FORETINIB IS EFFECTIVE THERAPY FOR METASTATIC SONIC HEDGEHOG MEDULLOBLASTOMA

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BACKGROUND: Expression profiling, molecular subgrouping and analysis of somatic copy number alterations were conducted on multiple independent cohorts of patient tumour samples to examine intermediates of the MET signaling pathway in medulloblastoma. To examine the in vitro and in vivo effects of foretinib treatment; MET signaling biochemical analysis; migration and invasion assays; and foretinib pharmacokinetic studies were performed. Medulloblastoma xenografts and transgenic mouse models were used to evaluate foretinib treatment in vivo. RESULTS: We analyzed three large non-overlapping cohorts of medulloblastoma patients (discovery cohort, n = 199; validation cohort 1, n = 439; validation cohort 2, n = 285) and demonstrated that cMET, known to be involved in tumor progression and dissemination, is a marker of sonic hedgehog (SHH) medulloblastoma. Importantly, immunohistochemical analysis of activated cMET (phosphorylated cMET) in another independent patient cohort (n = 385) revealed that cMET activation correlates with increased tumor relapse and a poor survival in pediatric patients with SHH medulloblastomas, thus defining a subset of patients that may benefit from cMET targeted therapy. We show that foretinib, an FDA approved inhibitor of cMET, suppresses cMET activation, decreases proliferation and induces apoptosis, both in medulloblastoma cell lines and in SHH medulloblastoma xenografts. Furthermore foretinib penetrates the blood-brain barrier and is effective both in the primary and in the metastatic compartments. Treatment of mouse xenografts and of an aggressive transgenic model of metastatic SHH medulloblastoma with foretinib reduced primary medulloblastoma growth, decreased the incidence of metastases by 36% and increased survival by 45%.

CONCLUSIONS: Our results provide strong rationale for advancing foretinib into clinical trials for SHH-driven medulloblastomas. SECONDARY CATEGORY: Tumor Biology.