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Abstracts

ET-16. MARIZOMIB (NPI-0052) ACTIVITY AS A SINGLE AGENT IN MALIGNANT GLIOMA

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Glioblastoma multiforme (GBM) is a highly aggressive brain tumor, which displays innate resistance to multiple treatment modalities. Previous studies have shown that proteasome inhibition can be used as a strategy for treating this malignancy. 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. While bortezomib and carfilzomib have only modest activity in gliomas, marizomib might potentially be a novel

therapeutic strategy for primary brain tumors. In these studies, we investigated the in vitro activities of marizomib in primary glioma cultures, neural stem/progenitor cells (NSC) and as well as in established human malignant glioma lines. The effect of marizomib on cell proliferation, proteasome activity, motility, apoptosis and Reactive Oxygen Species (ROS) were evaluated in glioma cell lines. 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 and NSC-derived cultures. Marizomib inhibited the proliferation of U251-MG and D54-MG cell lines with a half maximal effective concentration (EC50) of 52nM and 20nM respectively, along with a significant decrease in cell migration and invasion. Marizomib treatment of human glioma cells was associated with increased ROS 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). These preclinical studies demonstrate a significant anti-glioma effect of marizomib. Marizomib has relatively little effect on neural stem/progenitor cells suggesting minimal neurotoxicity. But importantly, unlike bortezomib and carfilzomib, marizomib can cross the blood brain barrier. Additional research into the use of marizomib in malignant gliomas orthotropic models is in progress and will be presented during the meeting.