AT-14. mTOR INHIBITION BLOCKS A KEY LIN28 DOWNSTREAM TARGET AND ENHANCES CISPLATIN MEDIATED CYTOTOXICITY LEADING TO EXTENDED SURVIVAL IN ATYPICAL TERATOID RHABDOID TUMORS

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LIN28 is a somatic cell reprogramming and stem cell factor that we have previously shown to be a key driver of atypical teratoid rhabdoid tumor (AT/RT) tumorigenicity. We hypothesize that disrupting LIN28 downstream pathways will extend survival in AT/RT. mTOR is a serine/threonine protein kinase that contributes to the aggressive phenotype of many tumors and multiple regulators of mTOR are known targets of the LIN28 pathway. MLN0128 is a dual TORC1/2 inhibitor with good brain penetration currently in phase I clinical trials. Treatment of AT/RT cell lines with MLN0128 inhibits TORC1/2 targets, suppressing cell proliferation at 10nM concentration (MTS assay p < 0.005 vs DMSO control; t-test) and inducing apoptosis (cleaved caspase 3 (CC3) assay p < 0.005 vs DMSO; t-test). MLN0128 treatment of AT/RT xenograft models nearly doubles mean overall survival (Kaplen-Meier test p < 0.005). MLN0128 acts synergistically with cisplatin therapy to slow tumor growth (MTS assay p < 0.005 vs DMSO control; t-test). Cisplatin, which is typically cytotoxic, induces the cytostatic process of autophagy in AT/RT, as determined by western Blot for LC3B, P62, c-PARP. Exogenous AKT expression in AT/RT cell lines further protects cells from cisplatin induced apoptosis (CC3 assay p < 0.05; t-test). MLN0128 inhibition of AKT suppresses autophagy and enhances cisplatin induced apoptosis. In conclusion, targeting the mTOR pathway with MLN0128 leads to potent in vitro and in vivo activity against AT/RT and acts synergistically in combination with cisplatin to slow tumor growth and prevent drug resistance. MLN0128 may be a candidate to combine with conventional AT/RT therapy in future clinical trials.