CANCER RESEARCH

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# Abstract 796: The BTK inhibitor BGB-3111 is synergistic with other anti-lymphoma targeted agents

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## Abstract

Introduction. BGB-3111 is a novel generation irreversible BTK inhibitor (Hu et al AACR2017) under active clinical investigation for lymphoid tumors. Here, we evaluated BGB-3111 in combination with other anti-cancer agents on a panel of human lymphoma cell lines.

Methods. Cell lines derived from activated B cell (ABC) diffuse large B cell lymphoma (DLBCL) (n=3), mantle cell lymphoma (MCL) (n=2) and chronic lymphocytic leukemia (CLL) (n=2) were exposed to increasing doses of BGB-3111 alone and in combination with increasing doses of other compounds (72h). Synergy was assessed with Chou-Talalay combination index (CI): synergism (<0.9), additive (0.9-1.1), antagonism/no benefit (> 1.1). Cell cycle analysis was performed after 24h of treatment.

Results. As single agent BGB-3111 showed anti-tumor activity in the nanomolar range in two ABC-DLBCL (TMD8, IC50 0.4 nM; OCI-LY-10, 1.5 nM) and in one MCL (REC1, IC50 0.9 nM) cell lines, while the remaining four cell lines resulted resistant (IC50s > 5μM). The pattern of activity was similar to what seen with ibrutinib and other 2$^{nd}$ generation BTK inhibitors (Gaudio et al, ENA 2016).

BGB-3111 was then valuated in combination with targeted agents. In ABC-DLBCL, synergism was achieved in 3/3 cell lines when BGB-3111 was combined with the MEK inhibitor pimasertib or with BCL2 inhibitor venetoclax. The

combination with BET inhibitor OTX-015 was synergistic in 2/3 cell lines, while the combination with the XPO1 antagonist selinexor was beneficial in 2/3 (1 synergism, 1 additive).

In CLL cell lines, the best combinations were BGB-3111 with OTX015 or with selinexor with 2/2 synergisms. The results of the combinations with pimasertib or venetoclax were discordant (pimasertib, 1 synergism, 1 no benefit; venetoclax, 1 synergism, 1 no benefit).

Both MCL cell lines achieved synergism combining BGB-3111 with pimasertib, or selinexor, or venetoclax. The combination with OTX-015 was also beneficial, but synergism was observed in only one of the two cell lines, and additive in the remaining.

The improved anti-tumor activity of the combination versus the single agents were confirmed performing cell cycle analysis in an ABC-DLBCL (OCI-LY-10) with an increased subG0 phase when BGB3111 was combined with venetoclax, pimasertib and OTX-015.

Conclusion. BGB-3111 was active as single and the combination with inhibitors of key regulatory pathways in cell lines derived from ABC-DLBCL, CLL and MCL.

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