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CP-05. MAPK PATHWAY ACTIVATION, CLONAL EVOLUTION, INCLUDING RARE TP53 LOSS, AND THE IMMUNE ENVIRONMENT OF RECURRENT CRANIOPHARYNGIOMA

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BACKGROUND: Craniopharyngiomas are rare challenging tumours, with around 25% of cases recurring despite surgery and/or radiotherapy. Relatively little is known about the biology of recurrence and there is an urgent need to develop new therapies. Our previous studies have suggested preclinical efficacy of MEKinhition with trametinib in human and murine adamantinomatous craniopharyngoioma (ACP) tissue. At ISPNO2022 we reported methylation and expression profiling results from a cohort of relapsed craniopharyngioma, identifying acquisition of chromosomal abnormalities across recurrence, the persistent activation of MAPK pathway at recurrence, the presence of myeloid cells and a rare case of malignant transformation associated with TP53 loss. METHODS: _Here we present an update from this study through exploring additional datasets, preclinical drug testing, and genetic manipulation of genetic engineered mouse models of ACP RESULTS: Exploration of whole genome sequencing data from 67 cases of ACP from Children's Brain Tumour Network has confirmed the presence of chromosomal arm changes in 7 (10%) of cases, including at diagnosis, confirming that the genomic landscape of ACP is more complex than previously thought. To further explore the potential of MAPK pathway inhibiton we have demonstrated efficacy of a further two clinically available MEK inbhiibtors, Selumetinib and Binimetinib, in reducing proliferation and inducing cell death in ex vivo explants of murine ACP. To explore the role of TP53 loss in aggressive craniopharyngioma, we show that Trp53 loss in a murine ACP model results in very aggressive tumours and reduced mouse survival. Finally, we have further characterised the tumour immune infiltrate showing differences in the cellular composition between ACP and Papillary CP, and revealing a diverse phenotype of macrophages in ACP. CONCLUSIONS: Together, this research provides further preclinical support for the ongoing evaluation of MAPK pathway inhibitors and immunomodulatory approaches in clinical trials in patients with craniopharyngioma.