C4 Therapeutics

CFT7455 Phase 1/2 Cohort A Data Investor Call

American Association for Cancer Research Annual Meeting 2022

Abstract CT186

April 8, 2022

Forward-looking Statements and Intellectual Property

Forward-looking Statements

The following presentation contains forward-looking statements. All statements other than statements of historical fact are forward-looking statements, which are often indicated by terms such as "anticipate," "believe," "could," "estimate," "expect," "goal," "intend," "look forward to," "may," "plan," "potential," "predict," "project," "should," "will," "would" and similar expressions. These forward-looking statements include, but are not limited to, statements regarding the therapeutic potential of C4 Therapeutics, Inc.'s technology and products. These forward-looking statements are not promises or guarantees and involve substantial risks and uncertainties. Among the factors that could cause actual results to differ materially from those described or projected herein include uncertainties associated generally with research and development, clinical trials and related regulatory reviews and approvals, as well as the fact that the product candidates that we are developing or may develop may not demonstrate success in clinical trials. Prospective investors are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date hereof. C4 Therapeutics, Inc. undertakes no obligation to update or revise the information contained in this presentation, whether as a result of new information, future events or circumstances or otherwise.

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Today's Agenda

Topic	Participants
Introductions	Kendra Adams, SVP Communications & Investor Relations
Opening Remarks	Andrew Hirsch, President and CEO
CFT7455 Pre-clinical Data	Adam Crystal, M.D., Ph.D., CMO
CFT7455 Phase 1 Data – Cohort A	Dr. Sagar Lonial, FACP Professor and Chair, Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University
Q&A Session	Dr. Sagar Lonial, Andrew Hirsch, Adam Crystal, and Stew Fisher, Ph.D., CSO

Robust Pipeline of Degrader Medicines Pursuing Meaningful Targets

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

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Number of targets represents the total number of active or potentially active research programs remaining under the applicable collaboration

New Orleans Convention Center, La Nouvelle Orleans

APRIL 8–13 • #AACR22

C4T Presentations at AACR Annual Meeting 2022

AACR American Association for Cancer Research ANNUAL MEETING 2022 New Orleans

Jim Henderson, Ph.D.,

Vice President of Chemistry, C4 Therapeutics

Abstract Number: 7922, Oral

Time: Monday, 4/11/22, 10:15 AM –11:45 AM CT

Location: La Nouvelle Orleans A-B

Session: New Drugs on the Horizon: Part 3

"The Discovery and Characterization of CFT7455: A potent, selective degrader of IKZF1/3 for the treatment of relapsed/refractory multiple myeloma"

Kate Jackson, Ph.D.,

Senior Director of Chemistry, C4 Therapeutics

Abstract Number: 7756, Oral

Time: Sunday, 4/10/22, 3:00 PM – 4:30 PM CT

Location: La Nouvelle Orleans A-B

Session: New Drugs on the Horizon: Part 2

"The Discovery and Characterization of CFT8634: A Potent and Selective Degrader of BRD9 for the treatment of SMARCB1-Perturbed Cancers"

Mathew Sowa, Ph.D.,

Senior Director, Proteomics and Ubiquitin Proteasome System Biology, C4 Therapeutics

Abstract Number: 2158, Oral

Time: Monday, 4/11/22, 2:30 PM – 4:30 PM CT

Location: Great Hall AD

Session: Emerging New Anticancer Agents

"Preclinical Evaluation of CFT1946 as a Selective Degrader of Mutant BRAF for the Treatment of BRAF Driven Cancers"

Chris Nasveschuk, Ph.D.,

Senior Vice President, Chemistry, C4 Therapeutics

Time: Friday, 4/8/22, 5:50 PM – 5:30 PM CT

Location: New Orleans Theater A

Session: Targeted Protein Degradation: Access to New Medicines by Drugging Challenging Targets

"Targeted Protein Degradation: Access to New Medicines by Drugging Challenging Targets"

Sagar Lonial, M.D., FACP

Chief Medical Officer Winship Cancer Institute of Emory University; Professor and Chair, Dept. Hematology and Medical Oncology, Emory University School of Medicine

Abstract Number: CT186, Poster

Time: Tuesday, 4/12/22, 9:00 AM - 12:30 PM CT

Location: Exhibit Halls D-H, Poster Section 33

"Pharmacokinetic (PK) Profile of a Novel IKZF1/3 Degrader, CFT7455, Enables Significant Potency Advantage over Other IKZF1/3 Degraders in Models of Multiple Myeloma (MM) and the Results of the Initial Treatment Cohort from a First-in-Human (FIH) Phase 1/2 Study of CFT7455 in MM"

Advancing Multiple Oncology Programs to Patients

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

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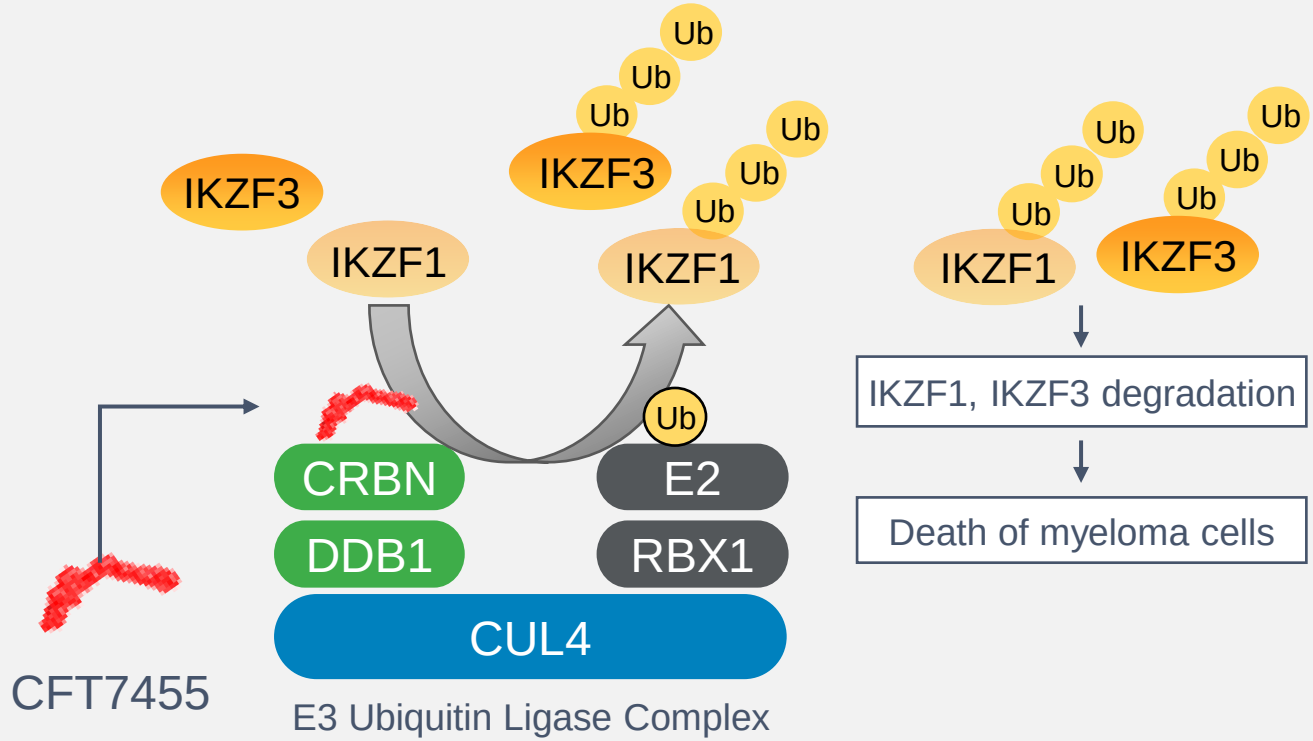
CFT7455: Potent Small Molecule IKZF1/3 Degrader with Enhanced Catalytic & Pharmacologic Properties

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

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
- 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; IMiD, immunomodulatory imide drug; monoDAC, monofunctional degradation activating compound; MM, multiple myeloma; RBX1, ring box protein 1; Ub, ubiquitin.

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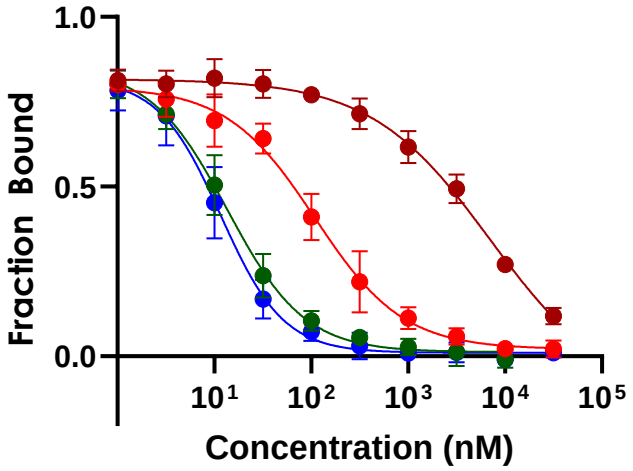
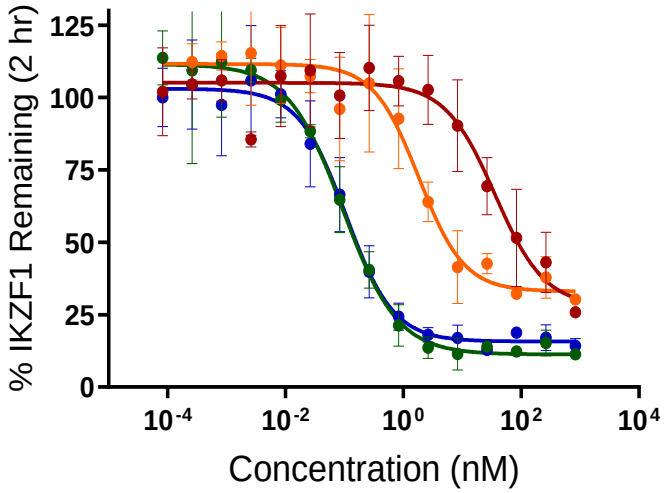
High Catalytic Activity of CFT7455 Improves Activity in H929 MM Cells Compared to Pomalidomide*

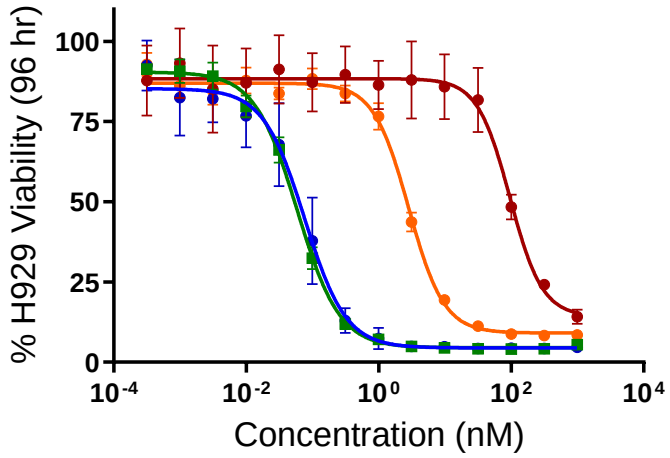
Binding Affinity (FP)



Degradation Kinetics



MM Cell Viability



Pomalidomide

CC-220

CC-92480

CFT7455

Key Takeaway:

- Catalytic activity enhancement resulted in >1000-fold improvement in potency vs. Pomalidomide

*Pomalidomide is an approved IKZF1/3 degrader while CC-220, CC-92480 and CFT7455 are all investigational compounds.
C4 Therapeutics data on file.

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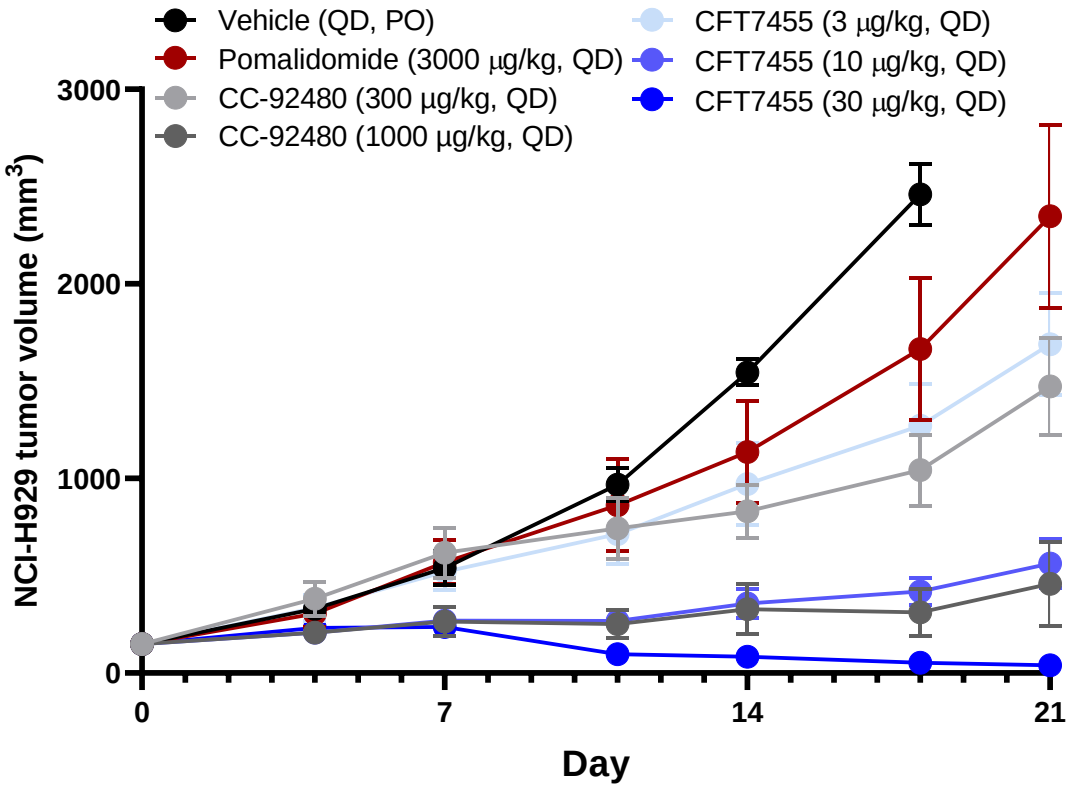
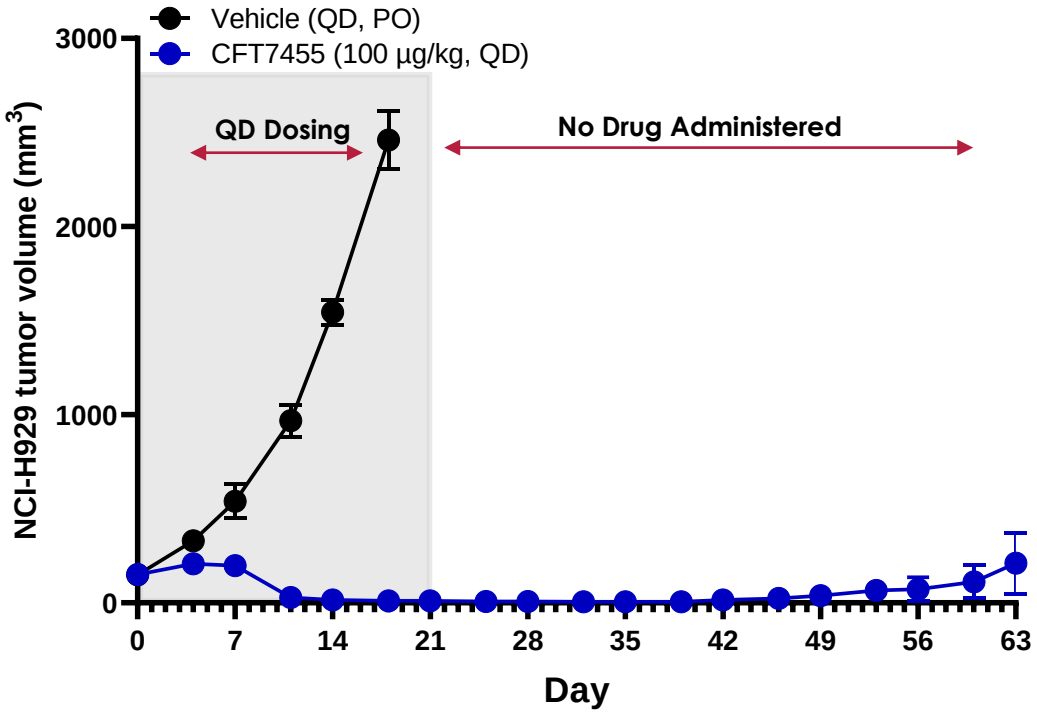
CFT7455 Demonstrates Superior Efficacy in NCI-H929 MM Xenograft Model

CFT7455 vs. Comparators



CFT7455 Results in Durable Complete Regression



Key Takeaways:

- In comparison to CC-92480, CFT7455 achieves equivalent efficacy at 1/100th of the dose
- In the NCI-H929 xenograft model, 100 µg/kg/day of CFT7455 resulted in durable tumor regressions

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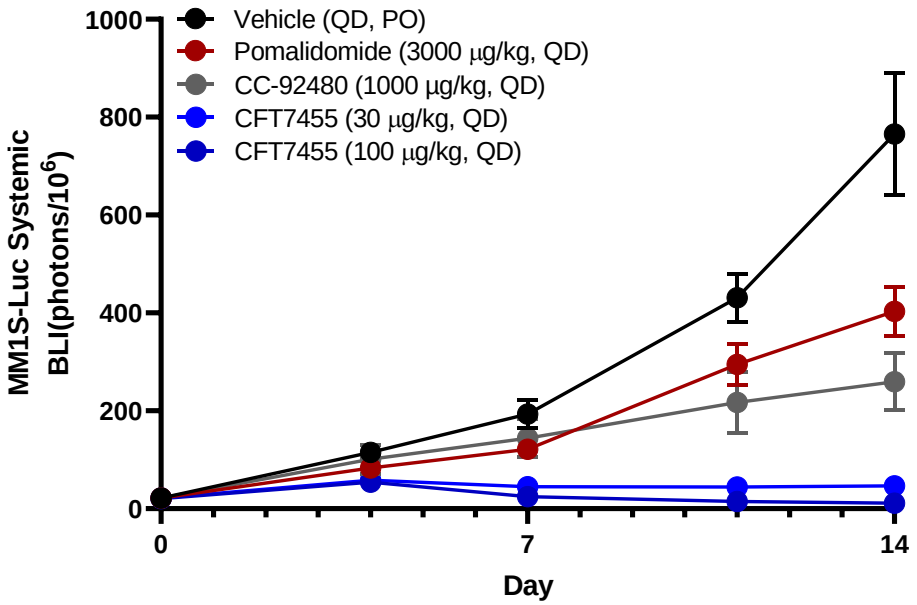
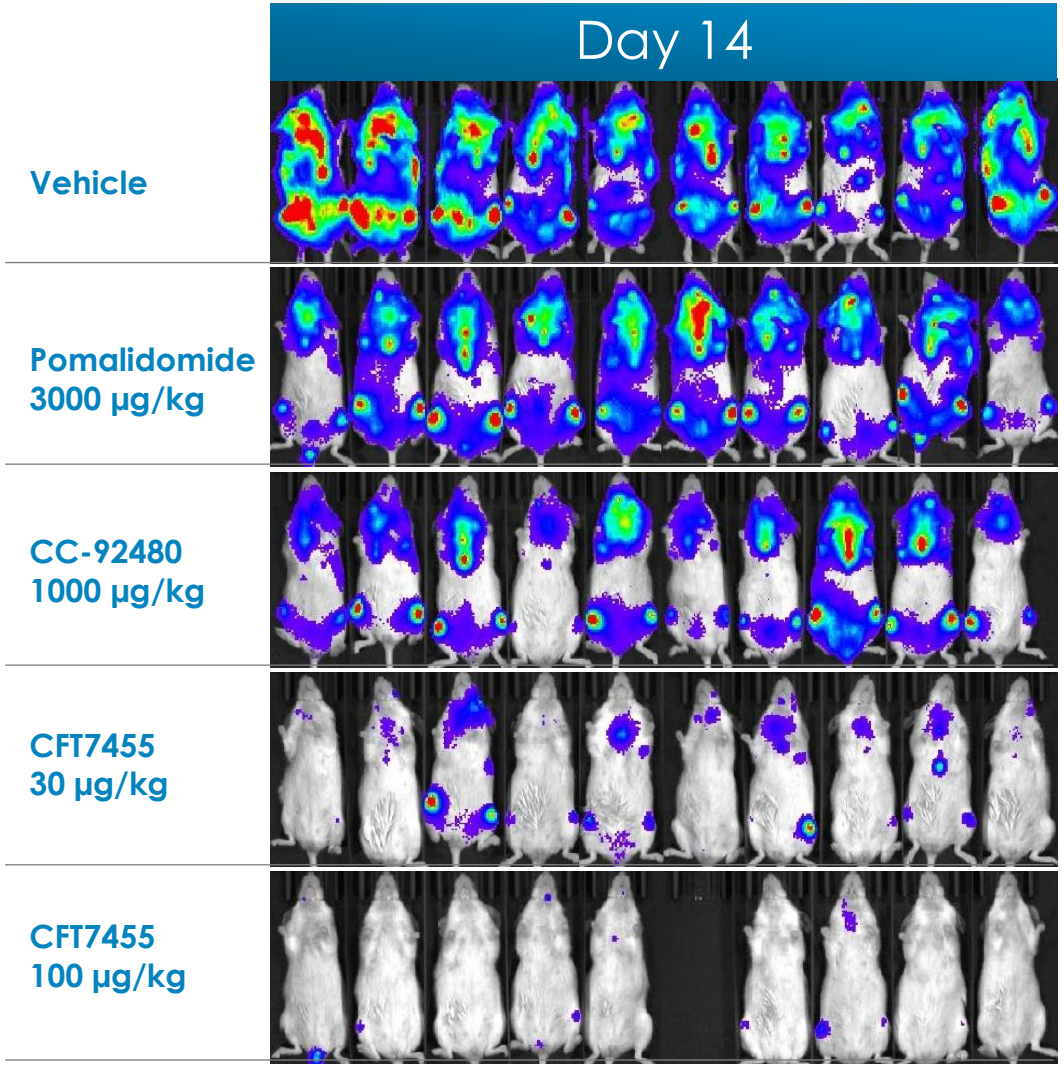
CFT7455 is Highly Efficacious in a Model of Systemic Multiple Myeloma

CFT7455 vs Comparators in a Model of Systemic MM





*Mouse missing in CFT7455 100 µg/kg group due to changes unrelated to treatment or disease

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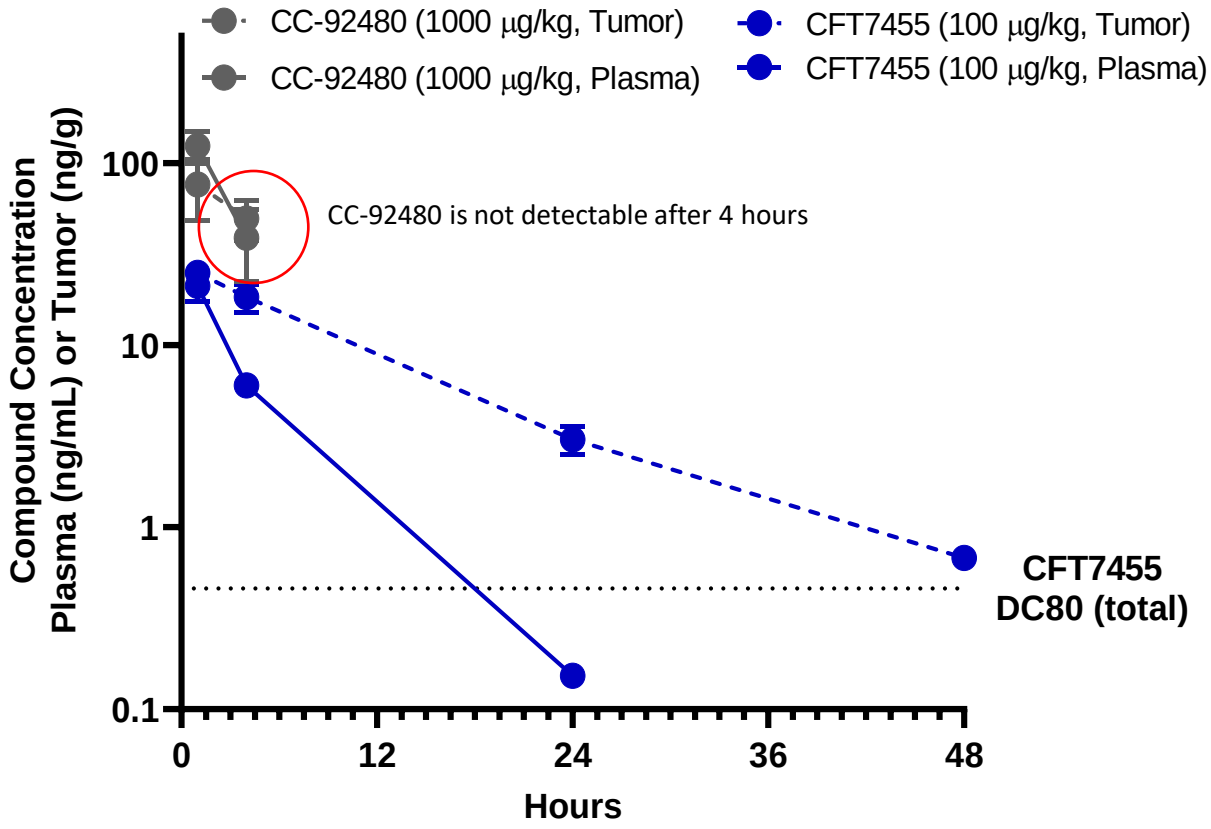
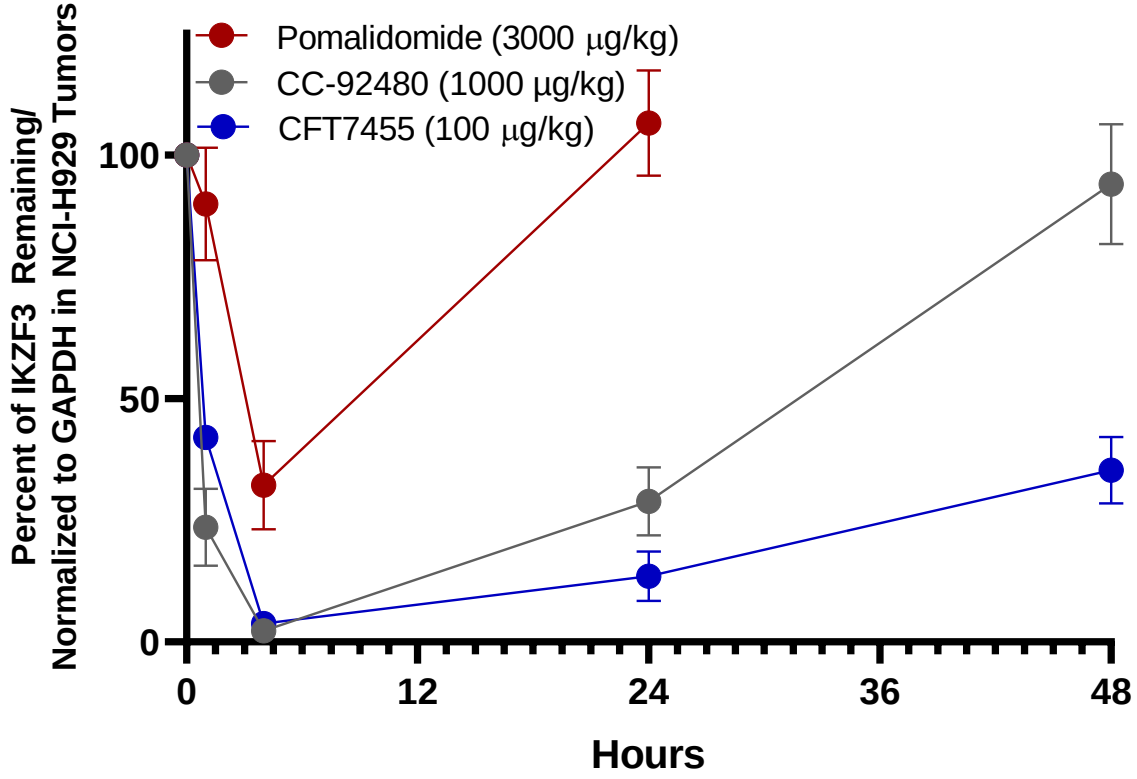
Single Dose PK/PD in H929 Xenografts Differentiates CFT7455 from CC-92480

CFT7455 and CC-92480* Tumor and Plasma Concentrations



Degradation Kinetics for CFT7455, CC-92480 and Pomalidomide



*CC-92480 was created in-house based on compound described in: Hansen JD, et al. *J Med Chem.* 2020;63(13):6648-6676.

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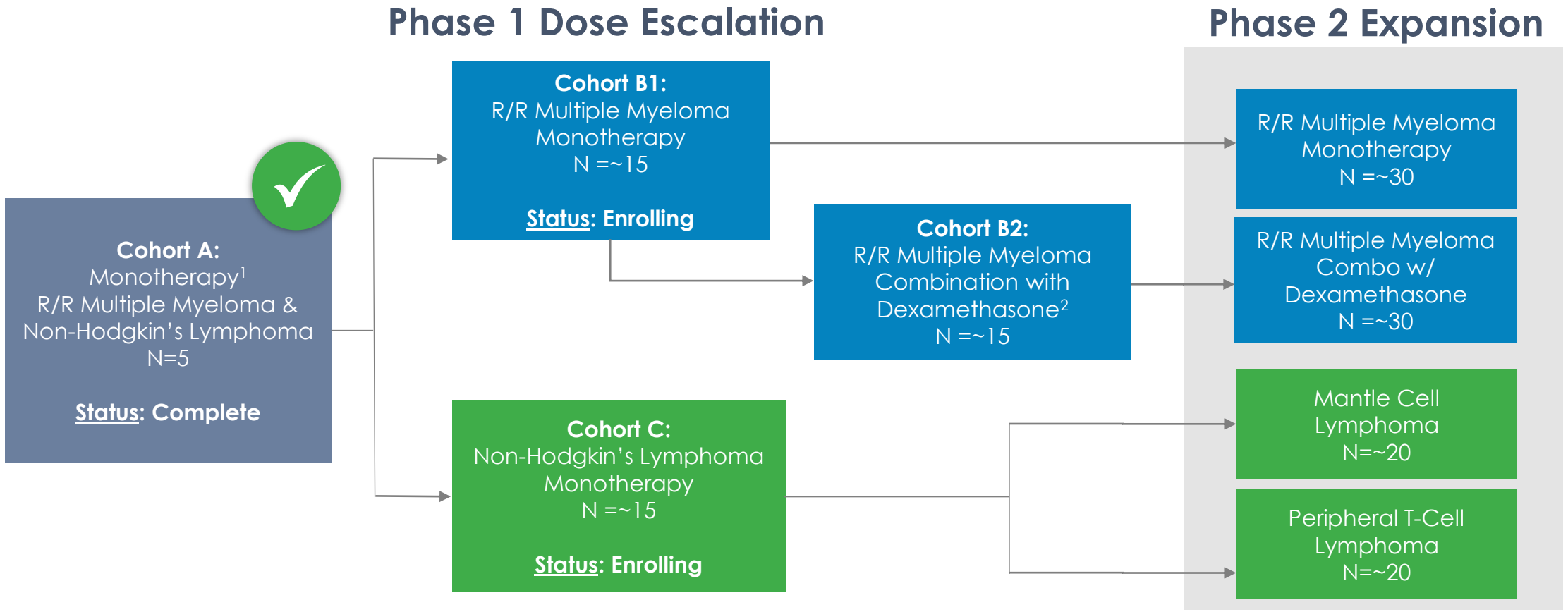
Pharmacokinetic (PK) Profile of a Novel IKZF1/3 Degrader, CFT7455, Enables Significant Potency Advantage over Other IKZF1/3 Degraders in Models of Multiple Myeloma (MM) and the Results of the Initial Treatment Cohort from a First-in-Human (FIH) Phase 1/2 Study of CFT7455 in MM

Sagar Lonial, MD, FACP[1], Shambavi Richard, MD[2], Jeffrey V. Matous, MD[3], Andrew J. Yee, MD[4], Urvi A. Shah, MD[5], Neha Mehta-Shah, MD, MSCI[6], Thomas Martin, MD[7], Eli Muchtar, MD[8], Sikander Ailawadhi, MD[9], Paul G. Richardson, MD[10], Manisha Bhutani, MD[11], Samantha Perino, B.S.[12], Jason Kirby, MSc[12], Roman V. Agafonov, PhD[12], Prasoon Chaturvedi, PhD[12], Bradley Class, MSc[12], Matthew Schnaderbeck, PhD[12], Michael R. Palmer, PhD[12], Cathleen Gorman, MSc.[12], Oliver Schoenborn-Kellenberger, MSc[12], Amanda Hoerres, PharmD[12], Stewart L. Fisher, PhD[12], Roy M. Pollock, PhD[12], Adam Crystal, MD, PhD[12], Michelle Mahler, MD[12] and Jesus G. Berdeja, MD[13]

CFT7455 Phase 1/2 Trial Design



Cohorts B1 & C Enrolling Patients to Determine Recommended Phase 2 Dose

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

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

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Cohort A Enrolled Heavily Pre-Treated and Highly Refractory MM Patients

N (%) of patients unless stated	N=5
Age in years, median (range)	63 (51,73)
Sex, male	3 (60)
Time since initial diagnosis, median (range), years	11 (4,21)
ECOG PS	
0	2 (40)
1	2 (40)
2	1 (20)
R-ISS stage at screening, n (%)	
Stage I	1 (20)
Stage II	1 (20)
Stage III	2 (40)
Missing	1 (20)
Presence of extramedullary plasmacytoma	3 (60)
Assessable serum free light chain	5 (100)

N (%) of patients unless stated	N=5
Number of lines of prior therapy, median (range)	5 (4–14)
Prior stem cell transplantation	3 (60)
IMiD agent refractory	5 (100)
POM	5 (100)
LEN	5 (100)
PI refractory	
BORT	4 (80)
CFZ	5 (100)
Prior anti-CD38 antibody	5 (100)
Prior CAR-T	2 (40)
Prior ADC	1 (20)
Prior bispecific antibody	1 (20)
Triple-class refractory (≥1 IMiD, ≥1 PI, and ≥1 anti-CD38 antibody)	5 (100)

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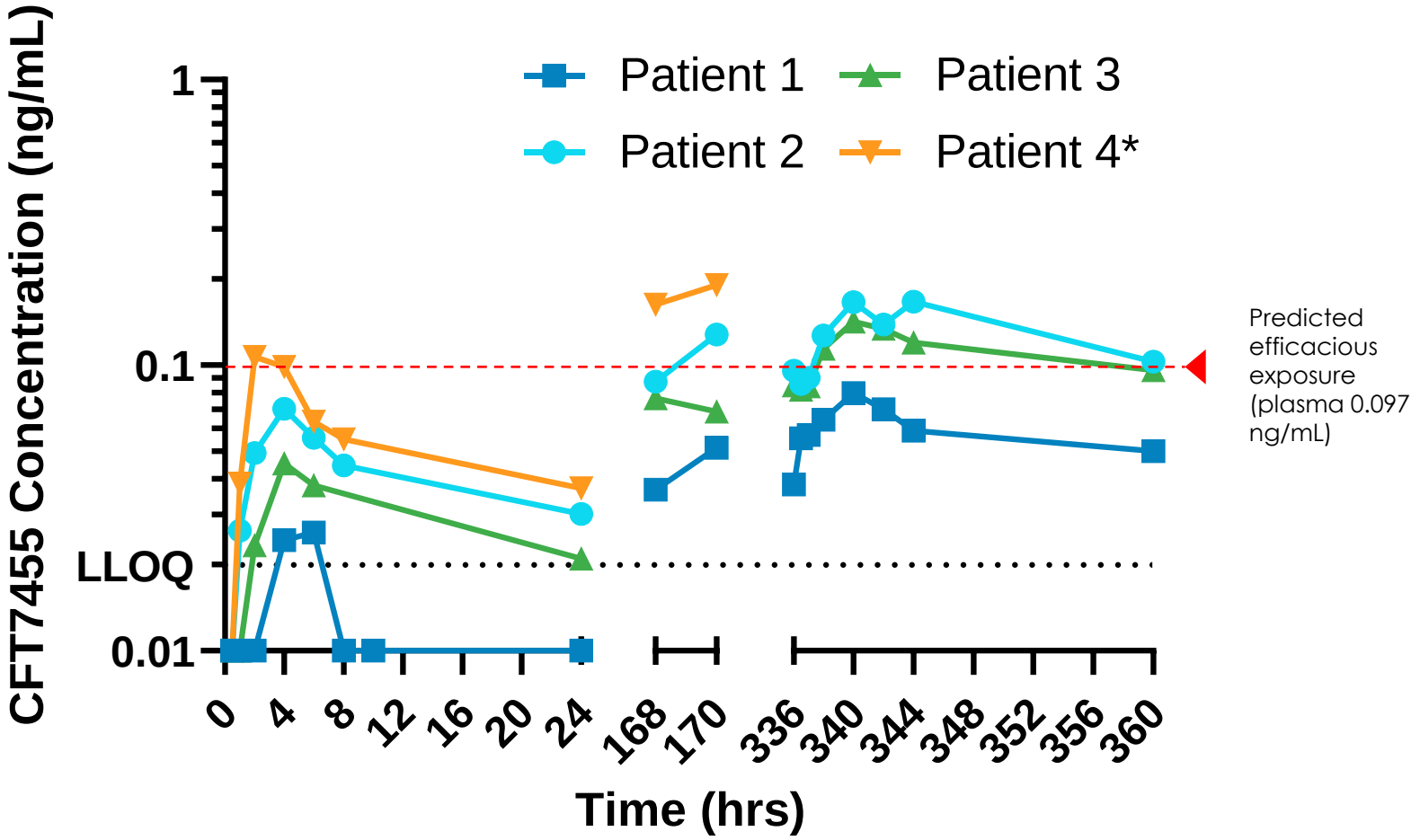
Observed Steady State Exposures Suggest CFT7455 50 µg QD Achieves Efficacious Exposures

Key Takeaways:

- The 50 µg dose achieved exposures which were active (and superior to pomalidomide) in pre-clinical models
- CFT7455 was rapidly absorbed, with a plasma half-life of approximately two days
- Accumulation of drug was observed up to four-fold by day 15 (360 hours)



* 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 available for Patient 5.

QD, every day

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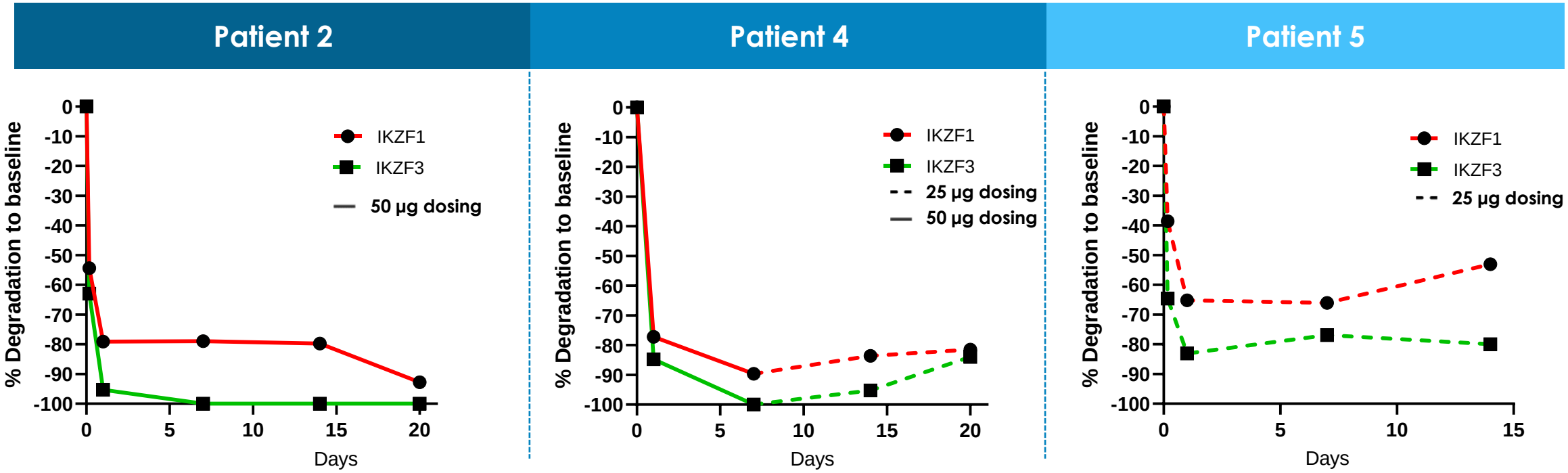
Deep and Sustained Degradation of IKZF1/3 Observed in Cycle 1 of Single Agent CFT7455



Key Takeaways:

- IKZF3 degradation was deeper in human PBMCs at 50 and 25 µg/day than was projected based on observed pre-clinical IKZF3 degradation of ~70% at equivalent exposures

Data not available for Patient 1 and Patient 3 due to compromised sample integrity
PBMC, peripheral blood mononuclear cells

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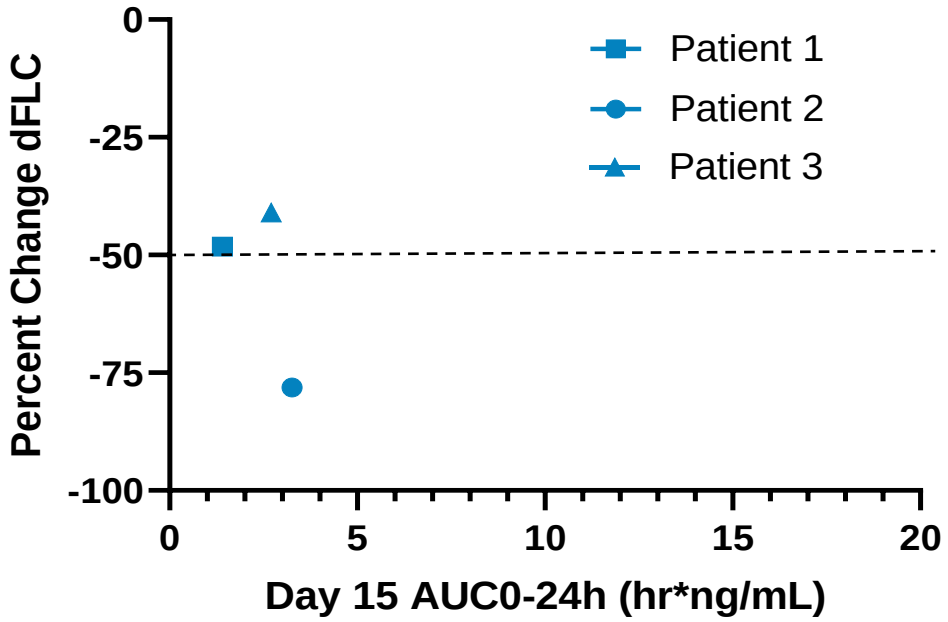
Meaningful Decreases in dFLC Achieved with Single Agent CFT7455 at Lower Exposure and Dose Than Seen with Another Investigational IKZF1/3 Degrader



✶ Patient 4 had an increase in dFLC of 56%, however it is not plotted as exposure data is not available; Patient 5 sample was not obtained

dFLC, difference between involved FLC and uninvolved FLC

dFLC equation: [Abnormal light chain$_{baseline}$- normal light chain$_{baseline}$]- [Abnormal light chain $_{nadir}$- normal light chain $_{nadir}$] /[Abnormal light chain$_{baseline}$- normal light chain$_{baseline}$] * 100

[1] From CC-92480 PD Poster at ASCO 2020 (Abstract 8531)

Key Takeaways:

- Meaningful reduction in differences in serum free light chain (at nadir) was observed at achieved steady state exposures
- Reductions in dFLC were observed in the 3 patients for whom data is available (all dosed at 50 µg) for plotting*
- Decreases in dFLC were observed at lower exposures in comparison to other clinical stage IKZF1/3 degraders
  - CFT7455: 50 µg resulted in active exposures with reduction (>40%) in dFLC in 3 patients
  - CC-92480: 100 µg (starting dose) + dexamethasone resulted in no reduction in dFLC[1]

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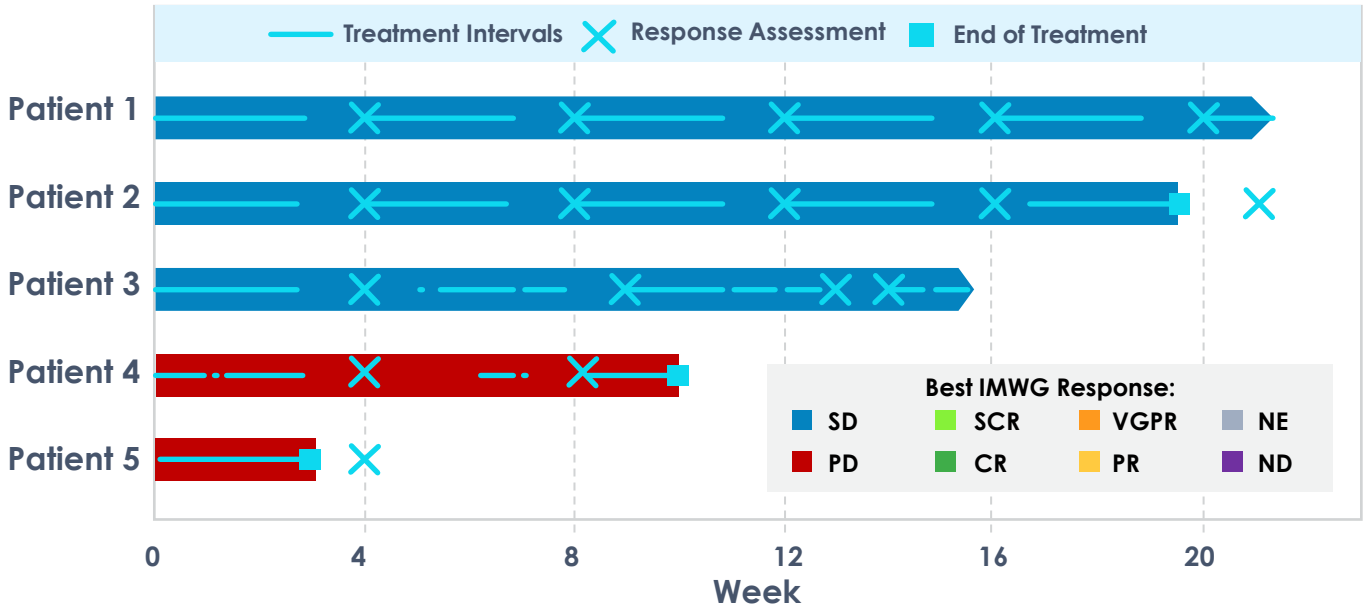
Responses to Single Agent CFT7455



First Actual Dose (µg)	Extramedullary Disease	% Change at Nadir in dFLC*
50	No	48.2 ▼
50	Multiple Plasmacytomas	78.1 ▼
50*	Lytic Bone Lesions	41.0 ▼
50*	No	▲ 56.3
25	Plasmacytomas and Bone Lesions	N/A

Key Takeaways:

- Across the five patients treated, a best response of SD was observed. Three patients achieved SD and two patients had a best response of PD.
- Patient 2 achieved a decrease in dFLC of 78%. This patient did not achieve PR due to the presence of measurable radiographically stable plasmacytomas.

* Patients were dose reduced from 50 µg to 25 µg
Each bar represents one patient in the study. Right arrow cap indicates continued on study.

dFLC, difference between iFLC and uninvolved FLC; SCR, Stringent Complete Response; CR, Complete Response; VGPR, Very Good Partial Response; PR, Partial Response; SD, Stable Disease; PD, Progressive Disease; NE, Non-evaluable; ND, Not done.

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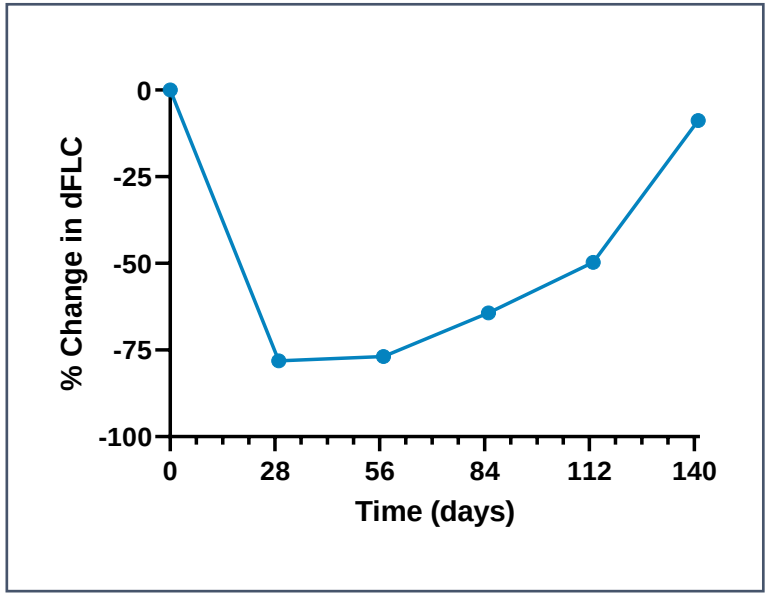
Patient 2 Vignette: Encouraging CFT7455 Singe Agent Activity in Heavily Pre-treated, High-risk MM Patient

- 60-year-old female enrolled 2 June 2021 into Cohort A
- Diagnosed with MM (IgG κ) Jan 2017
- **Heavily pretreated**

Line	Therapy	Best Response
1	Velcade+Dex	
1	Revlimid Velcade Dex/ Rev+Dex	CR
1	Melphalan	PD
1	RVD consolidation	VGPR
1	Autologous stem cell transplant (ASCT)	Stringent CR
2	Carfilzomib Dex	SD
3	Carfilzomib Pom Dex	SD
4	Dara +KPD	PD
5	GPRC5D Bispecific Antibody	PR



Per IMWG response criteria, patient achieved Stable Disease:

- Best response of 78.1% decrease in difference between light chains at nadir
- Best response of 26.5% percent radiographic reduction of plasmacytomas, from baseline

CR, complete response; Dara, daratumumab; Dex, dexamethasone; dFLC, difference between involved minus uninvolved serum free light chains; EMD, extramedullary disease; IKZF1/3, Ikaros family zinc finger proteins 1 and 3; IMWG, International Myeloma Working Group; KPD, carfilzomib–pomalidomide–dexamethasone; MM, multiple myeloma; PD; progressive disease; Pom, pomalidomide; PR, partial response; Rev, Revlimid; RVD, Revlimid-velcade-dexamethasone; SD, stable disease; VGPR, very good partial response.

Summary of Adverse Events

All TEAE's n (%)	Grade 1 (N=5)	Grade 2 (N=5)	Grade 3 (N=5)	Grade 4 (N=5)
Blood and lymphatic system disorders				
Neutropenia	0	0	1 (20)	3 (60)
Thrombocytopenia*	1 (20)	1 (20)	1 (20)	0
Anemia	0	0	1 (20)	0
Leukopenia	0	0	1 (20)	0
Investigations				
Aspartate aminotransferase increased	2 (40)	0	0	0
Alanine aminotransferase increased	1 (20)	0	0	0
Gastrointestinal disorders				
Diarrhea	1 (20)	0	0	0
General disorders and administration site conditions				
Fatigue	1 (20)	0	0	0
Pyrexia	1 (20)	0	0	0
Infections and infestations				
Rhinitis	1 (20)	0	0	0
Upper respiratory tract infection	1 (20)	0	0	0
Nervous system disorders				
Balance disorder	1 (20)	0	0	0
Headache	1 (20)	0	0	0
Renal and urinary disorders				
Nephrolithiasis	0	1 (20)	0	0

No Serious Adverse Events

*Thrombocytopenia includes the preferred term thrombocytopenia and platelet decreased

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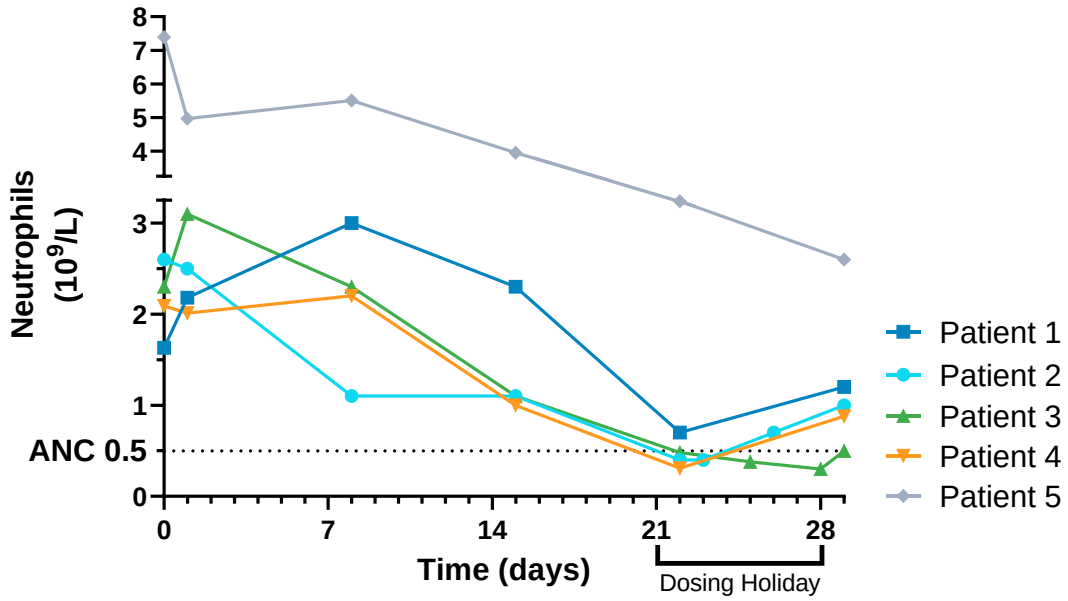
On-target Neutropenia Seen Across Patients; Most Severe at Day 21

Neutrophil Change Over Time



- Patient 4 received 50 µg for 8 days, followed by 25 µg
- Patient 5 received 25 µg dose

Key Takeaways:

- Neutropenia tended to worsen following day 15 and recovery was incomplete during the 7-day drug holiday
- The mechanism is considered due to on-target effects of degrading IKZF1 resulting in the downstream decrease in PU.1 causing transient neutrophil maturation arrest[1]
- Two DLTs were observed at the 50 µg per day dose, both consistent with on-target activity:
  - Grade 4 neutropenia lasting more than 5 days
  - A delay (more than 7 days) in initiating treatment in Cycle 2, in the setting of persistent Grade 3 neutropenia

DLT, dose-limiting toxicity

[1] Li S, et al. Blood Adv. 2018 Mar 13;2(5):492-504.

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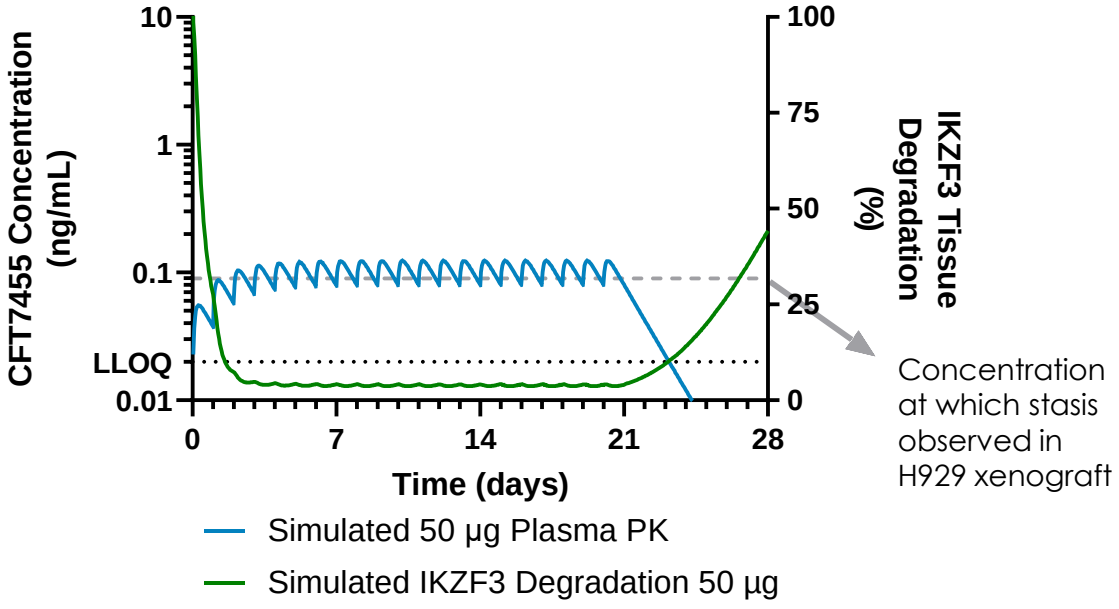
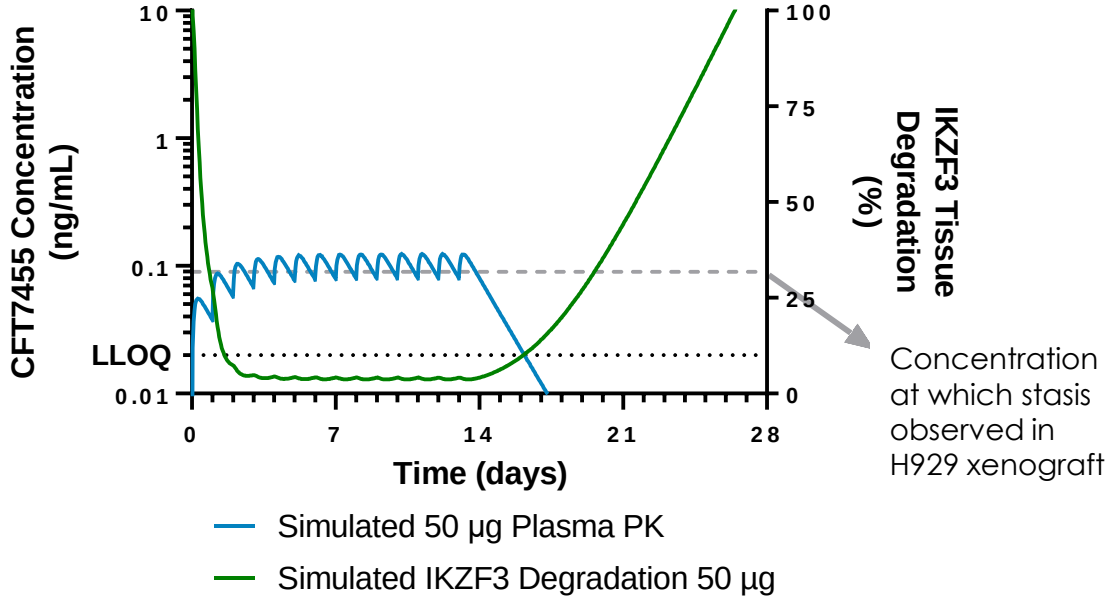
Alternative CFT7455 Dosing Schedule Expected to Increase Therapeutic Index

Modeling Based on Initial Dosing Schedule
21 Days On, 7 Days Off



Modeling Based on Planned Dosing Schedule
14 Days On, 14 Days Off



Key Takeaways:

- There is insufficient time for neutrophil recovery during the 21 day on, 7 day off schedule.
- A 14 day on, 14 day off schedule may limit neutropenia by permitting neutrophil maturation and recovery while effecting tumor apoptosis day 1-14 and limiting tumor recovery during break

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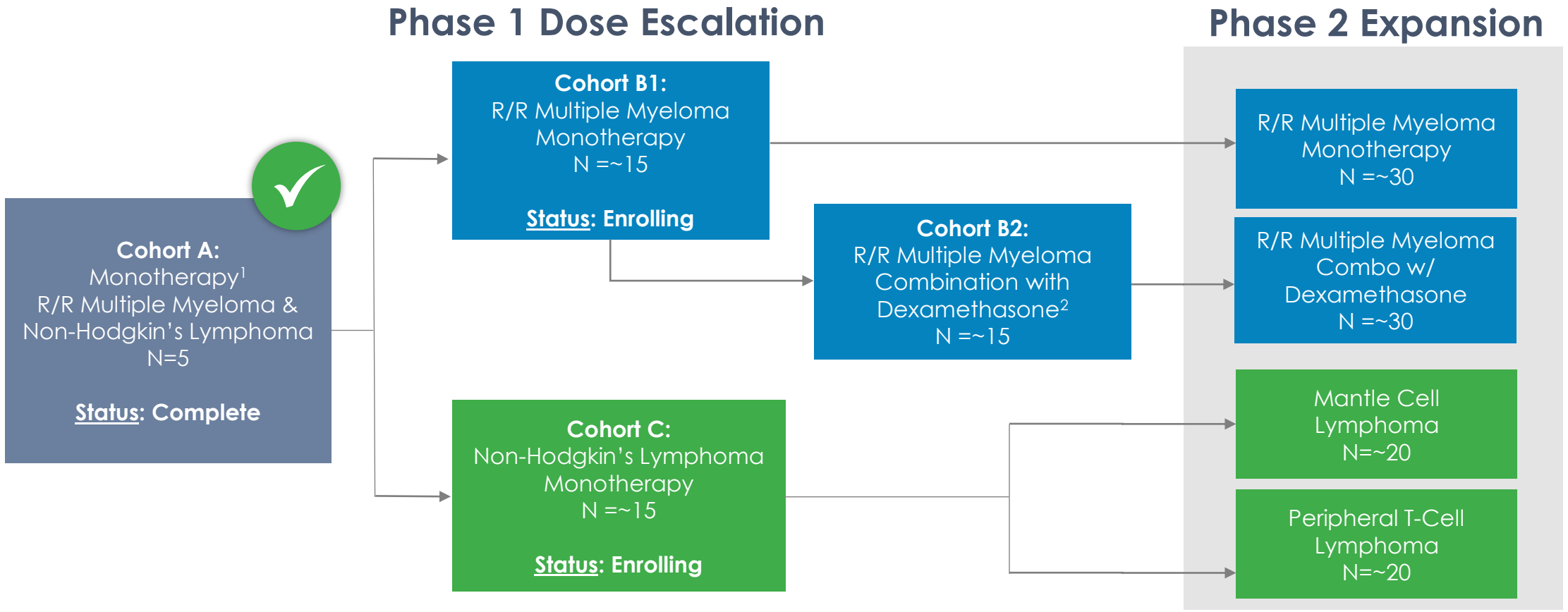
Summary

- Pre-clinically, single agent CFT7455 demonstrates increased activity *in vivo* in comparison to CC-92480
  - CFT7455 has longer exposure compared to CC-92480, resulting in sustained IKZF1/3 degradation in pre-clinical models
  - After 21 days of once-daily dosing, CFT7455 100 µg/kg/day resulted in durable tumor regressions for prolonged period after drug discontinuation
- Clinically, CFT7455 was well absorbed with a plasma $T_{1/2}$ of approximately 2 days, accumulation of drug was observed up to 4-fold by day 15 and achieved exposures at 50 µg, which are equivalent to predicted efficacious exposures from nonclinical studies
- On-target neutropenia was observed, including 3 patients with Grade 4 neutropenia resulting in 2 DLTs
- Early pharmacodynamic data suggests substantial potency and deeper degradation of the primary targets, IKZF1 and IKZF3 than initially projected at 50 µg
- Preliminary evidence of single agent CFT7455 activity was observed in this initial cohort of heavily pretreated MM patients, including meaningful decreases in dFLC

Cohorts B and C Enrolling At Starting Dose of 25 µg With Alternative Dosing Schedule



Modeling suggests that alternative dosing regimens expected to increase therapeutic index by allowing time for adequate neutrophil maturation during the days off drug with limited impact on efficacy

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

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

C4 Therapeutics

Q&A Session