Rational combination of pan-TEAD inhibitor SW-682 and MEK inhibitor mirdametinib in head and neck squamous cell carcinomas leads to synergistic response

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ENA Abstract #234
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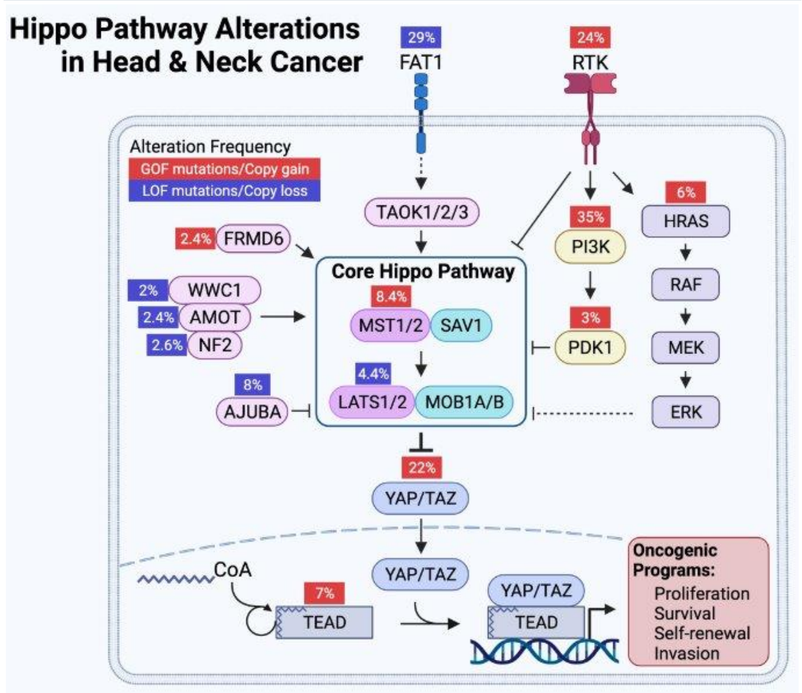
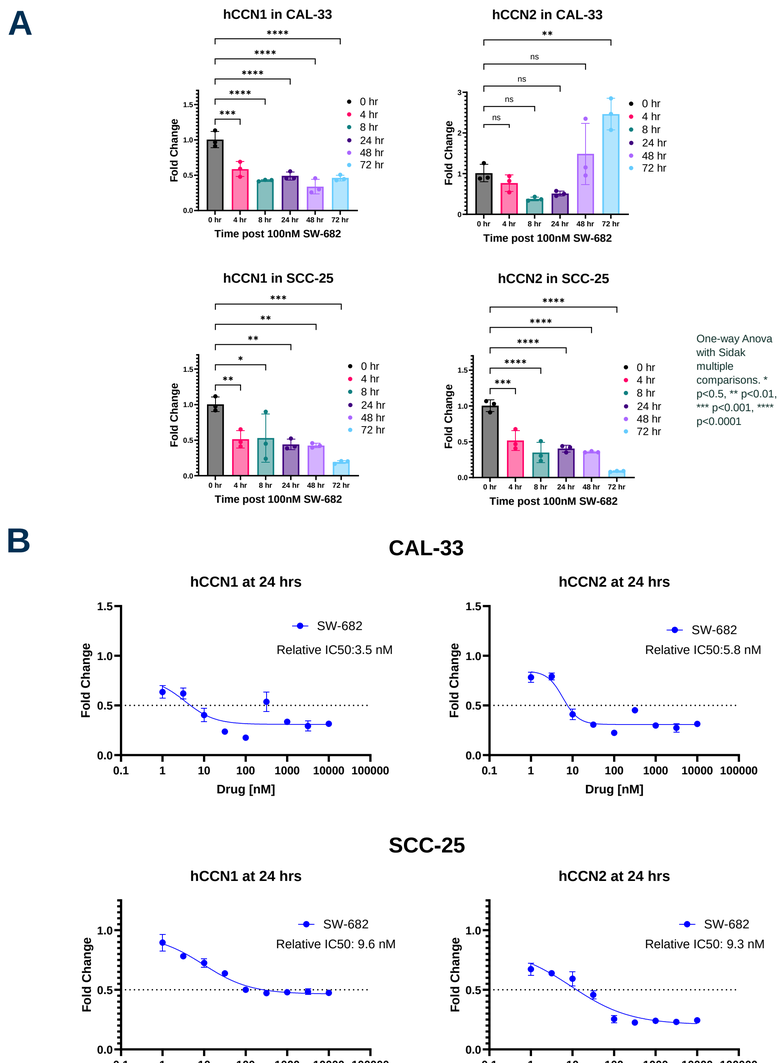
HNSCC exhibits alterations of the Hippo and MAPK signaling pathways



- Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer worldwide with a five-year mortality rate of 60%.[1]
- Mutational profiling of HNSCC shows that genetic alterations in the Hippo signaling pathway are common, with mutations in FAT1 (29%) and amplification of YAP1 (8%) or WWTR1 (TAZ) (14%) being the most frequent.[1]
- Elevated levels of phosphorylated ERK (pERK), indicative of activated MAPK signaling, are common and are associated with tumor growth, metastasis, and recurrence.[2]
- Aberrant Hippo pathway activity is a known resistance mechanism to MAPK pathway targeted therapy and the combination of targeting MAPK and Hippo pathways has shown synergy in preclinical HNSCC models.[3]

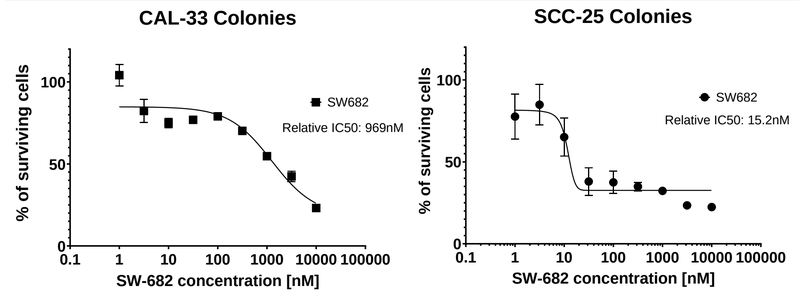
- **Hypothesis:** Combining SW-682, an investigational selective oral pan-TEAD inhibitor, with the investigational MEK inhibitor mirdametinib would lead to synergistic anti-tumor effects in HNSCC, providing a novel therapeutic approach in models harboring aberrations in the Hippo and MAPK pathways.

Dose-dependent inhibition of YAP/TEAD target gene expression by SW-682 in HNSCC

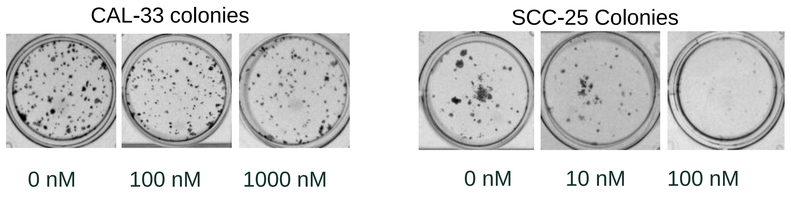


- CAL-33 and SCC-25 cell lines harboring biallelic loss of function of FAT1 showed:
  - A. Significant downregulation of target genes for up to 72 hours after SW-682 treatment.
  - B. Dose dependent effect of SW-682 treatment on Hippo pathway target gene expression.

SW-682 decreases colony formation in HNSCC FAT1 loss models

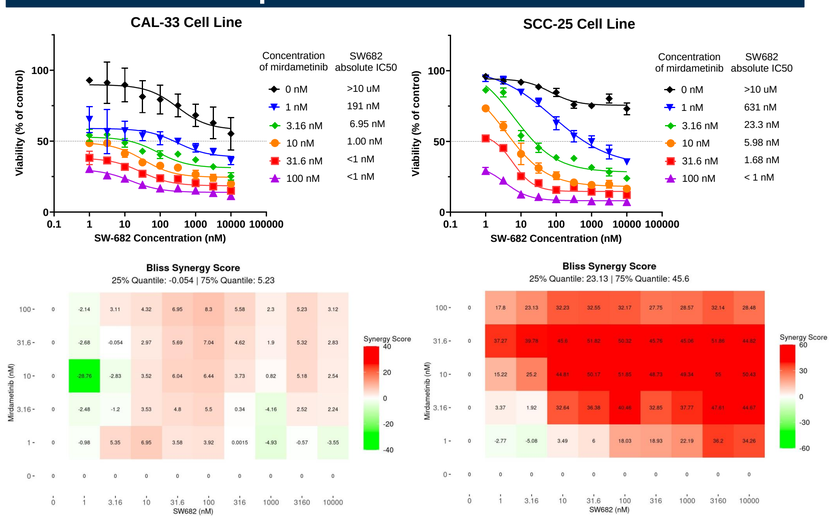


Representative images



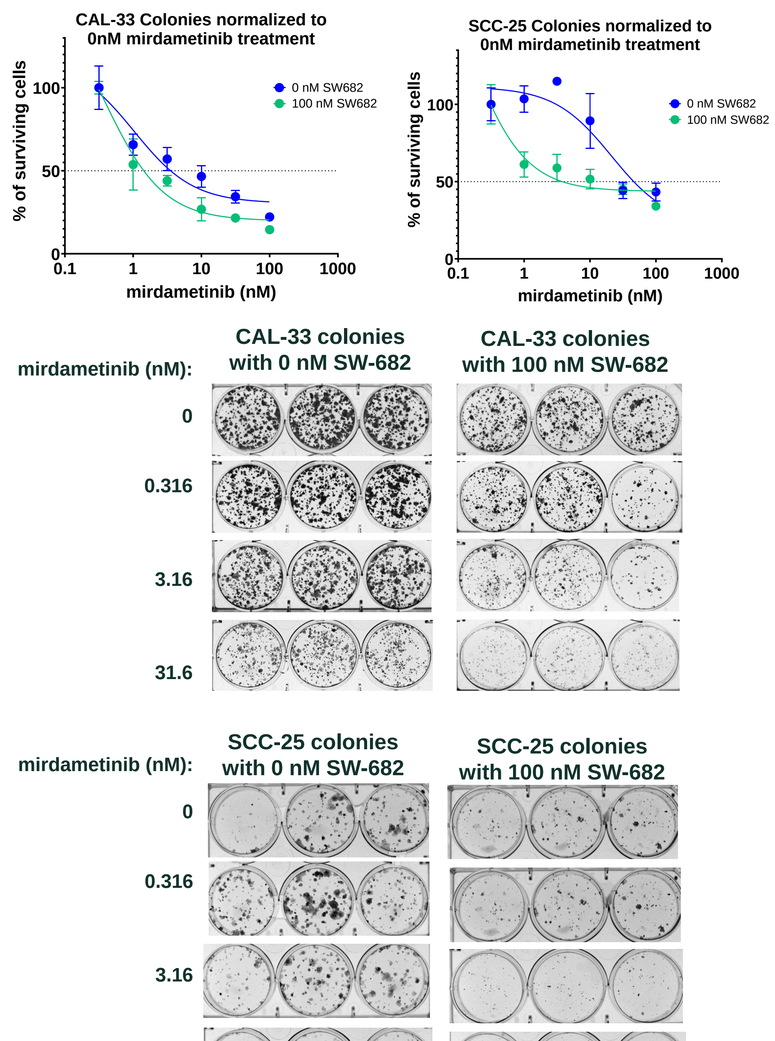
- Treatment with SW-682 results in a dose dependent decrease in CAL-33 and SCC-25 colony formation after 14 days.

Combination of mirdametinib and SW-682 synergized to reduce proliferation of HNSCC in vitro



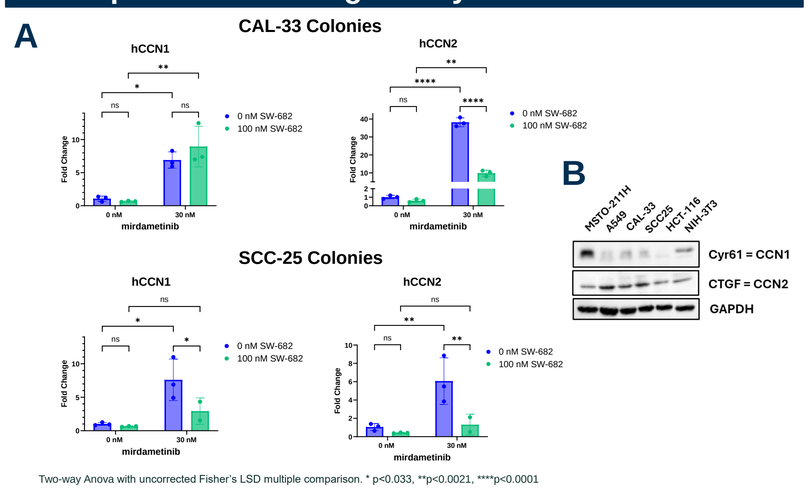
- Given the evidence of cooperative dependence between MAPK and Hippo pathways and the variable monotherapy response, in vitro combination effects of SW-682 with mirdametinib were evaluated.
- Higher synergy was observed in the SCC-25 model, with an average Bliss score of 24.4. CAL-33 showed a reduced Bliss score of 10.7.

Combination of mirdametinib and SW-682 further reduced colony formation when combined in HNSCC



- Addition of SW-682 to mirdametinib reduced clonogenic capacity of SCC-25 and CAL-33 cells.

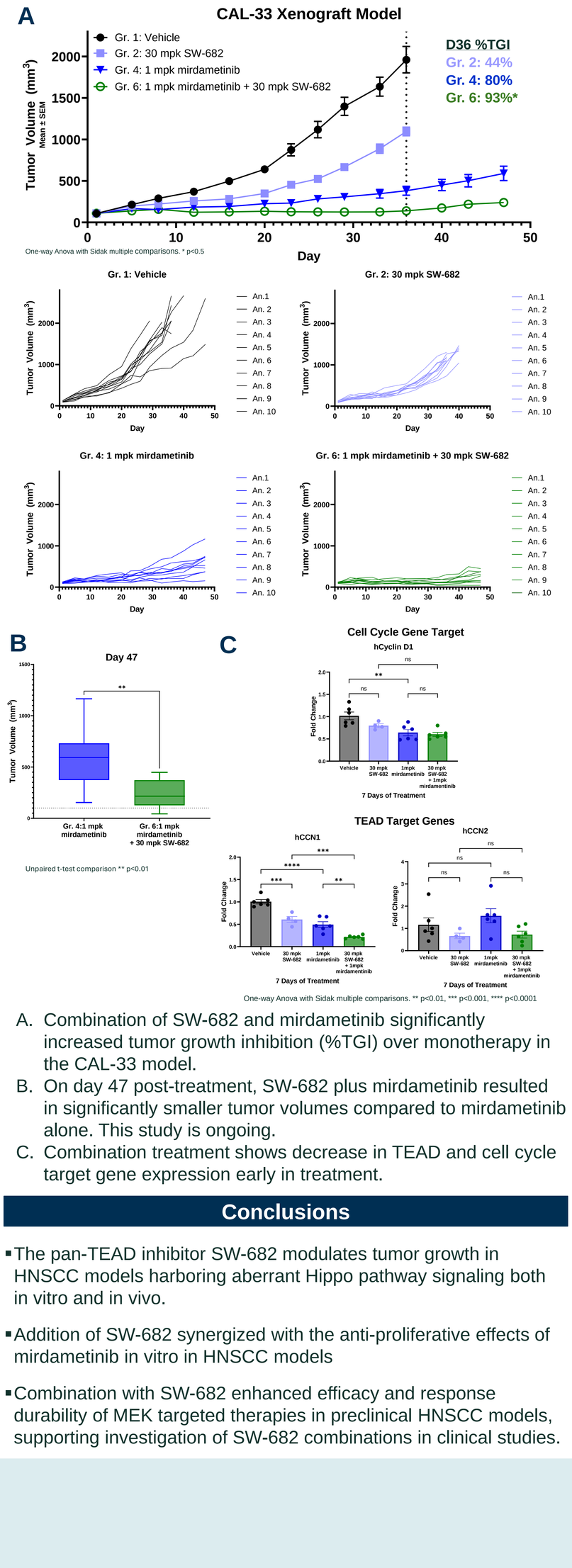
Mirdametinib-induced YAP/TEAD target gene expression is abrogated by SW-682 treatment



Two-way Anova with uncorrected Fisher's LSD multiple comparison. * p<0.033, **p<0.0021, ****p<0.0001

A. Mirdametinib treatment in colony assays increases CCN2 gene expression, which is abrogated by co-administration of SW-682.
B. CCN1 protein, as a compared to CCN2, is not abundantly expressed in HNSCC under endogenous conditions.

Combination of SW-682 and mirdametinib demonstrated increased anti-tumor activity in CAL-33 xenograft model



A. Combination of SW-682 and mirdametinib significantly increased tumor growth inhibition (%TGI) over monotherapy in the CAL-33 model.
B. On day 47 post-treatment, SW-682 plus mirdametinib resulted in significantly smaller tumor volumes compared to mirdametinib alone. This study is ongoing.
C. Combination treatment shows decrease in TEAD and cell cycle target gene expression early in treatment.

Conclusions

- The pan-TEAD inhibitor SW-682 modulates tumor growth in HNSCC models harboring aberrant Hippo pathway signaling both in vitro and in vivo.
- Addition of SW-682 synergized with the anti-proliferative effects of mirdametinib in vitro in HNSCC models
- Combination with SW-682 enhanced efficacy and response durability of MEK targeted therapies in preclinical HNSCC models, supporting investigation of SW-682 combinations in clinical studies.

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References:

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3. *Coggins GE, et al. Cancer Res*. 2019;79(24):6204–6214.

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