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MODL-02. ESTABLISHING THE TIME-DEPENDENCE OF CDK4/6 INHIBITOR EFFICACY IN PEDIATRIC BRAIN TUMORS AND FEASIBILITY OF METRONOMIC INTRATHECAL DELIVERY IN A PRECLINICAL MODEL
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This comprehensive study delves into the intricate dynamics of CDK4/6 inhibitors (abemaciclib, ribociclib, palbociclib) efficacy in the context of pediatric brain tumors, with a specific focus on establishing the temporal dependencies of their effectiveness. Beyond elucidating the time-dependent aspects, the research also explores into the feasibility and safety considerations associated with a metronomic intrathecal delivery with Palbociclib. This involves a thorough examination of pharmacokinetics and an analysis of liver and renal function through a panel assessment in vitro. By methodically exploring the optimal dosing within the brain after administration of Palbociclib via a systemic or intrathecal administration; the study aims to provide nuanced insights into enhancing therapeutic outcomes for pediatric brain tumors. Ultimately, we also provide a mechanistic understanding of the inhibition of CDK4/6 over time using RNAseq analysis; and an assessment of the efficacy of the proposed metronomic intrathecal delivery strategy in a preclinical mouse model of leptomeningeal ATRT. This multifaceted study not only expands our understanding of the temporal dynamics of CDK4/6 inhibitors but also lays the foundation for informed decision-making regarding the potential of this innovative therapeutic delivery method in the realm of pediatric brain tumor treatment.