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Circumscribed low-grade gliomas comprise roughly one-third of pediatric CNS tumors. Most of these tumors are caused by activating mutations in the mitogen-activated protein kinase (MAPK) pathway. Drugs targeting the MAPK pathway are effective in other cancers and are being utilized in low-grade gliomas. We describe treatment outcomes and toxicities in a series of thirteen low-grade glioma patients treated with trametinib. We performed a retrospective chart review to evaluate response on T2/FLAIR MRI images per updated RANO criteria, visual outcomes, tolerability, and durability of response in progressive low-grade glioma patients treated with trametinib. Thirteen patients age 22 months to 34 years were included. Best radiographic response on therapy included 2/13 partial response, 3/13 minimal response, 5/13 stable disease, and 3/13 progressive disease. Diagnoses included pilocytic astrocytoma (n=6), desmoplastic infantile ganglioglioma (DIG; n=1), and low-grade glial neoplasms (n=2). Molecular drivers included BRAF:KIAA1549 fusion (n=3), V600E mutation (n=1), and somatic NF1 mutation (n=1). Three patients had germline NF1. In patients with partial or minimal response, best response was seen after longer durations of therapy; 4 of 5 best responses occurred after at least 12 months on therapy. Five patients completed prescribed therapy. Three patients remain stable off therapy at 6, 12, and 21 months; two patients recurred at 1 and 10 months off therapy. Skin manifestations were the predominant form of toxicity. This was more severe in older males, and symptoms improved with intermittent dosing. All patients with optic pathway tumors showed at least stable vision throughout treatment, with some patients having dramatic improvement. Trametinib is effective and well-tolerated in patients with low-grade glioma. Dermatologic toxicity can be mitigated by intermittent dosing. Best responses tended to occur later in therapy, sometimes after relatively stable MRIs. Patients with optic pathway lesions showed stable to improved vision even in the absence of significant radiographic response.

### LGG-09. SENOLYTIC AGENT NAVITOCLAX TARGETS VINBLASTINE- AND MAPK INHIBITORS-INDUCED SENESCENT TUMOUR CELLS IN PAEDIATRIC LOW GRADE GLIOMAS

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Pilocytic astrocytoma (PA, WHO grade I), the most common paediatric brain tumour, is characterized by constitutive activation of the MAPK pathway. PA tumours show a slow growth, without tendency to progress to high-grade malignancies. However, a significant group of patients for whom a total resection is not feasible require additional therapy. The typical proliferative index of a PA, measured by Ki-67 staining, is 1–2%, whereas a large part of the tumour is Ki-67 negative and expresses markers of oncogene-induced senescence (OIS) such as SA-β-Gal positivity and the cell cycle inhibitors $p16^{INK4a}$ (CDKN2A) and $p21^{Cip1}$ (CDKN1A). Conventional treatments (i.e. chemotherapy) tend to target only proliferative cells and the effect of new molecularly targeted therapies (e.g., MAPK pathway inhibitors) on senescent cells remains unclear. Here, we discuss the opportunities to combine these therapies with new compounds targeting the senescent cells, referred to as senolytics, using three different PA models. (1) *Ex vivo* culture of human PA tumours (2) Two cell lines: the DKFZ-BT66 PA human cell line, carrying the oncogenic driver KIAA1549:BRAF-fusion, used as a model of OIS; and the proliferative BT40 cell line harbouring the $BRAF^{V600E}$ mutation; (3) *In vivo* xenograft model induced by orthotopic transplantation of BT40 cells. We have previously shown that OIS cells exhibit an increased sensitivity to senolytic compounds, such as navitoclax, a clinically approved BCL2/XL inhibitor, relative to proliferative controls *(Buhl et al, Clin Cancer Res. 2019)*. Our current research demonstrates that treatments with low doses of chemotherapy (e.g., vinblastine) or MAPK inhibitors (e.g., dabrafenib or trametinib) triggers a therapy-induced senescence response in proliferative cells (e.g., abolished proliferation, SA-β-Gal positivity, SASP production), making these senescent cells sensitive to senolytic compounds, including navitoclax. Together, our research provides a strong rationale supporting the combined use of senolytics with current conventional and targeted therapies against human PA.

### LGG-10. AN UNUSUAL PRESENTATION OF BILATERAL OPTIC NERVE GLIOMA IN CROUZON SYNDROME

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Optic pathway gliomas (OPGs) are low grade gliomas intrinsic to the visual pathway, frequently associated with Neurofibromatosis Type 1 (NF-1). Bilateral OPGs without chiasmatic involvement are almost pathognomonic for NF-1. We report an unusual case of bilateral optic nerve glioma without chiasmatic involvement in a 17-month old male patient with craniosynostosis and Crouzon Syndrome, an autosomal dominant disorder caused by activating *FGFR2* mutations associated with craniosynostosis and optic atrophy. The patient's c.1032 G>A pathogenic variant in *FGFR2* is a variant known to affect splicing and results in a protein that lacks part of an important domain involved in ligand binding. Although *FGFR1* mutations have been implicated in low-grade glioma through MAPK activation, *FGFR2* mutations have not yet been described in OPGs, although they have been described in epileptogenic low-grade gliomas and mixed neuronal-glial tumors. Our patient presented with worsening vision in the setting of known Crouzon Syndrome. An eye examination revealed bilateral primary optic atrophy. Brain and orbital MRIs demonstrated fusiform dilation and STIR hyperintensity of the intraorbital segments of the optic nerves bilaterally with normal pre-chiasmatic optic segments. There were no other radiographic or physical stigmata suggestive of NF-1. Next generation sequencing and copy number analysis from peripheral blood were negative for variants in *NF1*. RNA based studies for *NF1* aberrations are pending. Although follow up MRI scans demonstrated stable size of his OPGs, the risk of further visual deficit was considered significant due to his pre-existing optic atrophy and poor baseline visual acuity. Therefore, he was started on vincristine and carboplatin chemotherapy according to A9952, and induction therapy has been well tolerated. To our knowledge, this is the first patient with Crouzon Syndrome who has developed bilateral optic pathway gliomas. Orbital MRIs should be considered for these patients with worsening visual acuity not explained by other causes.

### LGG-11. BH3-MIMETICS TARGETING BCL-XL SELECTIVELY IMPACT THE SENESCENT COMPARTMENT OF PILOCYTIC ASTROCYTOMA

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Introduction: Pilocytic astrocytoma (PA) is the most common brain tumor in children. Activation of the mitogen-activated protein kinase (MAPK) pathway is a hallmark of PA. Complete remission in non-resectable tumors is infrequently observed with current therapeutic approaches. Most PA tumors cells are in oncogene-induced senescence (OIS), which may explain the benign growth behavior of PAs but also account for resistance to therapy. Therefore, treatment of PA with senolytic agents such as BH3-mimetics is a promising new approach. Methods: Three patient-derived PA cell lines, DKFZ-BT66, DKFZ-BT308 (both KIAA1549:BRAF-fusion positive) and DKFZ-BT314 (BRAF V600E-mutation positive) were used. Depending on inducible expression or repression of SV40 large T antigen all models can reflect both states of PA, proliferation and OIS.