The integrated stress activator BTM-3566 overcomes therapeutic resistance in mantle cell lymphoma

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ABSTRACT

Successive generations of BTK inhibitors and CAR T-cell therapy have transformed the treatment of mantle cell lymphoma (MCL). However, treatment resistance has inevitably emerged, creating significant medical need.[1] Recently a novel, clinical stage small molecule, BTM-3566, has been described that targets a mitochondrial process essential for Diffuse Large B-cell lymphoma (DLBCL) survival. BTM-3566 activates the mitochondrial protease OMA1, triggering the ATF4 integrated stress response (ISR).[2] BTM-3566 has robust in vitro efficacy in DLBCL cell lines irrespective of genomic background and elicits complete tumor regression in multiple cell line-derived xenograft (CDX) and patient-derived xenograft (PDX) mouse models of DLBCL. Based on the activity observed in DLBCL, we further explored the effectiveness of BTM-3566 in MCL models *in vitro* and in xenograft mouse models *in vivo*.

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INTRODUCTION

BTM-3566 induced the activation of the mitochondrial protease OMA1, leading to the cleavage of DELE1 and OPA1. OPA1 activation leads to fragmentation of the mitochondrial network. DELE1 cleavage leads to activation of HRI and downstream effector pathways leading to cancer cell death.

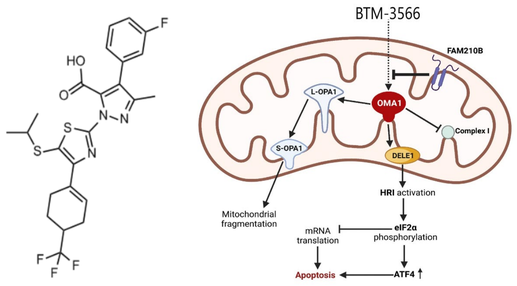

Figure 1. BTM-3566 induces apoptosis via the ISR pathway.

METHODS AND MATERIALS

- The CellTiter-Glo® cell viability assay (Promega) was employed to assess cell viability following a 72-hour treatment.
- Apoptosis inductive effects were measured through Annexin V/PI staining after 24h treatment.
- A JeKo-1 xenograft mouse model and four PDX mouse models, derived from patients exhibiting multiple clinical resistance, were passaged and utilized for *in vivo* screening.

RESULTS

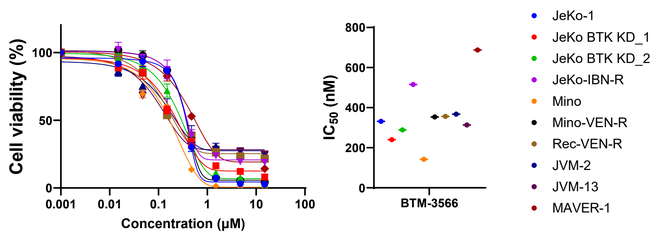

Figure 2. BTM-3566 inhibited cell growth in a panel of MCL cell lines.

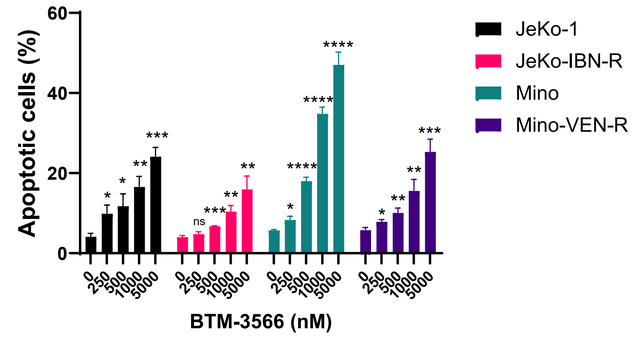

Figure 3. BTM-3566 induced apoptosis in MCL cell lines.
* p <0.1, ** p<0.01, ***P<0.001 and ****p<0.0001

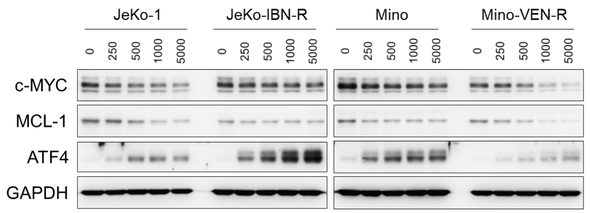

Figure 4. BTM-3566 reduced MCL-1 and c-MYC expression, while increased ATF4 expression after 24h treatment.

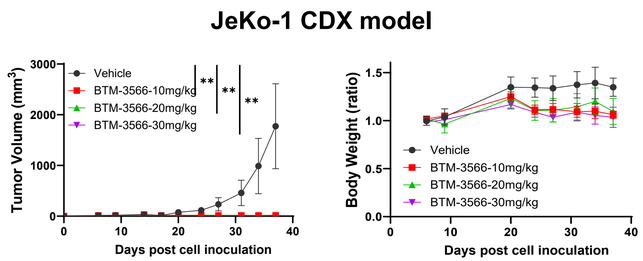

Figure 5. BTM-3566 inhibited tumor growth in JeKo-1 CDX model. ** p<0.01

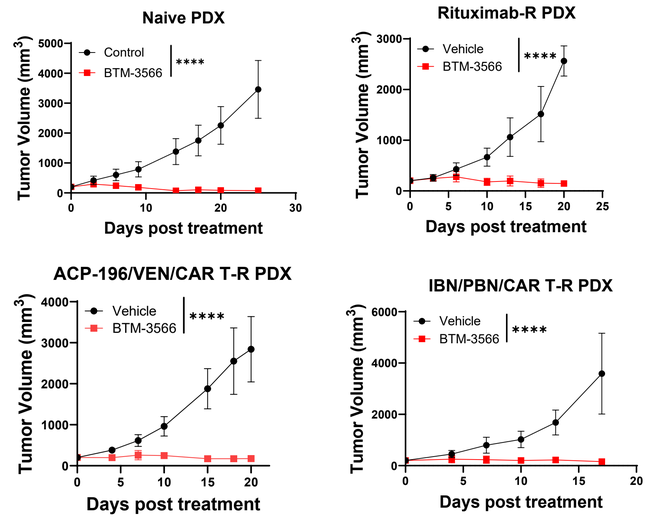

Figure 6. BTM-3566 (20 mg/kg) inhibited tumor growth in MCL PDX mouse models. IBN: ibrutinib; PBN: pirtobrutinib; VEN: venetoclax. ****p<0.0001.

CONCLUSIONS

- BTM-3566 inhibited cell proliferation and induced apoptosis across a panel of MCL cell lines, irrespective of resistance status to ibrutinib and venetoclax.
- BTM-3566 induced dose-dependent reductions in MCL-1 and c-MYC, accompanied by an increase in the transcription factor ATF4, indicative of activation of the stress response.
- BTM-3566 treatment resulted in nearly complete tumor growth inhibition in CDX and therapeutic resistant PDX mouse models.

REFERENCES

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