Cardio-safe Degrader CT-03p Degrades MCL-1 and Overcomes Venetoclax Resistance in AML

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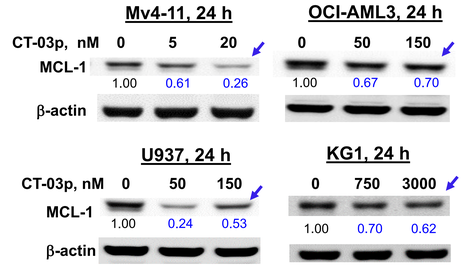
INTRODUCTION

- BCL-2 and MCL-1 are major anti-apoptotic proteins and play critical roles in survival and chemoresistance of AML
- The FDA-approved BCL-2 inhibitor venetoclax (VEN) and hypomethylation agent combinations have greatly improved outcomes in AML but most patients ultimately relapse
- MCL-1 is upregulated by multiple cell survival signaling proteins and is known to play a major role in resistance to BCL-2 inhibition
- MCL-1 also exerts other functions that support leukemia growth and survival including regulating metabolic activities and leukemia-stroma interactions (Carter BZ et al., Haematologica 2022)
- Potent and selective MCL-1 inhibitors were developed in recent years, but did not advance in clinical trials due to potential cardiotoxicity
- CT-03p is a cereblon-based MCL-1 bifunctional degrader with improved permeability, which does not affect non-human primate cardiac function *in vivo* at doses exceeding 100x the dose degrading 50% of MCL-1

AIM

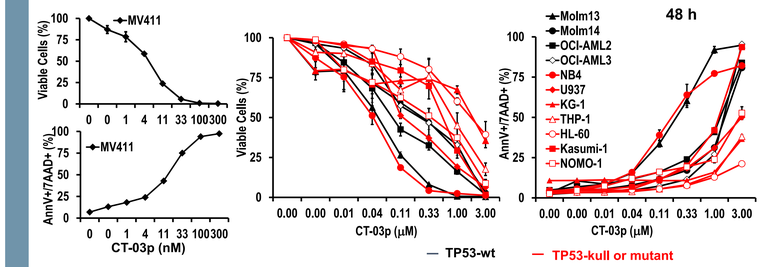
To investigate the activity of cardio-safe MCL-1 degrader CT-03p in AML, including VEN resistant AML

CT-03p Degrades MCL-1 in Leukemia cells

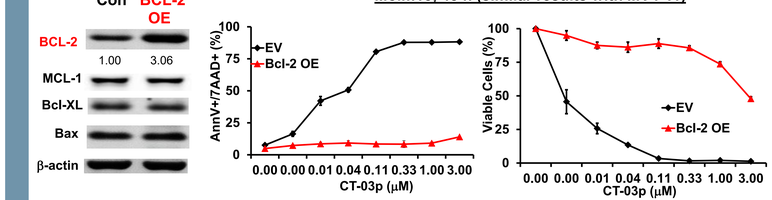


RESULTS

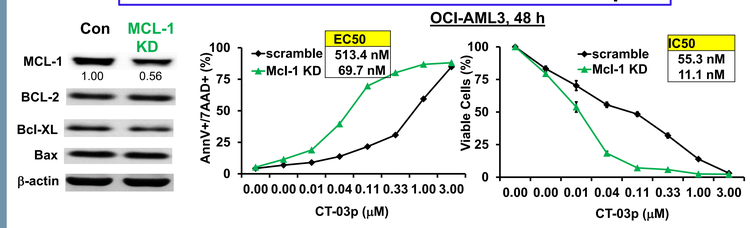
CT-03p Induces Apoptosis in Various Leukemia Cell Lines



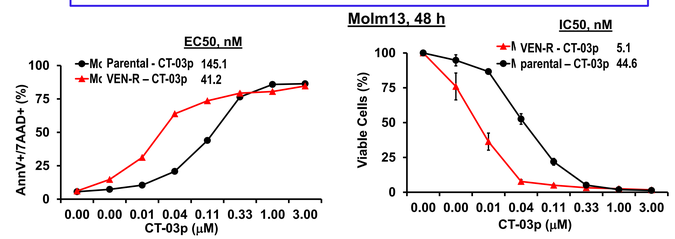
BCL-2 OE Cells Are Highly Resistant to CT-03p



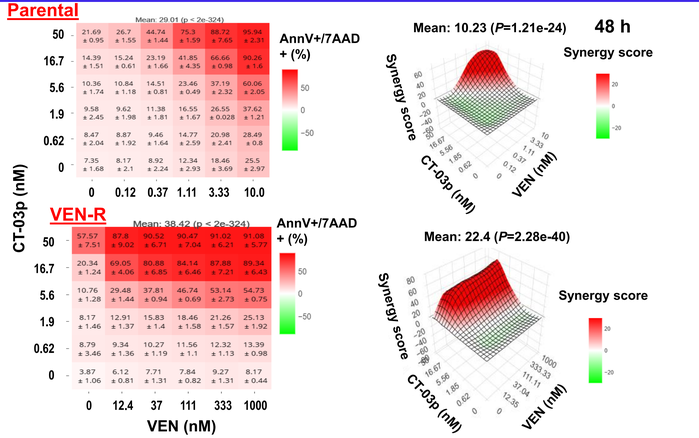
MCL-1 KD Sensitizes AML Cells to CT-03p



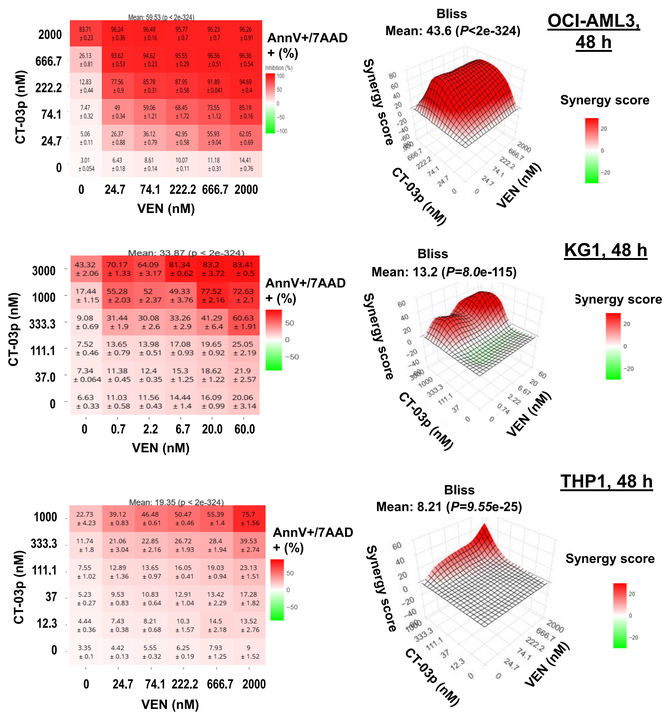
CT-03p Is Highly Active in AML Cells with Acquired Resistance to VEN



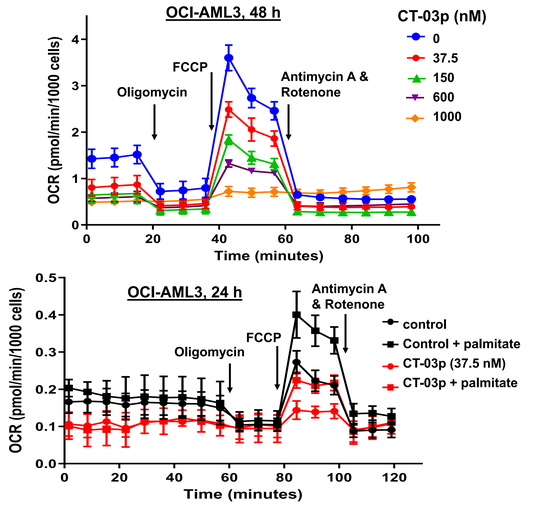
CT-03p Synergizes with VEN in both parental and VEN-R Molm13 Cells



Combination of CT-03p with VEN Is Highly Synergistic in VEN-R OCI-AML3, CT-03p resistant KG1, and VEN and CT-03p resistant THP1 Cells



CT-03p Inhibits Mitochondrial Metabolic Activities: Decreases OXPHOS and FAO



CONCLUSIONS

- CT-03p degrades MCL-1, induces cell death, and decreases viable cells in AML
- The degrader is highly active in AML cells with acquired resistance to VEN
- *TP53* mutation may be a resistance factor for MCL-1 degrader
- BCL-2 is a resistance factor to CT-03p
- The combination of CT-03p and VEN is highly synergistic in AML cells resistant to VEN, CT-03p, or both
- CT-03p inhibits metabolic activities of leukemia cells: reduces oxphos and FAO
- The importance of MCL-1 in AML therapy resistance and the lack of cardiotoxicity of CT-03p warrants future development of this degrader

CONTACT INFORMATION

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