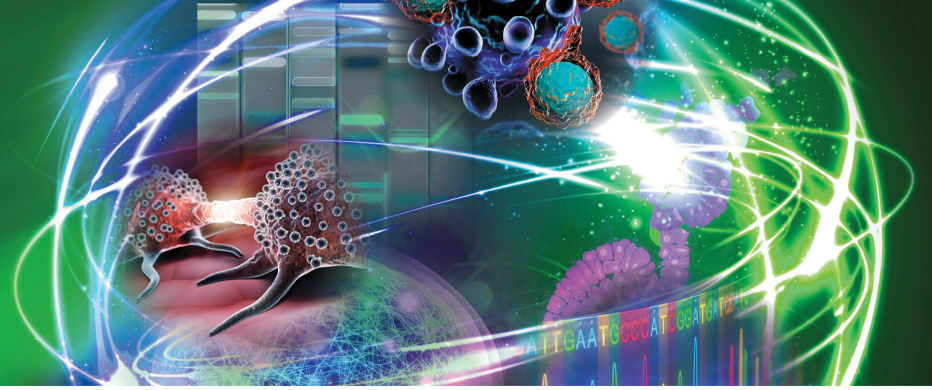
AACR American Association for Cancer Research
ANNUAL MEETING 2021
VIRTUAL #AACR21
APRIL 10-15, 2021 AND MAY 17-21, 2021 AACR.ORG AACR.ORG/AACR2021



CFT7455: A novel, IKZF1/3 degrader that demonstrates potent tumor regression in IMiD-resistant multiple myeloma (MM) xenograft models

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Disclosure Information

David Proia, PhD

- I have the following financial relationships to disclose:
  - Stockholder in: C4 Therapeutics
  - Employee of: C4 Therapeutics
- I will not discuss off label use and/or investigational use in my presentation.

Myeloma Therapies Have Improved OS But High Unmet Need Remains

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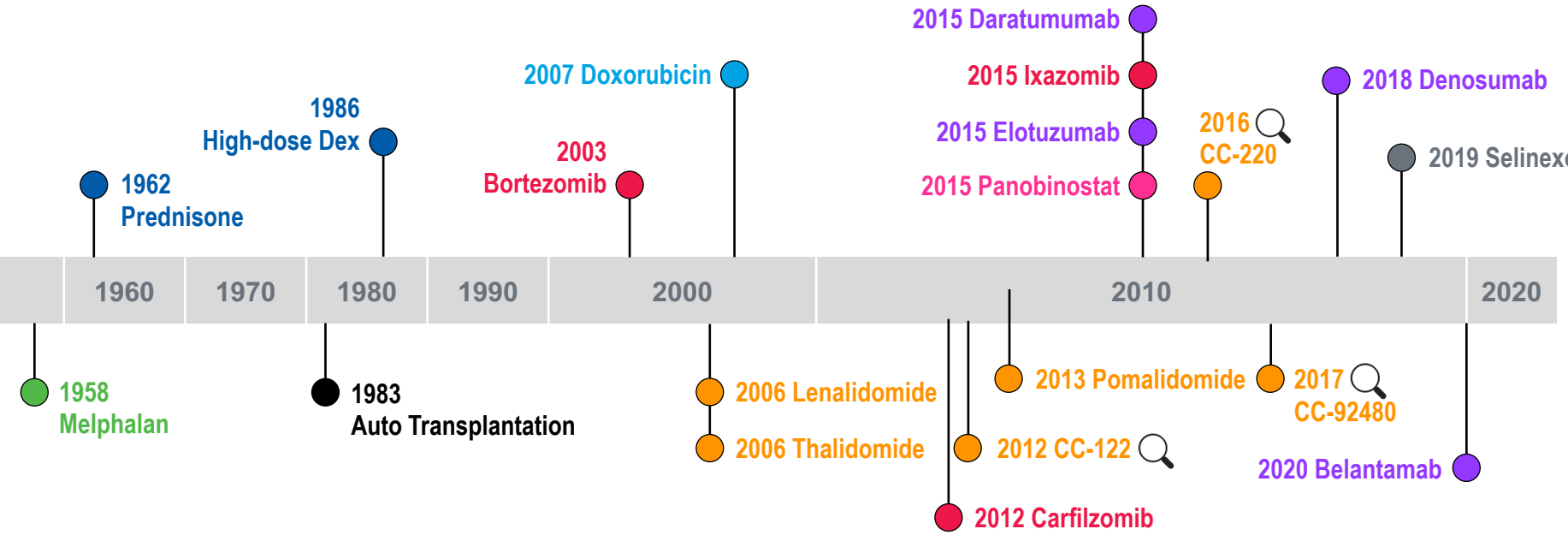
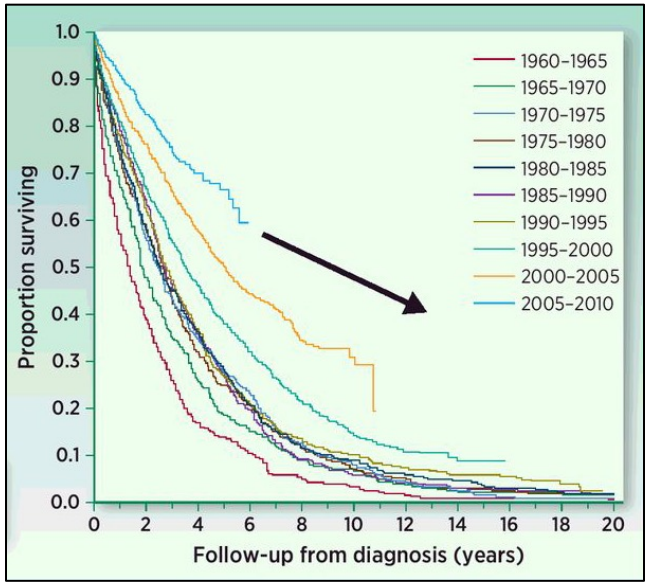


Improvement in OS
From Median of 3 Years to 8-10 Years



- Multiple myeloma (MM) is an incurable disease of the plasma cells
- MM patient survival has increased steadily since 2000, mirroring the introduction of several novel therapies
- IMiDs (thalidomide, lenalidomide, pomalidomide) are widely used in MM treatment regimens
- Relapsed/refractory MM remains a high unmet medical need

- Alkylators
- Steroid
- Anthracycline
- Proteasome inhibitors (“mibs”)
- Immunomodulators (“IMiDs” or “mids”)
- Monoclonal antibodies (“mAbs”)
- HDAC inhibitor
- XP01 inhibitor
- Investigational and not yet approved by the FDA

Auto, autologous; Dex, dexamethasone; IMiD, immunomodulatory imide drug; OS, overall survival
Figure adapted from Anderson KC. *Clin Cancer Res.* 2016;22:5419–27.

Ikaros Transcription Factors are Central to Lymphoid Differentiation and Myeloma

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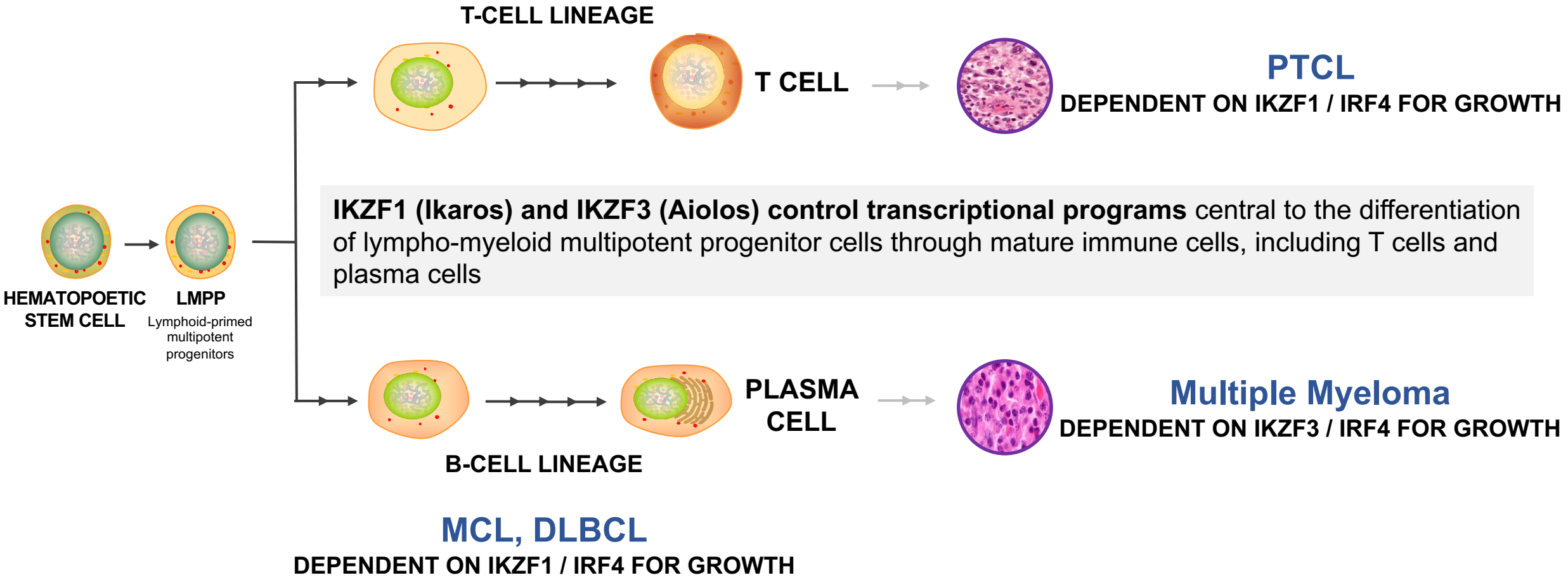

DLBCL, diffuse large B-cell lymphoma; MCL, mantle cell lymphoma; PTCL, peripheral T-cell lymphoma

CFT7455: Potent Small Molecule IKZF1/3 Degrader Optimized for Catalytic & Pharmacologic Properties

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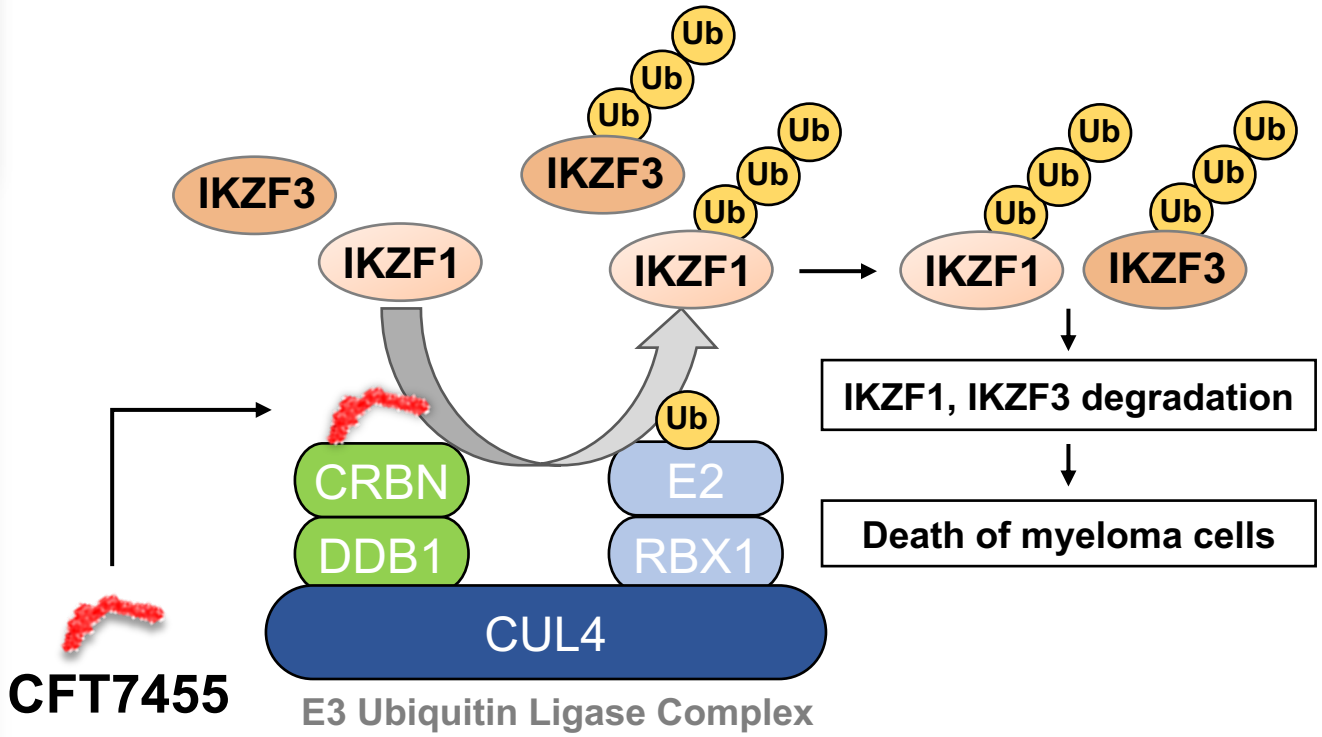
Goal: Develop an IKZF1/3 Monofunctional Degradation Activating Compound (MonoDAC) with these properties:

- 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
- Optimized pharmacologic profile to enable sustained IKZF1/3 degradation



High Catalytic Activity of CFT7455 Improves Anti-Cancer Activity in H929 MM Cells

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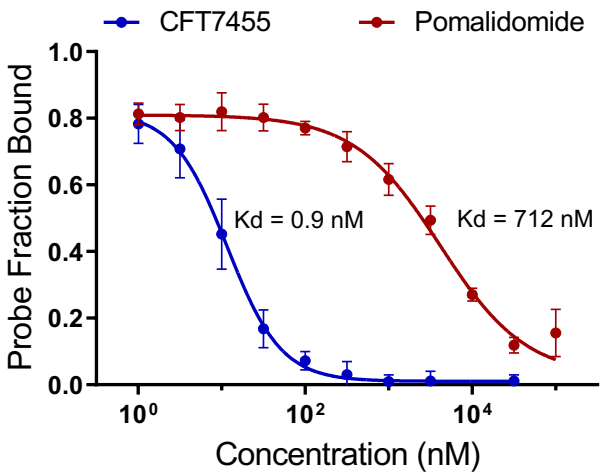
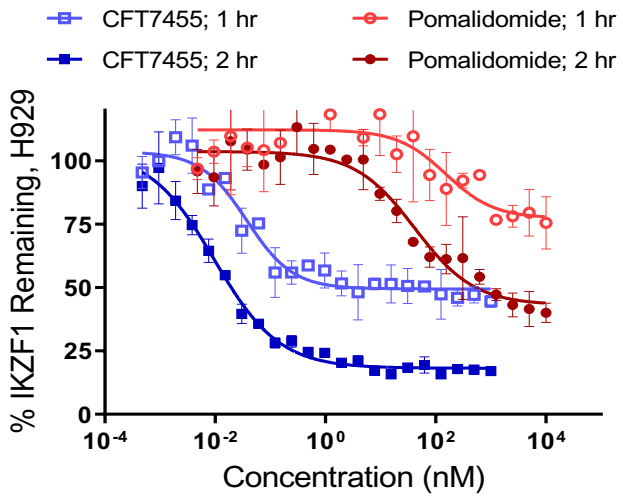
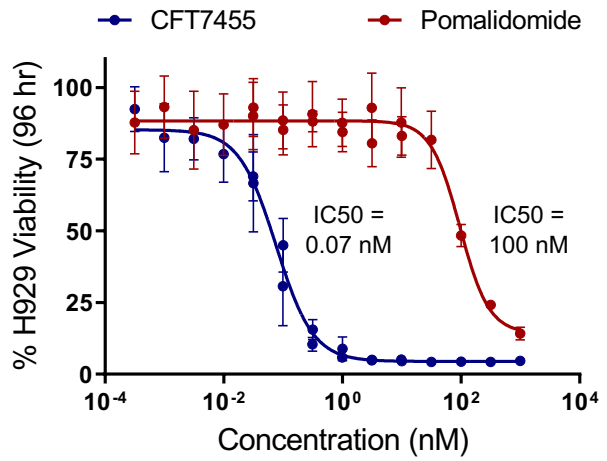
Binding Affinity (FP)



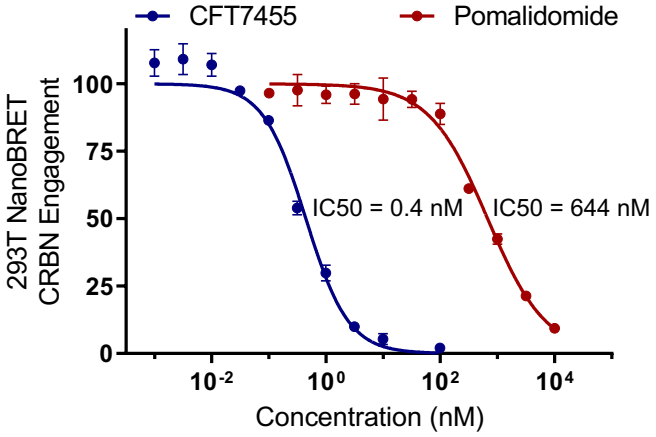
Degradation Kinetics



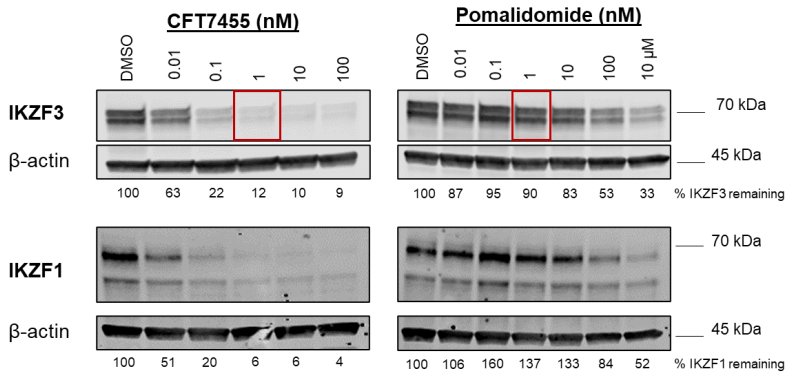
MM Cell Viability



In-Cell CRBN Competition

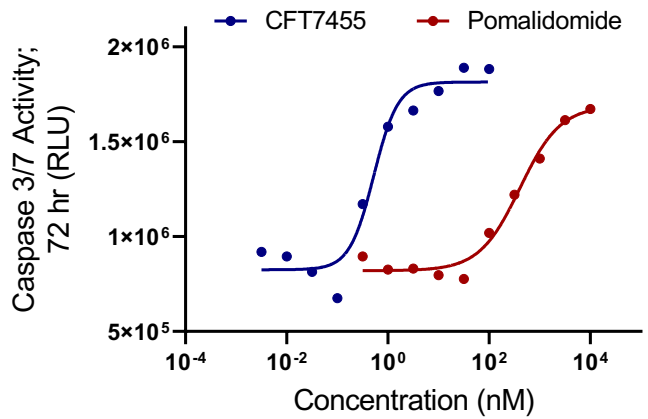


IKZF1/3 Degradation



H929 cells, 4 hr

Apoptosis



FP, fluorescence polarization

CFT7455 Demonstrates High Potency in MM Cell Lines and Xenografts

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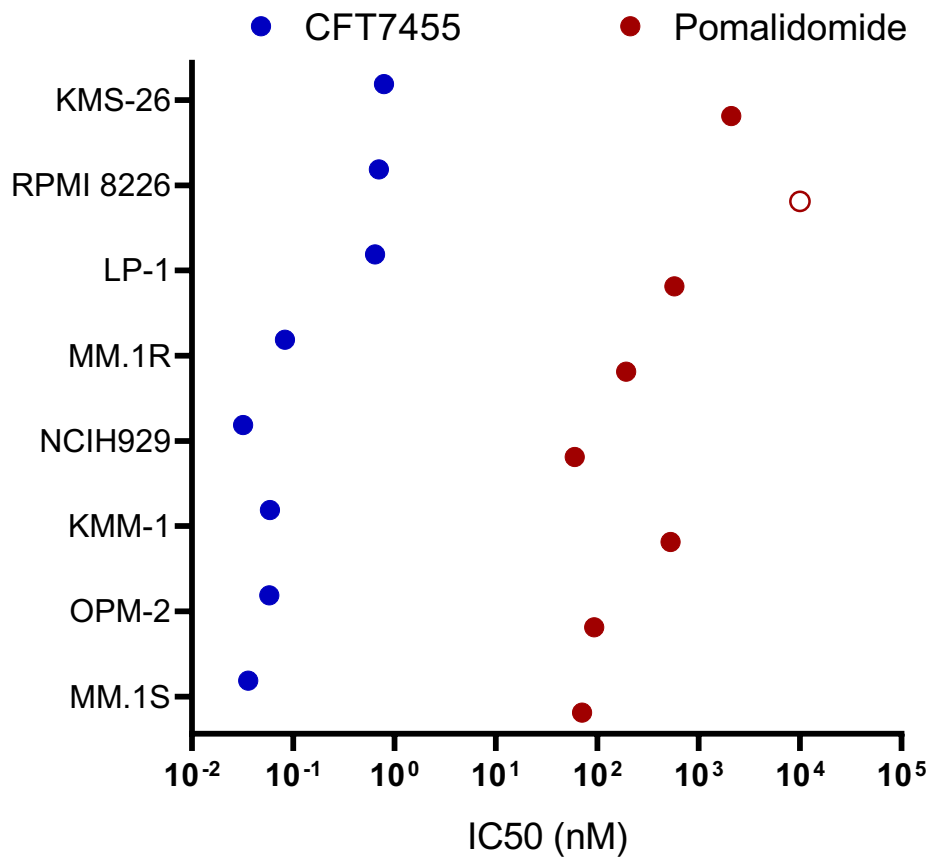
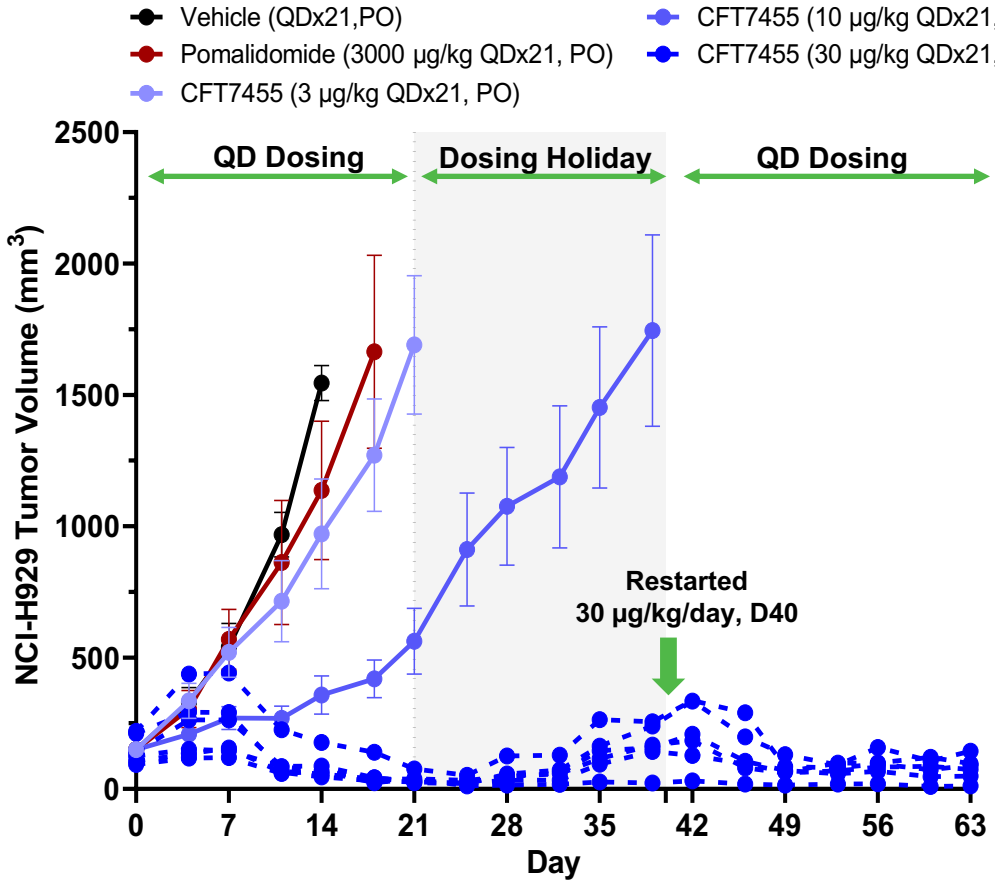
CFT7455 Has Broad Antiproliferative Activity



*Open symbol indicates highest tested concentration at which growth was not inhibited by more than 50%

CFT7455 Promotes Durable Tumor Regression



D, day; QD, once daily

CFT7455 Demonstrates High Potency in MM Cell Lines and Xenografts

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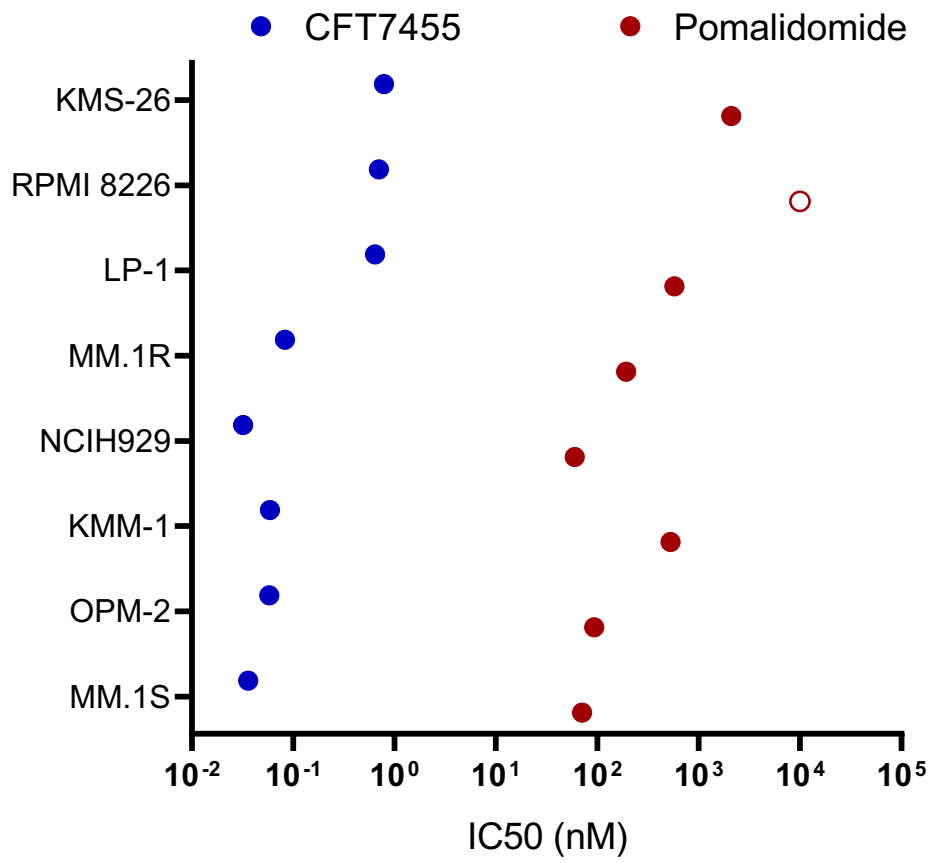
CFT7455 Has Broad Antiproliferative Activity



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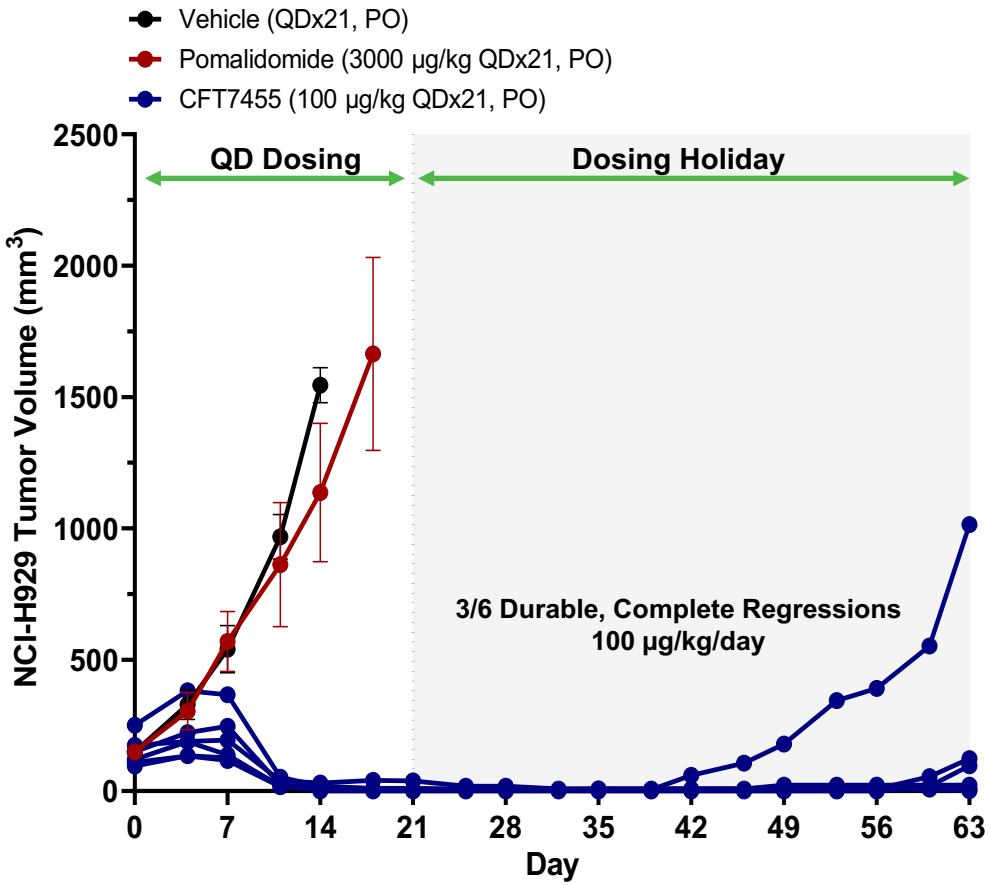
CFT7455 Promotes Durable Tumor Regression



D, day; QD, once daily

Durable CFT7455 Single-Agent Activity in a Systemic MM Tumor Model

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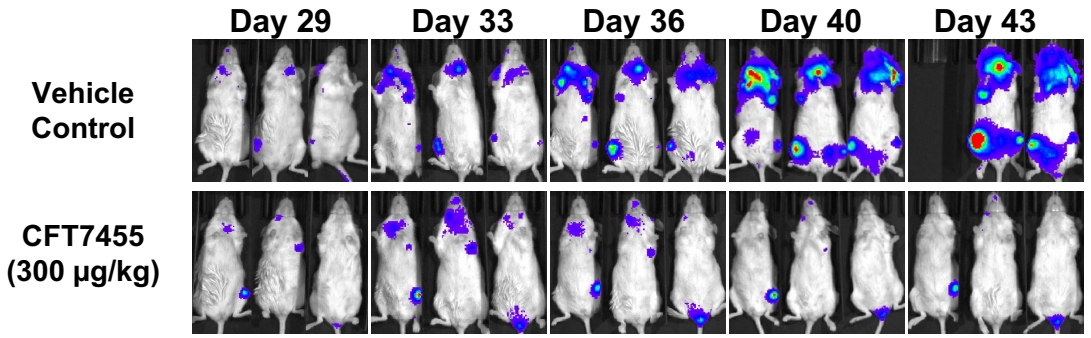
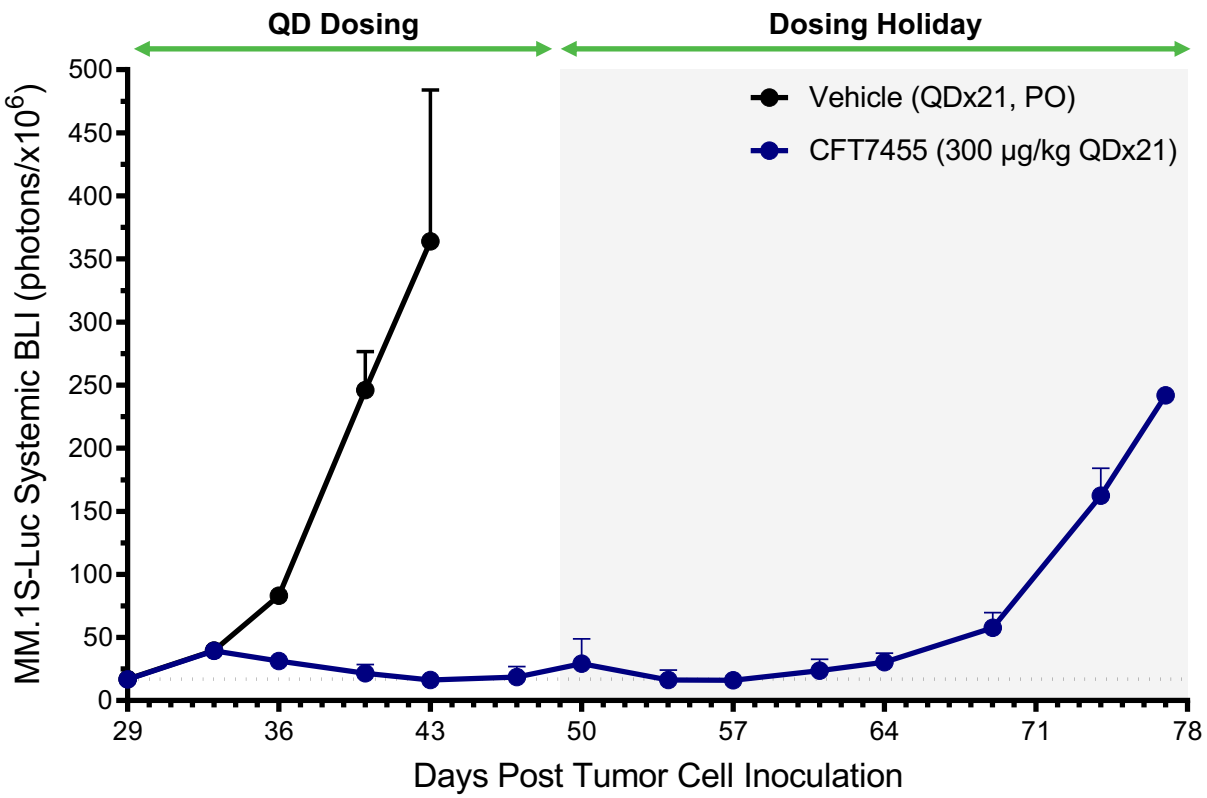
Lower Disease Burden in the MM.1S Model



Early and Stable Regression of Disease



BLI, bioluminescence imaging

Depth and Duration of IKZF3 Degradation Associated with CFT7455 Efficacy

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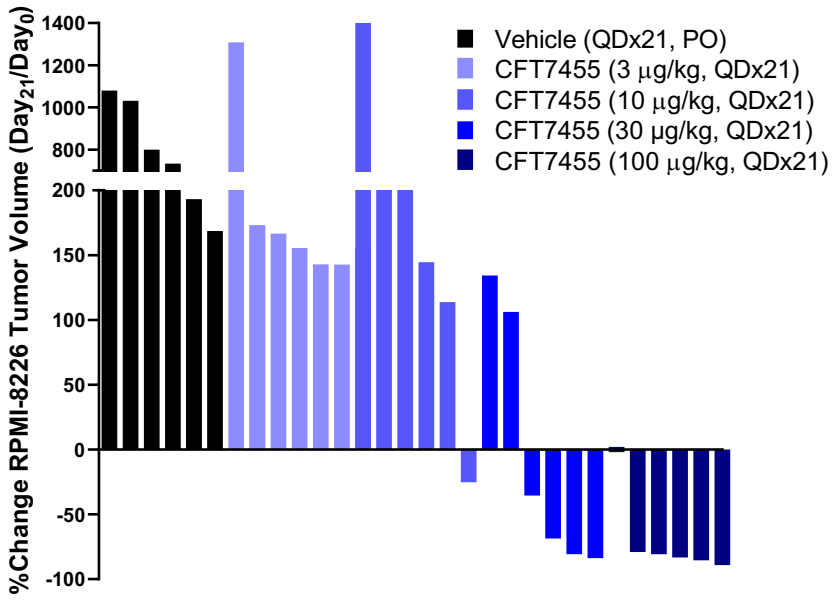
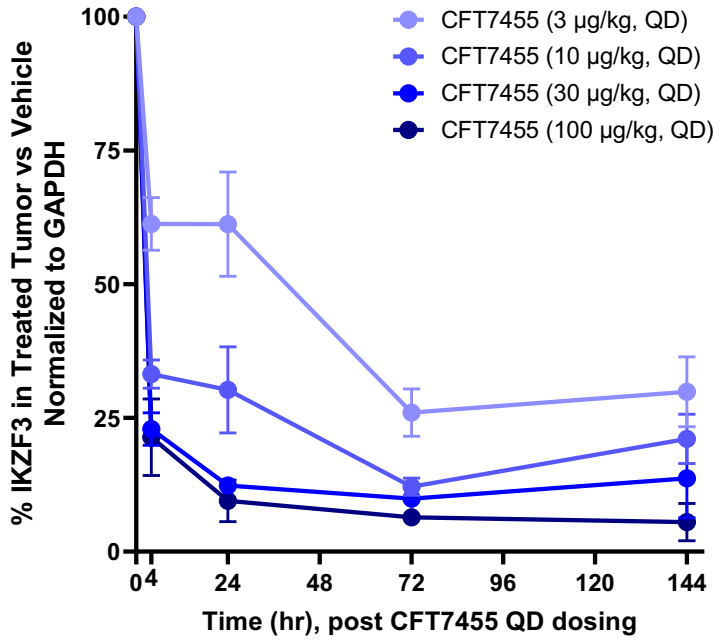
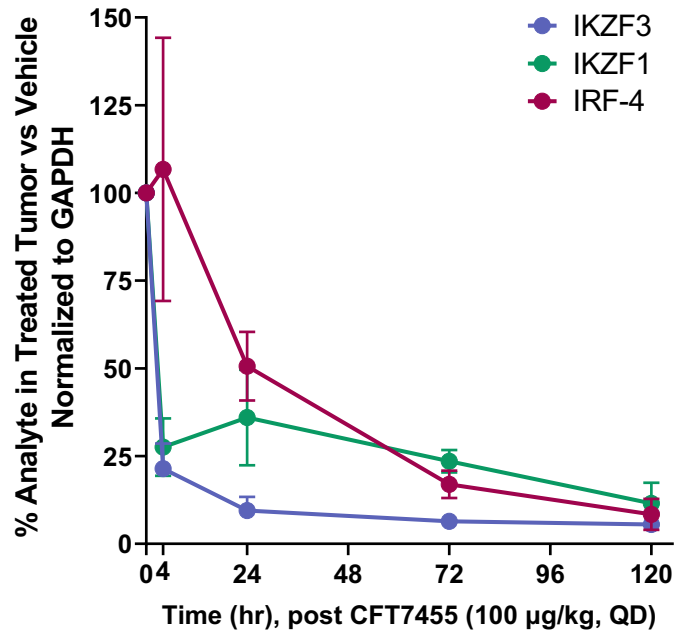
Dose Dependent Efficacy



Dose-Dependent IKZF3 Degradation



Loss of IRF-4 via IKZF1/3 Degradation



CFT7455 is Efficacious in MM Models Resistant or Insensitive to IMiDs

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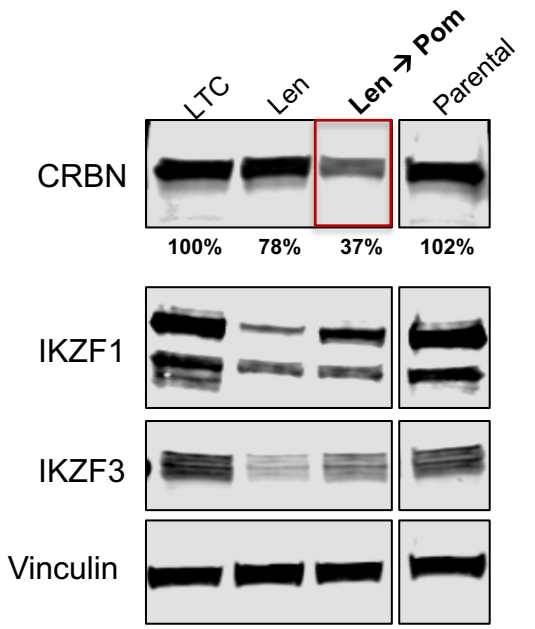
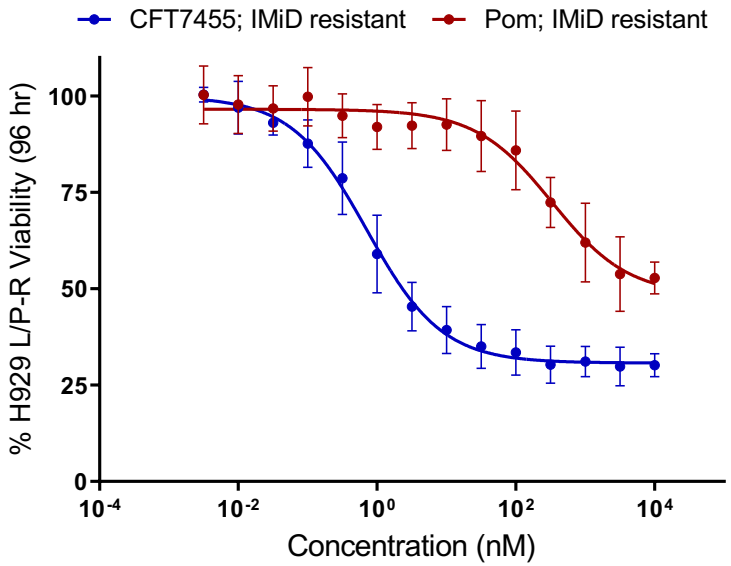
Reduction in CRBN Expression with Chronic IMiD Dosing

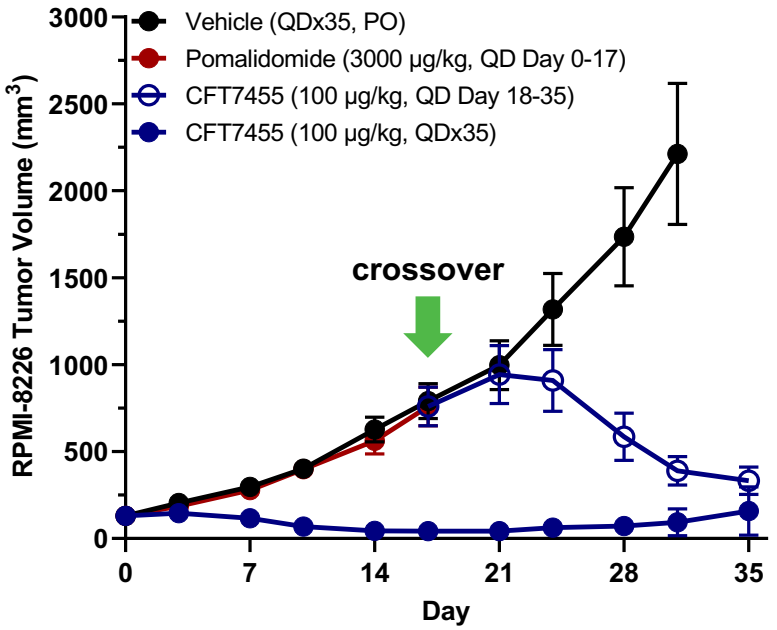


LTC = long term culture in DMSO
Parental = Original, naive H929 cells

CFT7455 Retains Activity in Len- & Pom-Resistant MM Cells



CFT7455 Promotes Regression in Tumors Insensitive to Pom



Len, lenalidomide; L/P-R, Len/Pom-Resistant

Expected Efficacy and Survival Outcomes When CFT7455 is Combined With Dexamethasone

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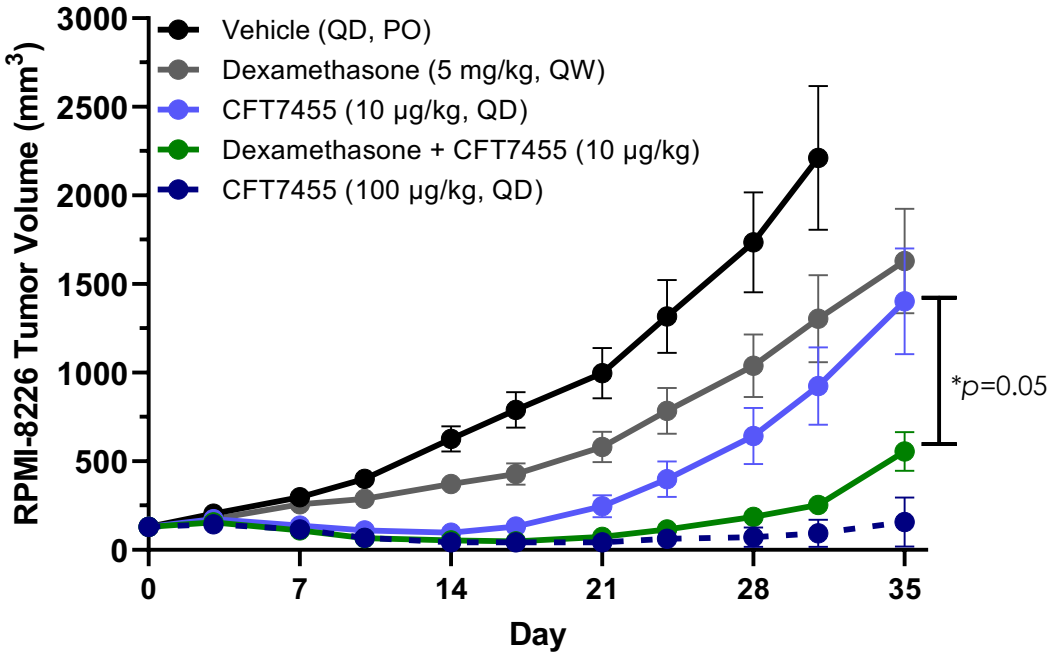
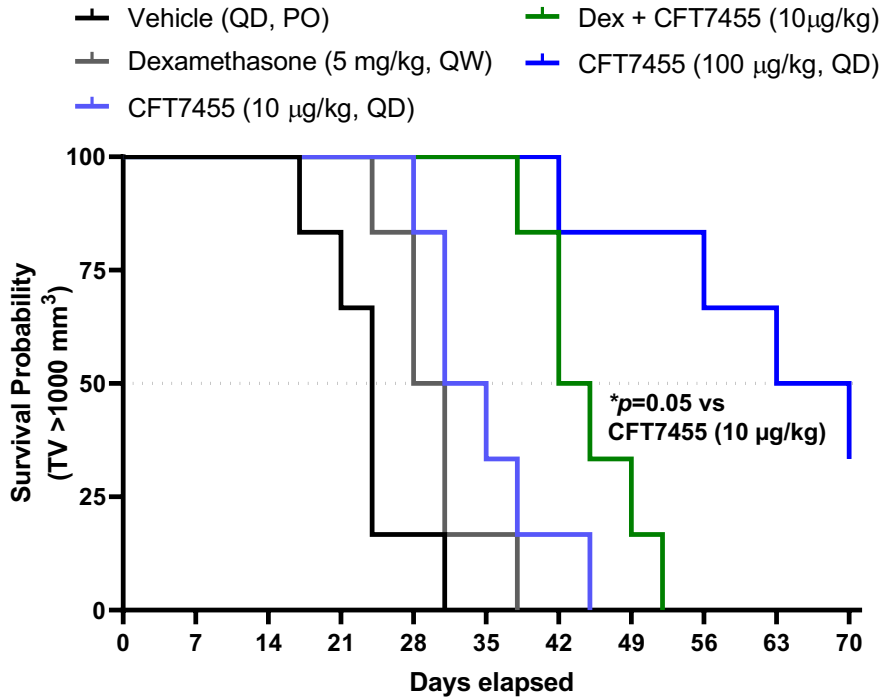
CFT7455 Yields Robust Efficacy as Monotherapy and in Combination with Dexamethasone



Significant Improvement in Survival with CFT7455 + Dexamethasone Combination



Dex, dexamethasone; QW, once weekly

Summary

- In vitro data with CFT7455 demonstrated:
  - High CRBN binding affinity (Kd = 0.9 nM)
  - Rapid, deep degradation of IKZF1/3 that is associated with apoptosis
  - Broad, potent antiproliferative activity in a panel of MM cell lines
- In vivo MM models treated with CFT7455 demonstrated:
  - Regression in multiple treatment-naïve MM tumor models at doses ≥10 µg/kg/day
  - Durable antitumor responses consistent with long-lived pharmacodynamic activity
  - Efficacy in models unresponsive to approved IMiDs
  - Expected efficacy and survival outcomes when combined with dexamethasone
- These encouraging data support the initiation of a first-in-human clinical trial to assess the safety and tolerability of CFT7455 in patients with R/R MM or non-Hodgkin lymphoma (NCT04756726) in the first half of 2021