Title:
Improving clinical trial access for people with rare CNS tumors: a phase I/II trial of PLX038 in tumors with MYC-C or MYC-N amplifications incorporating correlative studies and patient reported outcomes (PRO) – An NCI-CONNECT Clinical Trial

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MYC genes encode transcription factors that regulate the expression of genes involved in cell division. Supraphysiologic levels of MYC drive oncogenesis in many human cancers and induce conformational DNA changes leading to the formation of topoisome complexes, essential to manage the torsional strain. *MYC*/*MYCN* amplifications are seen in multiple primary CNS tumors including 30% of relapsed medulloblastomas (MB) and a subtype of ependymoma (EPN) where *MYCN* amplification defines the tumor. PLX038 is a PEGylated macromolecule containing the topoisomerase I inhibitor SN-38. PEGylations leads to longer half-life, tumor accumulation and decreased toxicity. We hypothesize that PLX038 will be efficacious in primary CNS tumors driven by *MYC*/*MYCN* amplifications by targeting the *MYC*-induced topoisome.
METHODS: Trial in development. Design and objectives: Phase I (N=12) – determine phase 2 dose of PLX038 in recurrent primary CNS tumors; TITE-BOIN design allowing continued accrual and real-time dose assignment. Phase II - 3 independent cohorts, N=30 for each group with interim analysis after 10 each: 2A - *MYCN* Amplified EPN post resection and radiotherapy (PFS); 2B - Recurrent *MYCN* Amplified EPN or *MYC*/*MYCN* Amplified MB (disease control rate, DCR); 2C - Other recurrent primary CNS tumors with *MYC*/*MYCN* amplifications (DCR). Additional measures include PROs from the Office of Patient-Centered Outcomes Research (OpCORe) web-based early phase trial endpoints and biomarkers of PLX038 distribution and response/resistance in peripheral blood, tumor tissue, hair follicles, and abdominal wall fat pad tissue. CONCLUSIONS: NCI-CONNECT is committed to innovative designs can mitigate some of the barriers to access experimental therapy for people with rare CNS tumors. This basket trial will enroll participants with unifying molecular features and potential susceptibility to PLX038 despite different histological diagnoses. Furthermore, incorporation of comprehensive PROs will help identify clinical benefit and tolerability, and correlative studies in tumor and other tissues will help identify biomarkers of response or resistance.

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