First-in-human results of STX-478, a mutant-selective PI3Kα inhibitor, in advanced solid tumor patients

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Background:

The PI3Kα pathway is commonly mutated in cancer. PI3Kα inhibitors have shown clinical benefit in hormone receptor positive (HR+), HER2- breast cancer (BC) in Phase 3 studies, but are limited by toxicities from wild type (WT) PI3Kα inhibition. STX-478 is an oral, allosteric, CNS-penetrant, mutant-selective PI3Kα inhibitor designed to improve efficacy while sparing WT toxicities. STX-478 led to robust efficacy without WT toxicities in PI3Kα mutant (PI3Kαm) tumors *in vivo*. Initial Phase 1 monotherapy trial results are reported.

Methods:

This first-in-human, Phase 1/2 study evaluated STX-478 alone or in combination in advanced PI3Kαm solid tumor patients. Dose escalation occurred per 3+3 design followed by expansion. Pre-diabetics/diabetics and those intolerant to PI3K inhibitors were permitted.

Results:

As of June 21st 2024, 61 patients (29 HR+/HER2- BC, 32 other solid tumors) were treated at STX-478 doses of 20 mg to 160 mg daily. 52% of patients were pre-diabetic/diabetic; 41% of BC patients had a prior PI3K pathway inhibitor. Median prior lines of therapy was 3 (range 1-7). STX-478 was well-tolerated with a MTD of 100 mg daily. Treatment-related adverse events (TRAEs) of ≥ 15% included: fatigue (30%), hyperglycemia (23%), nausea (20%) and diarrhea (15%). PI3Kα WT AEs (hyperglycemia, diarrhea and rash) were Grade 1/2. No patient discontinued due to an AE. STX-478 exposure was dose proportional up to the MTD and reached steady state by day 15. At doses ≥ 40mg, STX-478 achieved target coverage several fold higher than other PI3Kα inhibitors. In 43 evaluable patients, the confirmed/unconfirmed

ORR was 21%; 23% (5/22) in HR+/HER2- BC; and 44% (4/9) in gynecologic cancers. The disease control rate across tumors was 70%. Responses were seen in both kinase and helical domain mutant tumors; several deepened over time. PI3Kαm ctDNA levels markedly decreased on therapy in most patients.

Conclusions:

In heavily pre-treated patients, STX-478 was well-tolerated with favorable PI3Kα WT toxicity, including in diabetic patients or those intolerant to PI3K inhibitors. STX-478 was active in breast and non-breast cancers, with an ORR exceeding historical comparisons to other PI3K inhibitors. Enrollment is ongoing.

ABSTRACT (2000 character limit, excluding spaces, including title and body, author limit 20)

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