

## Remodeling and FoxO Activation in Multiple Myeloma

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### Introduction

Mezigdomide (Mezi, CC-92480) is a novel CRBN E3 ligase modulator (CELMoD) agent, that induces rapid and deep degradation of Ikaros and Aiolos, two transcription factors essential for multiple myeloma (MM). Elevated expression of PRC2 complex members, including the histone methyltransferase EZH2, is associated with inferior overall survival in MM. A recent clinical study (NCT05372354) demonstrated promising efficacy using a combination of Mezi, dexamethasone, and Tazemetostat (TAZ), an EZH2 inhibitor, in heavily pretreated MM patients<sup>1,2</sup>.

**Clinical note:** The Overall Response Rate (ORR) was 41% (41/101 pts) with the doublet (Mezi + Dex) and 54% (7/13 pts) with the triplet (Mezi + Dex + TAZ).

However, the molecular mechanisms underlying the impressive clinical activity remain poorly understood. Here, we employed integrated epigenomic and transcriptomic analyses to elucidate cell intrinsic mechanisms of the combination regimen.

### Methods

We evaluated the pharmacological effects of Mezi and TAZ, alone and in combination, across multiple MM cell line models.

- Synergistic cytotoxicity was evaluated using excess over Bliss scores and Incucyte across multiple MM cell lines.
- We utilized multi-omics approaches—including RNA-sequencing, Chromatin Immunoprecipitation sequencing (ChIP-seq) and Assay for Transposase-Accessible Chromatin using sequencing (ATAC-seq) to analyze differential impacts between single and combination treatments across three MM cell lines (36 and 72 hours post compound treatment).
- CRISPR-Cas9 technology was used to generate FoxO3 knockout cell lines to assess the contribution of FoxO signaling to the observed preclinical synergy.

### Results

- Synergistic Cytotoxicity and Transcriptional Reprogramming:
- Mezi showed strong synergy with TAZ in AMO1, U266, KMS12BM cell lines.
- Mezigdomide induced dose-dependent cell killing, reducing viability to below 50% at 0.1-1 nM (Figure 1A).

**Figure 1. Cytotoxic synergy of Mezi and TAZ demonstrated by bliss score and longitudinal cell growth.**

