TEAD inhibition by SW-682 potentiates activity of targeted therapies in NSCLC models

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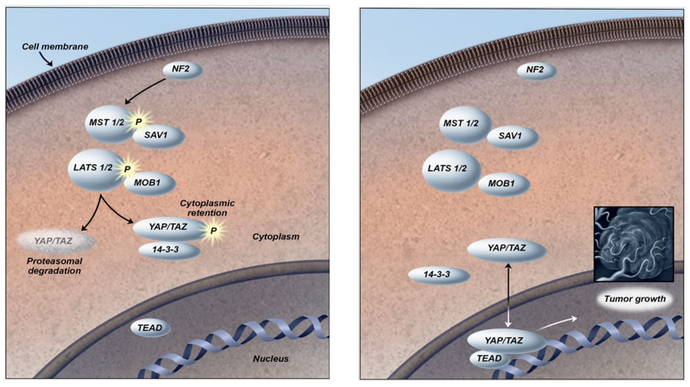
Introduction



- Genomic alterations in the Hippo signaling pathway occur in approximately 10% of cancers[1], leading to constitutive activation of transcriptional co-activators, YAP/TAZ[2]
- YAP/TAZ binds to the transcription factor TEAD, resulting in expression of target genes involved in cell proliferation and tumor progression[2]
- SW-682 is an investigational, small molecule pan-TEAD inhibitor that blocks TEAD-dependent transcription by binding to the palmitoylation pocket of all TEAD isoforms
- In Hippo-mutant mesothelioma models, SW-682 downregulates transcription of YAP/TAZ target genes, inhibits proliferation in vitro and results in tumor regression in vivo
- Oncogenic mutations in EGFR and RAS/MAPK signaling pathways are prevalent drivers of NSCLC; treatment with EGFR or RAS/MAPK inhibitors can hyperactivate YAP/TAZ signaling as a common mechanism of resistance[3], which presents an opportunity for combination therapy with TEAD inhibitors
- We investigated if TEAD inhibition by SW-682 could potentiate anti-tumor activity of EGFR and RAS/MAPK pathway inhibitors in NSCLC models

Materials and methods

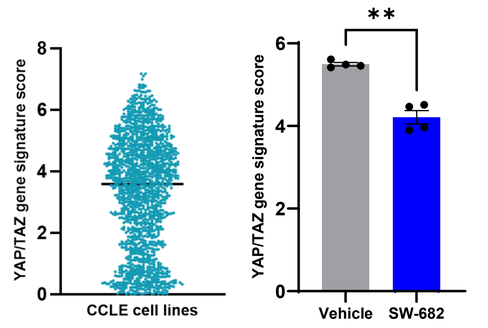
- NSCLC cell lines harboring oncogenic EGFR and KRAS G12C mutations were selected
- YAP/TAZ activity for each model was assessed by calculating a signature score for YAP/TAZ target genes
- Combination activity of SW-682 with inhibitors of EGFR (osimertinib) or KRAS G12C (sotorasib or adagrasib) was tested in respective mutant-specific cell lines
- SW-682 in combination with sotorasib was further evaluated in KRAS G12C NSCLC CDX models in vivo
- To assess the relationship between activated YAP/TAZ signaling and responses to SW-682 and sotorasib combination, KRAS G12C NSCLC PDX models with a range of YAP/TAZ gene signature scores were screened in vivo

Expression of YAP/TAZ target genes is a proxy for tumor intrinsic YAP/TAZ signaling

YAP/TAZ target genes

CYR61	CTGF	AMOTL2	ANKRD1
IGFBP3	F3	FJX1	NUAK2
LATS2	CRIM1	GADD45A	TGFB2
PTPN14	NT5E	FOXF2	AXL
DOCK5	ASAP1	RBMS3	MYOF
ARHGEF17		CCDC80	

Source: Wang et al., 2018[4]

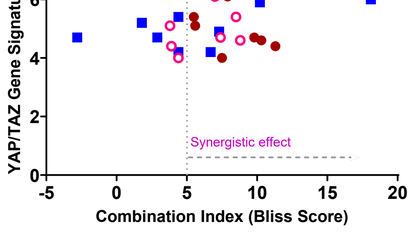


NCI-H226 tumors, SW-682 30 mg/kg QD, 35 days
** p ≤ 0.01, unpaired t test with Welch's correction

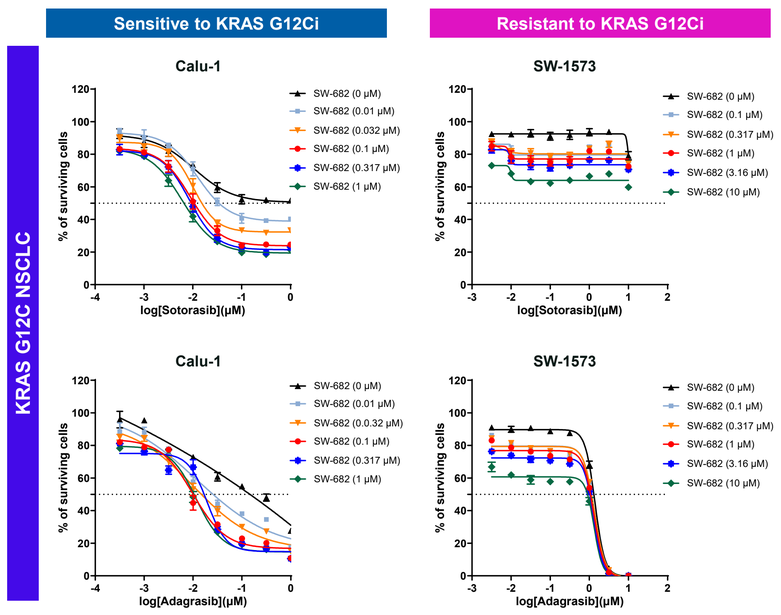
- YAP/TAZ target gene expression is associated with higher tumor intrinsic YAP/TAZ signaling[4]
- A composite YAP/TAZ gene signature score is derived from expression of 22 core YAP/TAZ target genes[4] and varies across CCLE cell lines
- YAP/TAZ target genes were significantly down-regulated in SW-682-treated mesothelioma NCI-H226 tumors
- We hypothesized that YAP/TAZ gene signature scores in EGFR or RAS/MAPK pathway mutated NSCLC models may predict responsiveness to combination therapy with SW-682

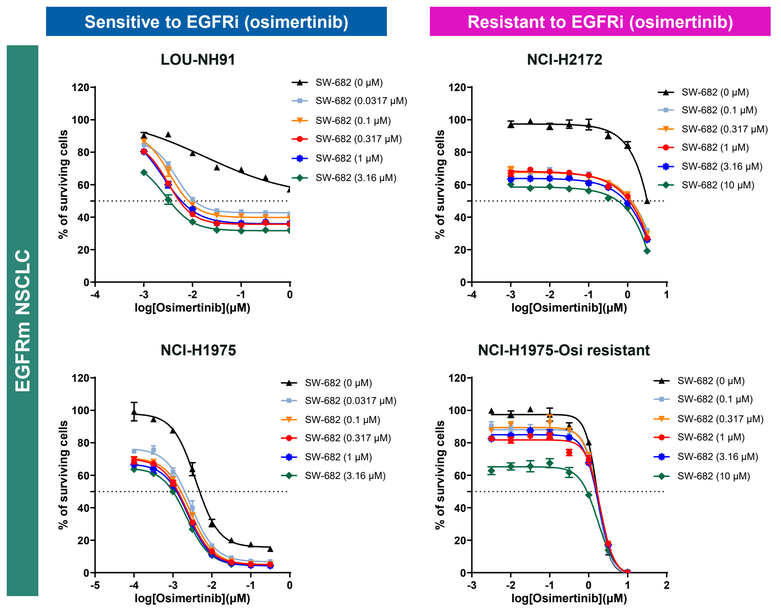
SW-682 synergized with osimertinib, sotorasib, and adagrasib in inhibiting cell proliferation in vitro

Category	Cell Line	YAP/TAZ Gene Signature Score	Combination Agent	Average Bliss Score
KRAS G12C NSCLC	Calu-1	6.6	Sotorasib	9.4
			Adagrasib	8.3
	SW 1573	6.1	Sotorasib	7.9
			Adagrasib	7.0
	NCI-H2030	5.4	Sotorasib	5.5
			Adagrasib	8.5
	HCC-44	5.1	Sotorasib	5.6
			Adagrasib	3.8
	NCI-H1792	4.7	Sotorasib	9.8
			Adagrasib	7.4
	NCI-H1373	4.6	Sotorasib	10.3
			Adagrasib	8.8
	NCI-H23	4.4	Sotorasib	11.3
			Adagrasib	3.9
	NCI-H358	4.0	Sotorasib	7.5
			Adagrasib	4.5
EGFRm NSCLC	LOU-NH91	6.0	Osimertinib	18.1
	HCC-2279	5.9		10.2
	HCC4006	5.4		4.4
	NCI-H2172	5.2		1.8
	HCC-827	4.9		7.3
	NCI-H1650	4.7		2.9
	NCI-H1975-Osi	4.7		-2.8
	NCI-H1975	4.2		6.7
	PC9	4.2		4.4



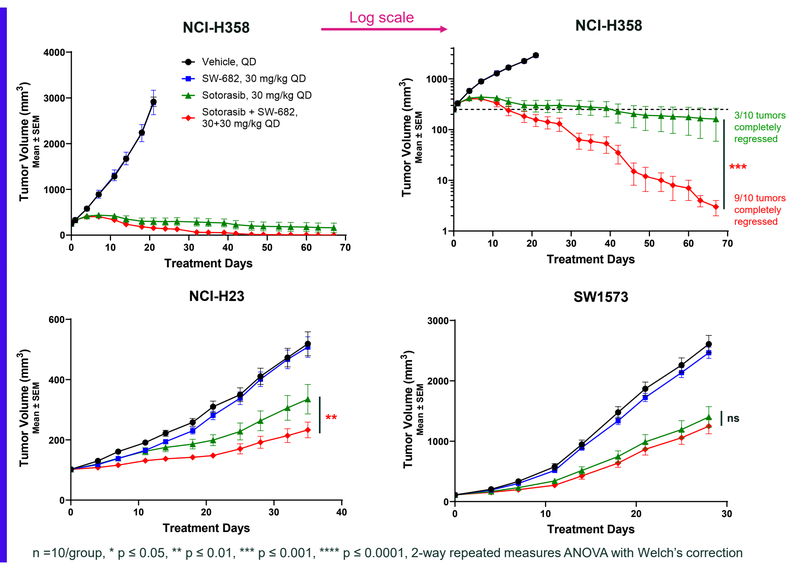
SW-682 synergized with osimertinib, sotorasib, and adagrasib in inhibiting cell proliferation in vitro



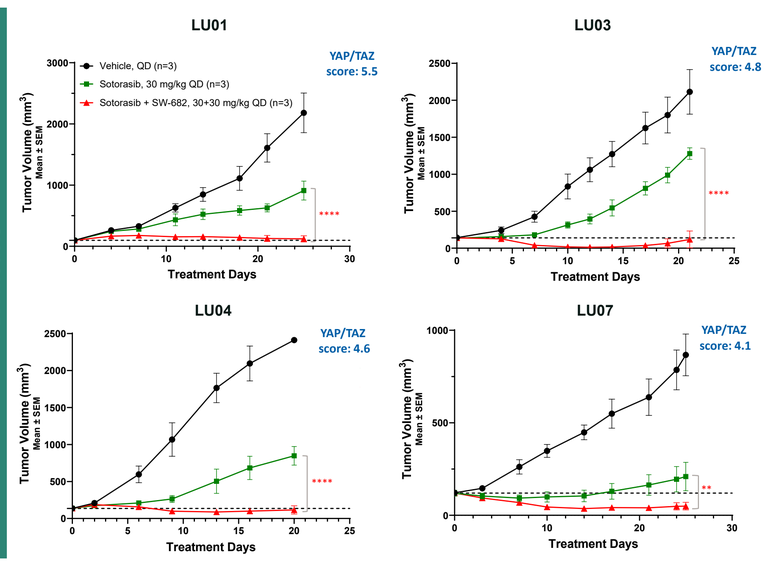


- Synergy was observed in a subset of NSCLC cell lines with intrinsic sensitivity to osimertinib, sotorasib, or adagrasib
- Combination with SW-682 enhanced potency of EGFR or KRAS G12C inhibitors and improved the depth of inhibition in a subset of NSCLC cell lines

SW-682 enhanced anti-tumor activity of sotorasib in NSCLC KRAS G12C CDX and PDX models in vivo

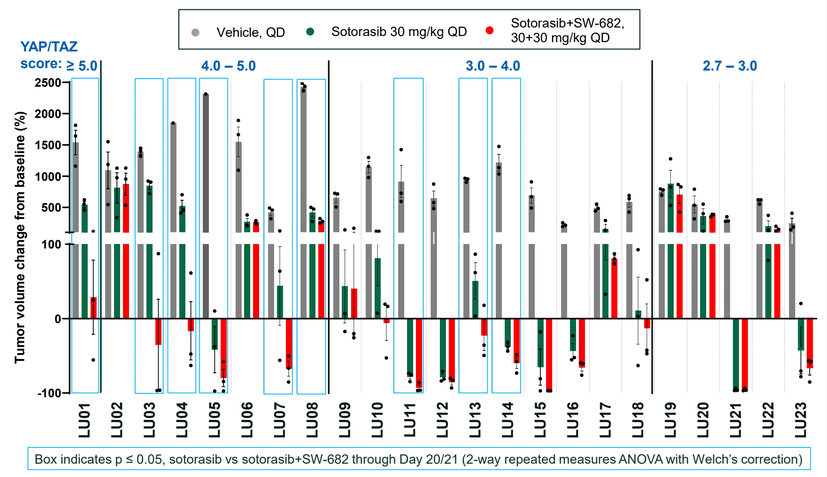


n =10/group, * p ≤ 0.05, ** p ≤ 0.01, *** p ≤ 0.001, **** p ≤ 0.0001, 2-way repeated measures ANOVA with Welch's correction



* p ≤ 0.05, ** p ≤ 0.01, *** p ≤ 0.001, **** p ≤ 0.0001, 2-way repeated measures ANOVA with Welch's correction

YAP/TAZ gene signatures help predict SW-682 + sotorasib combination activity in NSCLC PDX models

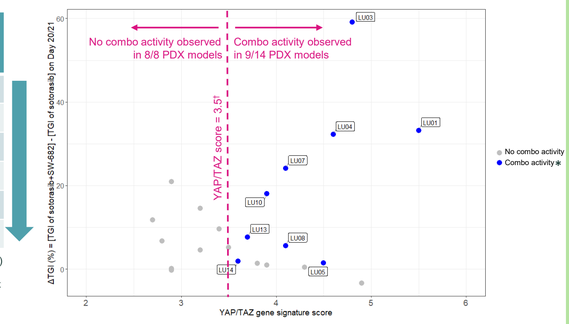


Box indicates p ≤ 0.05, sotorasib vs sotorasib+SW-682 through Day 20/21 (2-way repeated measures ANOVA with Welch's correction)

YAP/TAZ gene sig. score	# of models with combination activity*
> 5.0	1 / 1 (100%)
4.5 – 5.0	3 / 4 (75%)
4.0 – 4.5	2 / 3 (67%)
3.5 – 4.0	3 / 6 (50%)
3.0 – 3.5	0 / 3 (0%)
< 3.0	0 / 5 (0%)

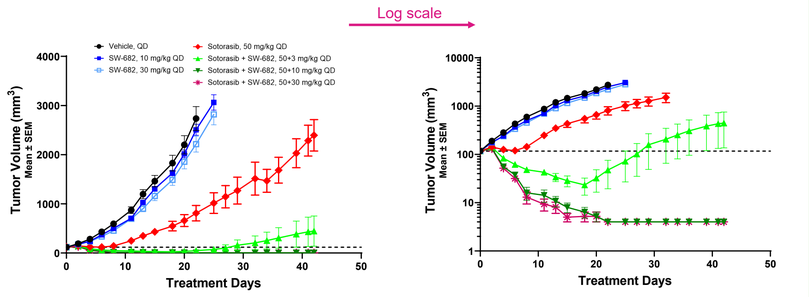
∗ Combination activity defined as significant (p < 0.05) by 2-way repeated measures ANOVA with Welch's correction test for sotorasib vs sotorasib+SW-682 at day 20/21

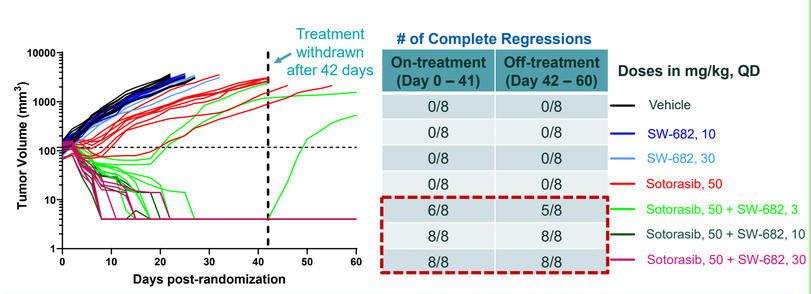
† Dashed line was drawn to indicate no observed combination activity in 8/8 PDX models tested with YAP/TAZ score < 3.5



- To determine if YAP/TAZ gene signature scores can predict combo benefit of SW-682 with sotorasib, an in vivo mini-screen was conducted in 23 KRAS G12C NSCLC PDX models with a range of YAP/TAZ gene signature scores
- Combination activity between SW-682 and sotorasib was observed more frequently in PDX models with higher YAP/TAZ gene signature scores and intrinsic sensitivity to sotorasib
- Therefore, relatively high YAP/TAZ gene signature scores and intrinsic sotorasib sensitivity may be necessary but not sufficient, for SW-682 to potentiate sotorasib anti-tumor activity

SW-682 potentiated anti-tumor activity of sotorasib in PDX model LU03, leading to tumor regressions





# of Complete Regressions

On-treatment (Day 0 – 41)	Off-treatment (Day 42 – 60)	Doses in mg/kg, QD
0/8	0/8	Vehicle
0/8	0/8	SW-682, 10
0/8	0/8	SW-682, 30
0/8	0/8	Sotorasib, 50
6/8	5/8	Sotorasib, 50 + SW-682, 3
8/8	8/8	Sotorasib, 50 + SW-682, 10
8/8	8/8	Sotorasib, 50 + SW-682, 30

- SW-682 enhanced tumor growth inhibition of 50 mg/kg of sotorasib in a dose-dependent manner in the PDX model LU03, resulting in complete tumor regressions
- Complete tumor regression was sustained for 18 days after treatment withdrawal in 21/22 tumors treated with combination of sotorasib and SW-682, suggesting an increased duration of response by the combination compared to sotorasib alone
- SW-682 single agent activity was not required for combination activity with sotorasib in PDX model LU03

Conclusions

- TEAD inhibition by SW-682 synergized with EGFR- and RAS/MAPK-directed therapies to inhibit cell proliferation in vitro
- SW-682 sensitized NSCLC KRAS G12C tumors to sotorasib treatment in CDX and PDX in vivo models
- Combination activity between SW-682 and sotorasib was observed more frequently in PDX models with elevated tumor intrinsic YAP/TAZ activity, indicating a potential patient stratification strategy
- Combination with SW-682 enhanced efficacy and response durability of sotorasib in preclinical NSCLC models, thus supporting investigation of SW-682 combinations in clinical studies

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