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### Title

HGG-13. FIRST REPORT OF TUMOR TREATING FIELDS USE IN COMBINATION WITH BEVACIZUMAB IN A PEDIATRIC PATIENT

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#### HGG-11. THE $\beta$ -CATENIN/CBP-ANTAGONIST ICG-001 INHIBITS PEDIATRIC GLIOMA GROWTH IN A WNT-INDEPENDENT MANNER

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Pediatric high-grade gliomas (pedHGG) belong to the most aggressive cancers in children with a poor prognosis due to a lack of efficient therapeutic strategies. The  $\beta$ -catenin/Wnt-signaling pathway was shown to hold promising potential as a treatment target in adult high-grade gliomas by abrogating tumor cell invasion and the acquisition of stem cell-like characteristics. Since pedHGG differ from their adult counterparts in genetically and biologically we aimed to investigate the effects of  $\beta$ -catenin/Wnt-signaling pathway-inhibition by the  $\beta$ -catenin/CBP antagonist ICG-001 in pedHGG cell lines. In contrast to adult HGG, pedHGG cells displayed minimal detectable canonical Wnt-signaling activity. Nevertheless, low doses of ICG-001 inhibited cell migration/invasion, tumorsphere- and colony formation, proliferation *in vitro* as well as tumor growth *in vivo/ovo*, suggesting that ICG-001 affects pedHGG tumor cell characteristics independent of  $\beta$ -catenin/Wnt-signaling. RNA-sequencing analyses support a Wnt/ $\beta$ -catenin-independent effect of ICG-001 on target gene transcription, revealing strong effects on genes involved in cellular metabolic/biosynthetic processes and cell cycle progression. Among these, high mRNA expression of cell cycle regulator *JDP2* was found to confer a better prognosis for pedHGG patients. In conclusion, ICG-001 might offer an effective treatment option for pedHGG patients functioning to regulate cell phenotype and gene expression programs in absence of Wnt/ $\beta$ -catenin signaling-activity.

#### HGG-12. HYPOXIA SEEMS TO BE FREQUENTLY UPREGULATED IN THE PEDIATRIC HIGH GRADE GLIOMA AND DIPG

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Pediatric high grade glioma (pHGGs), including sus-tentorial and DIPG, are known to have a very dismal prognosis. For instance, even an increased knowledge on molecular biology driving this brain tumor entity, there is no treatment able to cure those patients. Therefore, we were focusing on a translational pathway able to increase the cell resistance to treatment and to reprogram metabolically tumor cells, which are, then, adapting easily to a hypoxic microenvironment. We, previously, observed that the resistance to mTor and HIF1 inhibitions was completely linked to HIF2 hyperexpression spontaneously in the pHGG and DIPG cell lines. To establish, the crucial role of the hypoxic pathways in pHGG tumors themselves, we assessed their protein and transcriptomic deregulations in a pediatric cohort of pHGGs, as well as the metabolomic status. We tested 28 patients and could isolate 4 types of tumor profiles with immunohistochemical analyses. The first one was defined by the absence of HIF/HIF2 expression (6 tumors), the second one was just overexpressing HIF1 (9 tumors), the third one is the smaller with an isolated HIF2 hyperexpression (3 cases) and the last one where HIF1 and HIF2 and concomitantly expressed. The DIPG subgroup was statistically associated with HIF2 hyperexpression and the complete absence of mTor expression. At the transcriptomic level, most of the tumors were overexpressing constantly and mainly RAS, HIF1, RPS6KB1, VHL, ENG and VEGFA, whereas mTOR, AKT, CXCL12 and CXCR4 were modulated throughout the tumors' cohort. The metabolomic profiles showed a constant activated glycolysis in all tumors, whereas glutaminolysis and seronolysis were heterogeneously present. The only significant association was the presence of the lipolytic pathways and HIF2 hyperexpression, as already linked in our previous work. The combination of new drugs targeting hypoxia biomarkers and metabolic pathways like glycolysis and/or lipolysis might be a new approach in pHGG and DIPG.

#### HGG-13. FIRST REPORT OF TUMOR TREATING FIELDS USE IN COMBINATION WITH BEVACIZUMAB IN A PEDIATRIC PATIENT

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We report the first case of a pediatric patient with glioblastoma (GBM; WHO grade IV astrocytoma) successfully treated with tumor treating fields (TTF). The patient was diagnosed with GBM when 13 years of age and

progressed through surgical resection, radiotherapy and chemotherapy. Discrete tumor growth visualized on MRI with stable neurological examination was monitored for 6 months with subsequent stable disease observed radiographically and clinically for 7 months while adherent to Optune® (TTF). TTF thereby played a role in forestalling recurrent GBM growth in this young woman for 7 months without significant adverse effects. We propose that TTF therapy is a potential valuable treatment in this small, but sick, patient population.

#### HGG-14. IDENTIFICATION OF PERSONALIZED ACTIVE AGENTS IN PEDIATRIC GLIOMAS THROUGH HIGH-THROUGHPUT DRUG SCREENING IN MATCHING PAIRS OF PATIENT DERIVED ORTHOTOPIC XENOGRAFT (PDOX) NEUROSPHERE AND MONOLAYER CELLS

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Glioblastoma (GBM) is one of the deadliest brain tumors both in adults and children. The efficacy of targeting mutated genes/pathways has not been systematically analyzed. Additionally, it remains unknown if neurospheres and non-stem monolayer tumor cells will respond equally to the same target therapies. Relatively long-term treatment was achieved for high-throughput drug screening and revealed time- and dose-dependent effects in most of the 4,629 compounds that were active in at least one culture at one time point. When gene mutations were druggable, not all inhibitors of the same family were active. In IC-4687GBM, high NF1 mutation (>76–99% allele) frequency was found in patient tumor, xenografts, and cultured cells, but only 3/17 MEK inhibitors were active in neurospheres and 2/17 in monolayer cells on day 7. In IC-R0315GBM that carried PI3KA mutation (allele frequency 22–27%), 5/33 PI3K inhibitors were active in neurospheres and 8/33 in monolayer cells after 7 days. In IC-3752GBM (recurrent GBM) and ICb-1127AA, no druggable mutations were detected. The number of active drugs on day 7 was 366 in IC-4768GBM, 406 in IC-3752GBM, 284 in IC-R0315GBM, and 305 in ICb-1277AA. When the 4 matching pairs of neurospheres and monolayers were compared, the agents active in both cultures ranged from 36% to 60%, active only in neurosphere from 10.3% to 25%, and active only in monolayer cells from 14.8% to 53%. Subsequent *in vivo* validation using MLN8327 in IC-4687GBM and IC-R0315GBM showed that effective targeting of both neurosphere and monolayer was required for significantly-improved animal survival times. We showed that long-term treatment is feasible for high-throughput drug screening. Targeting druggable mutations can be achieved but only by a fraction of specific agents. Neurospheres and monolayer cells do not always respond equally toward the same drugs, and effective targeting of both subpopulations is needed to generate prolonged animal survival times.

#### HGG-15. MAPK PATHWAY ACTIVATION IN K27M MUTATED GLIOMAS – ASSOCIATION WITH CLINICAL PARAMETERS AND SURVIVAL

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K27M midline gliomas are defined by point mutations within the chromatin modifiers H3 and are represented as a new separate entity in the new version of the WHO classification for tumors of the central nervous system. These tumors arise in midline structures of the brain, the brain stem and the spinal cord. They occur in children and young adults and are usually associated with a bad clinical outcome. We and others previously reported Mitogen-activated protein kinase (MAPK) pathway activation via BRAF or FGFR1 hotspot mutations in single cases of K27M gliomas. In contrast to K27M mutations, MAPK activation is strongly associated with pediatric low-grade astrocytomas, that show a favorable survival. In the context of K27M glioma, the clinical significance of co-occurring BRAF or FGFR1 mutations remains unclear. We screened a cohort of patients with K27M mutated gliomas for BRAF or FGFR1 mutations. So far, we detected three cases with FGFR1 mutations (K656E and N546K) and two cases with BRAF V600E mutations. These cases showed a favorable survival in comparison to other K27M cases in our series and in comparison to previously reported patient cohorts of K27M glioma. Our results shed light on the frequency and clinical impact of MAPK pathway activation in K27M mutated gliomas with implications for targeted therapies and prognosis of patients.