CFT8634, a BRD9 BiDAC™ degrader, is active in a subset of multiple myeloma cell line models and synergistic when combined with pomalidomide or dexamethasone

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Introduction

BRD9 is a component of the noncanonical SWI/SNF (ncSWI/SNF) complex. Recent literature has shown that loss-of-function of BRD9 mediated by RNA interference or by BRD9 degrader compounds can inhibit proliferation of multiple myeloma (MM) cell lines and primary MM cells *in vitro*, as well as inhibit mouse MM xenograft tumor growth *in vivo*[1,2]. Additionally, *in vitro* synergy was observed when a BRD9 degrader was combined with either dexamethasone or pomalidomide.

CFT8634 is a potent and selective oral BiDAC™ degrader of BRD9 (Figure 1) that was being evaluated in a clinical trial for the treatment of SMARCB1-perturbed cancers, including synovial sarcoma and SMARCB1-null tumors. Pharmacokinetic and pharmacodynamic data from this trial demonstrated dose-proportional human plasma exposure and robust BRD9 degradation in patients[3].

Here we explored the anti-proliferative activity of CFT8634 in a larger subset of MM models at clinically relevant exposures. We observed that cell lines less sensitive to pomalidomide (POM) tend to be significantly more sensitive to CFT8634 treatment. As POM is a standard of care (SoC) treatment in MM, we interrogated the ability to combine CFT8634 and POM *in vivo* in MM models with varying sensitivity to CFT8634 *in vitro*.

In addition, the corticosteroid dexamethasone (DEX) is another SoC treatment given in combination with POM, we further explored the ability to combine DEX with CFT8634 in an *in vivo* model of MM that demonstrates moderate sensitivity to DEX alone.

CFT8634 is a potent and selective BRD9 oral degrader[4]

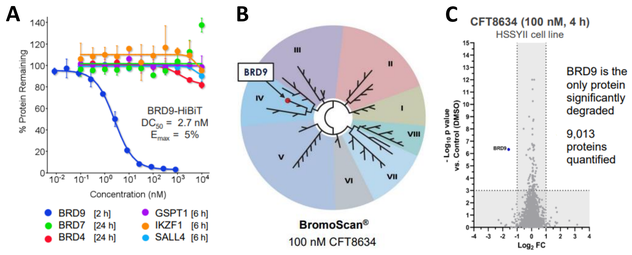


Figure 1: CFT8634 is a potent and selective BRD9 degrader. CFT8634 degrades BRD9 with selectivity over BRD4, BRD7, and neo-substrates of CRBN in HiBiT assays (A). Bromodomain binding specificity by BromoScan® Red dot is BRD9 binding activity (B). Global proteomic evaluation for CFT8634 in HSSYII synovial sarcoma cell line (C).

A panel of MM cell lines shows varying sensitivity to CFT8634 treatment in long-term proliferation assays

A

Multiple Myeloma Cell line	CFT8634 LCC* (nM)	CFT8634 Sensitivity
U266B1	5	High
OPM-2	13	
RPMI-8226	41	
KMS-12BM	41	
LP-1	370	
DELTA-47	370	
KMS-26	370	
KMS-34	370	
NCI-H929	3333	Medium
KMS-27	3333	
KMM-1	3333	
KMS-11	10000	Low
MM.1S	10000	
MM.1R	10000	
HunS1	10000	

*LCC is lowest cytotoxic concentration

B

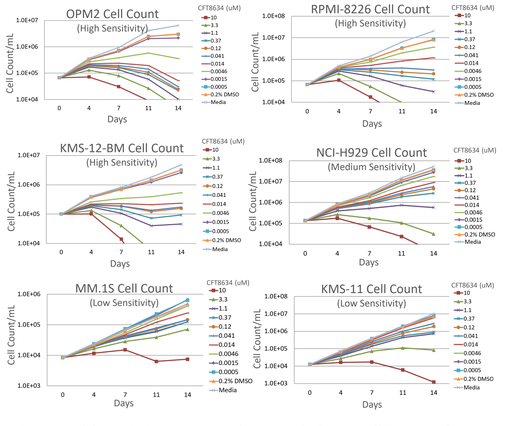


Figure 2: *In vitro* long-term proliferation (LTP) assay with CFT8634 treatment in a panel of MM cell lines. Fifteen MM cell lines were treated with a dose titration of CFT8634 for 14 days (re-fed on Days 4, 7, 11, and 14) and ranked based on the lowest cytotoxic concentration (LCC) on Day 14 (A). Representative MM cell line graphs showing cell counts after CFT8634 treatment in LTP assay (B).

In vivo CFT8634 as a single agent demonstrates varying efficacy in multiple myeloma xenograft models

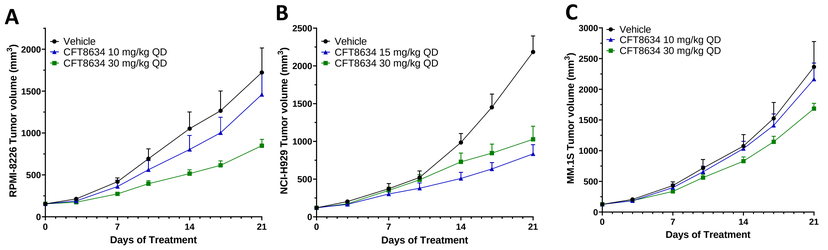


Figure 3: CFT8634 *in vivo* efficacy in multiple myeloma cell line xenograft models. Female CB17 SCID mice bearing established RPMI-8226 (A), NOD SCID mice bearing established NCI-H929 (B), and CB17 SCID mice bearing established MM.1S (C) tumors were treated orally (n=8) with Vehicle and clinically relevant exposures of CFT8634 (10, 15, or 30 mg/kg) once daily (QD) for 21 days. Efficacy data are expressed as mean tumor volumes + SEM.

CFT8634 synergizes with pomalidomide even in models where pomalidomide fails to show single agent activity

A

Multiple Myeloma Cell line	CFT8634 LTP Assay 14 d	POM CTG 96 h	
	LCC (nM)	IC_{50} (nM)	E_{max} %
U266B1	5	> 10000	60
OPM-2	13	93	18
RPMI-8226	41	> 10000	56
KMS-12BM	41	> 10000	71
LP-1	370	576	44
DELTA-47	370	> 10000	73
KMS-26	370	2093	48
KMS-34	370	>10000	N/A
NCI-H929	3333	60	0.6
MM.1S	10000	71	26

B

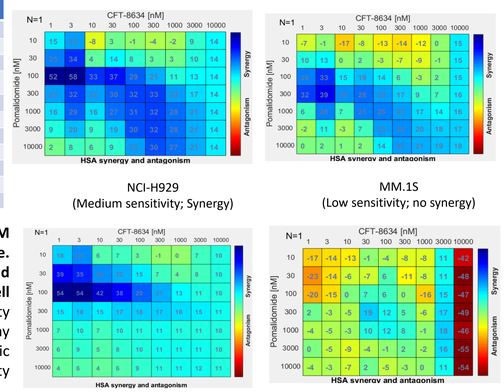


Figure 4: *In vitro* CFT8634 is active in MM cell lines not responsive to pomalidomide. Additionally, combination of CFT8634 and pomalidomide shows synergy in MM cell lines sensitive to CFT8634. CFT8634 activity measured in a long-term proliferation assay (Figure 2A) listed by lowest cytotoxic concentration and POM sensitivity measured by Cell Titer Glo (CTG) at 96 h to determine IC_{50} and E_{max}[5].(A). Viability measured by CTG. Cells were pretreated with CFT8634 for 96 h then treated with CFT8634 and POM for 144 h. Synergy was calculated using Combenefit HSA model (B).

The combination of CFT8634 and pomalidomide is synergistic in a MM xenograft model insensitive to pomalidomide alone

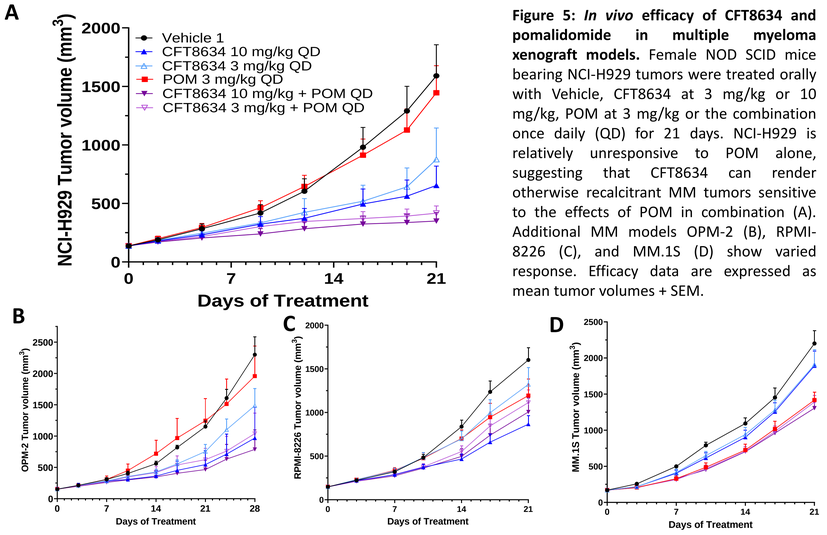
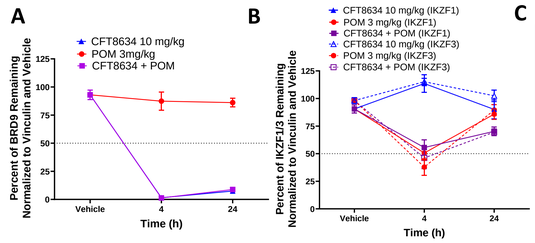


Figure 5: *In vivo* efficacy of CFT8634 and pomalidomide in multiple myeloma xenograft models. Female NOD SCID mice bearing NCI-H929 tumors were treated orally with Vehicle, CFT8634 at 3 mg/kg or 10 mg/kg, POM at 3 mg/kg or the combination once daily (QD) for 21 days. NCI-H929 is relatively unresponsive to POM alone, suggesting that CFT8634 can render otherwise recalcitrant MM tumors sensitive to the effects of POM in combination (A). Additional MM models OPM-2 (B), RPMI-8226 (C), and MM.1S (D) show varied response. Efficacy data are expressed as mean tumor volumes + SEM.

CFT8634 and pomalidomide do not interfere with each other's ability to degrade their respective targets



C

MM Xenograft Model	CFT8634 in vitro Sensitivity	PD % BRD9 degradation (10 mg/kg SD PD)	
		4h	24h
RPMI-8226	High	96.3	92.9
NCI-H929	Medium	98.5	92.5
MM.1S	Low	96.5	87.6

Figure 6: CFT8634, pomalidomide, and combination single dose (SD) tumor pharmacodynamics (PD) in multiple myeloma xenograft models. All mice were dosed orally with Vehicle, CFT8634 at 10 mg/kg, POM at 3 mg/kg, or the combination of CFT8634 (10 mg/kg) and POM (3 mg/kg). CFT8634 showed similar deep and durable BRD9 degradation as a single agent or in combination with POM in NCI-H929 (A). Combination of CFT8634 and POM did not affect POM's ability to degrade IKZF1/3 (B). Comparable BRD9 degradation in tumors was observed in MM xenograft models regardless of CFT8634 sensitivity (C).

In vivo administration of CFT8634 and dexamethasone leads to regression in MM xenograft model

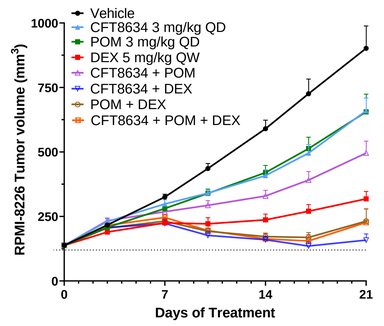


Figure 7: *In vivo* efficacy of CFT8634 and dexamethasone in a multiple myeloma xenograft model. Female CB17 SCID mice bearing RPMI-8226 tumors were treated orally with Vehicle, a clinically relevant dose of CFT8634 at 3 mg/kg or 10 mg/kg once daily (QD), POM at 3 mg/kg QD, dexamethasone (DEX) at 5 mg/kg once weekly (QW), CFT8634 + POM, CFT8634 + DEX, POM + DEX, or CFT8634 + POM + DEX for 21 days. The CFT8634 + DEX combination led to regression in 5/8 mice and demonstrated enhanced efficacy compared to the SoC combination of POM + DEX. The triple combination had no additional benefit. Efficacy data are expressed as mean tumor volumes + SEM.

Summary

- We demonstrate *in vitro* and *in vivo* single agent activity in an expanded set of MM models using a potent and selective oral BRD9 degrader.
- *In vitro*, the BRD9 degrader synergizes with pomalidomide even in models where pomalidomide fails to show single agent activity.
- We show *in vivo* synergy between BRD9 degradation and SoC agents pomalidomide and dexamethasone at clinically relevant doses suggesting combination benefit.
- The combination of two CRBN based degraders does not interfere with one another indicating that CRBN activity is not saturated.

References.

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AACR Annual Meeting, April 2024

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