UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM 8-K

CURRENT REPORT

Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): April 8, 2022

C4 THERAPEUTICS, INC.
(Exact name of Registrant as Specified in Its Charter)

Delaware	**001-39567**	**47-5617627**
(State or Other Jurisdiction of Incorporation)	**(Commission File Number)**	**(IRS Employer Identification No.)**
490 Arsenal Way, Suite 200 **Watertown, MA** **(Address of Principal Executive Offices)**		**02472** **(Zip Code)**

Registrant's Telephone Number, Including Area Code: (617) 231-0700

Not Applicable
(Former Name or Former Address, if Changed Since Last Report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, $0.0001 par value per share	CCCC	The Nasdaq Global Select Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§ 230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§ 240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 8.01 Other Events.

On April 8, 2022, C4 Therapeutics, Inc. (the "Company") issued a press release entitled "C4 Therapeutics Presents Clinical Data from Cohort A of the Ongoing Phase 1/2 Clinical Trial of CFT7455, a Novel IKZF1/3 Degrader." The Company also posted a corporate presentation on CFT7455 AACR Data for its investor webcast on its website at https://ir.c4therapeutics.com/events-presentations. A copy of the press release and the corporate presentation are filed as Exhibits 99.1 and 99.2, respectively, to this Current Report on Form 8-K and are incorporated herein by reference.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits.

Exhibit Number	Description
99.1	Press release issued April 8, 2022
99.2	Corporate Presentation of the Company dated April 8, 2022
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned thereunto duly authorized.

C4 Therapeutics, Inc.

Date: April 8, 2022

By: /s/ Lauren A. White

Lauren A. White
Chief Financial Officer and Treasurer

C4 Therapeutics Presents Clinical Data from Cohort A of the Ongoing Phase 1/2 Clinical Trial of CFT7455, a Novel IKZF1/3 Degrader

– *Single Agent CFT7455 Induces Deep and Durable Degradation of IKZF1/3 and Meaningful Decreases in Serum Free Light Chain at Doses Lower than Expected Based on Pre-clinical Studies* –

– *CFT7455 Exhibits Differentiated Pharmacokinetics (PK) and Potency Relative to Approved and Investigational IKZF1/3 Degraders* –

– *On-Target Dose Limiting Toxicity Observed; Modeling Suggests Differentiated Activity and PK Profile Provides Pathway to Increase Therapeutic Index with Alternative Dosing Schedule* –

– *Company to Host Conference Call and Webcast Today at 2 pm ET* –

WATERTOWN, Mass., April 8, 2022 -- C4 Therapeutics, Inc. (C4T) (Nasdaq: CCCC), a clinical-stage biopharmaceutical company dedicated to advancing targeted protein degradation science to develop a new generation of small-molecule medicines and transform how disease is treated, today presented data from Cohort A of its ongoing Phase 1/2 clinical trial of CFT7455, a novel degrader targeting IKZF1/3 for the treatment of multiple myeloma (MM) and non-Hodgkin's lymphomas (NHL). The data will be presented at the American Association for Cancer Research (AACR) Annual Meeting on Tuesday, April 12, 2022, at 9 AM CT by Sagar Lonial, M.D., FACP.

"The early clinical data from the ongoing Phase 1/2 trial demonstrates that CFT7455's differentiated pre-clinical profile, including enhanced PK and increased activity, has translated to the clinical setting," said Dr. Sagar Lonial, professor and chair, department of hematology and medical oncology, Winship Cancer Institute, Emory University. "Single agent CFT7455 has demonstrated preliminary evidence of clinical activity in a population of highly refractory and heavily pre-treated multiple myeloma patients. We continue to enroll patients in the ongoing clinical trial with the goal of providing a new treatment option for myeloma and lymphoma patients."

"We are encouraged by the early clinical observations and the potential of CFT7455 to be a next-generation therapy to treat multiple myeloma and non-Hodgkin's lymphomas," said Adam Crystal, M.D., Ph.D., chief medical officer of C4 Therapeutics. "We believe this initial data highlights the ability of our TORPEDO® platform to develop highly potent and selective degraders that have the potential to demonstrate deep and durable degradation of intended targets in the clinical setting. We will leverage the unique properties of CFT7455 to optimize its schedule and increase the therapeutic index as we progress to a recommended Phase 2 dose."

CFT7455 Phase 1/2 Clinical Trial

C4T designed CFT7455 to be highly potent and selective against its intended targets, IKZF1/3. The Phase 1/2 trial is designed to primarily investigate safety, tolerability, and anti-tumor

activity. Secondary and exploratory objectives are to characterize the PK and pharmacodynamic profile of CFT7455. The Phase 1 portion of the study explores CFT7455 as a single agent in patients with relapsed or refractory (RR) MM and NHL, as well as in combination with dexamethasone in patients with RRMM. Following identification of a recommended dose(s) and schedule(s), the Phase 2 portion of the trial is expected to expand to the following four investigational arms: (1) in RRMM, single agent CFT7455; (2) in RRMM, CFT7455 combined with dexamethasone; (3) in peripheral T-cell lymphoma, single agent CFT7455; and (4) in mantle cell lymphoma, single agent CFT7455.

Cohort A, the first cohort in the clinical trial, explored CFT7455 as a single agent and enrolled five patients with MM. All patients in Cohort A were highly refractory and heavily pre-treated, having received a median of five prior lines of therapy (range of 4-14), including both lenalidomide and pomalidomide. The starting dose in the trial was 50 µg and all patients in Cohort A received single agent CFT7455 for 21 days of the 28-day treatment cycle. The data cut-off date was January 14, 2022. At the time of this data cut-off, two patients remained on therapy; however, these patients have since discontinued treatment.

Summary of Data from Cohort A:

Safety

- Four patients received single agent CFT7455 at the starting dose of 50 µg per day. Two of these patients were dose reduced to 25 µg per day due to neutropenia, a known on-target toxicity associated with IKZF1/3 degraders.
- The fifth patient enrolled at a starting dose of 25 µg per day based on the recommendation of the safety review committee.
- Two dose-limiting toxicities (DLTs) were observed at the 50 µg per day starting dose, both consistent with on-target activity:
    1. Grade 4 neutropenia lasting more than 5 days
    2. A delay (more than 7 days) in initiating treatment in Cycle 2, in the setting of persistent Grade 3 neutropenia
- No patient experiencing neutropenia had a concurrent infection or fever.
- There were no serious adverse events reported and no adverse events resulted in death or treatment discontinuation.

Pharmacokinetics and Pharmacodynamics

- 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 and achieved exposures at 50 µg that were equivalent to predicted highly active exposures based on pre-clinical studies.
- CFT7455 demonstrated deep and durable degradation of IKZF1/3, as quantified by mass spectrometry, throughout Cycle 1.

Efficacy

- Responsiveness was measured based on International Myeloma Working Group (IMWG) criteria.

- Three patients had best observed reductions in the difference of serum free light chain (dFLC) ranging from 41 percent to 78 percent. One patient had an increase of 56 percent in dFLC.
- The patient who achieved a 78 percent reduction in dFLC did not achieve a partial response under IMWG criteria due to the presence of measurable plasmacytomas, which were assessed as stable.
- Three patients had a best response of stable disease. Two patients had a best response of progressive disease.

Next Steps for CFT7455

C4T has completed modeling of the Cohort A data and believes alternative dosing regimens are expected to increase the therapeutic index by allowing time for adequate neutrophil maturation during the days off drug, with limited impact on efficacy. Patients are enrolling in Cohort B1, exploring CFT7455 as a monotherapy for RRMM, and Cohort C, exploring CFT7455 as a monotherapy for NHL. Cohorts B1 and C have a starting dose of 25 μg per day at an alternative dosing schedule. Each cohort will proceed with dose finding in parallel, with the goal of achieving a recommended Phase 2 dose in each of MM and NHL.

Investor Webcast Information

C4T will host an investor webcast today, Friday, April 8, 2022, at 2 PM ET, with Sagar Lonial, M.D., FACP to discuss the CFT7455 clinical data being presented at AACR. To access the call, please dial 866-374-5140 or 404-400-0571 and provide the conference ID: 66856580. The webcast can be also accessed under “Events & Presentations” in the Investors section of the company’s website at www.c4therapeutics.com. A replay of the webcast will be available on C4T’s website for 30 days following the event.

About C4 Therapeutics®

C4 Therapeutics (C4T) (Nasdaq: CCCC) is a clinical-stage biopharmaceutical company dedicated to delivering on the promise of targeted protein degradation science to create a new generation of medicines that transform patients’ lives. C4T is leveraging its TORPEDO® platform to efficiently design and optimize small-molecule medicines that harness the body’s natural protein recycling system to rapidly degrade disease-causing proteins, offering the potential to overcome drug resistance, drug undruggable targets and improve patient outcomes. C4T is advancing multiple targeted oncology programs to the clinic and expanding its research platform to deliver the next wave of medicines for difficult-to-treat diseases. For more information, please visit www.c4therapeutics.com.

About CFT7455

CFT7455 is an orally bioavailable MonoDAC™ (Monofunctional Degradation Activating Compound) degrader designed to be highly potent and selective against its intended targets of Ikaros (IKZF1) and Aiolos (IKZF3). CFT7455 binds with high affinity to the E3 ligase adapter protein, cereblon, to target and degrade IKZF1/3 for the treatment of multiple myeloma and non-Hodgkin's lymphomas, including peripheral T cell lymphoma and mantle cell lymphoma. In early clinical data, CFT7455 demonstrated deep and durable degradation of IKZF1/3. C4T is

actively enrolling patients in its ongoing Phase 1/2 clinical trial. More information about this trial may be accessed at www.clinicaltrials.gov (identifier: NCT04756726).

Forward-Looking Statements
This press release contains "forward-looking statements" of C4 Therapeutics, Inc. within the meaning of the Private Securities Litigation Reform Act of 1995. These forward-looking statements may include, but may not be limited to, express or implied statements regarding our ability to develop potential therapies for patients; that alternative dosing regimens may increase the therapeutic index of CFT7455 with limited impact on efficacy; the design and potential efficacy of our therapeutic approaches; the predictive capability of our TORPEDO® platform in the development of novel, selective, orally bioavailable degraders; the potential timing, design and advancement of our pre-clinical studies and clinical trials, including the potential timing for regulatory authorization related to clinical trials; our ability and the potential to successfully manufacture and supply our product candidates for clinical trials; our ability to replicate results achieved in our pre-clinical studies or clinical trials in any future studies or trials; and regulatory developments in the United States and foreign countries. Any forward-looking statements in this press release are based on management's current expectations and beliefs of future events and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. These risks and uncertainties include, but are not limited to: uncertainties related to the initiation, timing, advancement and conduct of pre-clinical and clinical studies and other development requirements for our product candidates; the risk that any one or more of our product candidates will cost more to develop or may not be successfully developed and commercialized; and the risk that the results of pre-clinical studies and/or clinical trials will or will not be predictive of results in connection with future studies or trials. For a discussion of these and other risks and uncertainties, and other important factors, any of which could cause our actual results to differ from those contained in the forward-looking statements, see the section entitled "Risk Factors" in C4 Therapeutics' most recent Annual Report on Form 10-K and/or Quarterly Report on Form 10-Q, as filed with the Securities and Exchange Commission. All information in this press release is as of the date of the release, and C4 Therapeutics undertakes no duty to update this information unless required by law.

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Kendra.Adams@c4therapeutics.com

Media Contact:
Loraine Spreen
Director, Corporate Communications & Patient Advocacy
LSpreen@c4therapeutics.com

Exhibit 99.2

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.

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 presentation 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.

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, M.D., 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

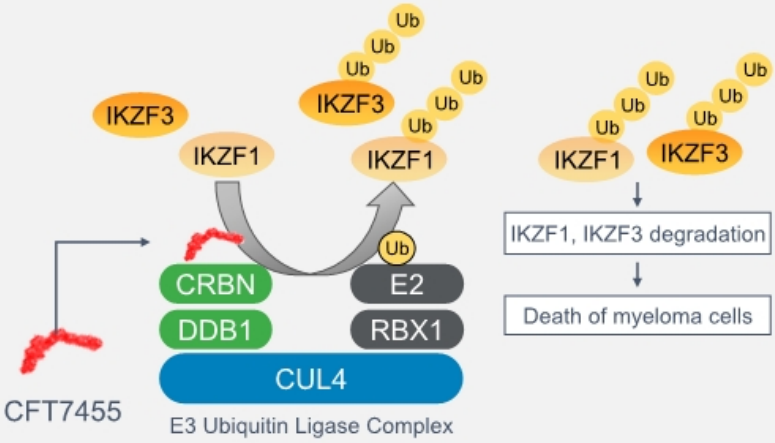
	2022 Milestones
CFT7455 (IKZF1/3)	✓ Present Cohort A Phase 1 data at AACR ✓ Present new pre-clinical data at AACR
CFT8634 (BRD9)	✓ Orphan Drug Designation ✓ Present pre-clinical data at AACR ❑ Initiate Phase 1 trial in 1H
CFT1946 (BRAF V600X)	✓ Present pre-clinical data at AACR ❑ Submit IND application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

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



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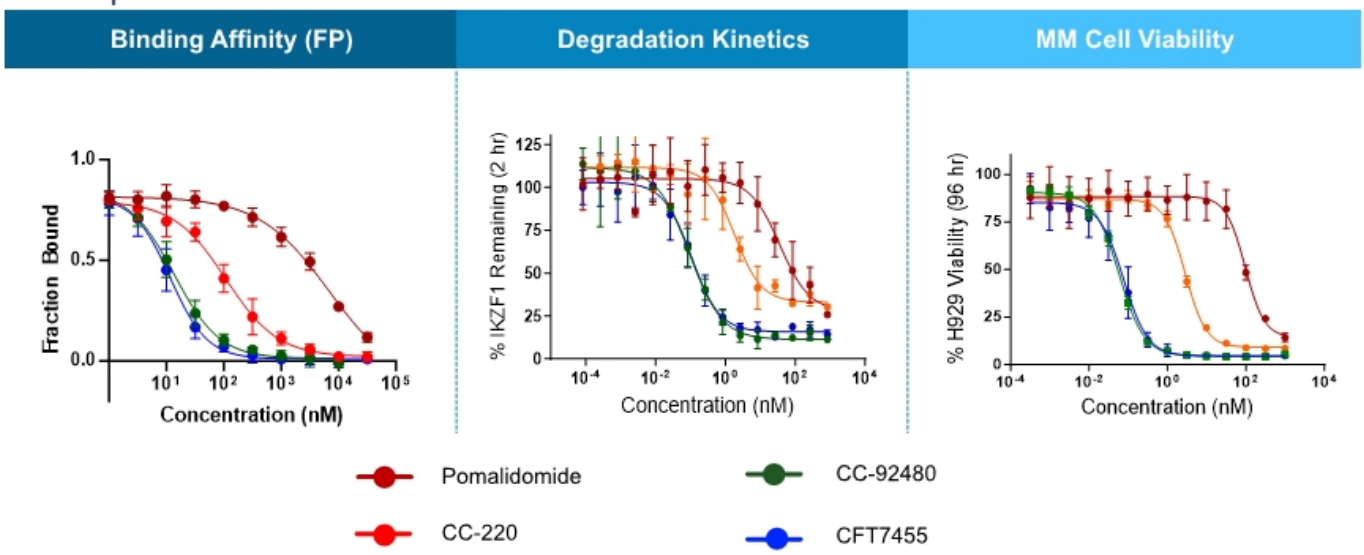
CRBN, cereblon; CUL4, cullin 4; DDB1, DNA damage-binding protein 1; IKZF1/3, Ikaros family zinc finger proteins 1 and 3; IMiD, immunomodulatory imide drug; monoDAC, monofunctional degradation activating compound; MM, multiple myeloma; RBX1, ring box protein 1; Ub, ubiquitin.

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



Key Takeaway:

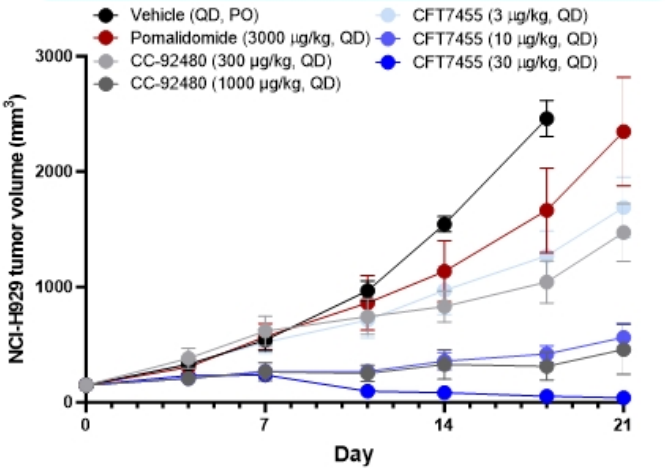
- Catalytic activity enhancement resulted in >1000-fold improvement in potency vs. Pomalidomide

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

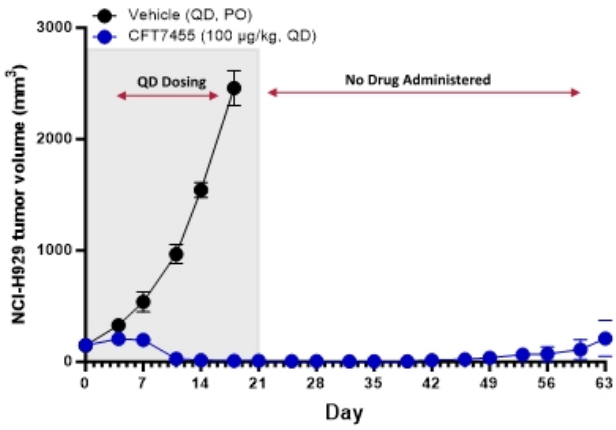
C4 Therapeutics

CFT7455 Demonstrates Superior Efficacy in NCI-H929 MM Xenograft Model

CFT7455 vs. Comparators



CFT7455 Results in Durable Complete Regression

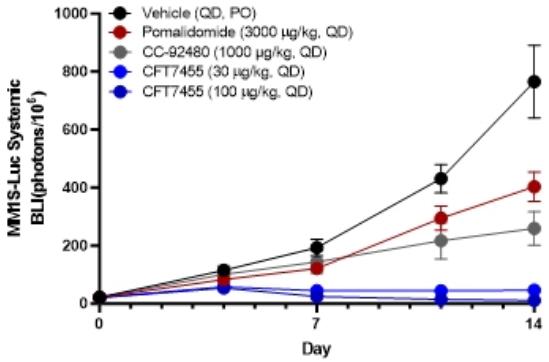


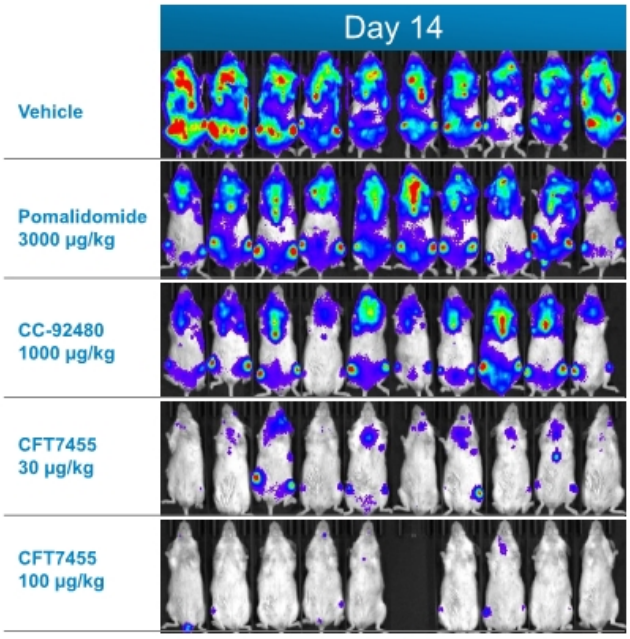
Key Takeaways:

- 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

CFT7455 is Highly Efficacious in a Model of Systemic Multiple Myeloma

CFT7455 vs Comparators in a Model of Systemic MM



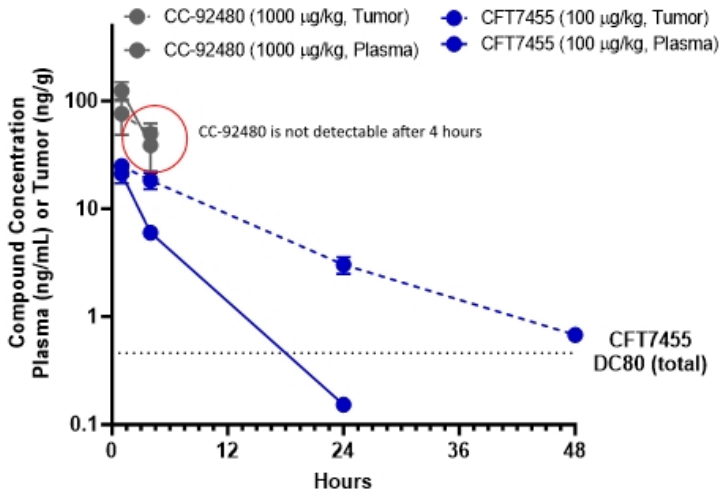


*Mouse missing in CFT7455 100 µg/kg group due to changes unrelated to treatment or disease

C4 Therapeutics

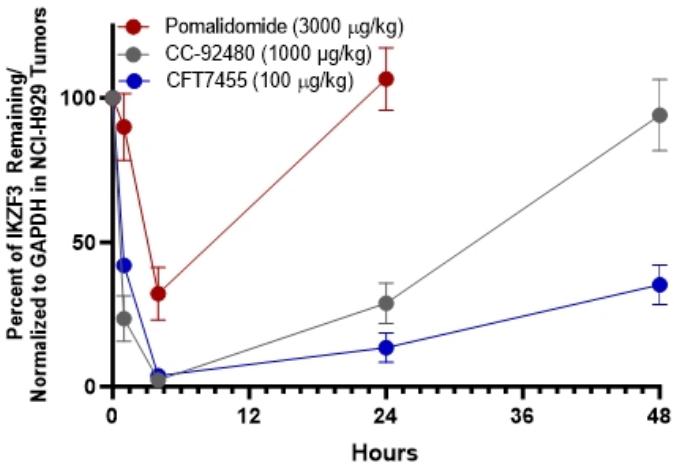
Single Dose PK/PD in H929 Xenografts Differentiates CFT7455 from CC-92480

CFT7455 and CC-92480* Tumor and Plasma Concentrations



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

Degradation Kinetics for CFT7455, CC-92480 and Pomalidomide

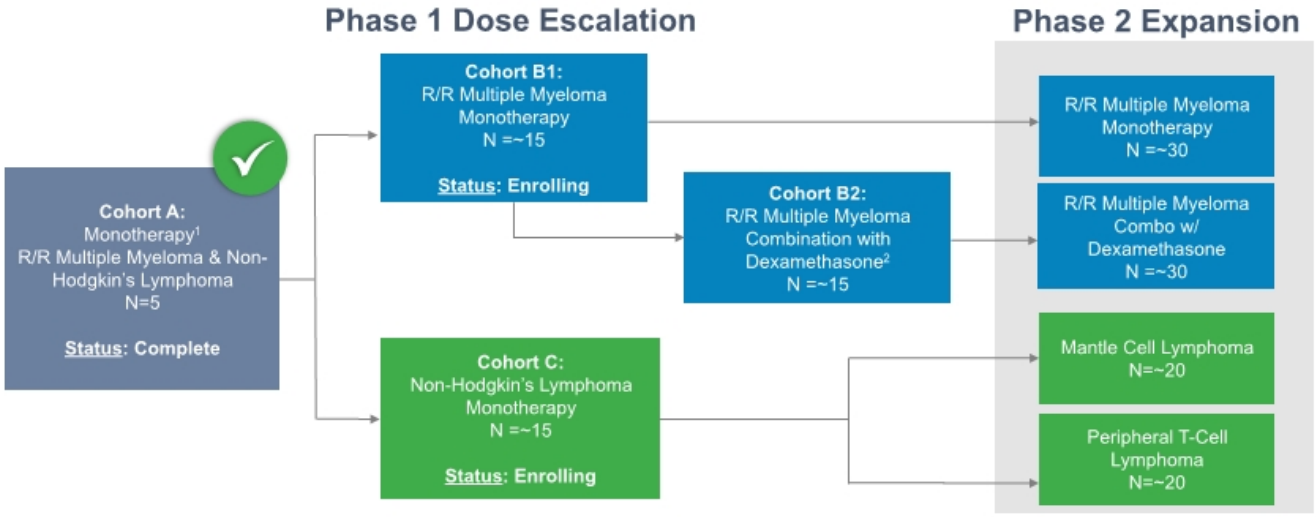


C4 Therapeutics

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

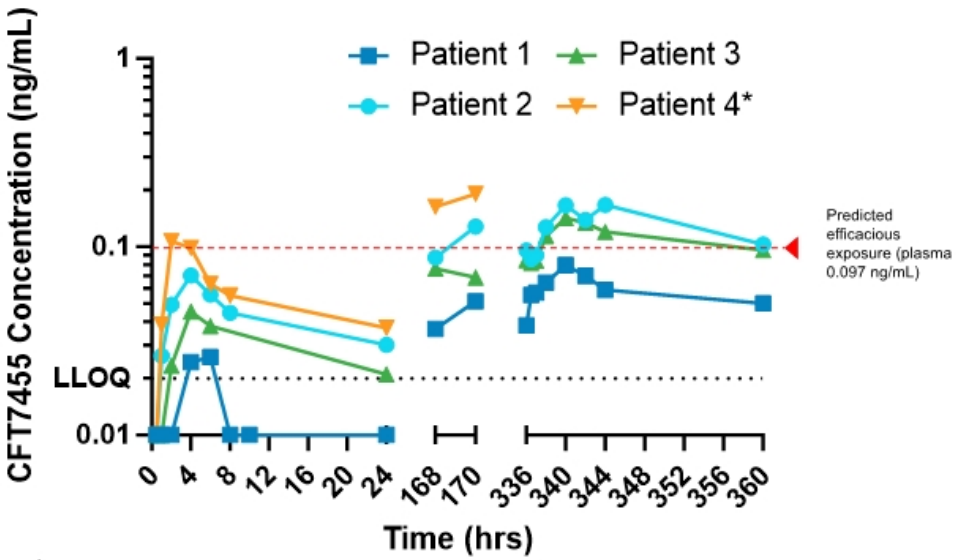
N (%) of patients unless stated	N=5
Age in years, median (range)	63 (51,73)
Sex, male	3 (60)
Time since initial diagnosis, median (range), years	11 (4,21)
ECOG PS	
0	2 (40)
1	2 (40)
2	1 (20)
R-ISS stage at screening, n (%)	
Stage I	1 (20)
Stage II	1 (20)
Stage III	2 (40)
Missing	1 (20)
Presence of extramedullary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

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)

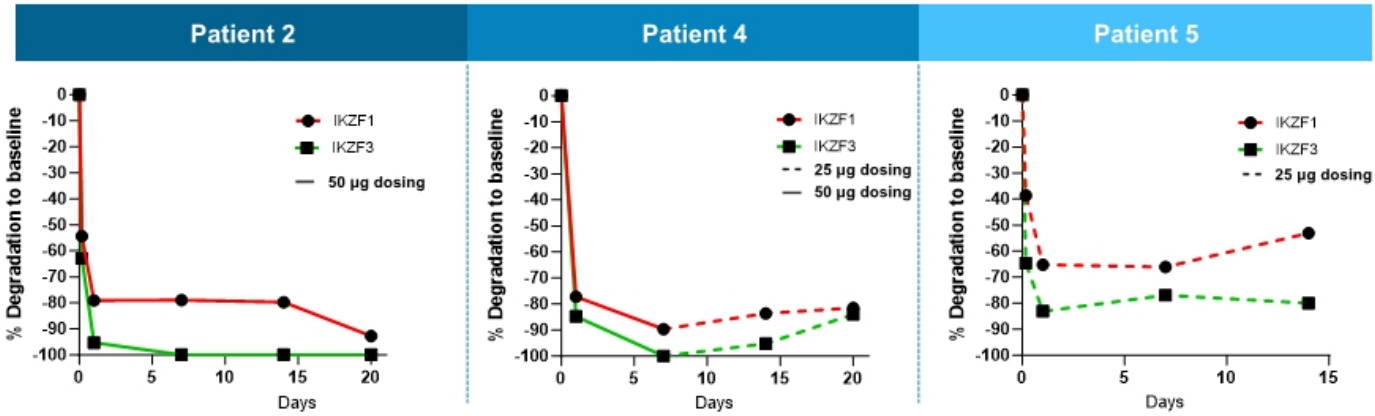


* Patient 4 received 50 µg for 8 days followed by 25 µg for 13 days followed by the regular 7-day rest period in Cycle 1; subsequent cycles continued at 25 µg 21 days on and 7 days off in a 28-day cycle. Data not available for Patient 5.

QD, every day

C4 Therapeutics

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

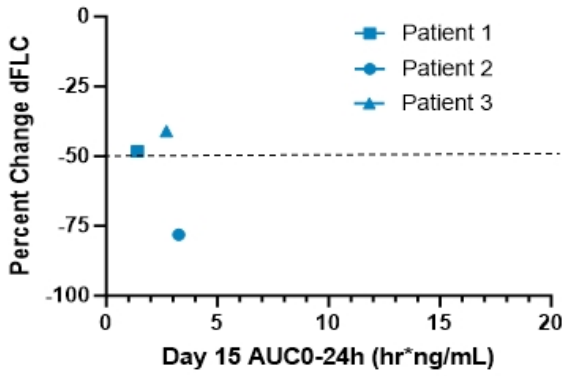


Key Takeaways:

- 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

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]

C4 Therapeutics

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.

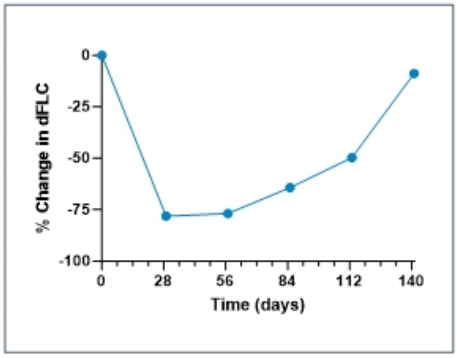
* Patients were dose reduced from 50 µg to 25 µg
Each bar represents one patient in the study. Right arrow cap indicates continued on study.

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.

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

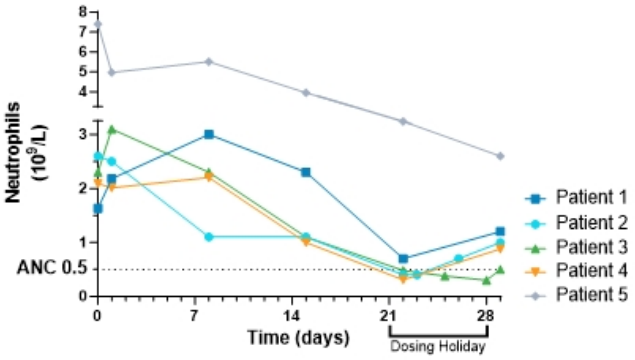
No Serious Adverse Events

*Thrombocytopenia includes the preferred term thrombocytopenia and platelet decreased

C4 Therapeutics

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

DLT, dose-limiting toxicity

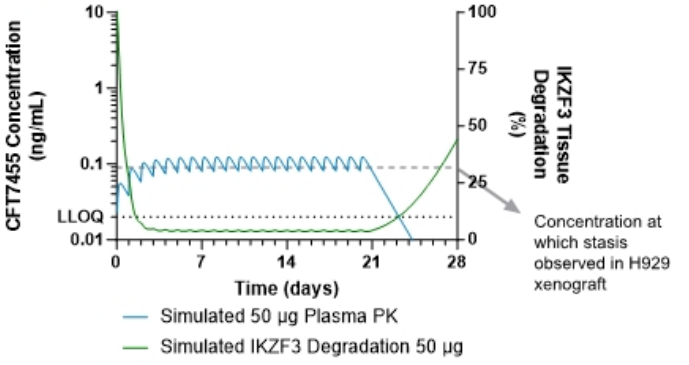
[1] Li S, et al. Blood Adv. 2018 Mar 13;2(5):492-504.

Key Takeaways:

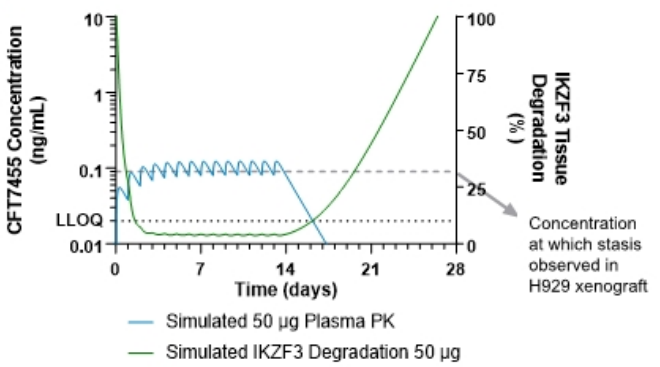
- Neutropenia tended to worsen following day 15 and recovery was incomplete during the 7-day drug holiday
- The mechanism is considered due to on-target effects of degrading IKZF1 resulting in the downstream decrease in PU.1 causing transient neutrophil maturation arrest[1]
- Two DLTs were observed at 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

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



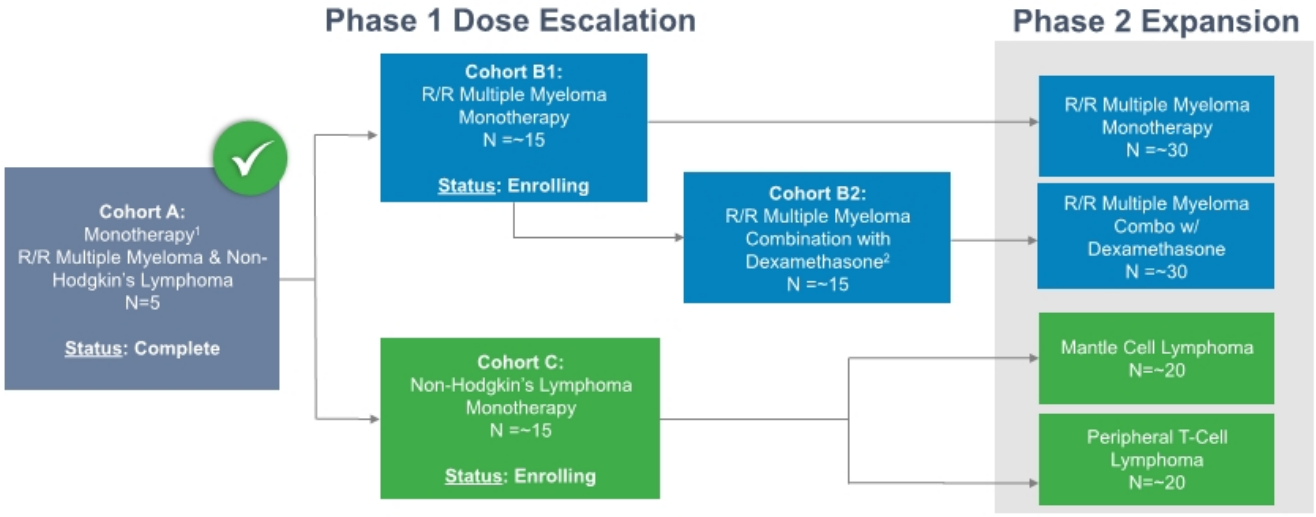
Key Takeaways:

- 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

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