GZ17-6.02 with proteasome inhibitors kills multiple myeloma cells

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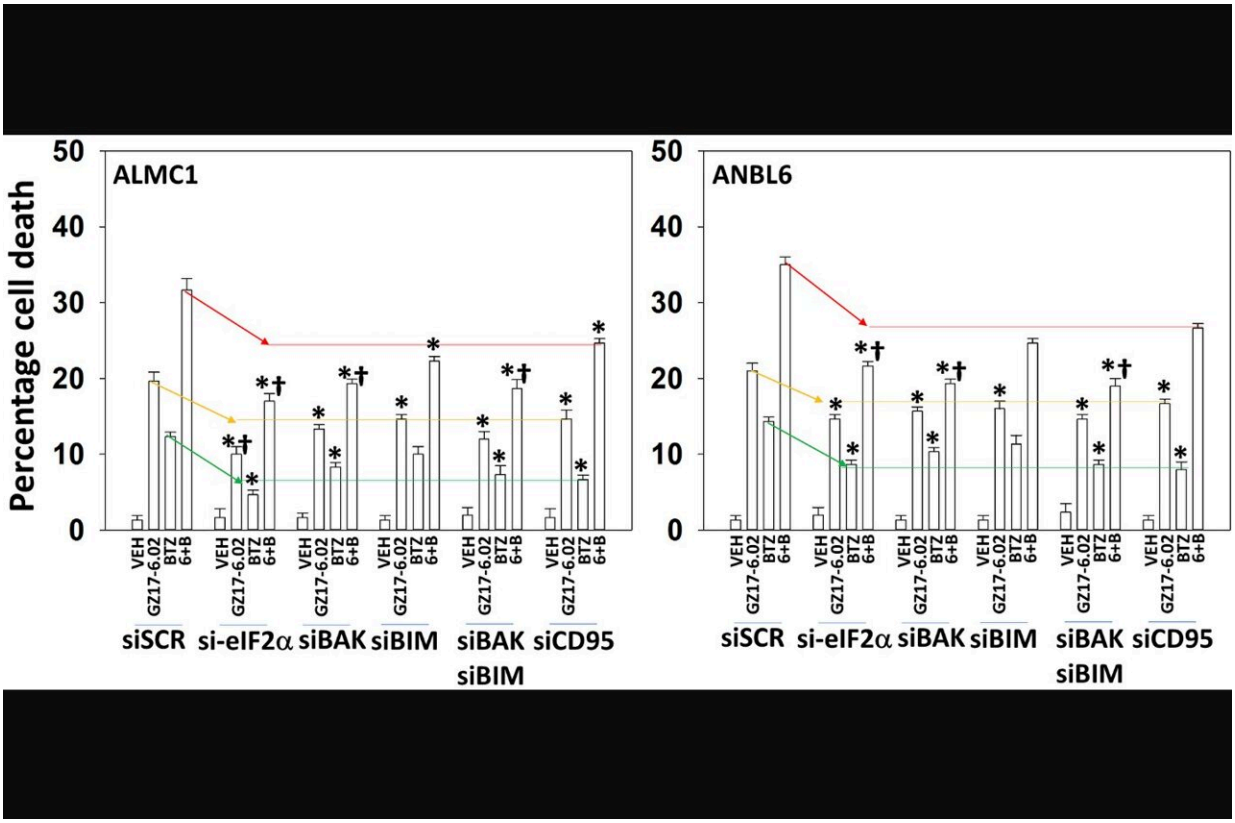

ER stress signaling plays an important role in mediating GZ17-6.02/bortezomib lethality. Credit: *Oncotarget* (2024). DOI: 10.18632/oncotarget.28558

A new research paper titled "GZ17-6.02 interacts with proteasome inhibitors to kill multiple myeloma cells" has been published in

Oncotarget.

In this new study, researchers Laurence Booth, Jane L. Roberts, Cameron West, and Paul Dent from Virginia Commonwealth University and Genzada Pharmaceuticals investigated GZ17-6.02, a synthetically manufactured compound containing isovanillin, harmine and curcumin, in multiple myeloma cells. GZ17-6.02 has undergone phase I evaluation in patients with solid tumors with a recommended phase 2 dose (RP2D) of 375 mg PO BID. GZ17-6.02 was more efficacious as a single agent at killing multiple myeloma cells than had previously been observed in solid tumor cell types.

"GZ17-6.02 interacted with proteasome inhibitors in a greater than additive fashion to kill myeloma cells and alone it killed inhibitor-resistant cells to a similar extent," the researchers note.

The drug combination of GZ17-6.02 and bortezomib activated ATM, the AMPK and PERK and inactivated ULK1, mTORC1, eIF2α, NFκB and the Hippo pathway. The combination increased ATG13 S318 phosphorylation and the expression of Beclin1, ATG5, BAK and BIM, and reduced the levels of BCL-XL and MCL1. GZ17-6.02 interacted with bortezomib to enhance autophagosome formation and autophagic flux, and knock down of ATM, AMPKα, ULK1, Beclin1 or ATG5 significantly reduced both autophagy and tumor cell killing. Knockdown of BAK and BIM significantly reduced tumor cell killing.

The expression of HDACs1/2/3 was significantly reduced beyond that previously observed in solid tumor cells and required autophagy. This was associated with increased acetylation and methylation of histone H3. Combined knockdown of HDACs1/2/3 caused activation of ATM and the AMPK and caused inactivation of ULK1, mTORC1, NFκB and the Hippo pathway. HDAC knockdown also enhanced ATG13 phosphorylation, increased BAK levels and reduced those of BCL-XL.

"Collectively, our present studies support performing additional in vivo studies with multiple myeloma cells," the researchers conclude.

More information: Laurence Booth et al, GZ17-6.02 interacts with proteasome inhibitors to kill multiple myeloma cells, *Oncotarget* (2024). DOI: 10.18632/oncotarget.28558

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