O4.08. AGI5198, AN INHIBITOR OF IDH1R132H, PROTECTS IDH1R132H HCT116 CELLS AGAINST IRRADIATION
R.J. Molenaar, D. Dimitrakopoulou, J. Stap, F.E. Bleeker, and C.J.F. Van Noorden; Academic Medical Center, Amsterdam, Netherlands

BACKGROUND: IDH1R132H mutations are both inaugural events in the formation of glioma and associated with prolonged glioma patient survival. The IDH1R132H mutation confers a neo-enzymatic function that results in accumulation of the oncometabolite D-2-hydroxyglutarate (D-2HG), which promotes gliomagenesis by inducing global DNA hypermethylation and HIF1α degradation. AGI5198 is an IDH1R132H inhibitor that reduces proliferation of IDH1R132H tumors and will soon be tested in clinical trials with patients with IDH1R132H glioma. METHODS: An IDH1R132H mutation was generated in HCT116 cells by AAV targeting technology GENESIS (Horizon Discovery Ltd). Both IDH1R132H and IDH1WT HCT116 cells were irradiated with 0-6 Gy γ-rays (IR) and/or incubated with 5 μM reactive oxygen species-scavenger N-acetyl cysteine (NAC) and/or 0-400 nM IDH1R132H inhibitor AGI5198. The effects were tested in clonogenic assays. Clones were chemically fixed and stained 10 days after IR. RESULTS: As compared with IDH1WT HCT116 cells, we observed a reduced surviving fraction of IDH1R132H HCT116 cells at all IR dosages. This suggests that IDH1WT HCT116 cells demonstrated increased sensitivity for IR. Pre-incubation of IDH1WT and IDH1R132H/HCT116 cells with AGI5198 before IR. With increasing concentrations of AGI5198, we observed a higher surviving fractions of IDH1R132H/HCT116 cells. There was no difference between the surviving fractions of AGI5198-treated and untreated IDH1WT/HCT116 cells. This indicates that AGI5198 protects IDH1R132H/HCT116 cells against IR in a dose-dependent fashion, but had no protecting effect against IR on IDH1WT/HCT116 cells. CONCLUSION: Our results show that prolonged survival of IDH1R132H glioma patients, as compared to IDH1WT glioma patients, may be at least partly explained by an increased sensitivity of IDH1R132H glioma patients to IR. In addition, our data suggest that AGI5198 reverses IR sensitivity of IDH1R132H/HCT116 cells. Since AGI5198 and IR counteract in our cell model, concomitant administration of IDH1R132H inhibitors and IR may be contraindicated because IDH1R132H inhibitors may decrease tumor response to IR.