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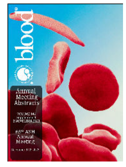

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

604.MOLECULAR PHARMACOLOGY AND DRUG RESISTANCE: MYELOID NEOPLASMS

Direct, Potent, and TP53-Independent Activity of Sting Agonists Against Acute Myeloid Leukaemia Enhances Venetoclax Efficacy *In Vivo*

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Introduction

TP53 mutation occurs in approximately 20% of patients with newly diagnosed acute myeloid leukaemia (AML). Treatment outcomes are universally poor and discovery of new therapies with TP53 independent activity represents an area of very high unmet need. Cyclic GMP-AMP synthase (cGAS) and stimulator of interferon genes (STING) sense cytoplasmic double-stranded DNA to elicit type I interferon production. Direct pharmacologic activation of STING has been investigated in clinical trials with the goal of enhancing immunogenicity. During apoptosis, activated caspases have been shown to suppress activation of the cGAS/STING pathway to render cell death immunologically silent. Whilst the canonical role of STING is stimulation of an inflammatory response, we now show that direct activation of STING by potent and clinically relevant agonists can induce apoptosis directly in cancerous cells by leveraging the high levels of expressed STING in a variety of blood cancers. Importantly, apoptosis induced by STING agonists may be enhanced through combination with diverse BH3-mimetic drugs in a TP53 independent manner (Diepstraten et al, submitted). In this abstract, we highlight the activity of STING agonists in AML and its potential for clinical testing, especially among patients with *TP53* mutated disease.

Methods

We tested the clinically relevant small molecule STING agonist diABZI (purchased from SYNthesis Med Chem), which is currently in early phase clinical trials (NCT03843359, NCT05424380). diABZI was tested alone or in combination with the BCL-2 specific BH3 mimetic drug venetoclax (purchased from Chemgood). Drug sensitivity assays were performed using human AML derived cell lines and primary bone marrow or peripheral blood mononuclear cells from patients with AML or myelodysplastic syndrome with excess blasts 2 (MDS-EB2). Cells were cultured for 48 hours, and cell death assessed by PI or DAPI staining. *In vivo* experiments were conducted by transplanting NOD- *scid*IL2Rgamma ^{null} (NSG) mice with MOLM-13 *TP53* wildtype (WT) or *TP53* knockout(KO) cells. Mice then received either no treatment (control), diABZI alone (1.5 mg/kg intravenously twice a week), venetoclax alone (50 mg/kg orally Monday-Friday), or combination diABZI and venetoclax for two weeks (*n*=5 per treatment arm). Survival analysis was performed using the log-rank (Mantel-Cox) test with Bonferroni correction.

Results

Single agent diABZI was active in 5/6 human AML cell lines tested, including cell lines with *TP53* mutation. Isogenic MOLM-13 *TP53* KO cells demonstrated the same sensitivity as the *TP53* WT parental cells. *BAX/BAK* KO and *STING* KO cell lines were resistant to diABZI, confirming that cell death occurred by apoptosis being dependent on BAX/BAK as well as STING. Combination of diABZI and venetoclax resulted in additive killing in MOLM-13 and OCI-AML3 cells (Bliss scores of 7.62 and 8.06, respectively).

Ex vivo testing was performed on 18 different primary specimens (16 AML and 2 MDS-EB2; 12/18 cases had high risk genetic or clinical features such *TP53* mutation, complex karyotype, secondary disease, or relapse after prior therapy) (Figure 1). Strikingly, diABZI was active as a single agent in 16/18 cases, with marked efficacy in 11 cases (IC_{50} <100 nM). The addition of venetoclax enhanced killing of AML cells, especially in cases resistant to STING agonist alone.

In vivo, diABZI monotherapy and combination therapy with venetoclax was well tolerated without significant weight loss or hematologic toxicity. Treatment with diABZI prolonged survival in the highly aggressive MOLM-13 xenograft model (Figure 2). In both the *TP53* WT and *TP53* KO context, single agent diABZI was superior to single agent venetoclax (p=0.012 and p=0.011, respectively), but survival was most prolonged in mice receiving combination therapy (p=0.013and p=0.012, respectively).

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Conclusion

Activation of STING can exert direct anti-tumour effects in blood cancers via induction of apoptosis. Human AML cells are highly sensitive to the pro-apoptotic effects of STING agonists. The combination of venetoclax and STING agonist shows marked efficacy in *ex vivo* and *in vivo* studies, including in models of *TP53* defective AML. Combining STING agonists with venetoclax represents a highly promising and novel therapeutic approach for AML and should be considered for accelerated early phase clinical trials.

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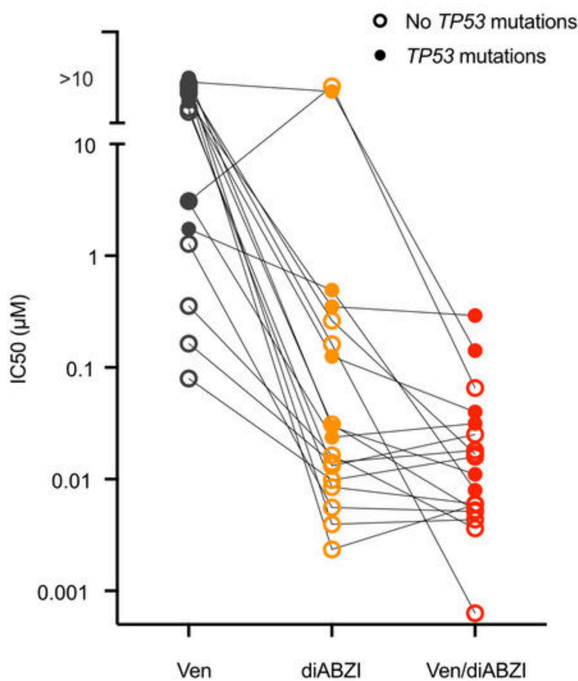

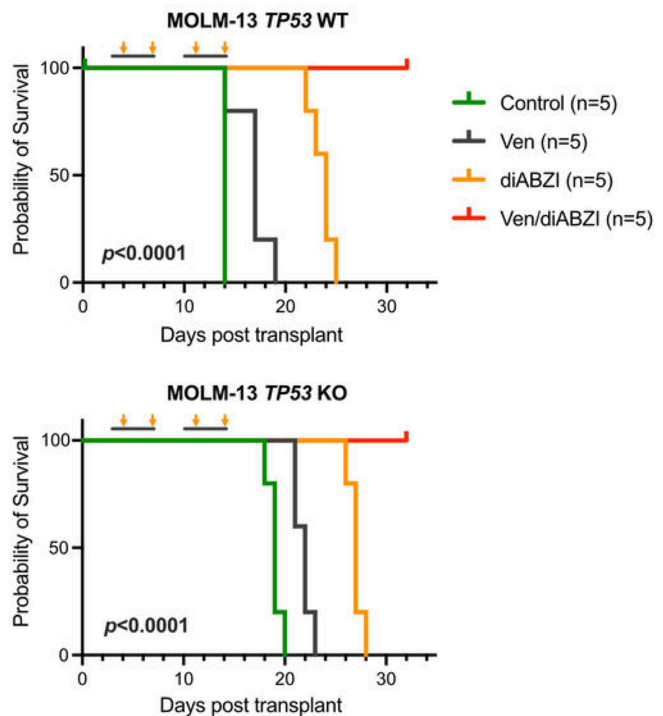

Figure 1

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