB Free Fraction: 0.018

**Mouse and human exposures are highly similar at equivalent doses, particularly with free fraction correction**

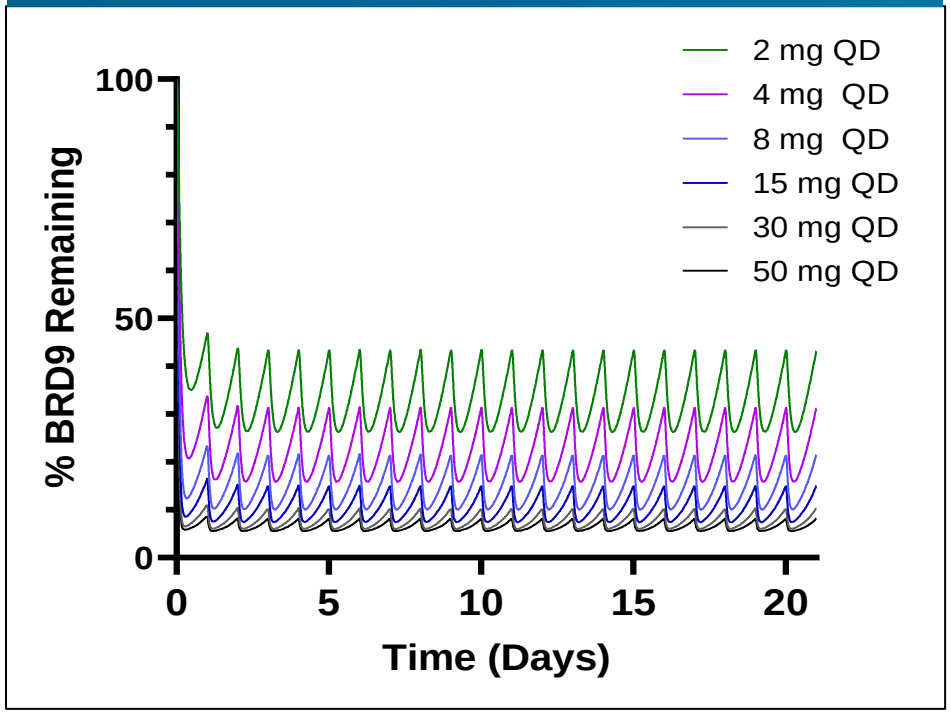
# Simulated PD Using Clinical Pharmacokinetics of CFT8634

## Human PK (Day 15, Steady State)



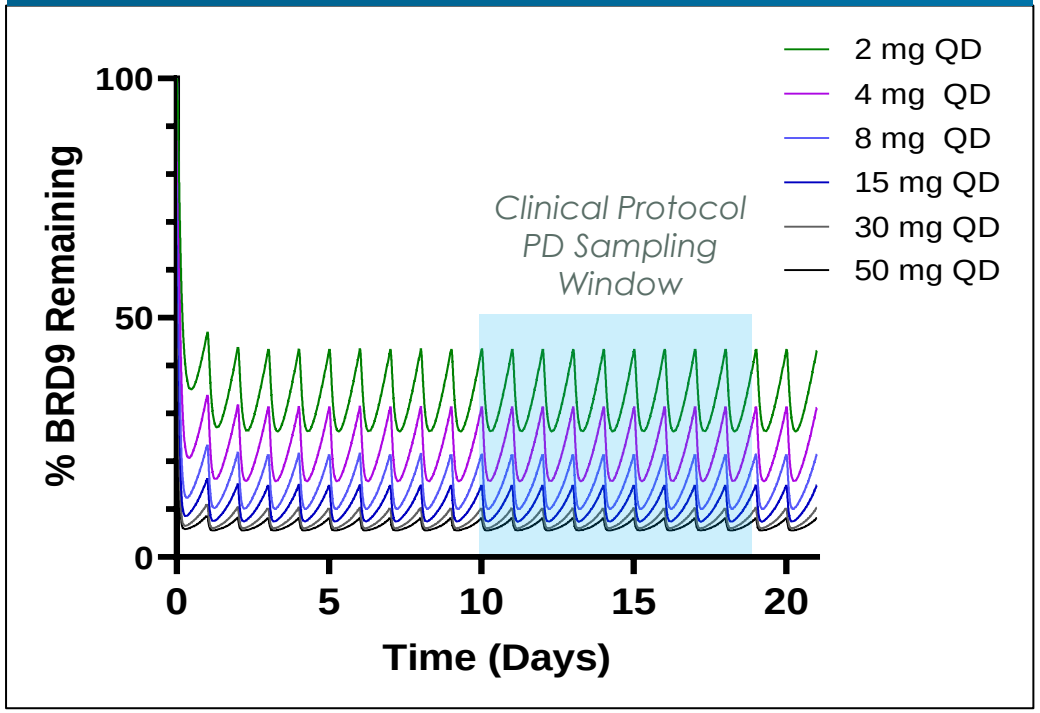

*Utilize kinetic degradation parameters from mouse PDX model*

## Predicted Human PD Response



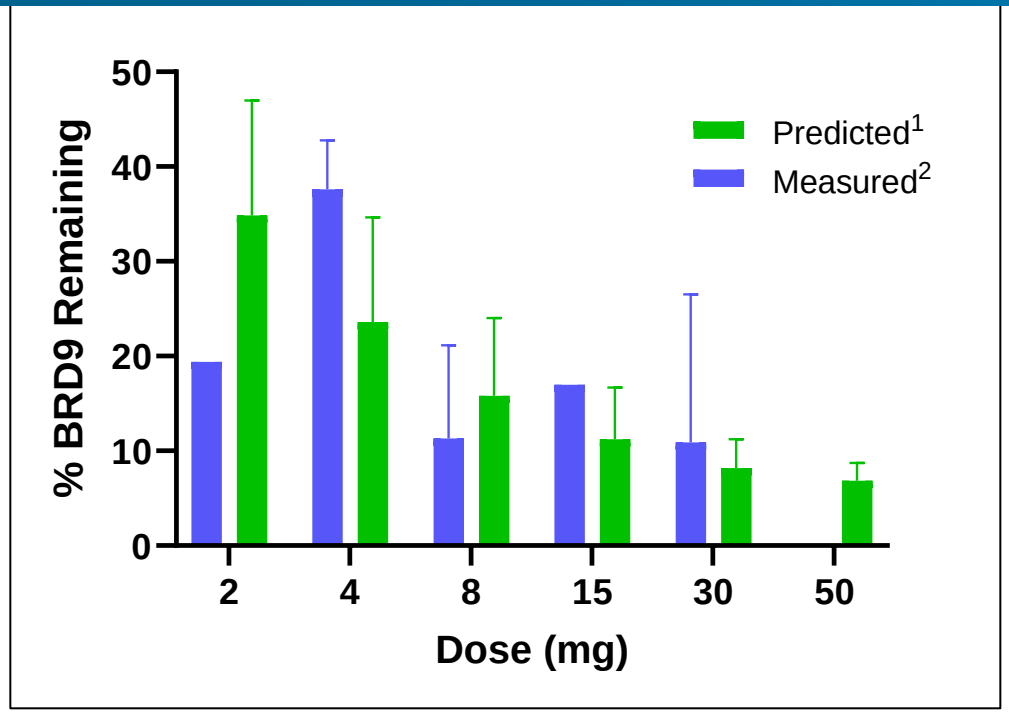
# Predicted vs Observed PD in Patients

## Predicted Human PD Response (Steady State)




*Predict PD response range per dose*

## Predicted Human PD Response (Clinical Protocol Sampling Window)



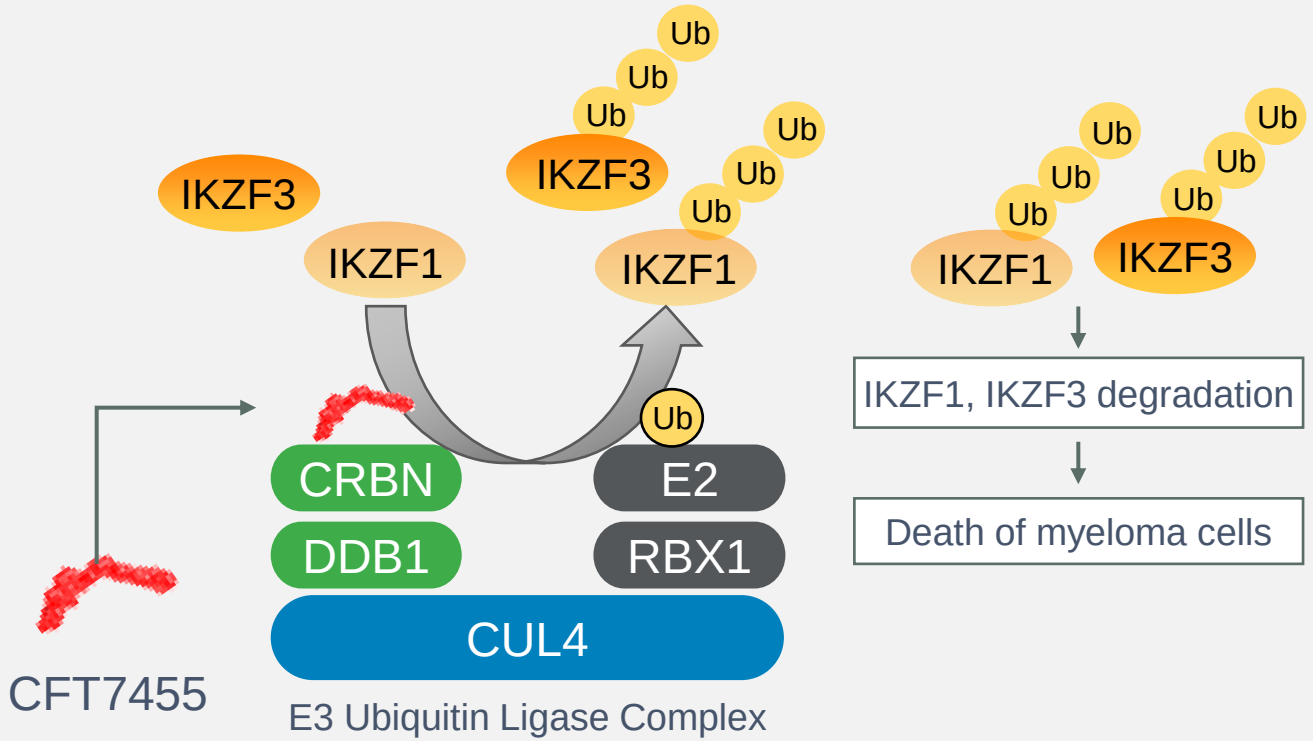

1. Error bars represent predicted range of response over 24 h
2. PD data were measured on tumor tissue by BRD9 IHC via H-score and normalized to the average H-score from all samples at baseline. Average of H-score and SD at all dose levels are reported on the graph.

# Cemsidomide: Potent Small Molecule IKZF1/3 Degrader with Enhanced Catalytic & Pharmacologic Properties

- IKZF1/3 are transcription factors required for cancer cell growth and survival in multiple myeloma (MM)
- Approved IKZF1/3 degraders (lenalidomide, pomalidomide) are widely used in MM treatment
- Relapsed/refractory MM remains a high unmet medical need

## Goal: Develop an IKZF1/3 MonoDAC™ Degrader with these properties:

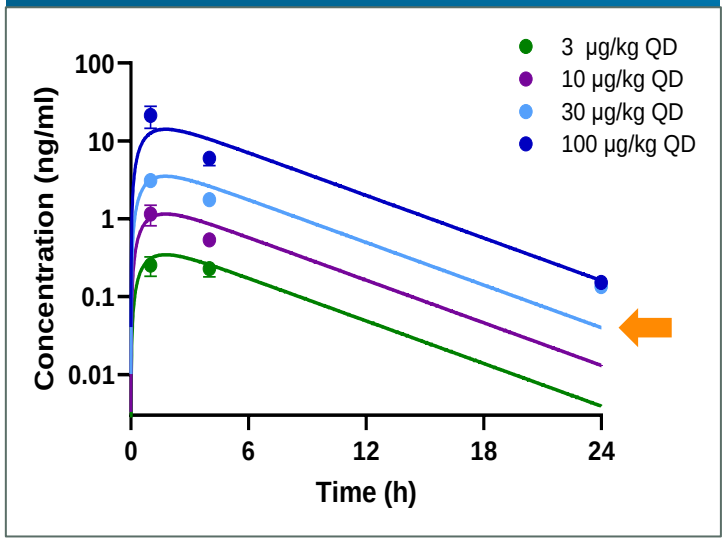
- Class-leading catalytic activity to enable potent, rapid, and deep target degradation
- High binding affinity to overcome resistance to lenalidomide and pomalidomide
- Selective to reduce off-target liabilities
- Pharmacologic profile that enables sustained IKZF1/3 degradation



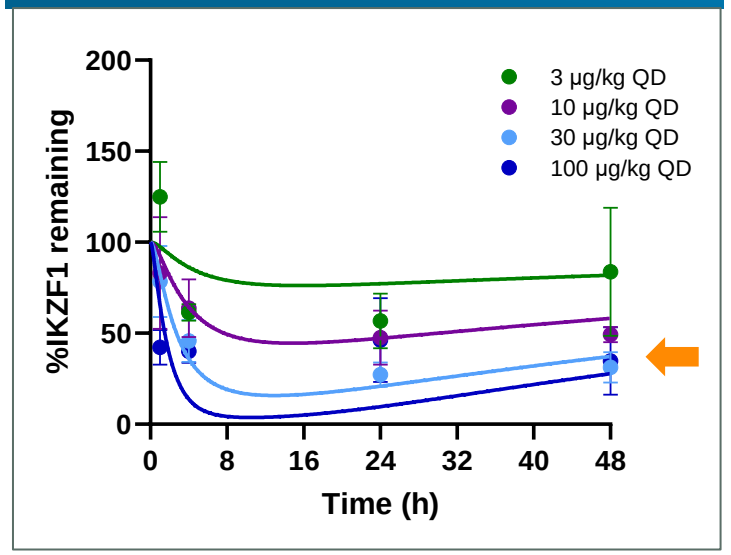

CRBN, cereblon; CUL4, cullin 4; DDB1, DNA damage-binding protein 1; IKZF1/3, Ikaros family zinc finger proteins 1 and 3; MonoDAC, monofunctional degradation activating compound; MM, multiple myeloma; RBX1, ring box protein 1; Ub, ubiquitin.

# PK/PD Modeling of Cemsidomide in Multiple Myeloma Mouse CDX Model

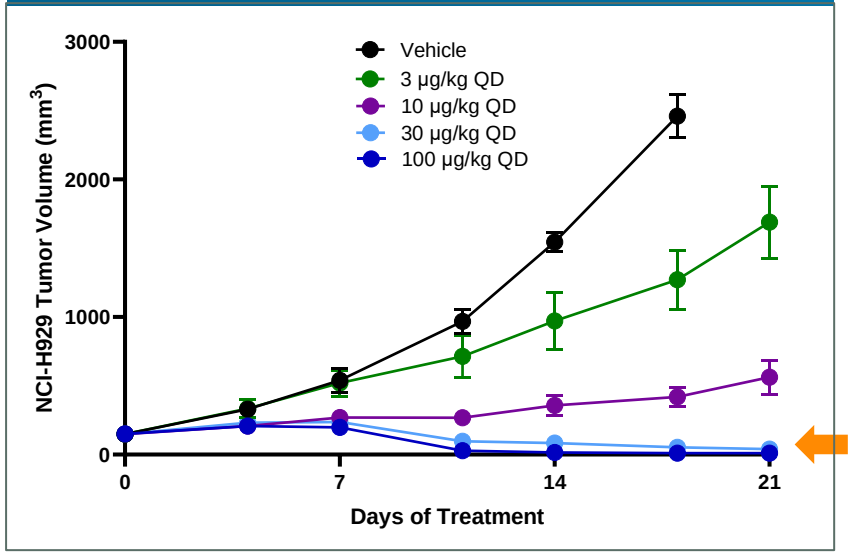
## Ascending Dose PK




## Pharmacodynamic Response[1]




## Dose Response Efficacy

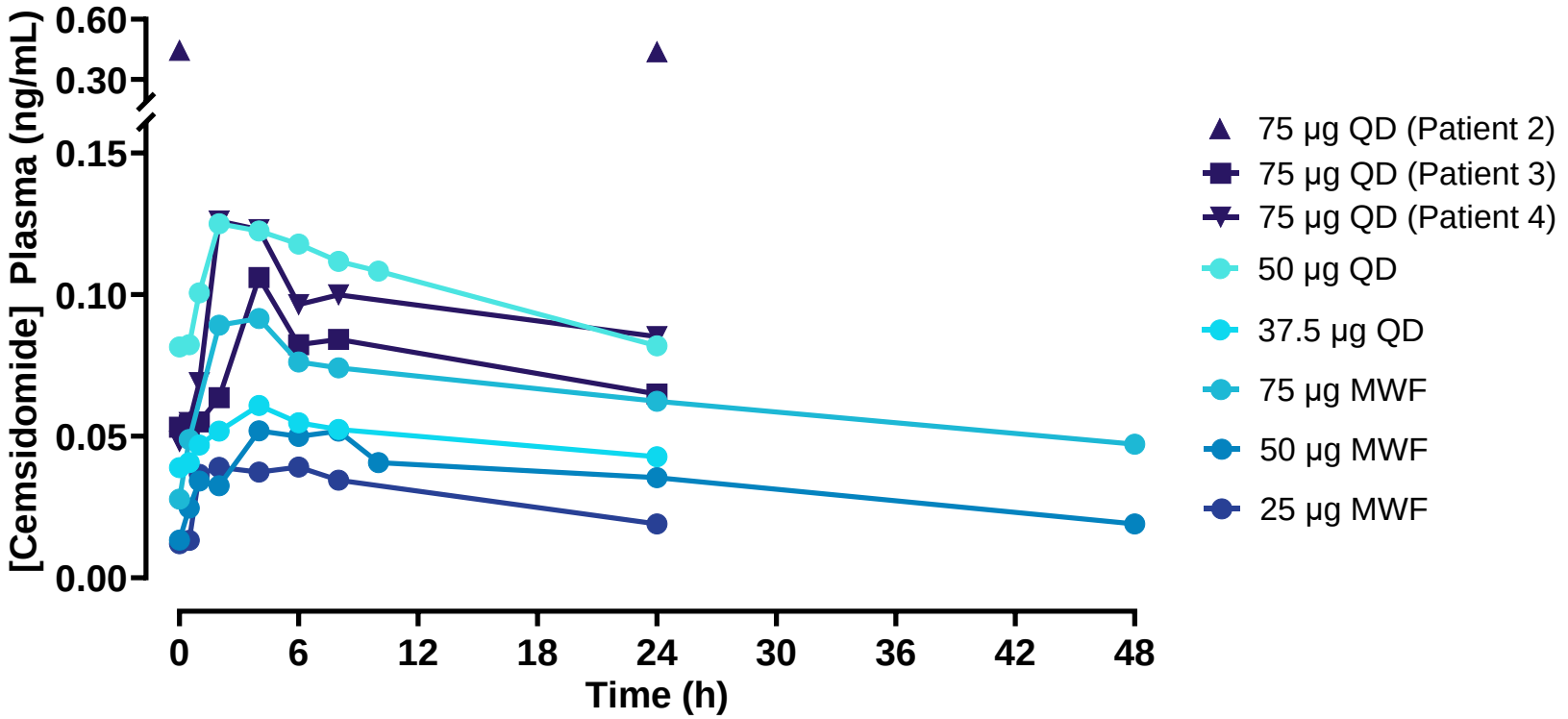



1. Similar response profile observed for IKZF3

**Dose response efficacy indicated that the 30 µg/kg dose should be used to set the pharmacodynamic threshold for PKPD modeling**

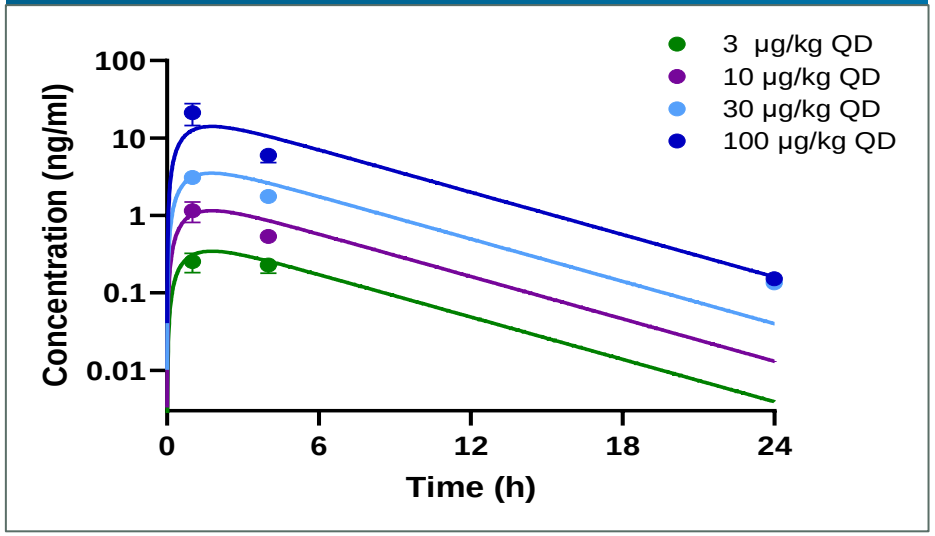
# Proportional Plasma Exposure Increase Observed with Cumulative Dose

## Steady State PK, Monotherapy (Plasma)



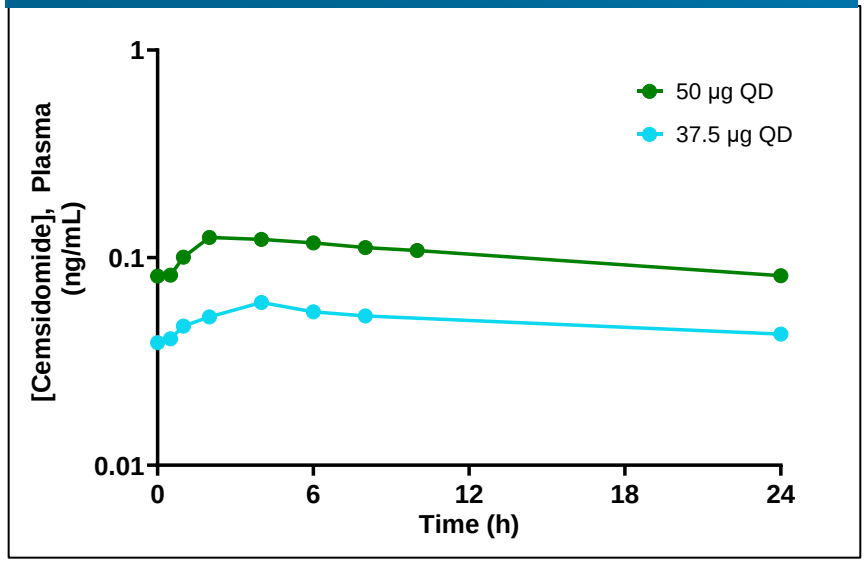
# Clinical PK Exhibits a Significant Disconnect from Mouse PK

## Mouse Pharmacokinetics (Single Dose, Plasma)




$T_{1/2} \approx 3$ h
No accumulation observed upon multi-day dosing

## Steady State Human Pharmacokinetics (Day 14, Plasma)



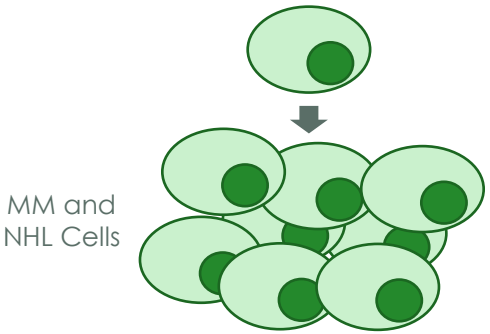

$T_{1/2} \approx 48$ h
Significant accumulation observed (≈ 3.5-fold)

Combined effect of 3-fold accumulation and much longer half-life results in
**~10-fold higher overall efficacious exposure in human than in mouse**

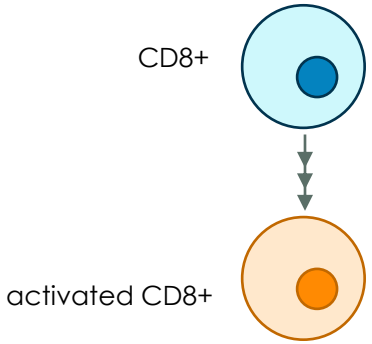
# IKZF1/3 Degradation Drives Three Distinct Areas of Hematopoietic Biology; Degrading IKZF1/3 is a Validated Therapeutic Strategy in MM and NHL

**IKZF1 / IKZF3 Transcription Factors**

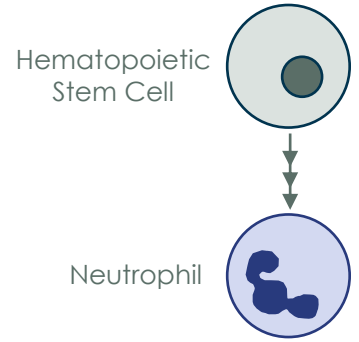
**Drive MM and NHL Cell Growth and Survival**




**Activate Fully Differentiated T-cells**




**Regulate Hematopoietic Stem Cell Differentiation**




## Consequences of IKZF1/3 Degradation:

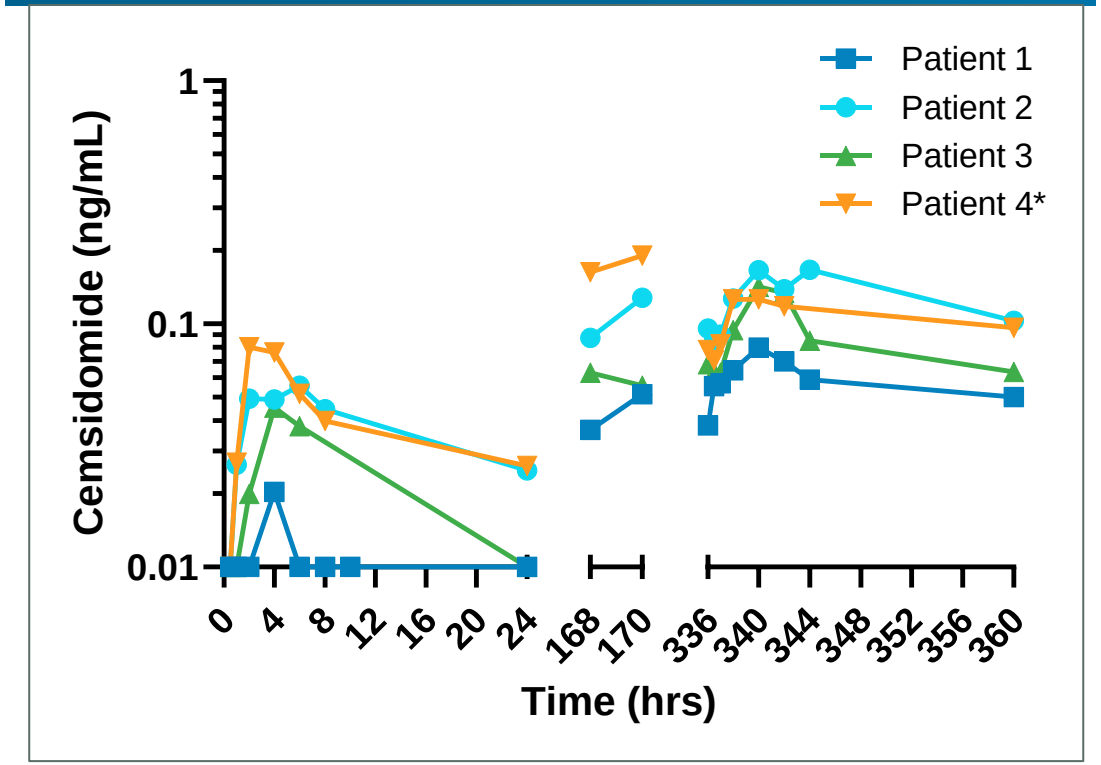
- **MM and NHL Cell Death**
- **T-cell Activation**
- **On-target Neutropenia**

Ikaros Family Zinc Finger proteins 1 and 3 (IKZF1/3); Multiple Myeloma (MM); Non-Hodgkin's Lymphoma (NHL).

C4 Therapeutics

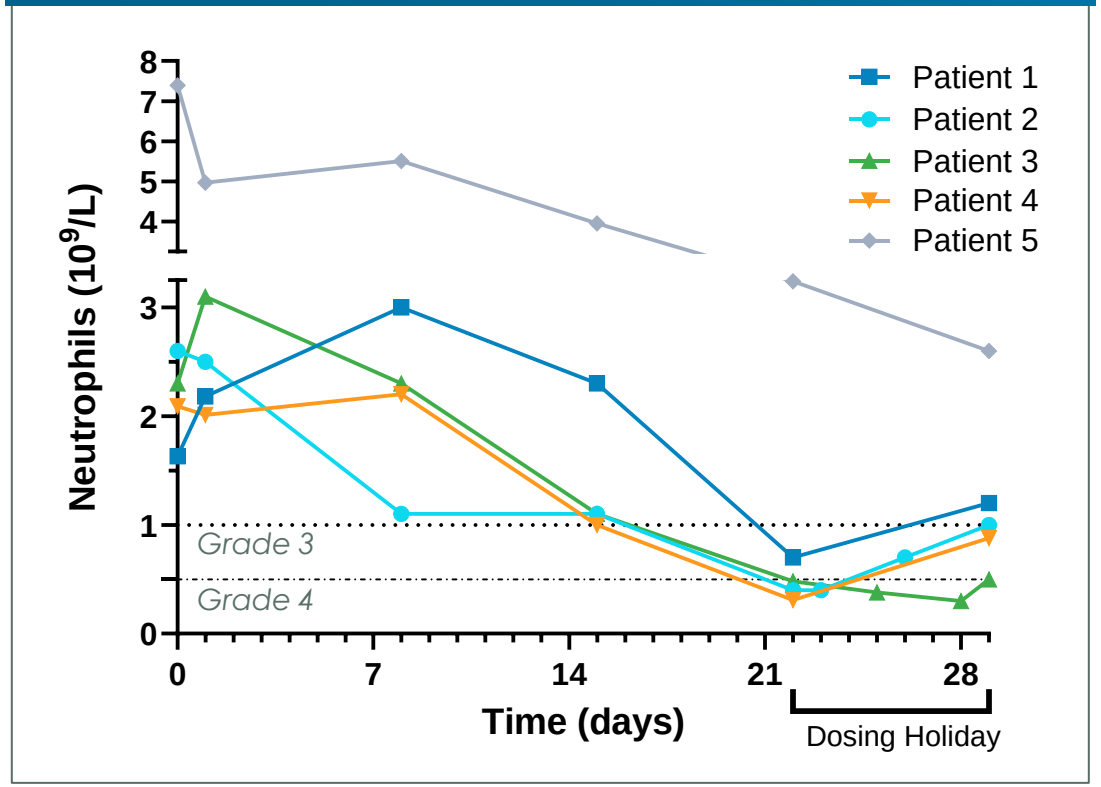
# Prolonged Steady State Exposure Is Associated With Clinical Neutropenia

## Cohort A, Cycle 1 Pharmacokinetics 21 Days on/7 Days off Schedule




*Patient 4 received 50 µg for 8 days followed by 25 µg for 13 days followed by the regular 7- day rest period in cycle 1, subsequent cycles continued at 25 µg 21 days on and 7 days off in a 28 -day cycle
Data not shown for Patient 5 who received 25 µg Dose
BQL (below quantification limit) results are shown at 0.01 for display only

## Cohort A, Cycle 1 Neutrophil Counts 21 Days on/7 Days off Schedule




Patient 4 received 50 µg for 8 days followed by 25 µg
Patient 5 received 25 µg Dose

C4 Therapeutics

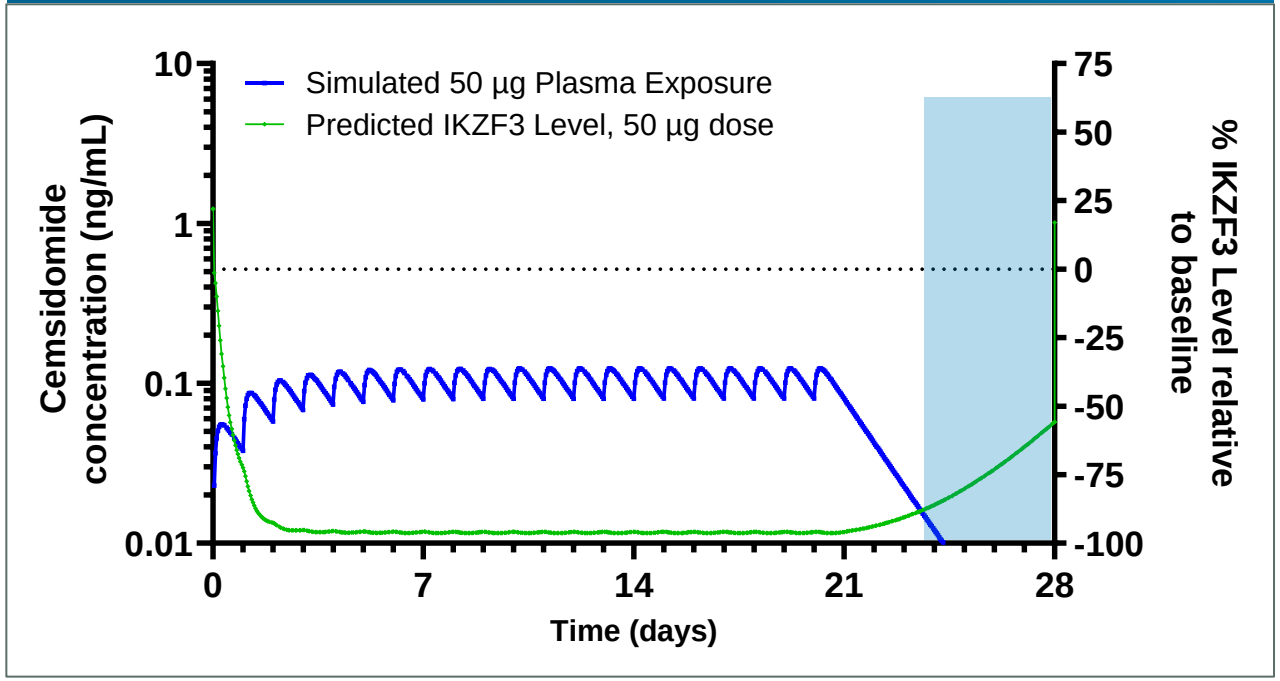




See Poster #1675, AACR 2022

# Clinical PD Confirms Sustained Suppression of IKZF1/3 With 21/7 Schedule

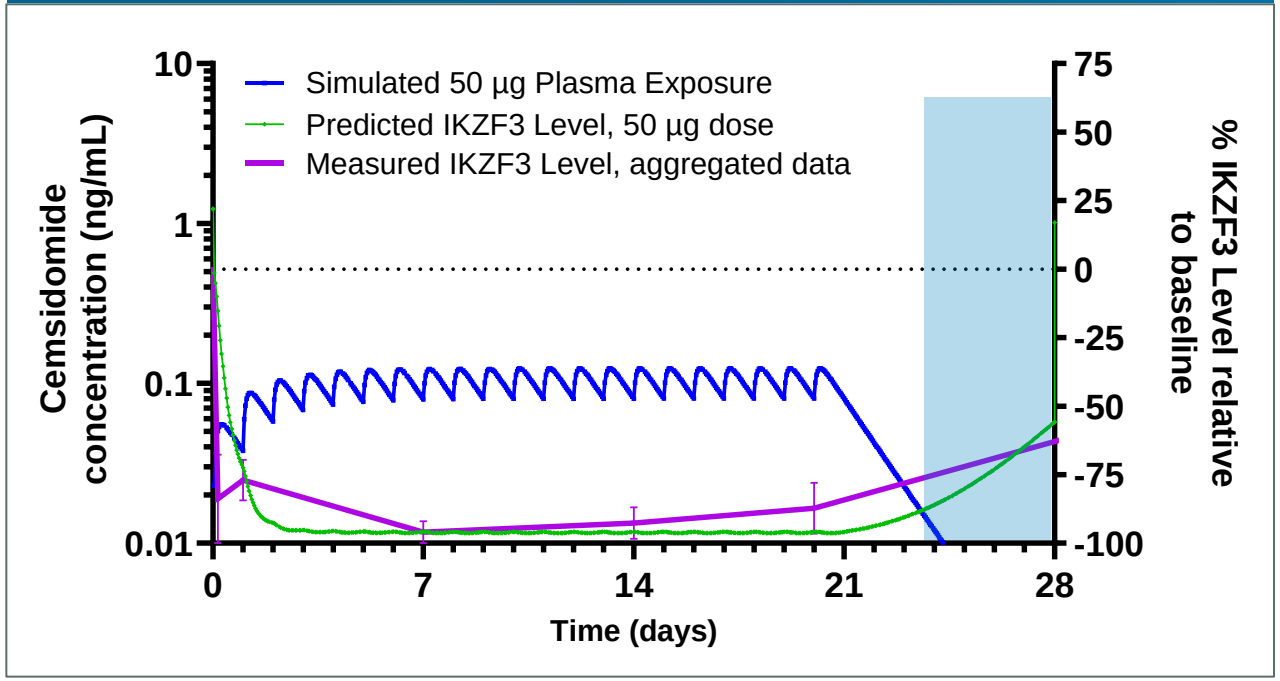
**Modeled PK/PD of 21 Days on/ 7 Days off Schedule**




**21/7 Schedule Does Not Provide Sufficient Time for Drug Clearance for Neutrophil Recovery**

# Clinical PD Confirms Sustained Suppression of IKZF1/3 With 21/7 Schedule

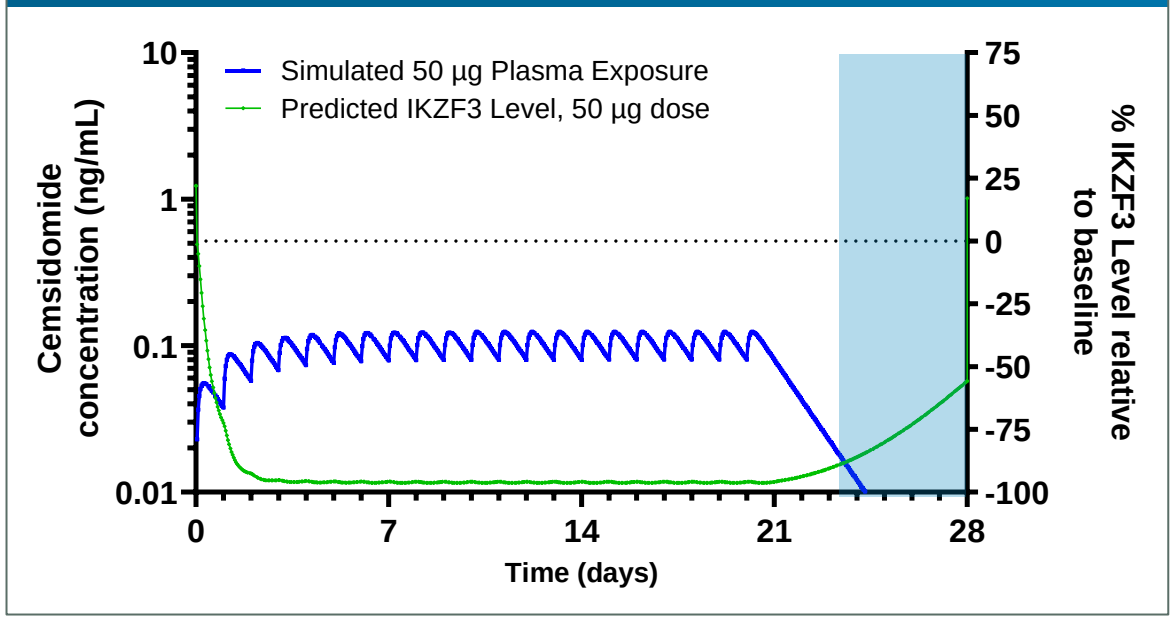
**Modeled PK/PD of 21 Days on/ 7 Days off Schedule**



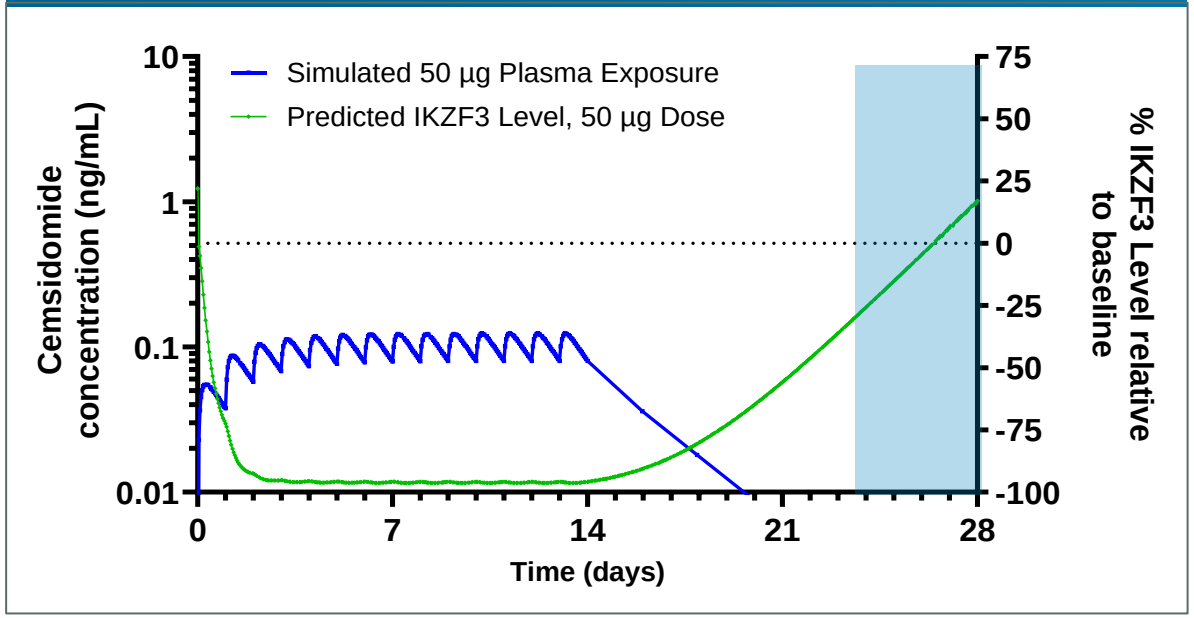

**21/7 Schedule Does Not Provide Sufficient Time for Drug Clearance for Neutrophil Recovery**

# PK/PD Modeling Supports 14 Days on/14 Days off Schedule as it Provides a Sufficient IKZF1/3 Degradation Holiday

## Modeled PK/PD of 21 Days on/ 7 Days off Schedule

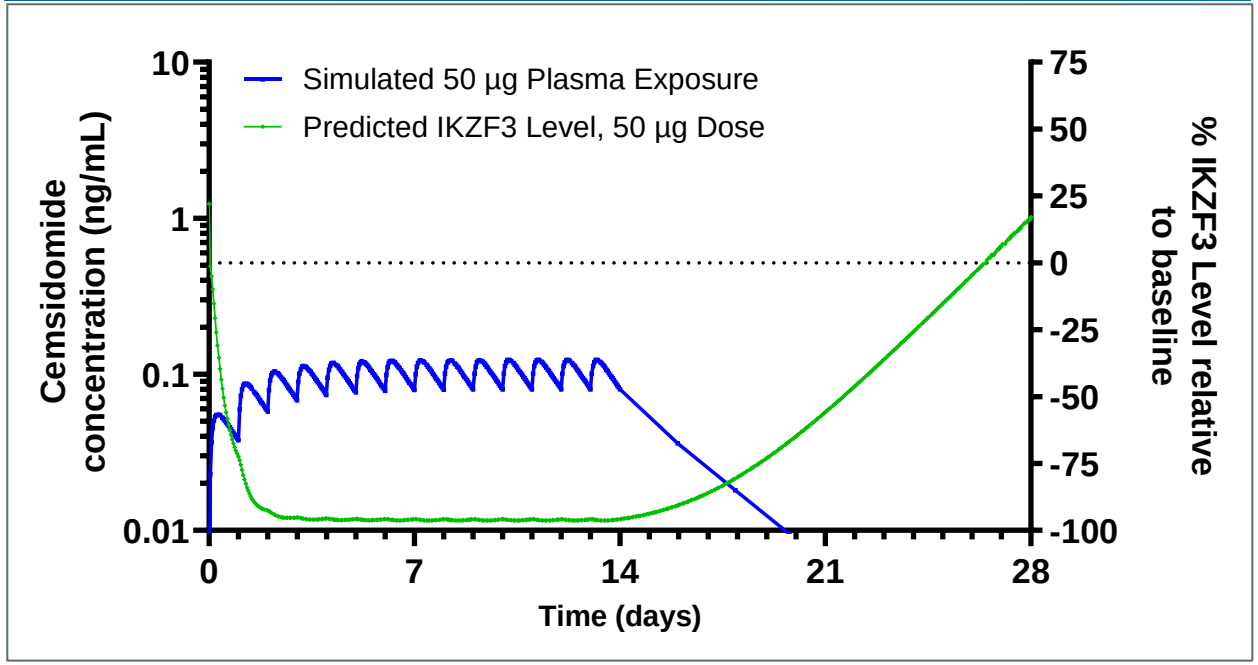



## Modeled PK/PD of 14 Days on/ 14 Days off Schedule



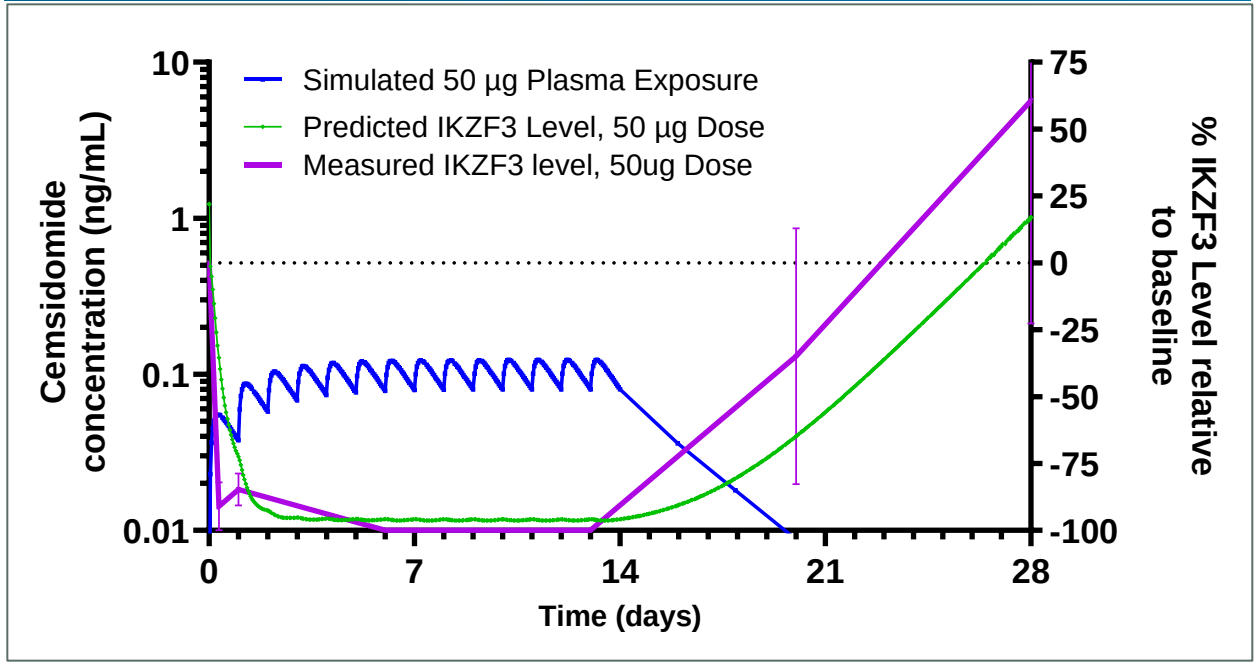
# Emerging Clinical Data is Consistent with PK/PD Modeling Prediction for 14 Days on / 14 Days off Schedule

**Modeled PK/PD of 14 Days on/ 14 Days off Schedule**



# Emerging Clinical Data is Consistent with PK/PD Modeling Prediction for 14 Days on / 14 Days off Schedule

**Modeled PK/PD of 14 Days on/ 14 Days off Schedule**



# Conclusions

- Semi-mechanistic PK/PD models that incorporate degradation kinetics parameters can be highly predictive of clinical PD response
  - Applicable to both heterobifunctional and monofunctional degraders
  - Demonstrated with different target classes
- In general, kinetic parameters determined from *in vitro* systems or fitting to *in vivo* models translate well to the clinic for oncology (CDX, PDX systems)
- Key factors that influence the predictions include pharmacokinetic differences between preclinical species and human exposure profiles
  - Plasma protein binding free fraction differences
  - Differences in tissue penetration or intrinsic clearance rates

# Acknowledgements


- We thank the patients and their families for participating in our clinical trials
- We thank all the investigators and their staff
- We thank the C4T employees, past and present, who contributed to the discovery and development of Cemsidomide and CFT8634, and the PK/PD modeling platform