IK-930, a Paralog Selective TEAD Inhibitor Effectively Attenuates Drug-Tolerant Persister Cell Proliferation

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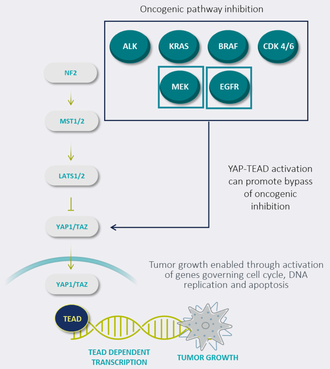
INTRODUCTION

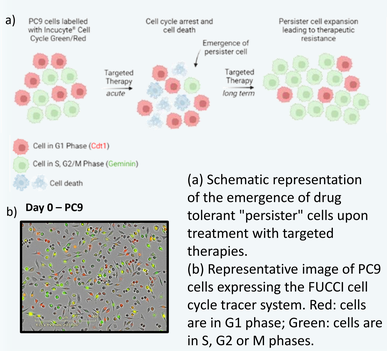
- The Hippo pathway kinase cascade negatively regulates the activity of transcription cofactor YAP/TAZ in a complex with DNA-bound transcription factor TEAD1-4
- Mutations in the Hippo pathway that result in activation of YAP/TAZ/TEADs are prevalent in multiple cancers (*Lin et al., Nature Genetics 2015; McGowan et al., Genes Cancer 2017*)
- **YAP/TAZ/TEADs transcriptional activity can also be induced upon inhibition of oncogenic drivers, leading to the emergence of drug tolerant "persister" cells and disease relapse** (*Kurppa et al., Cancer Cell 2020)*
- IK-930 is a TEAD1 selective palmitoylation inhibitor (see poster #1646) that effectively inhibits the transcriptional activity of YAP
- **IK-930 combined with EGFRi or MEKi can prevent the emergence of persister cells and attenuate resistance to these targeted therapies**
- IK-930 is currently in Phase 1 clinical development (NCT05228015)

Figure 1: YAP/TAZ/TEAD activation is an adaptive response to targeted therapies



Drug Tolerant (Persister) Cells Drive Therapeutic Resistance

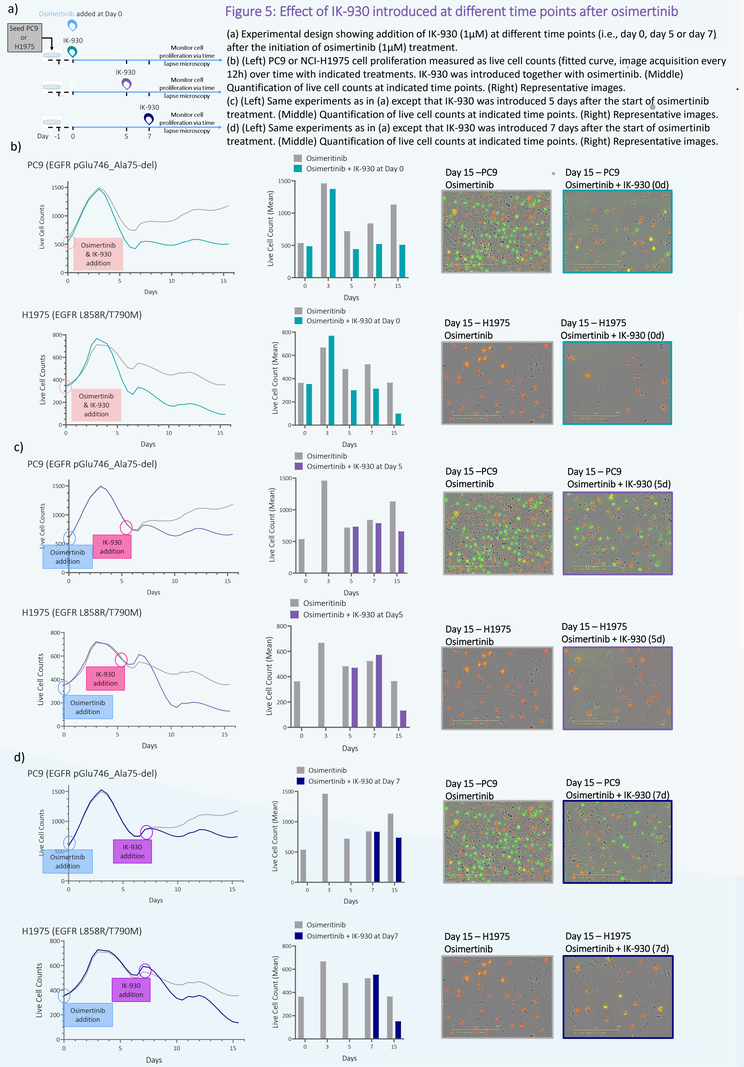
Figure 3: Real time monitoring of persister cell population by Fluorescence Ubiquitination Cell-Cycle Indicator (FUCCI)



(a) Schematic representation of the emergence of drug tolerant "persister" cells upon treatment with targeted therapies.
(b) Representative image of PC9 cells expressing the FUCCI cell cycle tracer system. Red: cells are in G1 phase; Green: cells are in S, G2 or M phases.

IK-930 Effectively Inhibits the Expansion of Osimertinib Tolerant Persister Cells Even After Their Emergence

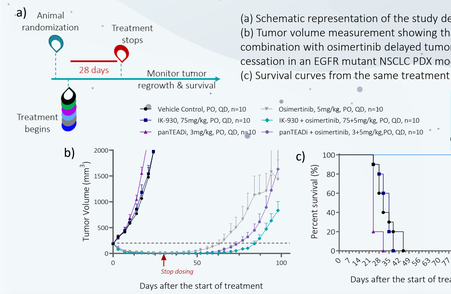
Figure 5: Effect of IK-930 introduced at different time points after osimertinib



(a) Experimental design showing addition of IK-930 (1μM) at different time points (i.e., day 0, day 5 or day 7) after the initiation of osimertinib (1μM) treatment.
(b) (Left) PC9 or NCI-H1975 cell proliferation measured as live cell counts (fitted curve, image acquisition every 12h) over time with indicated treatments. IK-930 was introduced together with osimertinib. (Middle) Quantification of live cell counts at indicated time points. (Right) Representative images.
(c) (Left) Same experiments as in (a) except that IK-930 was introduced 5 days after the start of osimertinib treatment. (Middle) Quantification of live cell counts at indicated time points. (Right) Representative images.
(d) (Left) Same experiments as in (a) except that IK-930 was introduced 7 days after the start of osimertinib treatment. (Middle) Quantification of live cell counts at indicated time points. (Right) Representative images.

IK-930 can Delay Tumor Recurrence in EGFRm Models

Figure 6: IK-930 + osimertinib combination delays tumor re-growth and prolongs survival in an EGFR mutant NSCLC PDX model

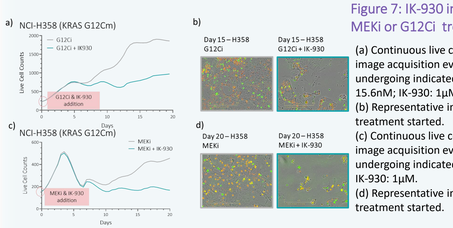


(a) Schematic representation of the study design.
(b) Tumor volume measurement showing that IK-930 (or panTEADi) in combination with osimertinib delayed tumor regrowth upon treatment cessation in an EGFR mutant NSCLC PDX model.
(c) Survival curves from the same treatment groups in (b).

No deaths in IK-930-osi combo group

IK-930 Shows Potential to Combat Resistance to MEKi or KRasG12Ci

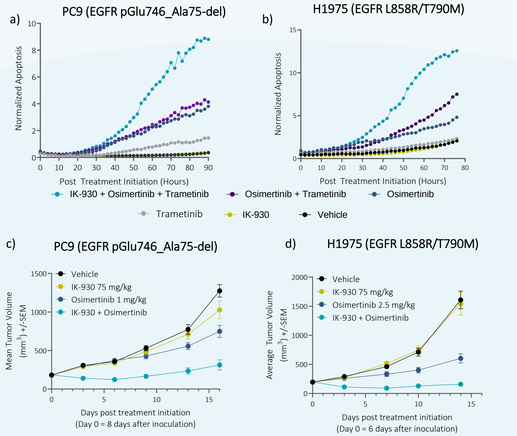
Figure 7: IK-930 inhibits expansion of MEKi or G12Ci treatment tolerant cells



(a) Continuous live cell counting (fitted curve, image acquisition every 12h) of NCI-H358 cells undergoing indicated treatments. G12Ci: 15.6nM; IK-930: 1μM.
(b) Representative images of (a) at day 15 after treatment started.
(c) Continuous live cell counting (fitted curve, image acquisition every 12h) of NCI-H358 cells undergoing indicated treatments. MEKi: 2μM; IK-930: 1μM.
(d) Representative images of (c) at day 20 after treatment started.

IK-930 Enhances Anti-Tumor Activity of Osimertinib *in vitro* and *in vivo*

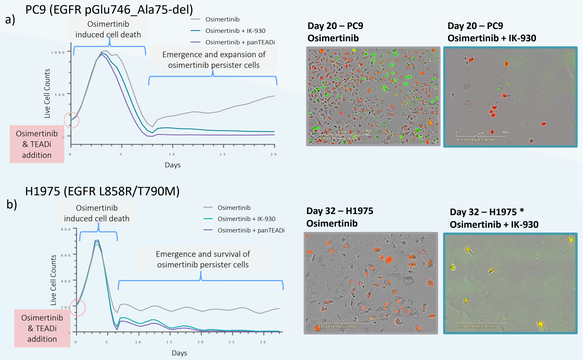
Figure 2: IK-930 enhances apoptosis induction *in vitro* and anti-tumor activity *in vivo* in combination with osimertinib



(a & b) A time course of apoptosis induction in PC9 or NCI-1975 cells upon IK-930, osimertinib and trametinib treatment as indicated.
(c & d) *in vivo* tumor growth inhibition activity of IK-930 and osimertinib, alone or in combination, in PC9 or NCI-H1975 xenografts.

TEAD1 Selective Palmitoylation Inhibitor IK-930 is Comparable to panTEADi in Preventing Emergence of EGFRi Resistant Persister Cells

Figure 4: IK-930 prevents emergence and expansion of persisters upon osimertinib treatment in EGFRmut NSCLC cells



(a) Continuous live cell counting (fitted curve, image acquisition every 12h) of PC9 cells (IncuCyte) undergoing indicated treatments. Media and inhibitors were replenished every 5 days. Osimertinb: 1μM; IK-930: 1μM; and panTEADi: 1μM. Representative images are shown to the right.
(b) Same experiment as (a) using NCI-H1975 cells. Representative images are shown to the right.

CONCLUSIONS

- IK-930 co-treatment is effective against the expansion of persister cells that emerge after targeted therapies including EGFRi, MEKi, and KRasG12Ci
- Consistent with the impact of IK-930 on persister cells, IK-930 co-treatment delayed tumor re-growth after treatment cessation *in vivo*
- Efficacy of TEAD1-selective IK-930 against osimertinib persister cells is comparable to that of a panTEAD palmitoylation inhibitor *in vitro* and *in vivo*

These data suggest multiple combination opportunities for IK-930 to treat patients with either EGFRmut or RASmut cancers. Ikena Oncology is planning clinical development of IK-930 in combination with multiple targeted therapies, the first of which is osimertinib in EGFRmut NSCLC.