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Synergistic activity of BET inhibitor BI 894999 with PLK inhibitor volasertib in AML *in vitro* and *in vivo*

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Abstract

Interactions between a new potent Bromodomain and extraterminal domain (BET) inhibitor BI 894999 and the polo-like kinase (PLK) inhibitor volasertib were studied in acute myeloid leukemia cell lines *in vitro* and in *vivo*. We provide data for the distinct mechanisms of action of these two compounds with a potential utility in AML based on gene expression, cell cycle profile and modulation of PD biomarkers such as MYC and HEXIM1. In contrast to BI 894999, volasertib treatment neither affects MYC nor HEXIM1 expression, but augments and prolongs the decrease of MYC expression caused by BI 894999 treatment. *In vitro* combination of both compounds leads to a decrease in S-Phase and to increased apoptosis. *In vitro* scheduling experiments guided *in vivo* experiments in disseminated AML mouse models. Co-administration of BI 894999 and volasertib dramatically reduces tumor burden accompanied by long-term survival of tumor-bearing mice and eradication of AML cells in mouse bone marrow.

Together, these preclinical findings provide evidence for the strong synergistic effect of BI 894999 and volasertib, warranting future clinical studies in patients with AML to investigate this paradigm.