Abstract# TPS3168 *TRIAL IN PROGRESS:* A Phase 1, First-in-Human Study of IK-930, an Oral TEAD Inhibitor Targeting the Hippo Pathway in Subjects with Advanced Solid Tumors

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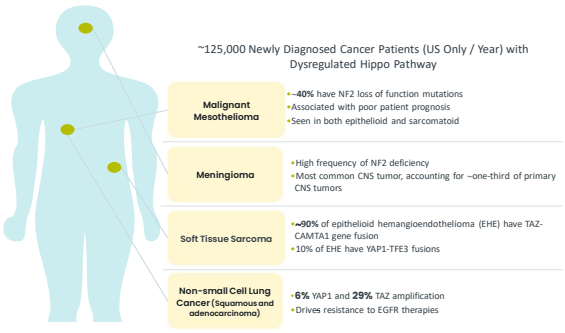
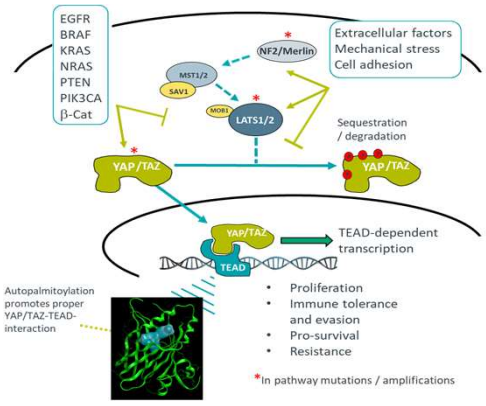
BACKGROUND

- The transcriptional enhanced associate domain (TEAD) proteins are transcription factors in the Hippo signal transduction pathway and are involved in modulating cell growth and survival
- The Hippo pathway is dysregulated in up to 10% of all solid tumors leading to nuclear localization of YAP1/TAZ and subsequent constitutive activation of TEAD which drives oncogenesis
- Increased nuclear YAP1/TAZ and TEAD activity are associated with poor patient outcome, and drive resistance to both chemotherapy and targeted therapy resulting in limited therapeutic options, thus constituting a significant unmet medical need
- Loss of function of NF2 and overexpression, amplification or gene fusion of YAP1 or TAZ frequently occur in specific tumors, such as malignant pleural mesothelioma (MPM), and rare tumors, such as epithelioid hemangioendothelioma (EHE)

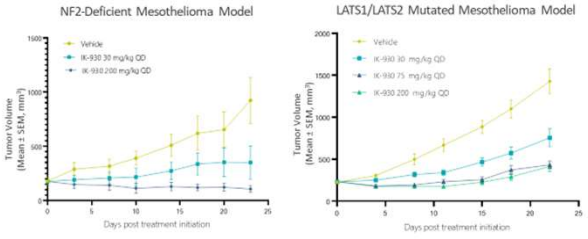


- IK-930 is a novel, selective, small molecule inhibitor that binds to the central lipid pocket of TEAD, prevents palmitate binding, and disrupts aberrant TEAD-dependent transcription



Rationale

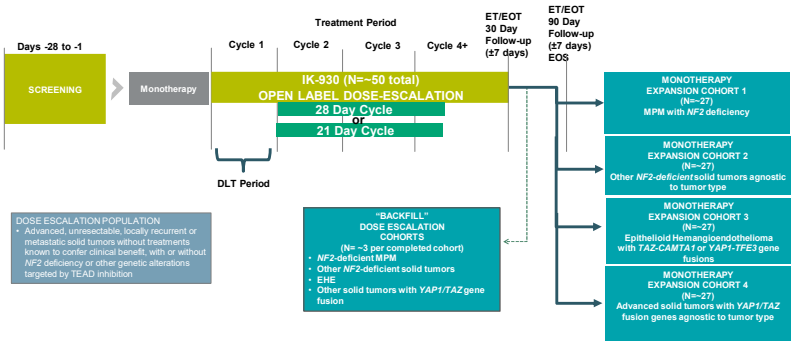
- IK-930 exhibits antitumor activity in tumor models of Mesothelioma with Hippo pathway mutations



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-930
- The monotherapy arm of the study will enroll approximately 158 patients and consists of 2 phases:
  - Dose escalation will enroll approximately 50 adult patients with advanced or metastatic solid tumors for whom there is no available therapy known to confer clinical benefit. Additionally, NF2-deficient MPM, other NF2-deficient solid tumors, and solid tumors harboring YAP1 or TAZ fusion genes, including EHE, will be enrolled for backfilling dose escalation cohorts
  - Dose expansion will enroll up to 27 patients each in four genetically defined cohorts of solid tumors, including: *NF2*-deficient MPM (Cohort 1), other *NF2*-deficient solid tumors agnostic to tumor type (Cohort 2), EHE with *TAZ-CAMTA1* or *YAP1-TFE3* gene fusions (Cohort 3), and solid tumors with *YAP1/TAZ* gene fusions agnostic to tumor type (Cohort 4)



Objectives and Endpoints

- Dose escalation:
  - Primary objectives: safety and tolerability of IK-930 and to determine RP2D and/or MTD
  - Secondary objectives: preliminary antitumor activity (DCR, TTR, DOR, and ORR) and PK of IK-930
- Dose expansion:
  - Primary objectives: safety and tolerability of IK-930 and preliminary antitumor activity (DCR, TTR, DOR, and ORR)
  - Secondary objectives: PK of IK-930, PFS, and OS
- Key exploratory objectives (dose expansion and escalation): pharmacodynamic effect of IK-930 on TEAD target genes, evaluation of baseline candidate biomarkers, evaluation of exploratory biomarkers of kidney injury

Key Eligibility Criteria

INCLUSION CRITERIA	EXCLUSION CRITERIA
Dose escalation: Subjects with advanced, unresectable, locally recurrent, or metastatic malignancy that has progressed on or following standard-of-care therapies and for whom there is no available therapy known to confer clinical benefit, regardless of genetic alterations of the Hippo pathway	Subjects with proteinuria >150mg/dL
Dose expansion: Subjects with NF2-deficient MPM, other NF2-deficient solid tumors agnostic to tumor type, EHE with TAZ-CAMTA1 or YAP1-TF3, or other solid tumors with YAP1/TAZ gene fusions determined as per local testing	Subjects with untreated or symptomatic primary central nervous system (CNS) tumors or with intracranial metastases (excluding primary CNS tumors that may be eligible for enrollment as part of Cohort 2)
No upper limit to the number of prior lines of anticancer therapy received	Has received prior radiotherapy for palliation within ≤ 2 weeks prior to the first dose of study treatment
Have measurable or evaluable disease per RECIST v1.1	Subjects taking strong CYP3A4/5 or CYP2C19 inhibitors or inducers unless they can be transferred to other medications ≥ 5 half-lives prior to dosing

Statistical Considerations

- During dose escalation, at least 3 subjects will be enrolled in each dose level cohort using the BOIN design
- Backfilling will be allowed with at least 3 additional subjects once a dose escalation level is deemed safe by the Safety Review Committee
- A Simon 2-Stage design will be used in each of the four cohorts during dose expansion

STUDY STATUS

The study began in January 2022 and is actively enrolling patients. Clinical trial information: NCT05228015

REFERENCES

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