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Abstract CT268: Preliminary results from a first-in-human study of IK-595, an oral MEK/RAF molecular glue, in patients with RAS- or RAF-altered advanced solid tumors

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Abstract

Background:

The clinical utility of MEK inhibitors is limited to BRAF V600X mutant cancers and NF1 mutant neurofibromas due to early emergence of resistance and low therapeutic indices. IK-595, a novel MEK-RAF molecular glue, traps MEK in an inactive complex with all RAF isoforms and durably blocks MEK and ERK phosphorylation. IK-595 overcomes the key resistance mechanisms to approved MEK inhibitors including CRAF-mediated MEK reactivation and kinase independent CRAF activity. Moreover, the PK profile of IK-595 enables robust but intermittent pathway inhibition, which drives apoptosis in MAPK-pathway dependent cancers while minimizing toxicity to healthy cells.

Methods:

This is a phase 1, first-in-human, open-label, multicenter study to evaluate IK-595 as monotherapy in pts with RAS- or RAF-altered advanced solid tumors for whom there are no treatment options known to confer clinical benefit. The study consists of a Dose Escalation phase using a Bayesian Optimal Interval design, followed by a Dose Expansion phase. In Dose Escalation, IK-595 was administered orally at doses ranging from 0.5-8 mg on intermittent dosing schedules (QOD, Q3D, QW, and BIW). Study objectives included evaluation of safety, PK, PD, and antitumor activity (RECIST 1.1).

Results:

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As of Jan 06, 2025, 51 pts enrolled in the Dose Escalation phase across 8 dose regimens. Median age was 61 years (range 35-84); 88% of pts had RAS mutations and 12% had RAF mutations; median number of prior lines of therapy was 3. More than half (53%) of the pts had a

primary diagnosis of CRC, followed by pancreatic cancer (23.5%), and others (23.5%). The treatment was well tolerated and the most common treatment-related adverse events were grade 1 or 2 rash, diarrhea, nausea, fatigue, vomiting, and retinopathy. IK-595 exposure increased dose proportionally and the $t_{½}$ was ~24 hrs. Robust pERK inhibition was demonstrated in a blood PD assay. Saturating inhibition occurred with doses ≥1 mg 4 hrs after dosing. The durability of inhibition increased with increased dose; 6mg resulted in a PD response of ~90% at 24 hrs and ~80% at 72 hrs. Blood samples were collected to evaluate ctDNA dynamics and will be presented. The overall DCR was 44% (15/34) in disease-evaluable pts. Significant tumor reduction was observed in 5 pts; 2 cPRs occurred in KRAS G12D gastric (2 prior lines tx) and KRAS G12D ovarian cancer (3 prior lines tx including MEKi); 1 uPR occurred in KRAS G12R pancreatic cancer with liver metastases (1 prior line tx) with responses ongoing; 2 prolonged SD occurred in Class III BRAF mutant urothelial cancer (7 lines prior tx) for 29 weeks and KRAS G12D CRC (2 lines prior tx) for 30 weeks and ongoing.

Conclusion:

IK-595 is well tolerated in pts with low-grade skin and GI toxicities as the most frequently observed adverse events. Encouraging target inhibition and early antitumor activity in RAS- and RAF-altered solid tumors was observed. Clinical trial information: NCT06270082

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