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The BTK-degrader BGB-16673 and the BCL2-inhibitor sonrotoclax are active as single agents and in combination in marginal zone lymphoma models

Alberto J. Arribas [1,2], Elisa Civanelli [1], Camilla Scalise [1], Luciano Cascione [1,2], Andrea Rinaldi [1], Davide Rossi [1,3], Emanuele Zucca [1,3], Francesco Bertoni [1,3].

[1] Institute of Oncology Research, Faculty of Biomedical Sciences, USI, Bellinzona, Switzerland; [2] SIB Swiss Institute of Bioinformatics, Lausanne, Switzerland; [3] Oncology Institute of Southern Switzerland, Ente Ospedaliero Cantonale, Bellinzona, Switzerland.

1 - BACKGROUND

Targeting the B cell receptor signaling with BTK and PI3K inhibitors (i) is efficacious in treating patients with lymphoid tumors, including marginal zone lymphoma (MZL). Unfortunately, resistance occurs, indicating the need for combinations and novel approaches. BGB-16673 (BTK-d) is a first-in-class cereblon-mediated BTK degrader currently in phase 1 in refractory/relapsed B-cell lymphoma. Here, we assessed BTK-d in MZL models as a single agent and in combination with clinically relevant compounds to provide the rationale for future trials.

2 - METHODS

Cell viability was assessed by MTT assay after 5 days of exposure to increasing concentrations of drugs or DMSO (control) in six MZL models and in resistant derivatives to PI3K-i, BTK-i and BCL2-i (n.=7). Analyses included apoptosis and cell cycle analyses, immunoblotting, and RNA-Seq.

4 - CONCLUSION

Its ability to degrade BTK, combined with its synergy with other targeted therapies, positions BTK-d as a promising candidate for further development in MZL patients. The 2nd generation BCL2-i sonrotoclax appears as another drug to be explored in the same patient populations, possibly combining the two molecules.

Contacts:
Francesco Bertoni, Institute of Oncology Research, Bellinzona, Switzerland; e-mail: francesco.bertoni@ior.usi.ch.

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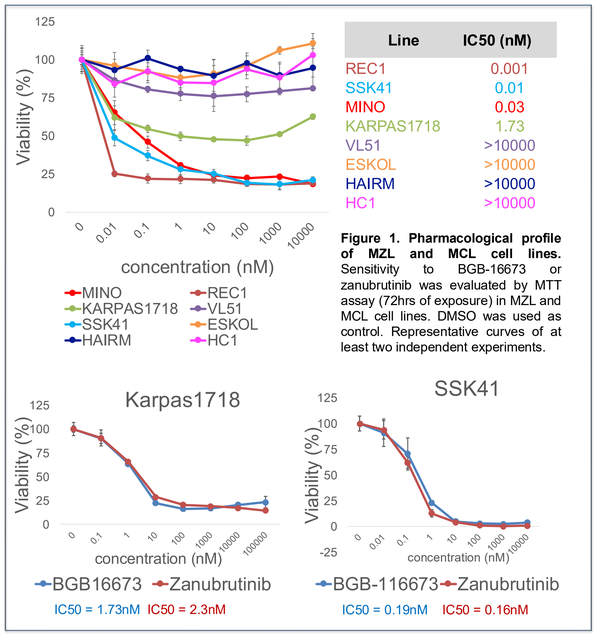
3 - RESULTS

Six MZL cell lines (SSK41, Karpas1718, VL51, HC1, HAIRM, and ESKOL), and two mantle cell lymphoma (MCL, as positive control for response to BTK-targeted agents) were treated with the BTK degrader BGB-16673 at a concentration of up to 10µM. The BTK degrader was very active in 2 models (SSK41, IC50=0.1 nM; Karpas1718, 1.7 nM). VL51 achieved a maximal reduction in proliferation of 25% at 10 nM. Less than 20% of the reduction was observed in HC1, HAIRM and ESKOL (Figure 1 top). The activity of BGB-16673 did not differ from the BTK inhibitor zanubrutinib (Figure 1 bottom) and, accordingly, was limited in cells resistant to ibrutinib (n.=2), idelalisib (n.=2), copanlisib (n.=1), and copanlisib/venetoclax (n.=2) (Figure 2). BGB-16673 induced apoptosis and cell cycle arrest in sensitive Karpas1718 and SSK41. It importantly inhibited p-BTK(Tyr223) and decreased total BTK protein levels in all six cell lines (Figure 3).
RNA-Seq was performed on Karpas1718 exposed to BGB-16673, zanubrutinib or DMSO. Both molecules down-regulated the BCR-TLR-NF-κB signaling pathway, MYC target genes, and upregulated genes involved in DNA damage. Oxidative phosphorylation, commonly associated with resistance to multiple therapies, was repressed by BGB-16673 but upregulated by zanubrutinib (Figure 4).
BTK-d was combined with conventional and targeted agents. Combination with BTK-d improved the activity of single agents, with synergism with BCL2-i (venetoclax, sonrotoclax), lenalidomide, and rituximab (Figure 5). BTK-d exposure was associated with down-regulation of BCL-XL and MCL1. Combination of sonrotoclax with BGB-16673 induces apoptosis and is cytotoxic in MZL models *in vitro* (Figure 6). Notably, the new BCL2-i sonrotoclax was over ten times more active than venetoclax in HC1 and K1718 and equally active in the remaining two SSK41 and VL51 (Figure 7).



Line	IC50 (nM)
REC1	0.001
SSK41	0.01
MINO	0.03
KARPAS1718	1.73
VL51	>10000
ESKOL	>10000
HAIRM	>10000
HC1	>10000

Figure 1. Pharmacological profile of MZL and MCL cell lines. Sensitivity to BGB-16673 or zanubrutinib was evaluated by MTT assay (72hrs of exposure) in MZL and MCL cell lines. DMSO was used as control. Representative curves of at least two independent experiments.

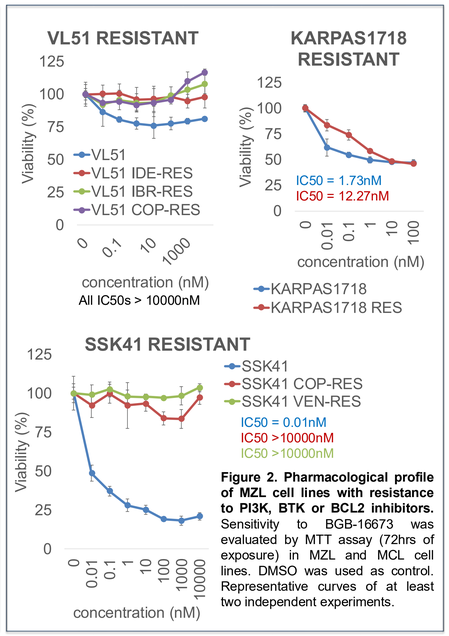


Figure 2. Pharmacological profile of MZL cell lines with resistance to PI3K, BTK or BCL2 inhibitors. Sensitivity to BGB-16673 was evaluated by MTT assay (72hrs of exposure) in MZL and MCL cell lines. DMSO was used as control. Representative curves of at least two independent experiments.

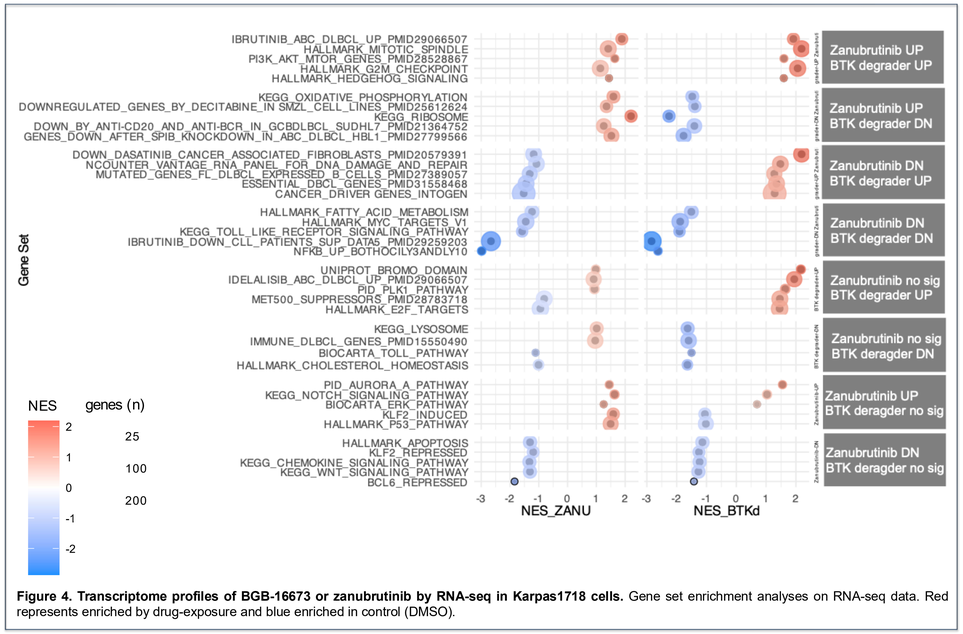


Figure 4. Transcriptome profiles of BGB-16673 or zanubrutinib by RNA-seq in Karpas1718 cells. Gene set enrichment analyses on RNA-seq data. Red represents enriched by drug-exposure and blue enriched in control (DMSO).

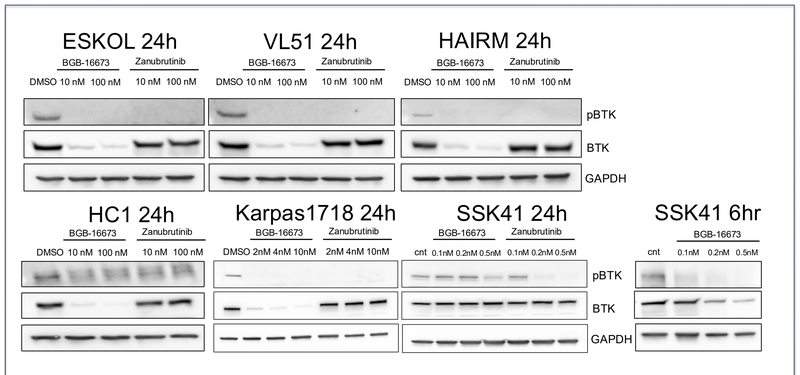


Figure 4. pBTK/BTK expression by immunoblotting in MZL cell lines. Protein expression of phospho (p-) and total BTK upon BGB-16673 or zanubrutinib upon 6 or 72 hours in MZL cell lines. GAPDH was used as a housekeeping gene.

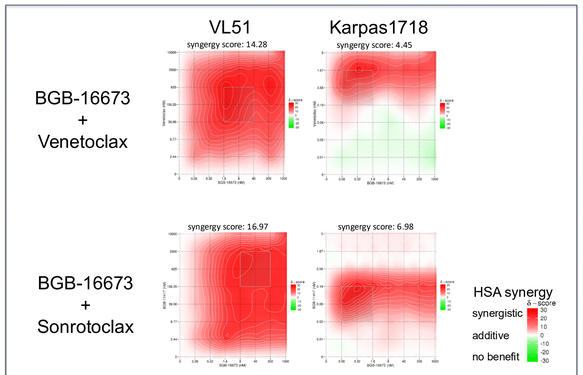


Figure 5. Combination of BGB-16673 and BCL2 inhibitors. VL51 and Karpas1718 cells were exposed BGB-16673 in combination with venentocax or sonrotoclax (72 hrs, MTT assay). Synergy was evaluated by the Highset Single Agent /(HSA) model in the SynergyFinder online tool.

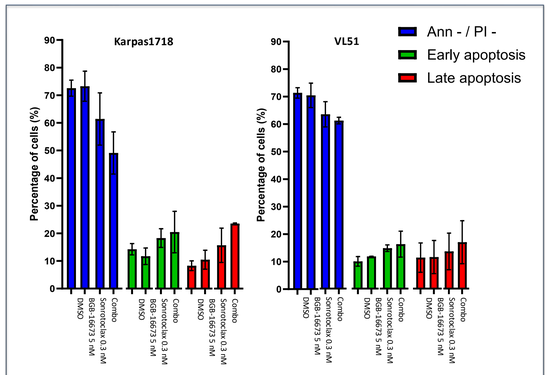


Figure 6. Apoptosis assay in Karpas1718 and VL51 cells. Cells were exposed to BGB-16673, sonrotoclax, as single agents or in combination for 24hr. Apoptosis and necrosis was evaluated by flow cytometry upon Annexin-V (FITC) and PI staining respectively. Representative results of two independent experiments.

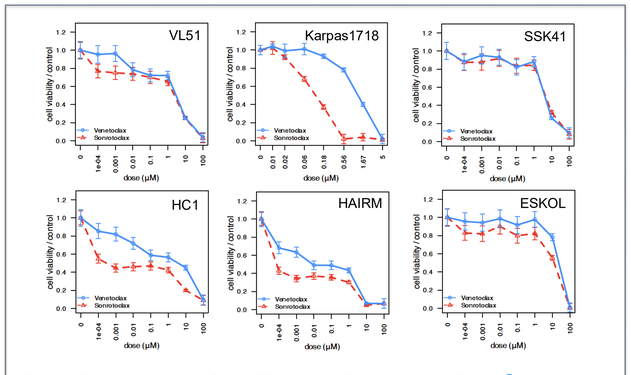


Figure 7. Pharmacological profile of MZL cell lines. Sensitivity to the BCL2 inhibitors venetoclax (blue) or sonrotoclax (red) was evaluated by MTT assay (72hrs of exposure) in MZL cell lines. DMSO was used as control. Representative curves of at least two independent experiments.