Somatic mutations in ACVR1 are found in a quarter of children with diffuse intrinsic pontine glioma (DIPG), however, there are no ACVR1 inhibitors licensed for the disease. Using an Artificial Intelligence-based platform to search for approved compounds for ACVR1-mutant DIPG, the combination of vandetanib and everolimus was identified as a possible therapeutic approach. Vandetanib, an inhibitor of VEGFR/RET/EGFR, was found to target ACVR1 (Kd=150nM) and reduce DIPG cell viability in vitro but has limited ability to cross the blood brain barrier. In addition to mTOR, everolimus inhibits ABCG2 (BCRP) and ABCB1 (P-gp) transporters and was synergistic in DIPG cells when combined with vandetanib in vitro. This combination is well-tolerated in vivo, and significantly extended survival and reduced tumor burden in an orthotopic ACVR1-mutant patient-derived DIPG xenograft model. Four patients with ACVR1-mutant DIPG were treated with vandetanib plus mTOR inhibitor, informing the dosing and toxicity profile of this combination for future clinical studies [1)].

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