BACKGROUND: Infant-type hemispheric gliomas (IHG) are epigenetically distinct from pediatric-type diffuse high-grade glioma (pHGG) and often present with a poor outcome.

METHODS: We identify the current clinical practice and outcomes for previously reported and one unpublished IHG with survival data obtained from published literature and/or via the authors of the publications. Our analysis is based on 131 patients (84% of all patients with IHG). Survival analysis was conducted using the Kaplan-Meier method.

RESULTS: Based on multivariate analysis, complete resection resulted in better event-free survival (EFS) outcomes compared to patients with partial resection. In addition, a few drugs demonstrated increased efficacy with radiotherapy (RT) that have not been explored, especially as first line treatment.

OUTLOOK AND CONCLUSION: We will currently perform clonogenic assays to prioritize the most effective drug-RT combinations for trials. OUTLOOK AND CONCLUSION: We will currently perform clonogenic assays to prioritize the most effective drug-RT combinations for trials.
BACKGROUND: Pediatric high-grade glioma (pHGG) is associated with poor overall survival and standard care has remained unchanged for the past decade. BRAFV600E mutations occur in 5-10% and dabrafenib in combination with mekinist is approved in this subtype. Nevertheless, acquired resistance to targeted therapeutics is a common setback in highly aggressive tumors. Homozygous CDKN2A/B loss co-occurs in approximately 60% of this pHGG subtype. Taking advantage of those combined molecular alterations and exploiting acquired resistance mechanisms is of utmost importance to increase overall survival in these patients. METHODS: Four pHGG cell models with BRAFV600E mutation and homozygous CDKN2A/B loss were tested for the effects of CDK4/6 inhibitor monotherapy (palbociclib, ribociclib, abemaciclib) and/or combination treatment with trametinib on cell survival, cell cycle, apoptosis and senescence. RESULTS: Abemaciclib showed the highest efficacy of CDK4/6 inhibitors comparable to trametinib monotherapy in our cell models. Abemaciclib led to a cell cycle arrest and combined treatment with trametinib induced distinctly increased levels of apoptosis in our tumor models when compared to monotherapy and a great proportion of surviving cells were senescent. One cell model was orthotopically implanted in mice and abemaciclib and combined treatment with trametinib showed a slightly increased response when compared to trametinib alone. CONCLUSIONS: Summarizing, treatment with abemaciclib showed promising therapeutic effects in HGG cell models with BRAFV600E mutation and homozygous CDKN2A/B loss comparable to trametinib alone. Levels of apoptosis were distinctly higher with combinatorial abemaciclib and trametinib treatment when compared to monotherapy alone and senescence was induced in a great number of surviving cells. In vivo abemaciclib was more efficient when compared to trametinib alone. Currently we are working on in vivo experiments and the effect on sustained induction of senescence and mechanisms of tumor cell growth after discontinuation of therapy and in a combinatorial metronomic approach and in combination with radiotherapy.