The BTK inhibitor BGB-3111 is synergistic with other anti-lymphoma targeted agents

Abstract n. 796

Chiara Tarantelli [1], Lu Zhang [2], Elisabetta Curti [1], Filippo Spriano [1], Eugenio Gaudio [1], Luciano Cascione [1], Alberto Arribas [1], Emanuele Zucca [2], Anastasios Stathis [2], Davide Rossi [1,2], Francesco Bertoni [1,2]

[1] Università della Svizzera italiana, Institute of Oncology Research, Bellinzona, Switzerland; [2] Oncology Institute of Southern Switzerland, Bellinzona, Switzerland.

BACKGROUND

BGB-3111 is a 2nd generation irreversible BTK inhibitor (Hu et al AACR2017) under active clinical investigation for lymphoid tumors. We evaluated BGB-3111 in combination with other anti-cancer agents on lymphoma cell lines.

Material and 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)

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) (Table 1). The pattern of activity was similar to what seen with ibrutinib and other 2nd 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 (MK8628/birabresib) 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/MK8628/birabresib 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.

HISTOTYPE	CELL LINE	DRUG	IC50 VALUE (nM)
ABC-DLBCL	TMD8	BGB3111	0.42
ABC-DLBCL	OCI-LY-10	BGB3111	1.53
ABC-DLBCL	SUDHL-2	BGB3111	>5000
MCL	REC1	BGB3111	0.86
MCL	JEKO-1	BGB3111	>5000
CLL	PCL-12	BGB3111	>5000
CLL	MEC-1	BGB3111	>5000

Table 1. Activity of BGB-3111 in lymphoma cell lines. Seven lymphoma cell lines) were exposed to increasing concentrations of BGB-3111 for 72h. IC50 were calculated and showed in the table.

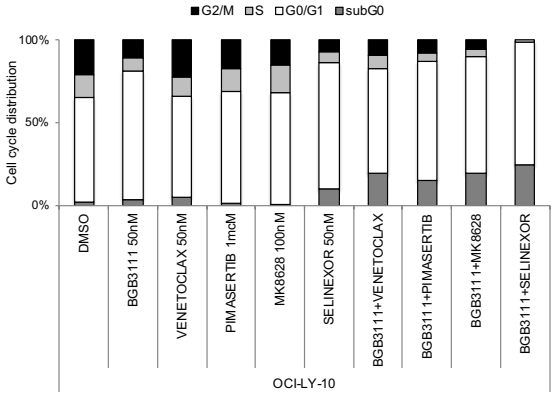

Figure 2. Cell cycle distribution after BGB-3111 as a single or combined with venetoclax, pimasertib and OTX015 at specific concentrations in OCI-LY-10 cell line (24h).

CONCLUSIONS

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.

CONTACT

Francesco Bertoni, Institute of Oncology Research, via Vela 6, 6500 Bellinzona, Switzerland; phone: +41918200367; e-mail: frbertoni@mac.com

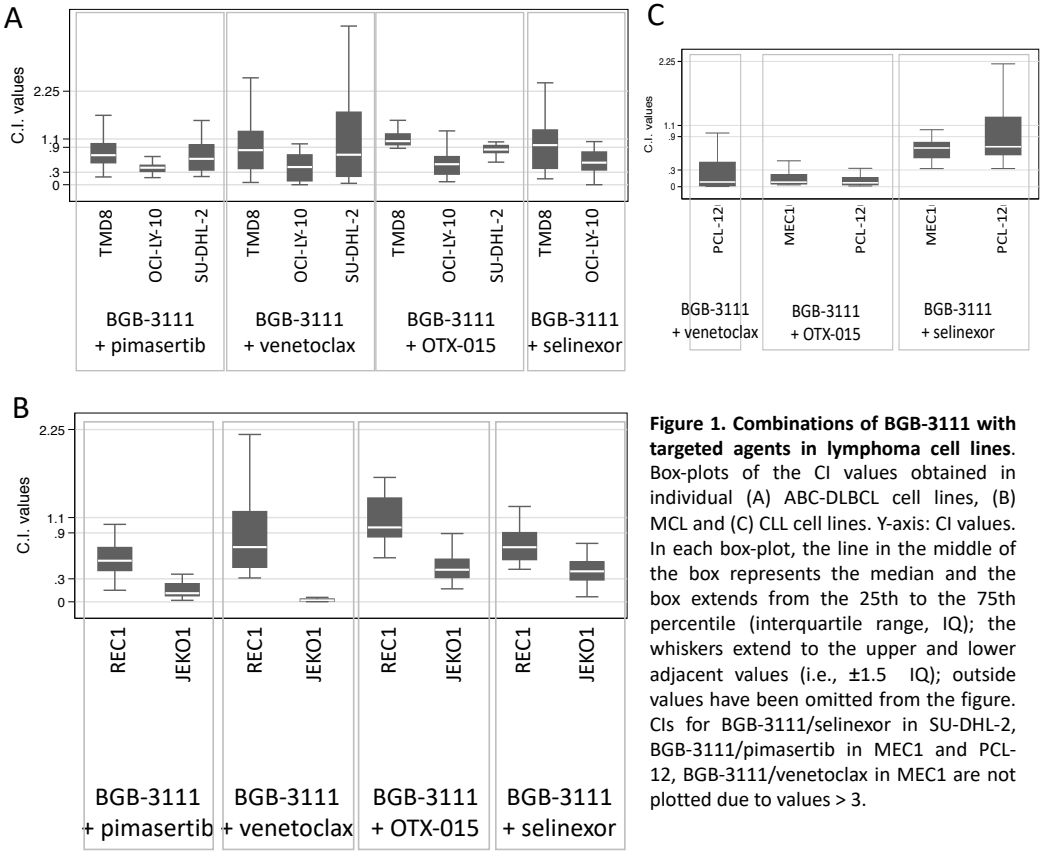

Figure 1. Combinations of BGB-3111 with targeted agents in lymphoma cell lines. Box-plots of the CI values obtained in individual (A) ABC-DLBCL cell lines, (B) MCL and (C) CLL cell lines. Y-axis: CI values. In each box-plot, the line in the middle of the box represents the median and the box extends from the 25th to the 75th percentile (interquartile range, IQ); the whiskers extend to the upper and lower adjacent values (i.e., ±1.5 IQ); outside values have been omitted from the figure. CIs for BGB-3111/selinexor in SU-DHL-2, BGB-3111/pimasertib in MEC1 and PCL-12, BGB-3111/venetoclax in MEC1 are not plotted due to values > 3.