

Experimental drug combined with radiation kills brain tumors in pre-clinical studies

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A new study led by scientists at VCU Massey Cancer Center has shown that an experimental drug known as AZ32 selectively sensitizes brain tumors to radiation and significantly extends the survival of mouse models with human glioblastoma multiforme (GBM), the most common

and deadly form of brain cancer. Published in the journal *Molecular Cancer Therapeutics*, the study builds on the research of principal investigator Kristoffer Valerie, Ph.D., and has paved the way for a phase 1 clinical trial testing a similar but more effective experimental drug, AZ1390, in combination with radiation therapy for the treatment of brain cancer. An accompanying study on AZ1390 that Valerie co-authored was recently published in *Science Advances*.

AZ32 is a member of a family of compounds referred to as ATM kinase inhibitors. ATM, or ataxia telangiectasia mutated, is an enzyme that facilitates repair of DNA damage in cells. Radiation therapy is first-line treatment for GBM; however, glioma stem cells are often able to resist DNA damage caused by radiation. By inhibiting ATM, AZ32 was shown to disrupt the process by which brain [cancer](#) cells resist radiation while sparing and potentially protecting healthy brain tissue.

"In 2009 and 2013, we were the first to show that an ATM kinase inhibitor could make [brain cancer](#) cells and tumors sensitive to radiation," says Valerie, a member of the Developmental Therapeutics research program at Massey, in reference to his prior research published in *Molecular Cancer Therapeutics and Clinical Cancer Research*. "This time with AZ32, we used an ATM kinase inhibitor that penetrates the blood-brain barrier. The combination of AZ32 and radiation was highly effective against GBM cells with mutant versions of the p53 tumor suppressor gene, which normally acts to promote radiation resistance."

As many as 80 percent of GBM patients have cancers with mutant or dysfunctional p53 signaling. The combination therapy forced GBM [cells](#) to undergo mitotic catastrophe, which occurs when external stressors cause a cell to inappropriately enter into mitosis, a phase of the cell cycle where cell division occurs, and ultimately led to cell death.

"Our study is the first to show that an ATM kinase inhibitor that can be

taken orally and able to penetrate the blood- brain barrier radiosensitizes GBM in mouse models. It is also the first to explain the p53-based mechanism by which ATM kinase inhibitors selectively sensitize brain cancers to radiation," says Valerie. "We are excited to translate these findings into a clinical trial and hopefully bring more effective therapies to patients who typically do not have good outcomes."

This study laid the groundwork for a phase 1 clinical trial (NCT03423628) led by AstraZeneca that will test AZ1390 in combination with [radiation therapy](#) for the treatment of brain tumors. It will assess the safety and tolerability of increasing doses of AZ1390 in combination with different regimens of [radiation](#) therapy for recurrent GBM, [brain](#) metastases and newly diagnosed GBM. The trial is estimated to enroll 132 patients at seven medical centers in the US and the UK, including VCU Massey Cancer Center.

More information: Jeremy Karlin et al. Orally bioavailable and blood-brain-barrier penetrating ATM inhibitor (AZ32) radiosensitizes intracranial gliomas in mice., *Molecular Cancer Therapeutics* (2018). [DOI: 10.1158/1535-7163.MCT-17-0975](https://doi.org/10.1158/1535-7163.MCT-17-0975)

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