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Authors

Di, Kaijun
Gong, Xing
Curticiu, Dana M
[et al.](#)

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Abstract 1809: Marizomib (NPI-0052) activity as a single agent in malignant glioma

Kaijun Di, Xing Gong, Dana M. Curticiu, Michael A. Palladino, and Daniela A. Bota

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Abstract

Background: Glioblastoma multiforme (GBM) is a highly aggressive brain tumor, which displays innate resistance to multiple treatment modalities. Previous studies have shown that the proteasome plays a vital role in the physiology of GBM, and that proteasome inhibition can be used as a strategy for treating malignant gliomas. Marizomib (NPI-0052) is a second generation irreversible proteasome inhibitor, which has a more lipophilic structure and has a broader and more prolonged inhibition profile for 20S proteasome activities compared to bortezomib and carfilzomib, two proteasome inhibitors approved by FDA for treatment of multiple myeloma. While bortezomib and carfilzomib have only modest activity as a treatment of malignant gliomas, marizomib might potentially be a novel therapeutic strategy for primary brain tumors. Unfortunately, to date, the number of studies that have analyzed the effect of marizomib on glioma is limited.

Methods: In these studies, we investigated the in vitro activities of marizomib in primary cell cultures derived from a multitude of human brain tumors (high-grade and low-grade gliomas and meningiomas), normal neural stem/progenitor cells (NSC) and as well as in the established human malignant glioma lines U251-MG and D54-MG. The effect of marizomib on cell proliferation, proteasome activity, motility, apoptosis and Reactive Oxygen Species (ROS) were evaluated in glioma cell lines. The inhibition of marizomib by the ROS quenching agent, N-acetyl cysteine (NAC) was also tested.

Results: The sensitivities varied in function of the pathology of the tumor, with the malignant glioma stem-like cells being the most severely affected, in contrast with the low-grade glioma, meningioma and NSC-derived cultures. Marizomib inhibited the proliferation of U251-MG and D54-MG cell lines with a half maximal effective concentration (EC_{50}) of 52nM and 20nM respectively, along with a significant decrease in cell migration and invasion. Treatment

with marizomib at a concentration of 60nM for 4 hours inhibited proteasome chymotrypsin-like (CT-L, β 5) activity by 85% in U251-MG and D54-MG cells. Marizomib treatment of human glioma cells was associated with increased free radical production and apoptosis, along with activation of caspase-3 and cleavage of PARP. Those effects of marizomib can be suppressed by exposure to the ROS quenching agent N-acetyl cysteine (NAC).

Conclusion: These preclinical studies demonstrate a significant anti-tumor effect of marizomib in malignant glioma cells. Marizomib has relatively little effect on neural stem/progenitor cells suggesting minimal neurotoxicity, while severely affecting both malignant glioma stem cells and glioma cell lines. But importantly, unlike bortezomib and carfilzomib, marizomib can cross the blood brain barrier. Additional research into the use of marizomib as a potential treatment for malignant gliomas as a single agent or in combination with SOC therapies for glioma is warranted.

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