IK-930, a Novel TEAD-inhibitor, Overcomes Hippo/YAP-mediated Adaptive Response to MEK and EGFR-targeted Therapies

Mihir Rajurkar, Marta Sanchez-Martin, Daniel Hidalgo, Nathan Young, Benjamin Amidon, Sakeena Syed, X. Michelle Zhang, Jeffrey Ecsedy, Lan Xu.

Ikena Oncology, 645 Summer Street, Suite 101, Boston, MA, USA

Download this poster and visit our website

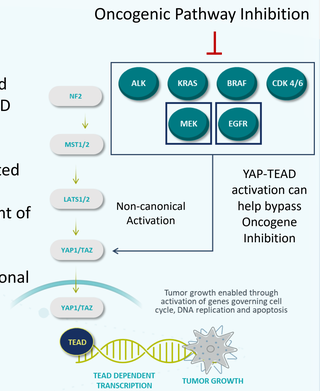
Introduction

The Hippo/YAP/TEAD signaling pathway plays a key role in the regulation of cell proliferation, survival, and tissue homeostasis.. Dysregulated Hippo signaling due to genetic alterations or crosstalk with other oncogenic pathways has been associated with tumorigenesis in multiple cancer types such as mesothelioma, meningioma and NSCLC among others. Additionally, inhibition of pathways such as RAS, MAPK, and EGFR has been shown to drive YAP-TEAD signaling suggesting YAP-TEAD signaling as an important mechanism of resistance to oncogene targeted therapies. To investigate the mechanism of YAP/TAZ activation upon treatment with targeted therapies, KRAS or EGFR mutant cell lines were engineered to express a TEAD-luciferase reporter, and then treated with multiple MEK and EGFR inhibitors. These studies demonstrated that inhibition of MEK or EGFR with small molecules induces activation of YAP-TEAD signaling in a dose dependent manner suggestive of TEAD pathway upregulation as an adaptative response to oncogene inhibition in cancer. Furthermore, treatment with multiple MEK inhibitors with different mechanism of action, or with EGFR inhibitors resulted in nuclear translocation of YAP, as demonstrated in immunofluorescence experiments. Importantly, the addition of Ikena's TEAD inhibitor IK-930, resulted in abrogation of TEAD-mediated transcription induced by MEK or EGFR inhibitors. Consistently, combination of IK-930 with MEKi and EGFRi resulted in apoptosis in vitro and led to strong antitumor activity in vivo in KRAS and EGFR mutant xenografts models of CRC and NSCLC. Importantly, we find that treatment with IK930 prevented the emergence of EGFRi resistant "persister" cells, thus overcoming the Hippo/YAP-mediated adaptive response to EGFR inhibition.

Our findings provide a strong rationale for combined targeting of TEAD with MEK and EGFR, and support clinical evaluation of the IK-930 in combination with targeted therapies in oncogene driven solid tumors.

Hippo/YAP/TEAD activation is an adaptive response to targeted therapy

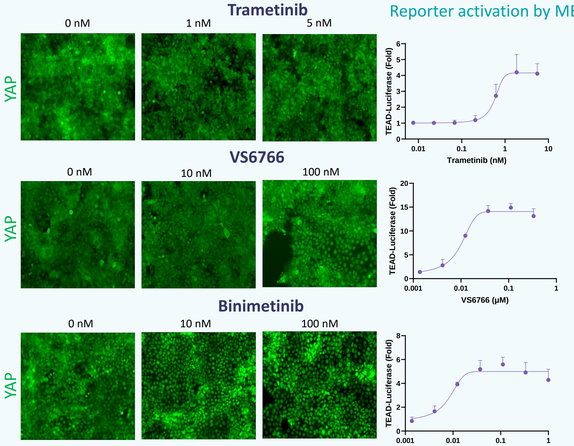
- YAP/TAZ translocate to the nucleus, and activate transcriptional activity via TEAD family transcription factors
- YAP/TAZ can be non-canonically activated in cancer cells upon treatment with oncogene-targeted agents, independent of upstream Hippo signaling
- Abnormal TEAD-dependent transcriptional activation is a potential mechanism of resistance to targeted therapies



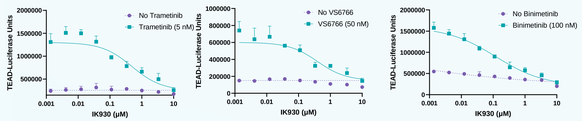
YAP-TEAD signaling is activated in response to MEK inhibitors in HCT116 (KRAS G13D) cells

YAP IF: Increased Nuclear Localization with MEKi

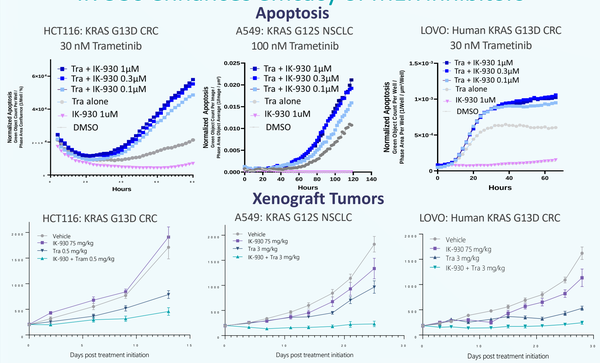
Dose-dependent TEAD-Reporter activation by MEKi



IK-930 inhibits MEKi induced Adaptive YAP-TEAD signaling

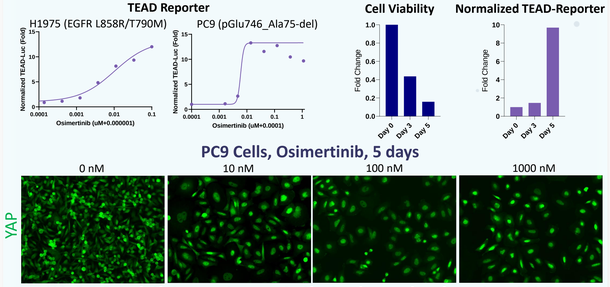


IK-930 enhances efficacy of MEK inhibitors

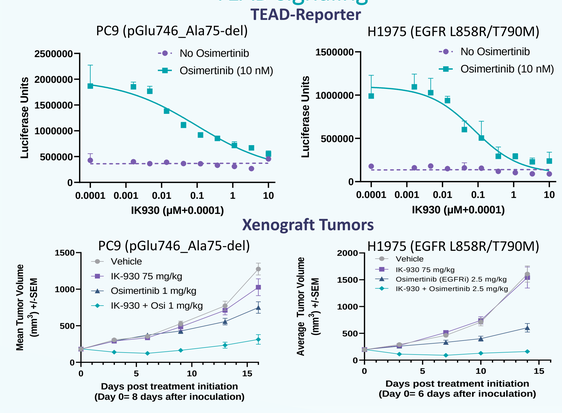


EGFRi osimertinib activates YAP-TEAD signaling in EGFR-mut NSCLC cells

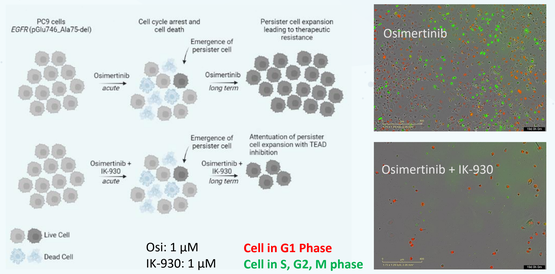
Dose-dependent TEAD-reporter activation by osimertinib



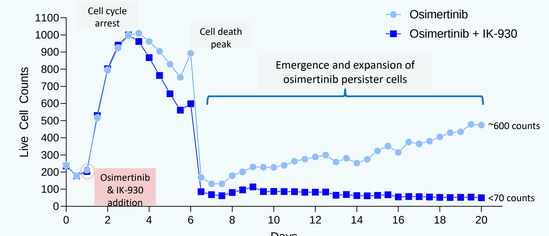
IK-930 inhibits osimertinib-induced adaptive YAP-TEAD signaling



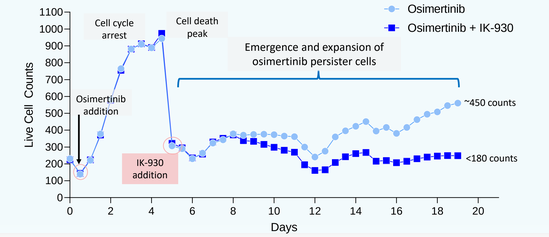
Efficacy of IK-930 against osimertinib-refractory "persister" cells



IK-930 + osi combined treatment prevents emergence of persisters



IK-930 addition after persister emergence attenuates expansion



IK-930 combination therapy: An opportunity to overcome adaptive response to oncogene-targeting

- The Hippo pathway is implicated in resistance to multiple targeted therapies
- Ikena's TEAD-palmitoylation inhibitor, IK-930, prevents Hippo/YAP-mediated adaptive response to targeted therapies
- IK-930 enhances anti-tumor activity of MEK and EGFR inhibitors
- IK-930 prevents emergence, and expansion of EGFRi osimertinib-resistant "persister" cells
- These data support clinical evaluation of IK-930 in combination with MEKi in *KRAS*-mut cancers and EGFRi in *EGFR*-mut cancers
- IK-930 is currently being evaluated in a Phase 1a/b clinical trial as a monotherapy in Hippo pathway-mutated cancers, with planned combo cohorts with EGFRi and MEKi

Visit clinicaltrials.gov for more on the trial