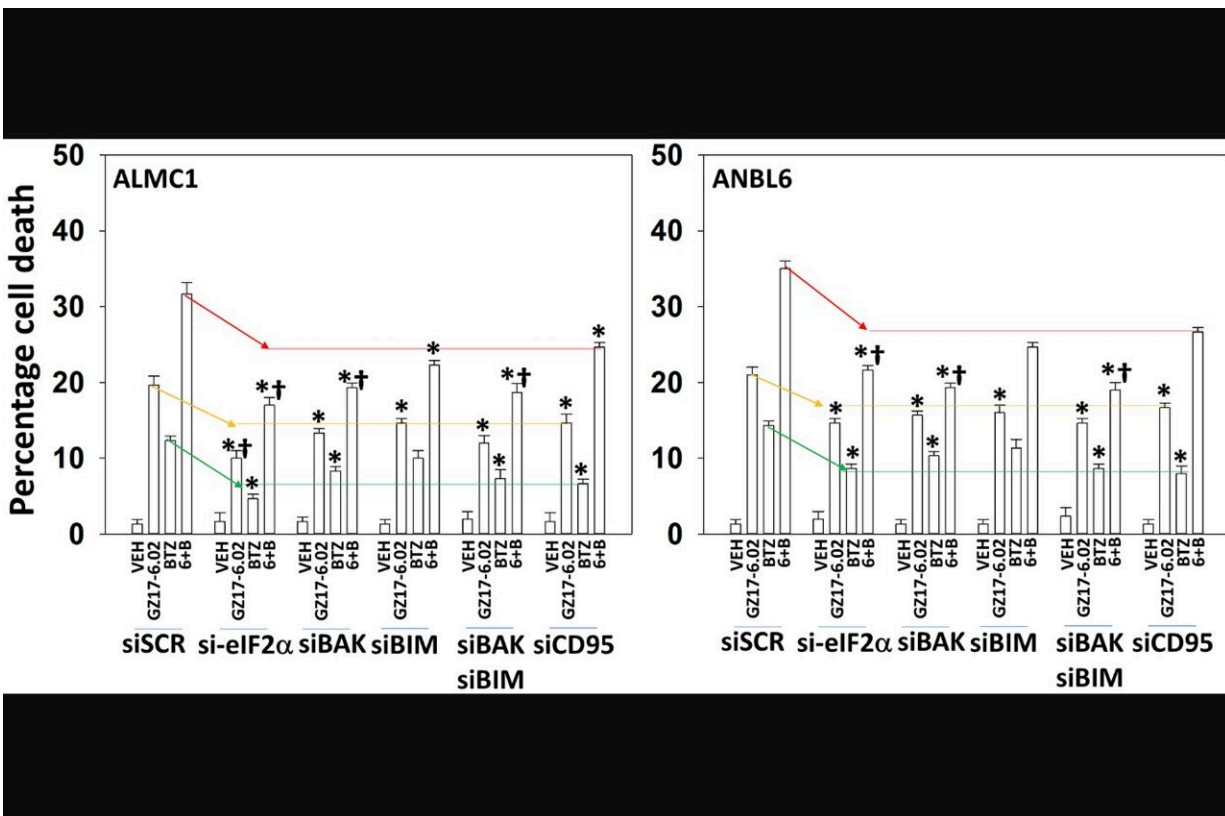


GZ17-6.02 with proteasome inhibitors kills multiple myeloma cells

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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, eIF2 α , NF κ B 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, AMPK α , 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, NF κ B 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](https://doi.org/10.18632/oncotarget.28558)

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