Hippo Pathway Relationship to RAS / EGFR Signaling; Therapeutic Potential

Hippo Pathway Targeted Drug Development Summit

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May 26 2022

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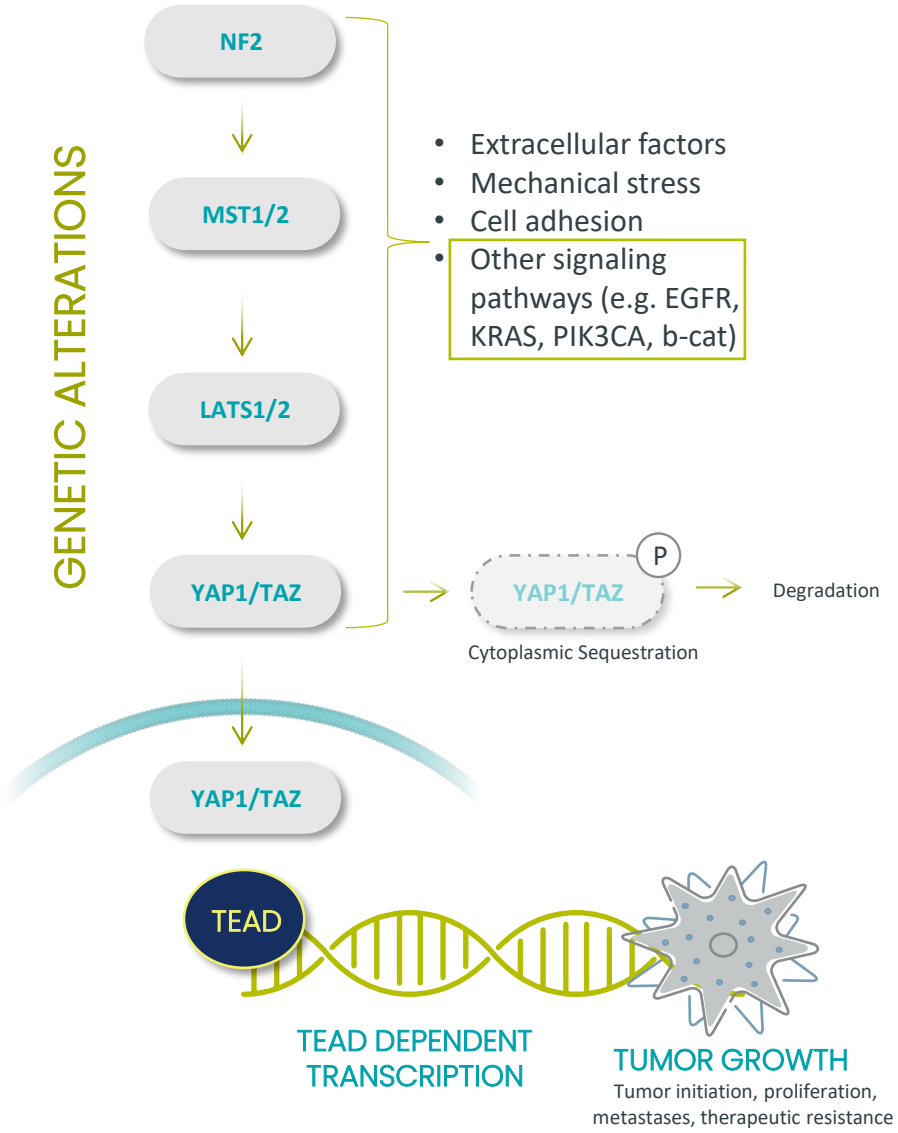
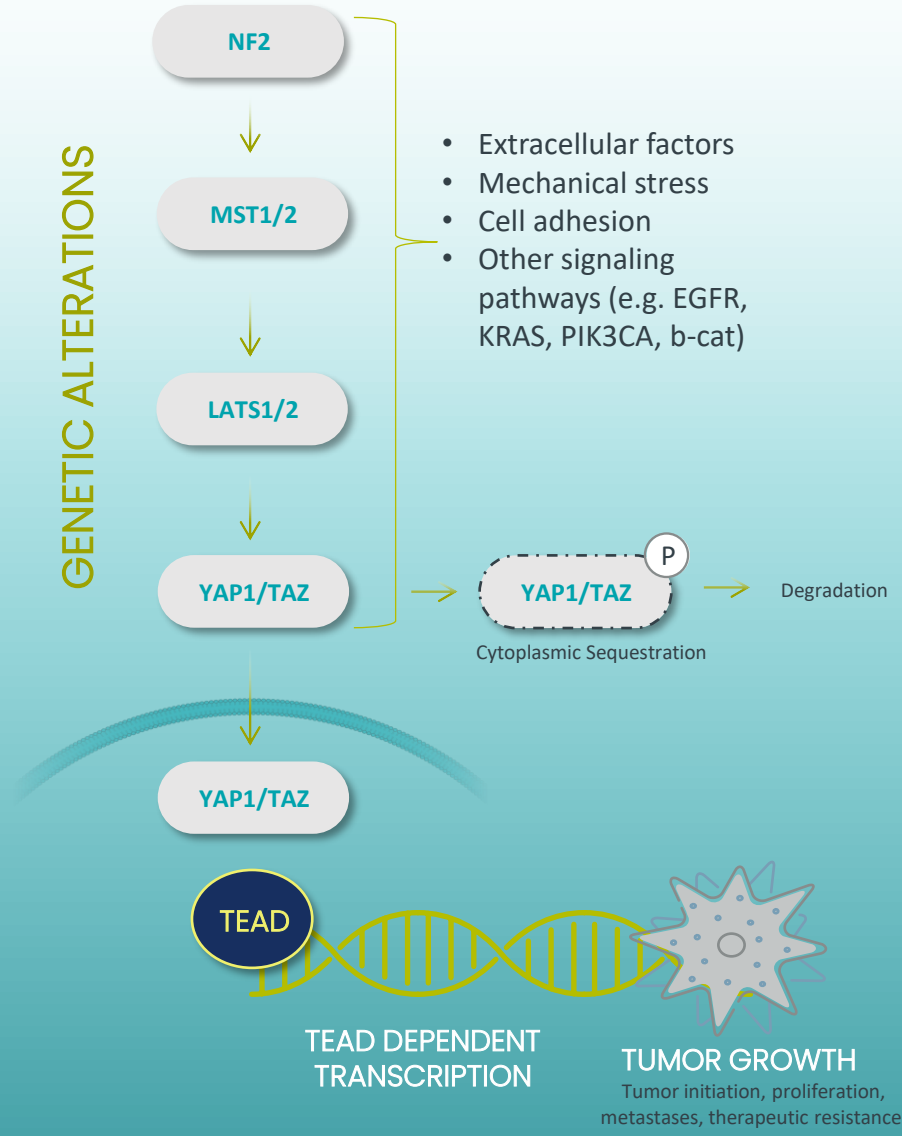
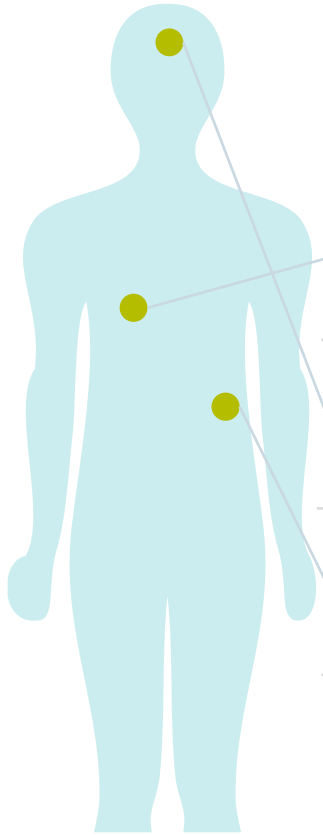
Hippo Signal Transduction Pathway in Cancer



- Multiple activating signals drive
  YAP/TAZ nuclear localization ⇢ TEAD binding ⇢ gene expression of proliferation / pro-survival pathways
- TEAD transcription dysregulated in many cancers
  Numerous tumor suppressor / oncogenes lead to TEAD activation
  Increased nuclear YAP1/TAZ, TEAD activity associated with poor outcome
- Key mechanism of therapeutic resistance

Genetic Alterations in Hippo Pathway Drive Oncogenesis in Patients Across Multiple Indications





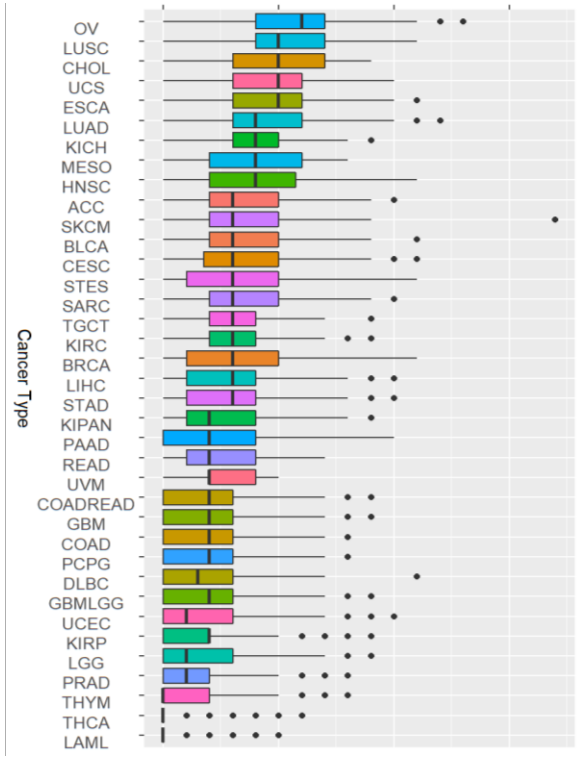
~125,000 Newly Diagnosed Cancer Patients (US Only / Year) with Deregulated Hippo Pathway

Malignant Mesothelioma	• ~**40%** have NF2 loss of function mutations • Associated with poor patient prognosis • In both epithelioid and sarcomatoid
Meningioma	• High frequency of NF2 deficiency • Most common CNS tumor, accounting for ~one-third of primary CNS tumors
Soft Tissue Sarcoma	• **~90%** of epithelioid hemangioendothelioma, or EHE, have TAZ-CAMTA1 fusions • 10% of EHE have YAP1-TFE3 fusions

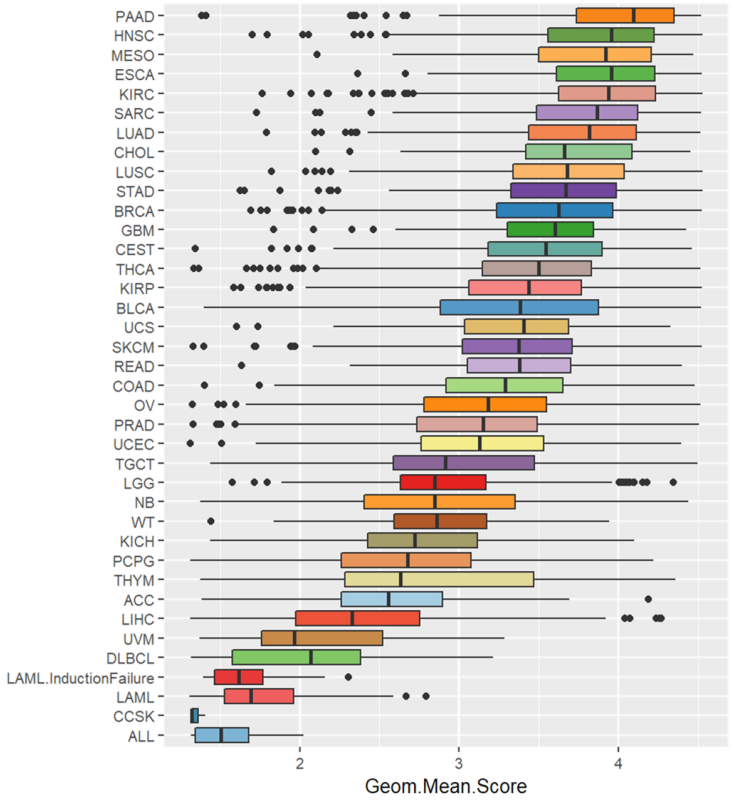
Translational Data to Drive Indication Selection

Bioinformatics Analyses

NF2, YAP1, TAZ, LATS1/2, MST1/2, BAP1 Alterations



YAP1/TAZ Activity Score*

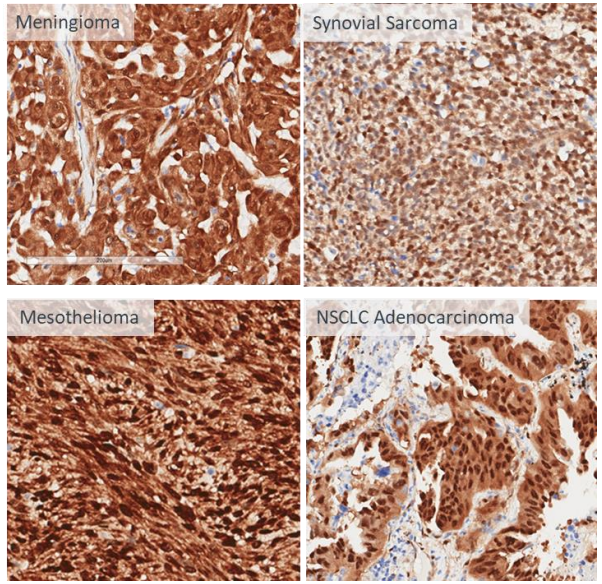


Overlapping Tumors

MESO, HNSCC, CHOL, NSCLC, ESCA, KIRC/CH

**Signature derived from Pham et al 2021*

YAP/TAZ Nuclear Localization

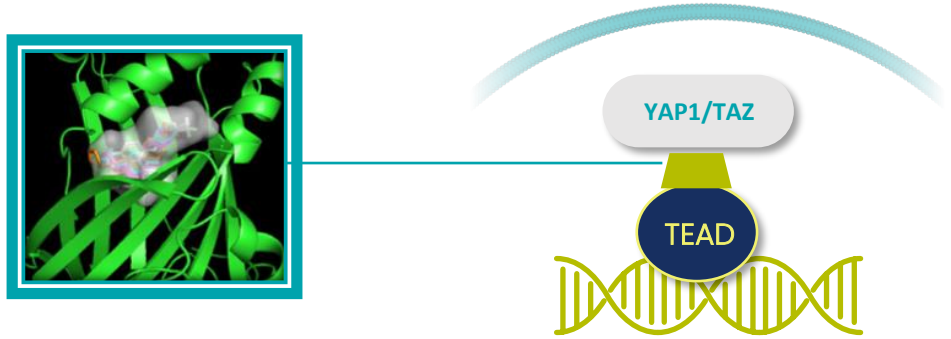


High YAP1 nuclear protein expression indicative of pathway activation in select indications

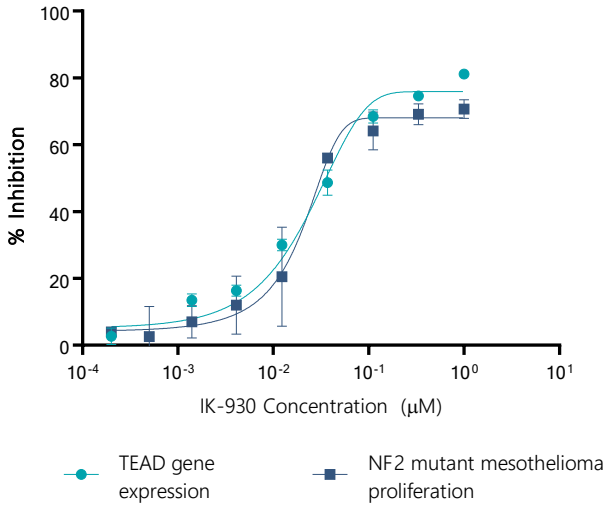
	%YAP1 +2 +3	%TAZ +2 +3
Meningioma	76	**8**
Sarcoma	56	**11**
Mesothelioma	46	**19**
HNSCC	**43**	**1**
Cholangiocarcinoma	31	**4**
NSCLC	25	**10**
Pancreas	20	**4**
Thymoma	10	**5**
Liver/Hepatocellular	3	**1**

IK-930 is an Oral, Selective, Potent TEAD Inhibitor

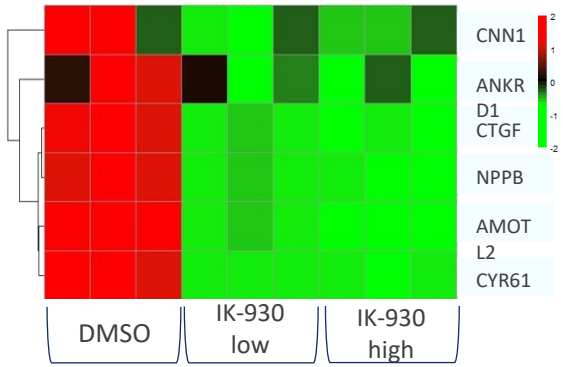
Binding the Central Lipid Pocket of TEAD



Potent TEAD Inhibition

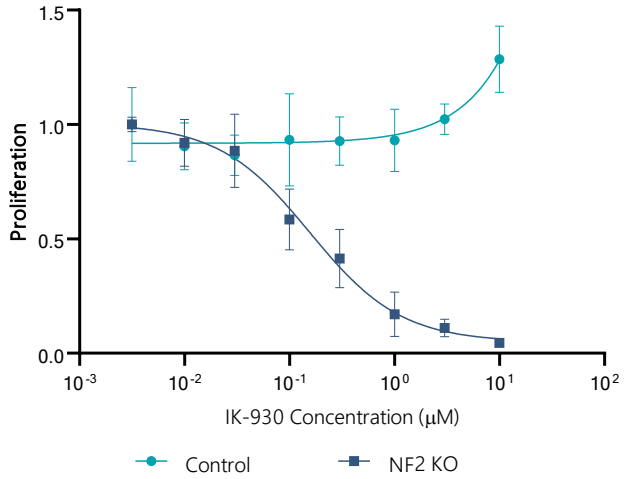


Robust Inhibition TEAD Target Gene Expression



TEAD activated cell line

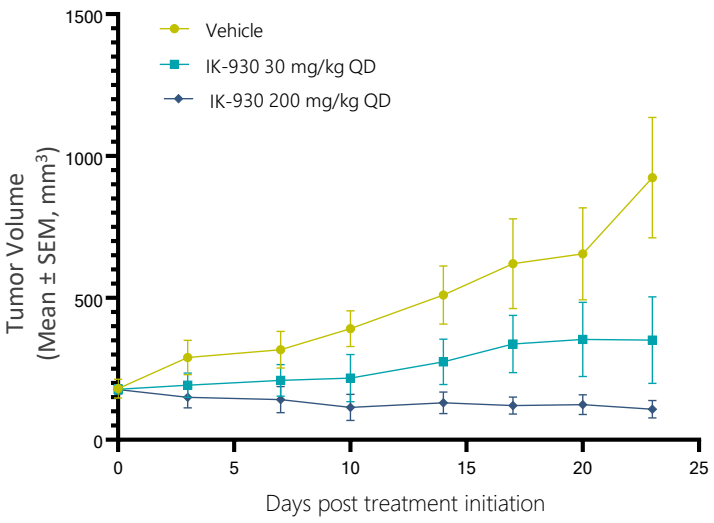
Selective Activity in Hippo-Mutated Cells



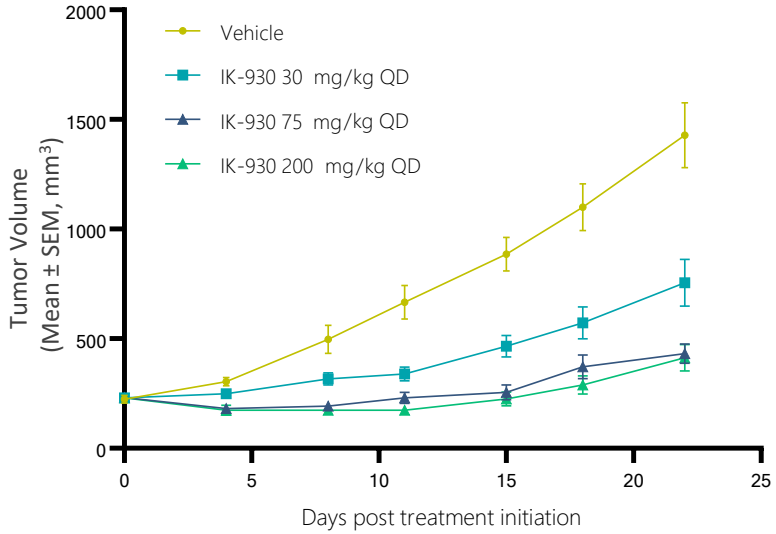
IK-930 Demonstrated Anti-Tumor Activity in Tumor Models with Hippo Pathway Mutations

Potential for Monotherapy Across Genetic Mutations

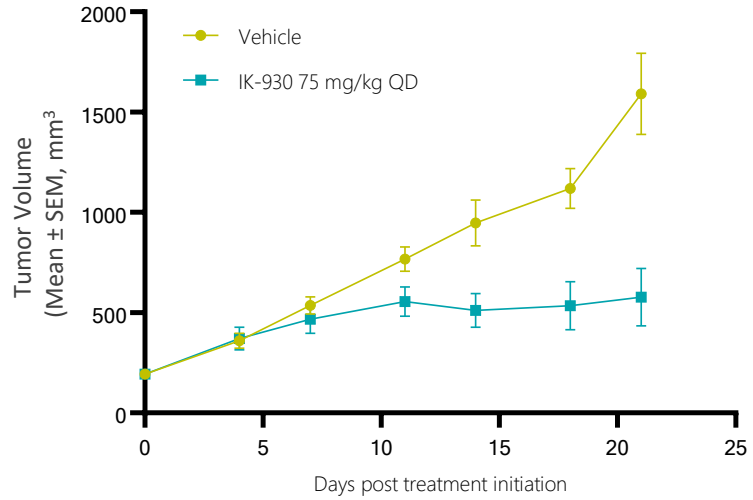
NF2 Deficient Mesothelioma Model



LATS1/LATS2 Mutated Mesothelioma Model



YAP1 Amplified HNSCC Model



IK-930 is a Well Tolerated TEAD Inhibitor with Favorable ADME/PK Profile

- ✓ Highly selective across a receptor, enzyme, ion channel safety panel (> 50 fold over H226 IC_{50})
- ✓ Minimal inhibition of hERG in automated patch clamp assay (IC_{50} > 200 fold over H226 IC_{50})
- ✓ Minimal Cyp inhibition - low potential to drug-drug-interactions
- ✓ Not a substrate of P-gp or BCRP transporters
- ✓ Moderate and similar plasma protein binding across species
- ✓ Very good oral bioavailability in mouse, rat, dog, and monkey
- ✓ Brain penetrant

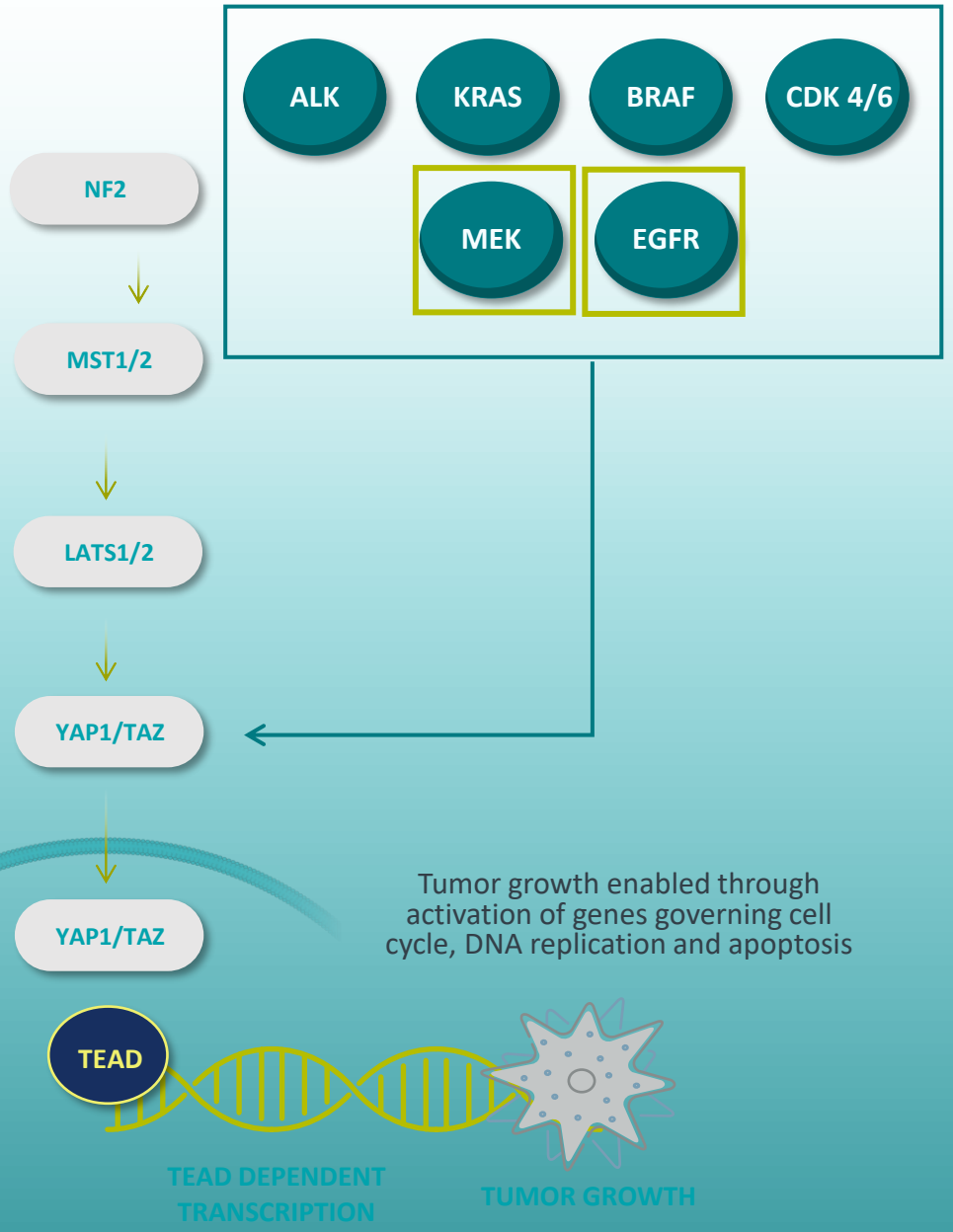
Cyp, hERG and Safety Panel Profiling Suggest Low Risk for Drug-drug Interaction and Off Target Toxicity Concerns

CYP Inhibition, IC_{50}	
Cyp1A2	>10 uM
Cyp2B6	>10 uM
Cyp2C9	>10 uM
Cyp2C19	7.6 uM
Cyp2D6	>10 uM
Cyp3A4-M	9.0 uM
Cyp3A4-T	>10 uM

Plasma protein binding, free fraction	
Mouse	2.8%
Rat	1.7%
Dog	2.1%
Monkey	2.3%
Human	4.3%

Nonclinical PK Summary		
Mouse	T1/2	1.6 h
	Vd	2.7 L/kg
	Oral bioavailability	55%
Rat	T1/2	1.7 h
	Vd	2.8 L/kg
	Oral bioavailability	56%
Dog	T1/2	1.8 h
	Vd	3.1 L/kg
	Oral bioavailability	52%
Monkey	T1/2	2.2 h
	Vd	2.8 L/Kg
	Oral bioavailability	49%

Role of Hippo Pathway in Therapeutic Resistance; Multiple Opportunities for Combination with IK-930

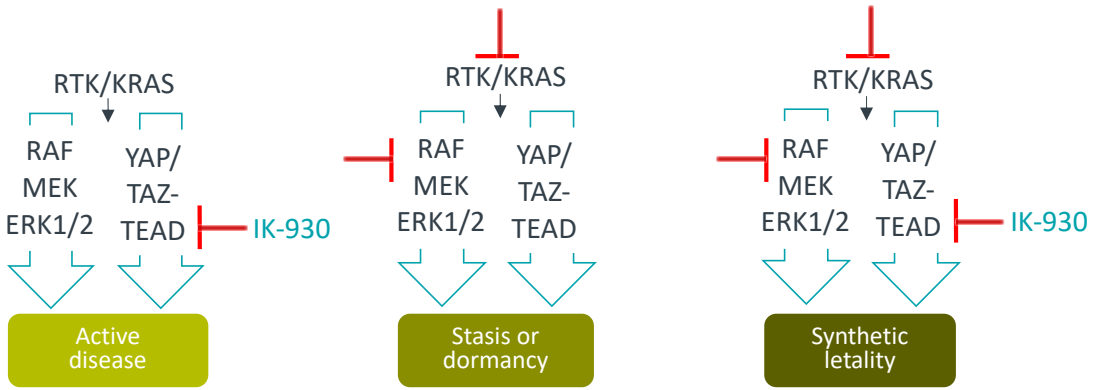


Screens identifying Hippo-mediated resistance

Cancer	Condition	Hit	Format	Reference
Melanoma	BRAFi	NF2	CRISPR	Shalem, O. et al. (2014) Science, 343, 84
Melanoma	BRAFi	EMICERI*	CRISPR	Joung, J. et al. (2017) Nature, 548, 343
BRAF mut lung	BRAFi	YAP	shRNA	Lin, et al., (2015) Nat Genet, Mar; 47(3): 250
Kras mut CRC	Kras KD	YAP	cDNA	Shao et al., (2014) Cell, 3;158(1):171
PDAC	Kras KO	YAP amp	GEMM	Kapoor, A. et al. (2014) Cell, 158, 185
NSCLC	EGFRi	TEAD Gene signature	RNASeq	Kurppa, K et al. (2020) Cell, 37 (104-22)
NSCLC	EGFRi	NF2	CRISPR	Zeng, H. et al (2019 Elife, 8:e50223

* EMICERI : Increase MOB3B (component of MST1/2 and LATS1/2 inhibitor complex) expression

Combined TEAD and RTK or KRAS / MAPK inhibition synthetically lethal in BRAF- and KRAS mutant tumors

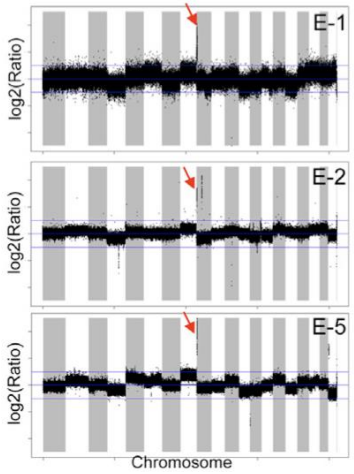


Adapted from Lin, et al., (2015) Nat Genet, Mar; 47(3): 250

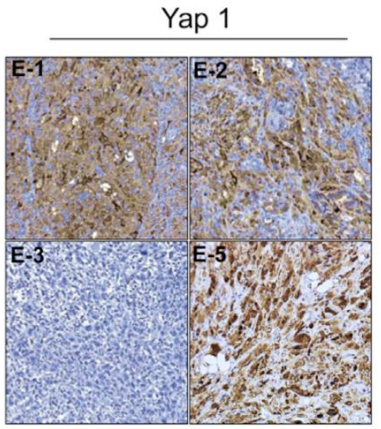
Role of YAP1/TEAD in KRAS Mutated Pancreatic Cancer

- Yap required for progression to invasive PDAC in mutant Kras or Kras:Trp53 mice (Zhang Sci Signal, 2014)
- YAP1/TEAD mediates tumor recurrence in PDAC GEMM upon $KRAS^{G12D}$ withdrawal (Kapoor et al Cancer Cell 2014)
  - $KRAS^{G12D}$ extinction induced rapid tumor regression
  - Subset of relapsed tumors lacking $KRAS^{G12D}$ mediated by YAP1/TEAD
- YAP1 activation mediates pancreatic cancer progression upon wild-type KRAS allele loss (Yan et al Oncogene 2021)

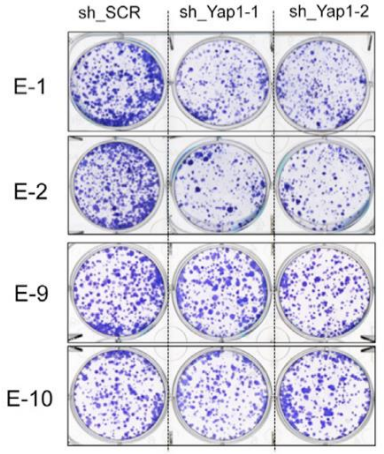
9qA1 (Yap1) amplification by aCGH

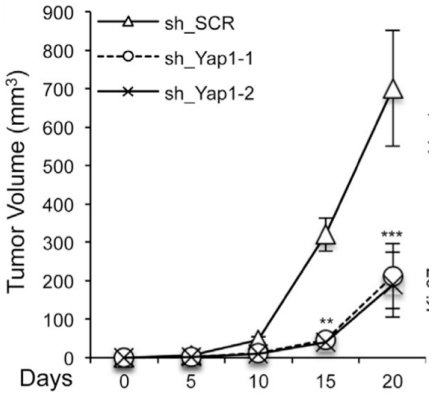


YAP1 IHC in KRAS independent tumors



YAP1 dependent tumor growth in KRAS independent tumors (E-1, E-2)

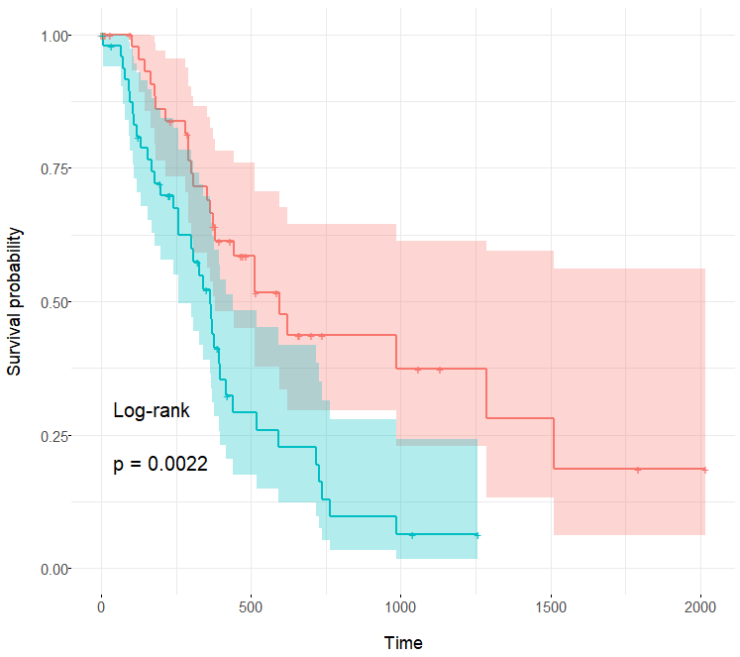




Kapoor et al Cancer Cell 2014 (DOI: 10.1016/j.cell.2014.06.003)

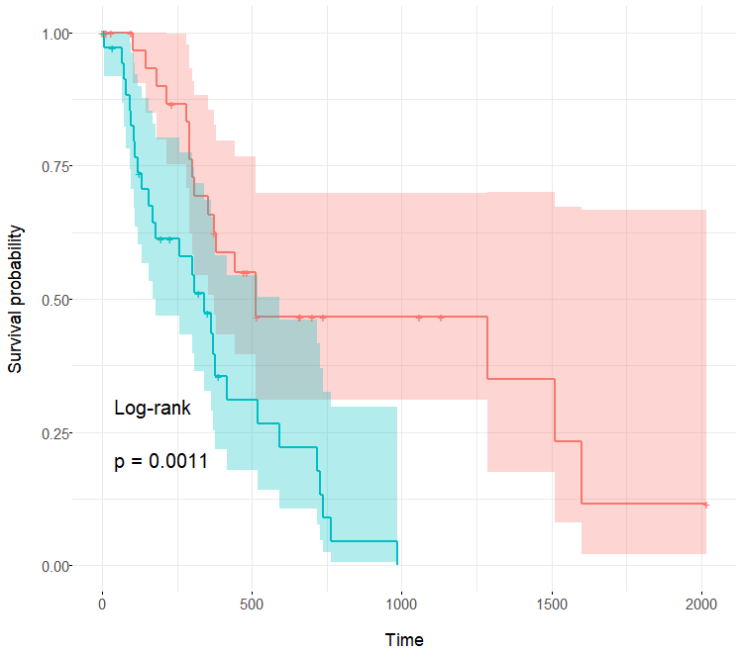
Hippo/YAP1 Transcriptional Signature Associated with Poor Outcome in KRAS Mutated Pancreatic Cancer

All samples (n = 149)



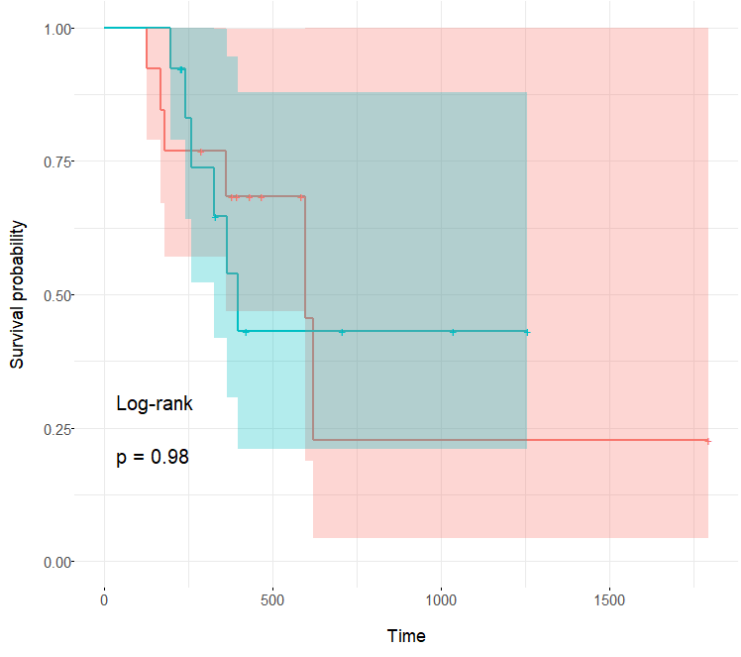
$p_{continuous}$ = 4.3E-05

KRAS mutant (n = 109)



$p_{continuous}$ = 5.9E-05

KRAS wild-type (n = 40)



$P_{continuous}$ = 0.49

Bottom 33% of samples by expression

Top 33% of samples by expression

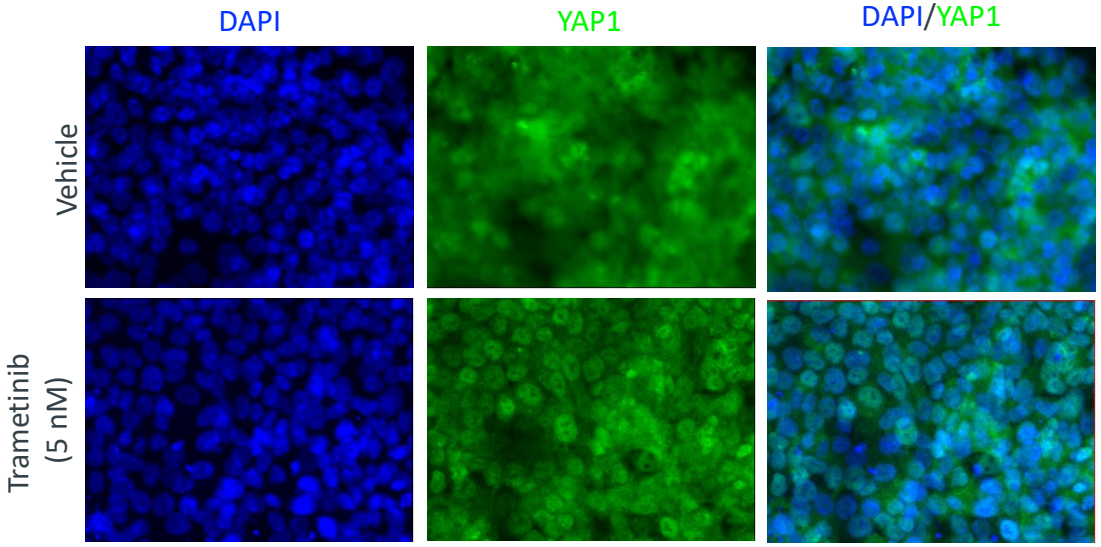
Signature also associated with decreased OS in KRAS mutated NSCLC

Hippo signature derived from Pham et al *Can Dis* 2021

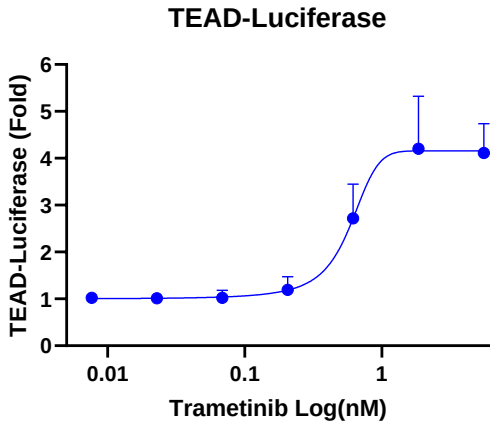
11

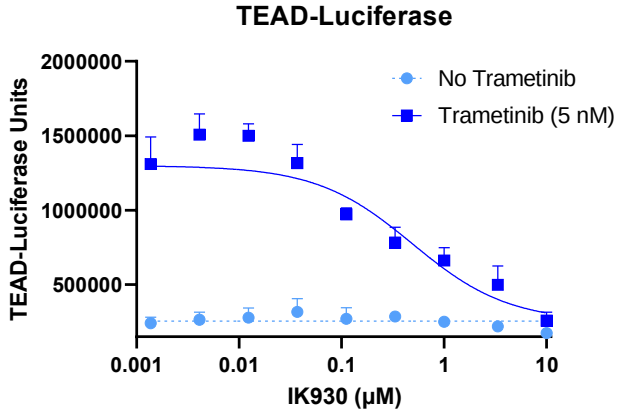
MEK Inhibitor Induces YAP1 Nuclear Localization and TEAD Dependent Transcription

HCT116 cells (KRAS G13D)



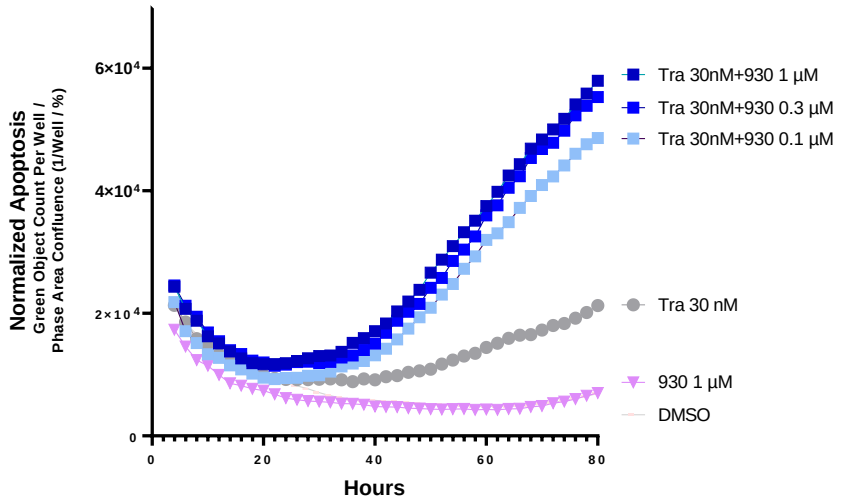
HCT116 cells (KRAS G13D)



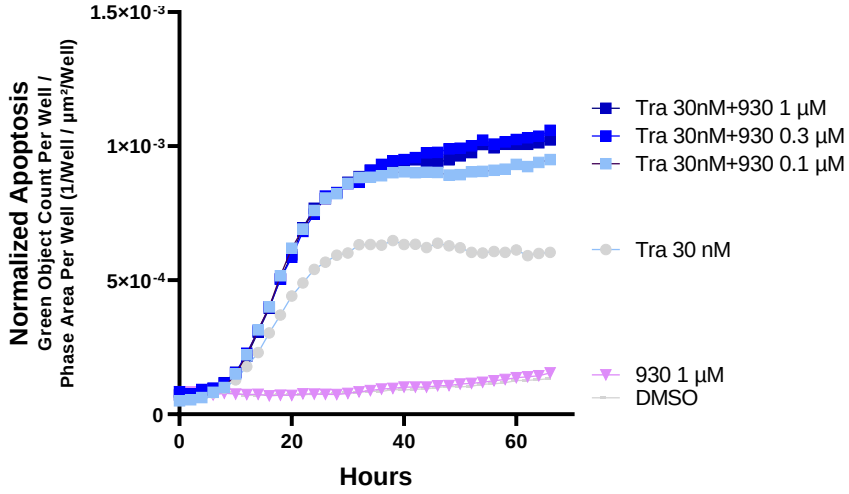


IK-930 Enhances Apoptosis in Trametinib-Treated KRAS Mutant Cells

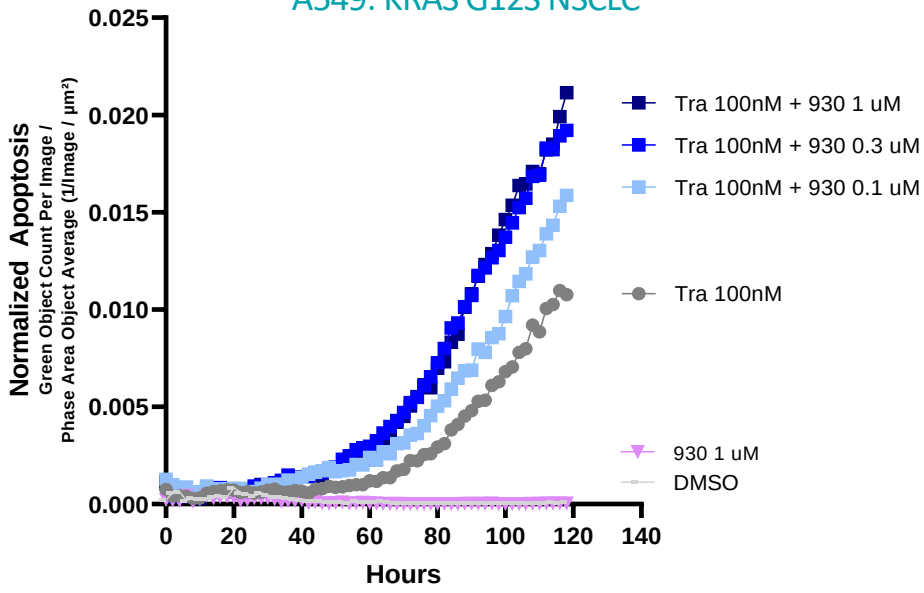
HCT116: KRAS G13D CRC



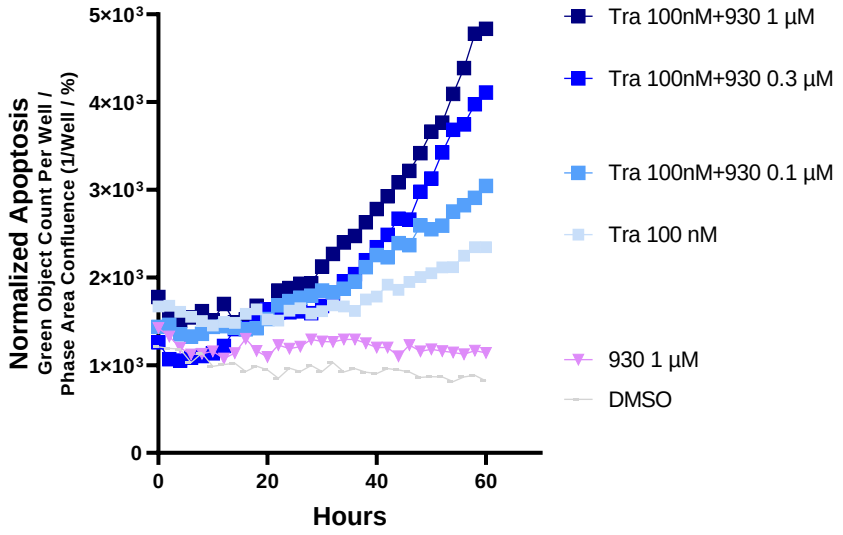
LOVO: Human KRAS G13D CRC



A549: KRAS G12S NSCLC

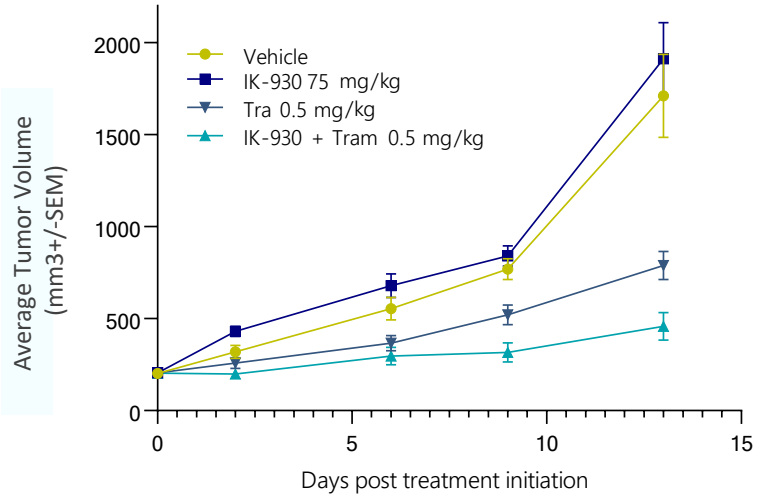


Calu-1: KRAS G12C NSCLC

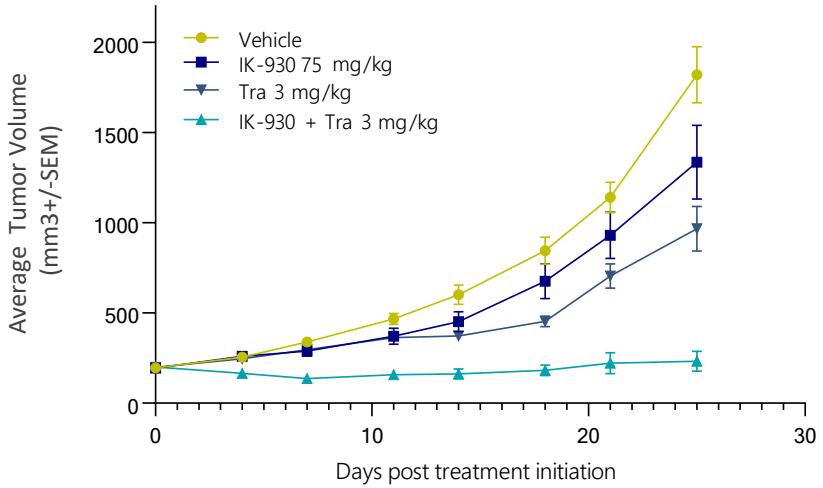


Increased Anti-Tumor Effect of IK-930 in Combination with MEK Inhibitor in KRAS Mutant Tumors In Vivo

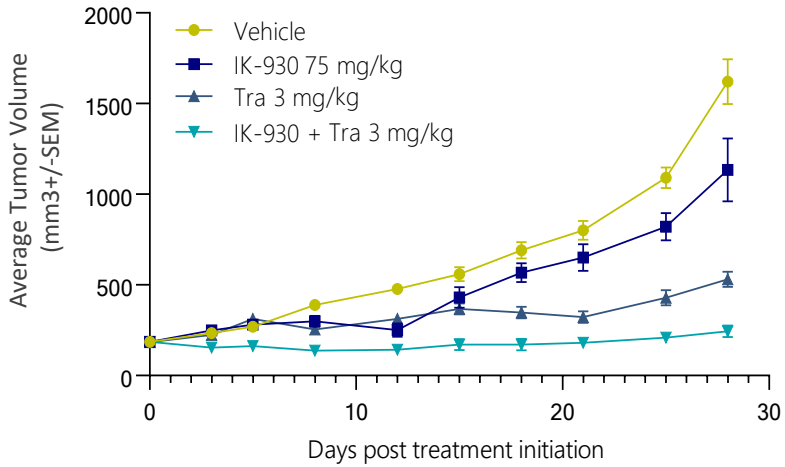
Impact Across Tumor Models for KRASm CRC and NSCLC



HCT116: KRAS G13D CRC



A549: KRAS G12S NSCLC

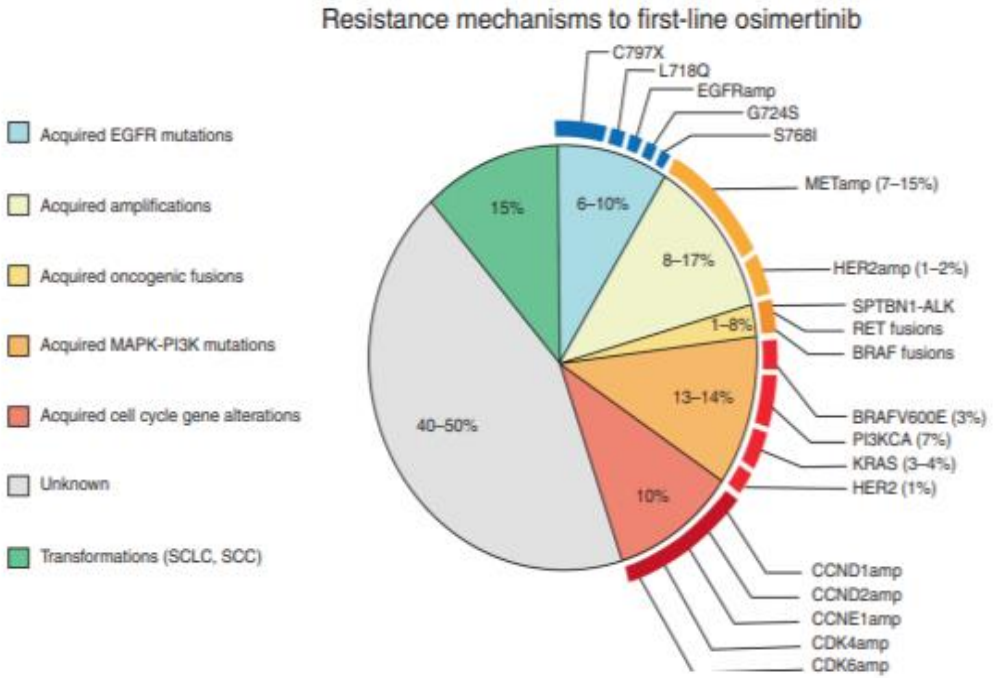


LOVO: Human KRAS G13D CRC

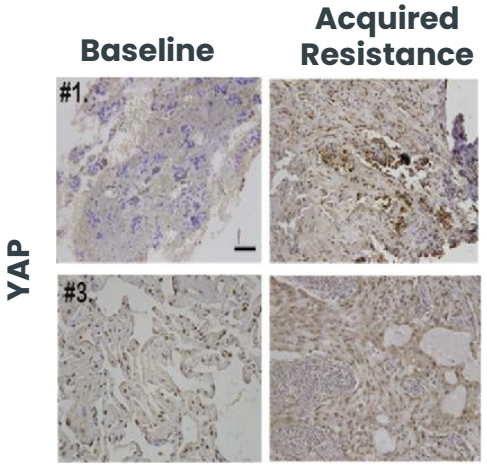
Model	HCT116	A549	Lovo
In vivo TGI Combination	83% (1mg/kg MEKi)	78% (0.5mg/kg MEKi)	75% (1mg/kg MEKi)

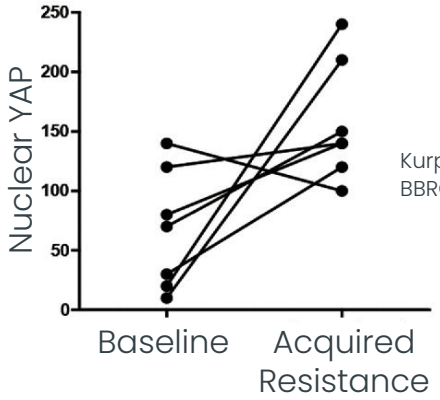
IK-930 Opportunity to Address Emerging Resistance Associated With Early use of Osimertinib in EGFRm NSCLC

Resistance mechanisms to osimertinib in *EGFR*-mutated non-small cell…
A Leonetti et al.



- Success of osimertinib (3rd Gen EGFRi) as 1L and adjuvant tx of EGFRm NSCLC
- Resistance is related to acquired EGFRm, MET amplifications, oncogenic fusions, histological transformation, BUT…
- At least 40% of these cases do not have an identified mechanism of resistance and represents a significant unmet medical need
- Literature suggests that Hippo/Yap1 activation associated with acquired resistance



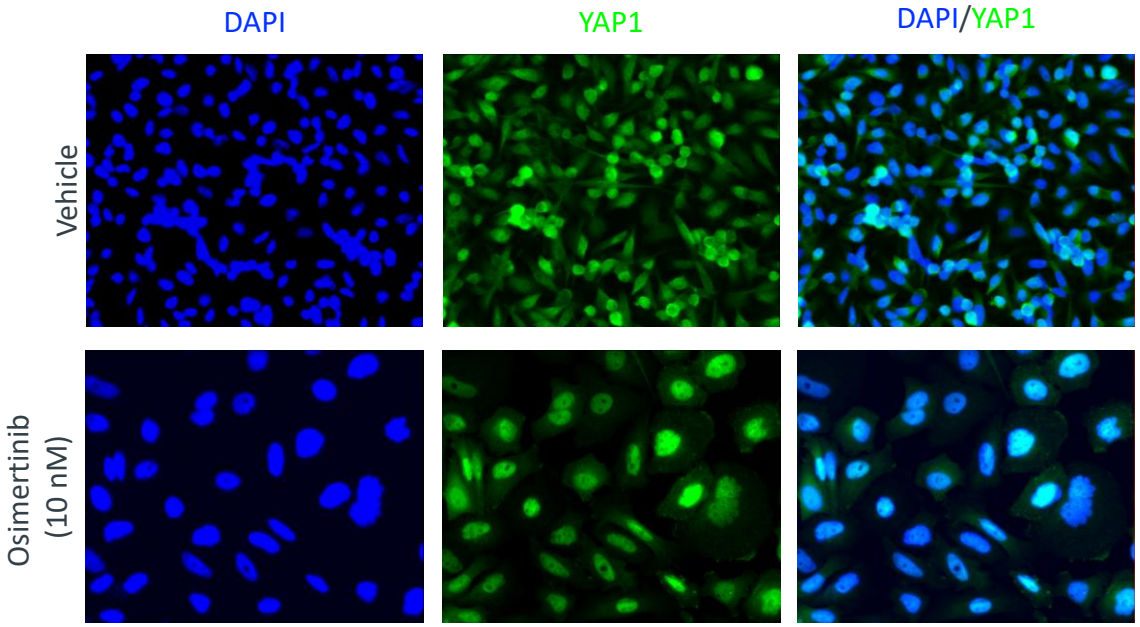


Kurppa 2020; Bratch 2019
BBRC. 2016 May 20;474(1):154

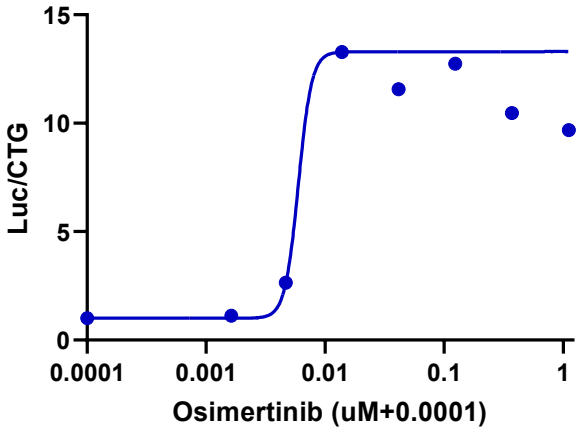
- Opportunity for IK-930 based combinations to address acquired Osimertinib resistance (post 1L /adjuvant)
- Opportunity to identify subset of patients in whom addition of IK930 combo can delay/prevent the emergence of resistance (1L)

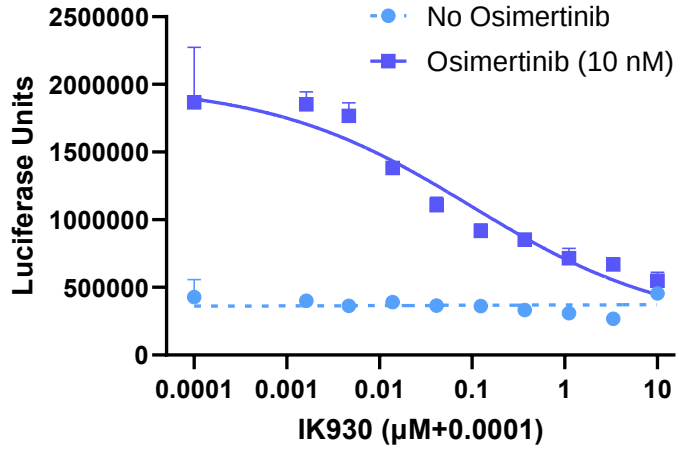
EGFR Inhibitor Induces YAP1 Nuclear Localization and TEAD Dependent Transcription

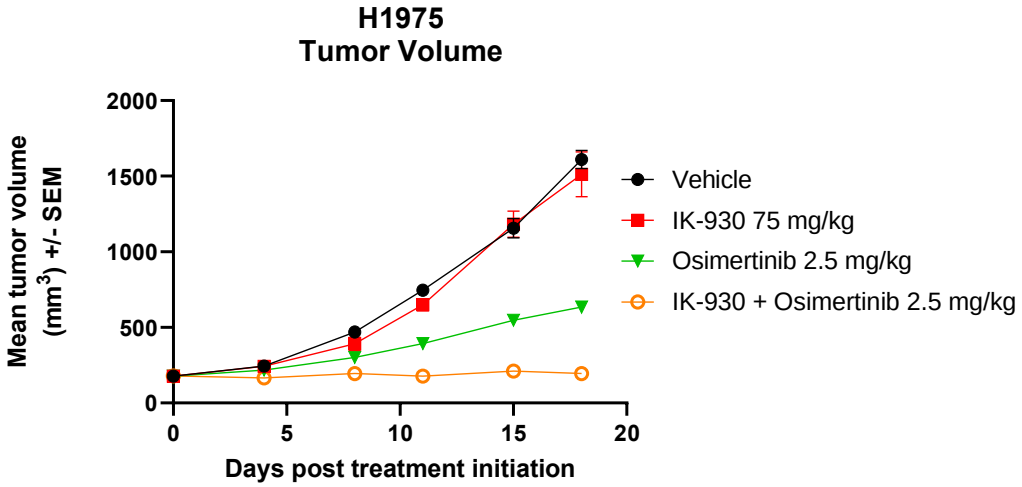
PC9 cells (EGFR p.Glu746_Ala75-del)
5 days treatment

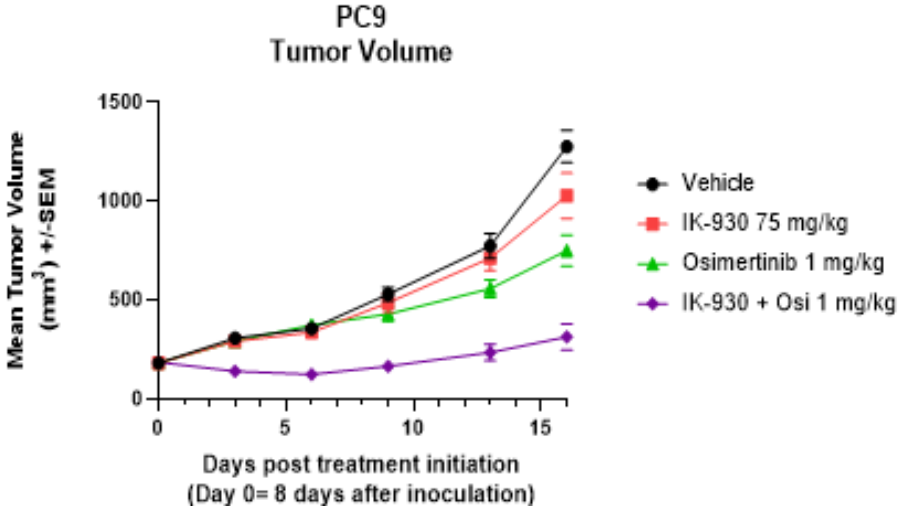


PC9 cells (EGFR p.Glu746_Ala75-del)
5 days treatment



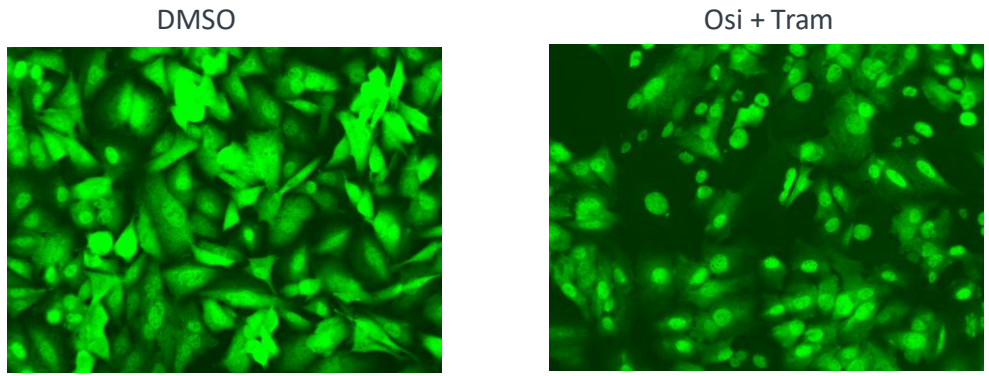






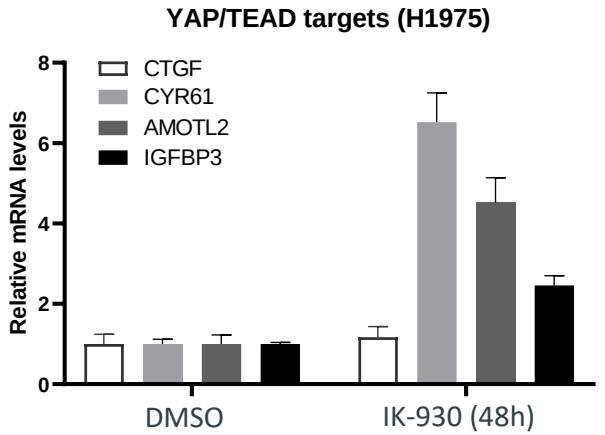
Anti-Tumor Activity of IK-930 Combined with EGFR and MEK Inhibitors

YAP1 nuclear localization in EGFR mutant H1975

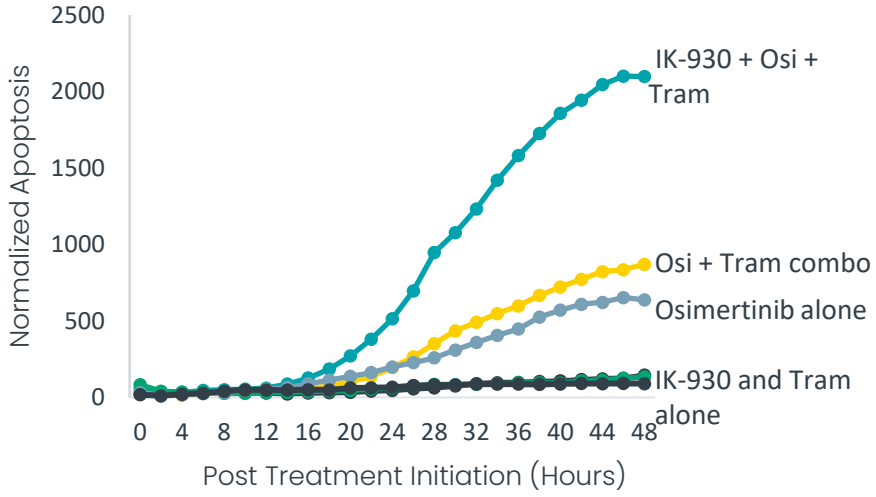


IF: α-YAP1

TEAD-dependent genes induced by EGFRi + MEKi in H1975

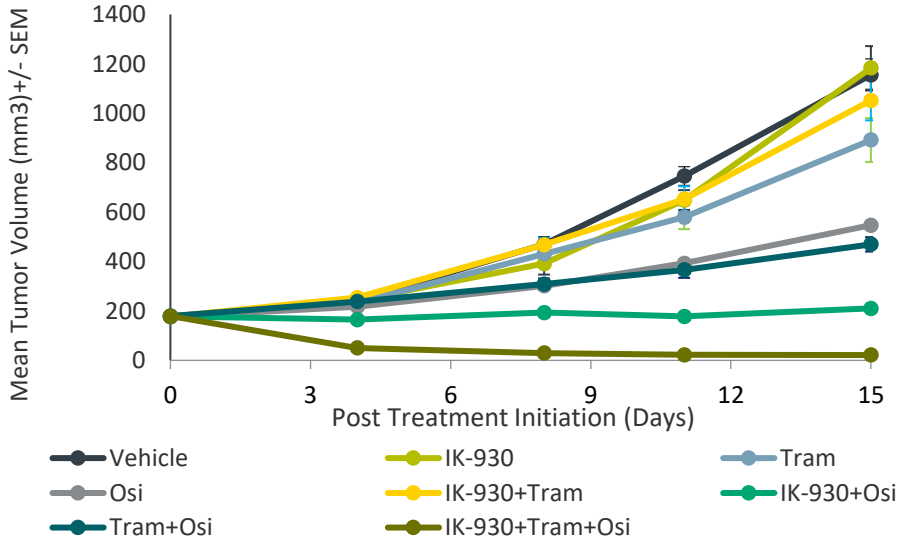


IK-930 enhances apoptosis in vitro in EGFR mutant H1975

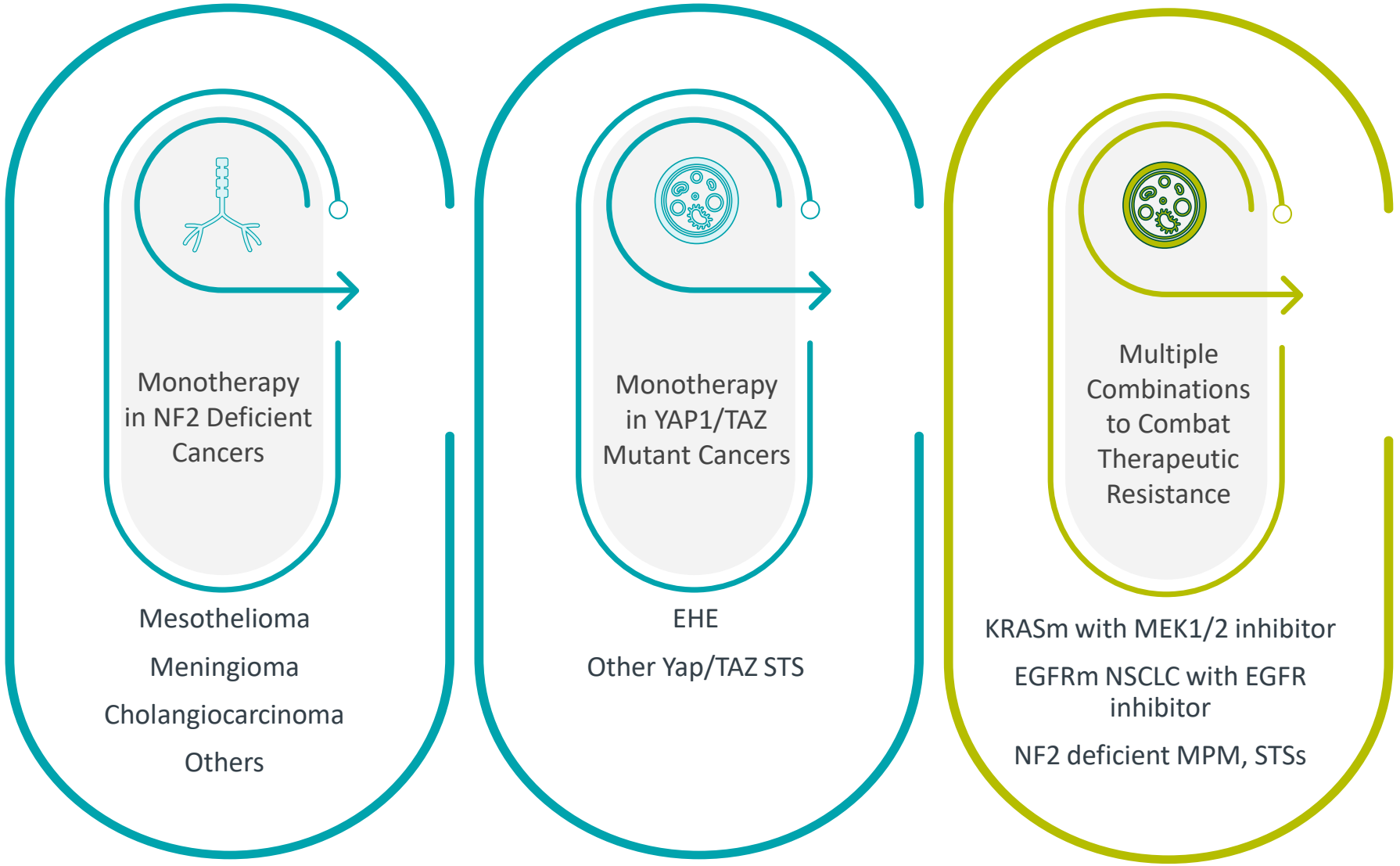


IK-930 increased apoptosis of osimertinib treated H1975 cells at 48h in a separate experiment

IK-930 synergy with EGFRi and MEKi in vivo



Developing First-in-Class TEAD Inhibitor for Genetically Altered Cancers and Therapeutic Resistance



Monotherapy strategy focused on NF2- deficient orphan indications including NF2 deficient MPM, EHE and other solid tumors with prevalent YAP/TAZ fusion genes

Combination strategy to explore multiple with targeted agent combos to reverse mechanism of resistance in broader indications

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