THE SELECTIVE CDK9 INHIBITOR ENITOCICLIB OVERCAME THERAPEUTIC RESISTANCE IN MANTLE CELL LYMPHOMA

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INTRODUCTION

Mantle cell lymphoma (MCL) is an aggressive subtype of non-Hodgkin lymphoma. Even advanced therapies such as BTK inhibitors (BTKi), the BCL2 inhibitor venetoclax, and anti-CD19 CAR-T cells are generally followed by resistance and relapse, creating an urgent need for novel drugs to overcome resistance. CDK9 is a transcriptional regulator that is critical in cancer cell survival and overexpression of oncogenes including MYC and anti-apoptotic proteins including MCL-1. It is overexpressed in tumors after relapse and is thus a promising therapeutic target. Enitociclib is a highly potent and selective CDK9 inhibitor under preclinical and early clinical development. In this study, we assessed the *in vitro* and *in vivo* efficacy of enitociclib (formerly VIP152 and BAY-1125152) in targeting MCL and in overcoming therapeutic resistance using cell line-derived and patient-derived preclinical models.

AIM

To assess the in vitro and in vivo efficacy of CDK9 specific inhibitor enitociclib in targeting MCL and in overcoming therapeutic resistance.

METHODS

- **Single-cell RNA-seq**: to investigate enriched cancer hallmarks in MCL.
- **Cell viability assays**: to assess the *in vitro* efficacy of enitociclib in MCL cell lines
- **Apoptosis assays**: to determine if enitociclib induces apoptosis in MCL cell lines
- **Western blots**: to identify relevant pathways in bypassing resistances.
- **Cell line-derived xenograft and patient-derived xenograft models of MCL**: established in immunodeficient mice and used to monitor tumor growth and thus determine the *in vivo* efficacy of enitociclib

RESULTS

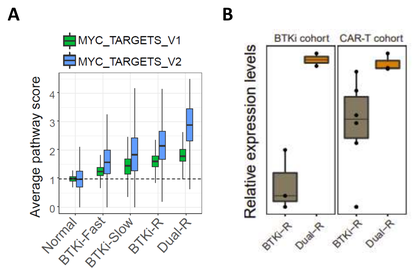
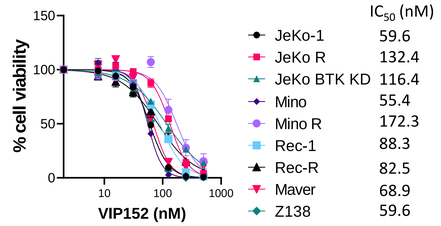


Figure 1. Enrichment of MYC_TARGETS_v1 and MYC upregulation in MCL patients with therapeutic resistance. (**A**) Single-cell RNA sequencing revealed that MYC_TARGETS_v1 is gradually enriched in BTKi-Fast, BTKi-Slow, BTKi-R, and BTKi-CAR-T Dual-R MCL cells. (**B**) CDK9 expression is higher in BTKi-CAR-T Dual-R MCL cells compared to BTKi-R cells.



	IC_{50} (nM)
JeKo-1	59.6
JeKo R	132.4
JeKo BTK KD	116.4
Mino	55.4
Mino R	172.3
Rec-1	88.3
Rec-R	82.5
Maver	68.9
Z138	59.6

Figure 2. CDK9 specific inhibitor enitociclib is potent in killing MCL cells. IC_{50} values were generated in 9 MCL cell lines based on 8-dose 2 cell viability assay.

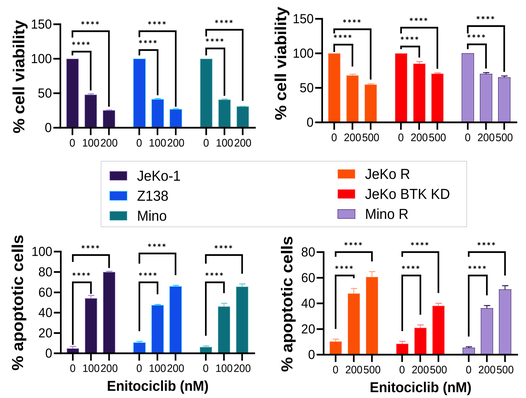


Figure 3. VIP152 inhibits cell viability and induces apoptosis at 24 h post treatment.

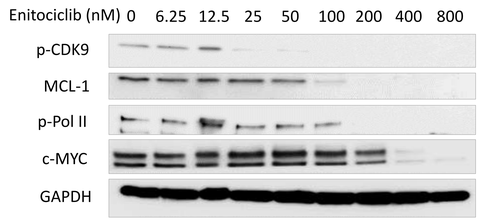


Figure 4. Enitociclib dose-dependently suppressed CDK9 phosphorylation, Pol II phosphorylation, and expression of c-MYC and MCL-1 at 6 hr after treatment.

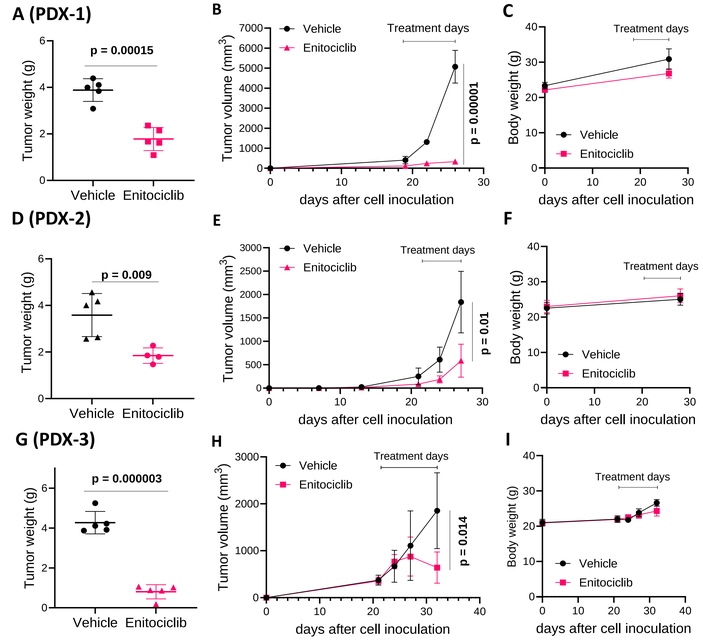


Figure 5. Enitociclib potently inhibited MCL cell growth in MCL patient-derived xenografts (PDX) models in mice. Enitociclib (10 mg/kg, IV, twice a week) effectively inhibited tumor growth in PDX models with ibrutinib resistance (**A-C, PDX-1**), ibrutinib-venetoclax dual resistance (**D-F, PDX-2**), or dual resistance to ibrutinib and CAR-T therapy (**G-I, PDX-3**). Mouse tumors were dissected and weighed (**A, D and G**). Tumor size (**B, E and H**), and mouse body weight (**C, F and I**) are plotted.

CONCLUSIONS

- ✓ Targeting CDK9 with enitociclib led to potent anti-lymphoma activity in vitro and in vivo.
- ✓ Enitociclib induced rapid CDK9 inhibition and a rapid decline in c-MYC, MCL-1, and cyclin D1.
- ✓ Enitociclib potently inhibited tumor growth in PDX models.
- ✓ CDK9 is a promising target for overcoming therapeutic resistance in MCL.

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