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Final Results from a First-in-Human Phase 1 Study of the Dual Isocitrate Dehydrogenase (IDH) 1/2 Inhibitor, LY3410738, in Advanced Solid Tumors Harboring IDH1 or IDH2 Mutations

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Abstract

Background: Isocitrate dehydrogenase (IDH) 1/2-isoform inhibitors have clinical efficacy in IDH1/IDH2-mutated (mIDH1/mIDH2) neoplasms. However, primary and secondary resistance limits their therapeutic potential. LY3410738, an oral, brain penetrant, dual mIDH1/mIDH2 isoform-selective inhibitor was designed to overcome resistance.

Methods: This global, multicenter, open-label, phase 1 study of patients with IDH-mutant solid tumors evaluated LY3410738 as monotherapy (dose-escalation) for advanced solid tumors in combination with cisplatin-gemcitabine for newly diagnosed cholangiocarcinoma or with durvalumab for relapsed/refractory cholangiocarcinoma (dose-expansion) (NCT04521686). Primary objectives were the maximum tolerated dose (MTD), recommended phase 2 dose, and preliminary antitumor activity. Safety, pharmacokinetics, inhibition of D-2-hydroxyglutarate, and circulating tumor DNA (ctDNA) were assessed.

Results: Overall, 119 patients received LY3410738 alone (N=94) or in combination with cisplatin-gemcitabine (N=19) or durvalumab (N=6). No dose-limiting toxicities (DLTs) were observed; the MTD was not determined. Common adverse events included nausea, vomiting, and decreased appetite. Overall response rates of 5.2% and 11.1%, and disease control rates of 56.9% and 63.0%, were observed for patients with relapsed/refractory IDH1- or IDH2-mutant cholangiocarcinoma or IDH1-mutant glioma, respectively. D-2-hydroxyglutarate normalization was rapid and durable. In dose-expansion cohorts, combination treatments were tolerable, with one DLT in the durvalumab cohort. LY3410738 plus cisplatin-gemcitabine demonstrated a response rate of 42.1%, median DOR of 8.1 months, median PFS of 10.2 months for patients with newly diagnosed IDH-mutant cholangiocarcinoma.

Conclusions: LY3410738 demonstrated largely cytostatic antitumor activity in IDH1- or IDH2-mutated cholangiocarcinoma and IDH1-mutated gliomas. LY3410738 plus cisplatin-gemcitabine exhibited favorable antitumor activity in patients with treatment-naïve IDH-mutated cholangiocarcinoma, warranting further exploration as a treatment strategy.