Abstract # TPS3185: *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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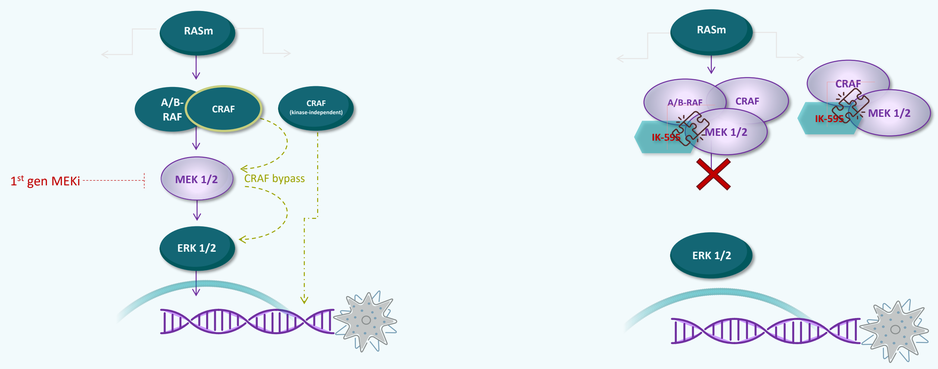
Background

- The RAS pathway is implicated in at least half a million new cancer diagnoses each year in the United States
- Current approved MEK inhibitors block MEK kinase activity, however ERK-mediated negative feedback triggers a CRAF bypass mechanism leading to reactivation of the MEK pathway[1]
- Additionally, CRAF has kinase-independent activity that promotes tumor growth[2] that is not inhibited by 1st generation MEK inhibitors
- CRAF plays a critical role in the therapeutic resistance of approved MEK inhibitors in RAS mutant cancer patients[1]

First gen MEK inhibitors trigger CRAF mediated pathway reactivation

IK-595 traps MEK & RAF in an inactive complex to prevent CRAF bypass and kinase-independent CRAF function



IK-595 is a best-in-class MEK/RAF molecular glue that traps MEK in an inactive complex with all RAF isoforms blocking ERK pathway reactivation and broadly impacting the RAS therapeutic space

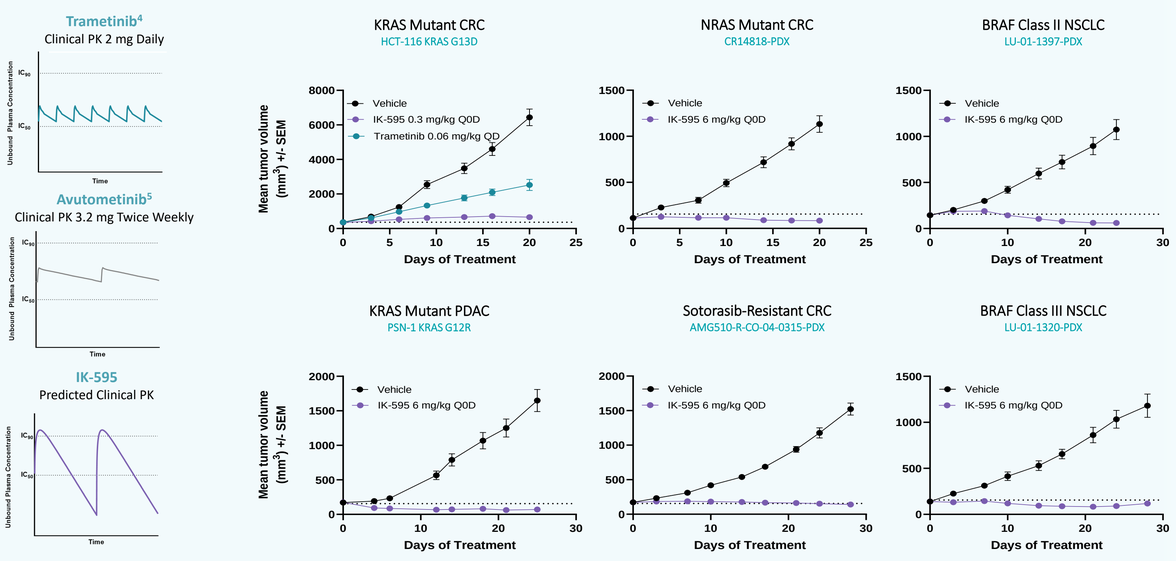
Rationale

IK-595 was designed to overcome key vulnerabilities of first generation and clinical stage MEK inhibitors[3]

- ✓ Inhibit MEK mediated ERK1/2 phosphorylation
- ✓ Prevent MEK phosphorylation by RAF
- ✓ Alleviate therapeutic resistance through CRAF mediated bypass and pathway reactivation
- ✓ Block CRAF kinase independent activities
- ✓ Optimized PK profile to target IC90 plasma concentrations widening the therapeutic window

IK-595 may address cancers other MEK inhibitors have been unable to treat[3]

- ✓ IK-595 has demonstrated robust antitumor activity in preclinical models, including KRAS, NRAS, and non-V600E BRAF mutated tumors as well as RAS-inhibitor resistant models
- ✓ IK-595 could be active in KRAS and NRAS tumors by preventing both feedback activation and by inhibiting the kinase independent function of CRAF



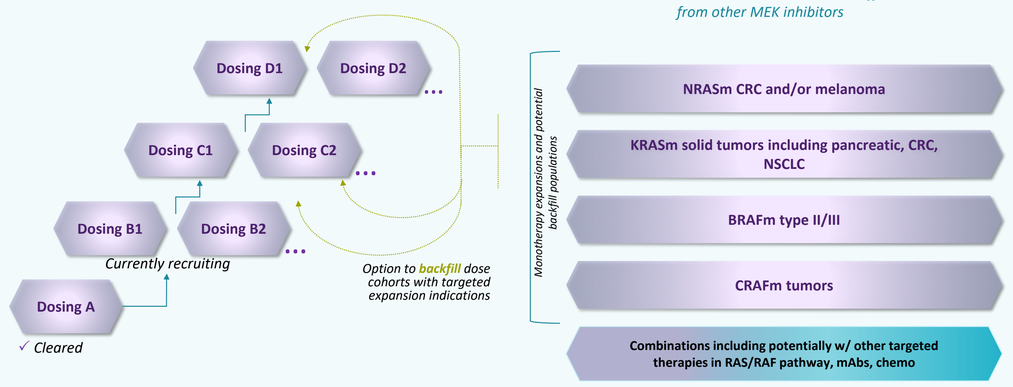
Methods

Study Design

- Phase 1, first-in-human, open-label, multicenter study to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and preliminary antitumor activity of IK-595
- IK-595 is an oral drug administered intermittently with the flexibility to explore additional dosing schedules
- Backfilling will be allowed with ≥ 3 patients per dose level once a dose escalation level is deemed safe and sufficient plasma exposures have been achieved

Dose Escalation & Dose Schedule Exploration
Recruiting only targeted patients into dose escalation including any with RAS or RAF mutations

Dose Expansion and Combinations Following Dose Schedule Selection
Potential indications where IK-595 could be differentiated from other MEK inhibitors



Key Eligibility Criteria

- Advanced and unresectable or metastatic solid tumors with no available therapy known to confer clinical benefit
- Documented RAS/RAF gene alteration determined by local testing
- ECOG performance status of 0 or 1
- Fresh pre-treatment tumor biopsy

Objectives and Endpoints

Primary Objectives/Endpoints

- To determine the safety and tolerability of IK-595
  - *Frequency and severity of adverse events*
  - *Number of patients with dose-limiting toxicities (dose escalation only)*
- To determine the RP2D and/or MTD of IK-595 (dose escalation only)

Secondary Objectives/Endpoints

- To determine the PK of IK-595
- To evaluate the pharmacodynamic effects of IK-595 on pERK in paired tumor biopsies
- To assess preliminary antitumor activity
  - *ORR, TTR, DOR, DCR, and PFS*

Key Exploratory Objectives/Endpoints

- Overall survival (OS)
- Target engagement and pharmacodynamic activity of IK-595 in peripheral blood cells by measuring changes in pERK levels
- Evaluate the association of baseline tumor biomarkers (mutations, gene or pathway expression) with clinical response
- Monitor changes in tumor burden and evaluate molecular response in longitudinal blood sample collections

Statistical Considerations

- During dose escalation, a minimum of 3 patients will be enrolled in each dose level per the BOIN design
- Backfilling will be allowed with at least 3 additional patients once a dose has been deemed safe by the Safety Review Committee
- A Simon 2-stage adaptive design will be used in dose expansion

References

1- Lito *et al.* Cancer Cell 2014
2- Venkatanarayan *et al.* Cell Reports 2022
3- Haines *et al.* AACR Meeting 2024
4- Infante *et al.* Lancet Oncology 2012
5- Martinex-Garcia *et al.* Clin Cancer Res 2012

Study Status

- The study opened in December 2023 and is actively enrolling
- Enrollment in the first 2 cohorts was completed with no DLTs and dose escalation continues
- Clinical Trial information: NCT06270082

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