

RT schedules for DIPG while administering the same systemic treatment. **METHODS:** Patients: 2-21 years-old with a not-pretreated radiologically verified DIPG (MRI blindly reviewed at diagnosis and every 12 weeks thereafter) and symptoms duration below 6 months. Biopsy was required if suggested by atypical imaging. Vinorelbine 20 mg/m<sup>2</sup>-nimotuzumab 150 mg/m<sup>2</sup> were administered weekly for 12 weeks; thereafter every other week until tumor progression or for up to 2 years. Standard(ST) arm included focal RT at total dose of 54Gy (1.8Gy/day); for local progression re-irradiation was proposed at 19.8Gy, in case of dissemination craniospinal irradiation(CSI) at 36Gy was adopted. Experimental(SP) arm included three elective courses of RT at defined timepoints at 36Gy, 19.8Gy and 19.8Gy with possible reirradiation for relapse at 9 Gy. Incidences of local(L) and distant(D) progression were assessed in a competing risk setting. **RESULTS:** Aggregated preliminary results are given for 4 Italian centers. 54 pts were screened and 51 included, 27 in ST, 28 males, median age 7 years (range 3-17). Median time of observation was 17.9 months. Twelve patients needed a shunt, 10 during treatment; 20 were biopsied, in 18 cases according local protocols. 19/20 tumors had H3.3 K27 mutation. 41 relapsed, 28 locally, 13 with a component of dissemination. 36 died, one for tracheotomy bleeding. SP irradiation was feasible and never produced significant radionecrosis. Median EFS/OS were 7.3/12.9 months, respectively; EFS/OS at 1 year were 19.0%/57.3%, not differing between patients with local vs. disseminated relapses. Patients submitted to biopsies had more dissemination (P=0.04) and less local progression (P=0.077). **CONCLUSIONS:** Treatment was feasible and OS confirmed previous results obtained in a single center. Randomization results will be later reported.

#### DIPG-05. HOW DO POTASSIUM CHANNELS CONTRIBUTE TO THE GROWTH AND INVASION OF HIGHLY-AGGRESSIVE BRAIN CANCERS?

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Glioblastoma (GBM) is a lethal form of high-grade glioma with a dismal median survival time of just 15 months. Characterised by its' highly diffuse and intrinsic growth pattern, GBM invades the healthy brain at an alarming rate. While diffuse midline glioma (DMG) is a much rarer disease, it is even more lethal, with a 5-year survival rate of just 2%. Though GBM is largely diagnosed in adults, DMG primarily affects young children aged 5-9 years and accounts for 10% of all childhood CNS cancers. Thus, while rare, DMG is highly aggressive and currently has no effective treatments to extend survival times beyond the median of 9 months. There is a pressing need for the development of novel and improved targeted therapies for each of these devastating diseases. Ion channels have long been implicated in the progression of numerous cancer types, due to their integral roles in proliferation, cell cycle transition, apoptosis, migration, and cellular plasticity. Voltage-gated potassium channels (VGKCs), in particular, have strong links to the key processes of proliferation, migration and invasion in GBM tumours. Given that the majority of GBM-related deaths are attributed to secondary tumours and metastasis, targeting proteins that are integral to these processes could result in reduced recurrence. Preliminary evidence suggests a potential role for the VGKC subtypes Kv5.1, Kv7.2, and the Kv4 subfamily in GBM and DMG, due to observed upregulation of these genes in both patient-derived cell lines and tumour samples. These particular VGKC subtypes are highly novel with regards to these cancers, while their significant upregulation suggests they may be associated with tumour progression. Thus, we aim to further explore the relationship between ion channel function and tumorigenesis in GBM and DMG, with a specific focus on VGKC subtypes and their potential therapeutic value.

#### DIPG-06. UNCOVERING THE FACTS IN DIFFUSE MIDLINE GLIOMA (DMG)

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Effective treatments are urgently needed for the incurable paediatric brainstem tumour Diffuse Midline Glioma (DMG). Most DMGs contain Histone H3 mutations (H3K27M), which produce extensive epigenetic dysregulation by inhibiting EZH2-mediated trimethylation of H3K27 (H3K27me3). Global depletion of the repressive H3K27me3 modification results in aberrantly open chromatin and is central to DMG tumorigenesis. Thus, targeting the epigenome is a promising avenue of treatment for DMG. We found that targeting the histone chaperone complex Facilitates Chromatin Transcription (FACT) with the curaxin drug CBL0137 has low potential pre-clinical efficacy against DMG, leading to a paediatric Phase I/II clinical trial for CBL0137 which includes a DMG/DIPG cohort (NCT04870944). In this project we aim to elucidate CBL0137's molecular mechanism in

DMG. FACT is critical for maintaining chromatin homeostasis during DNA replication, transcription, and repair. We therefore hypothesised that FACT maintains the aberrant epigenetic landscape resulting from H3K27M. Consistently, we found CBL0137 to be more cytotoxic against H3K27M-mutant, compared to H3-WT or isogenic DMG cells lacking the mutation. Furthermore, FACT directly interacts with H3K27M, and FACT inhibition increases both EZH2 catalytic activity and global H3K27me3 levels. We are now using ChIP-seq to discover the genome-wide distribution of FACT and H3K27M, and will interrogate the consequence of CBL0137 treatment on the epigenome and transcriptome. Preliminary results suggest that FACT is located at certain genes co-occupied by H3K27M, the active histone mark H3K27ac, and the BET protein BRD4. This implies that FACT is involved in maintaining open chromatin and perhaps transcription at these regions. Combining CBL0137 with other epigenetic drugs, such as BET inhibitors, could therefore represent a rational therapeutic opportunity for DMG. This work will ultimately inform mechanism-based targeted therapies to combine with CBL0137 to improve its efficacy and uncover valuable new insights into DMG epigenetics and pathobiology.

#### DIPG-07. PRECLINICAL AND CASE STUDY RESULTS UNDERPINNING THE PHASE II CLINICAL TRIAL TESTING THE COMBINATION OF ONC201 AND PAXALISIB FOR THE TREATMENT OF PATIENTS WITH DIFFUSE MIDLINE GLIOMA (NCT05009992)

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Diffuse midline gliomas (DMG), including those of the brainstem (diffuse intrinsic pontine glioma - DIPG), are pediatric CNS tumors recognized as the most lethal of all children's cancers. Palliative radiotherapy is the only ap-