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The SGK1 Inhibitor THRV-1257 Induces Robust Tumor Regression and Overcomes Resistance to Standard of Care Dabrafenib Plus Trametinib in a Mouse Model of Anaplastic Thyroid Cancer (ATC) with BRAF V600E Mutation

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BACKGROUND

- ATC is a rare form of highly aggressive thyroid cancer with a progression-free survival of ~ 6 months and limited treatment options.
- ATC is characterized by frequent mutations in genes involved in RAS/MAPK signaling.
- The combination of the BRAF inhibitor dabrafenib and MEK inhibitor trametinib is currently the standard of care for ATC patients whose tumors have the BRAF V600E mutation, however resistance rapidly develops.
- Inhibition of Serum and Glucocorticoid Regulated Kinase 1 (SGK1) was shown to limit the proliferation of ATC cell lines, regardless of their oncogenic driver[1].
- We previously described novel inhibitors of SGK1 with improved drug-like properties[2].
- THRV-1257 is an orally available SGK1 inhibitor that shows efficacy in preclinical ATC models and is scheduled to start Phase 1 clinical trials in Q1 2024 (TRIFEKTA Study).

SGK1 IS INVOLVED IN CROSSTALK AND MAINTENANCE BETWEEN RAS/MAPK AND PI3K SIGNALING

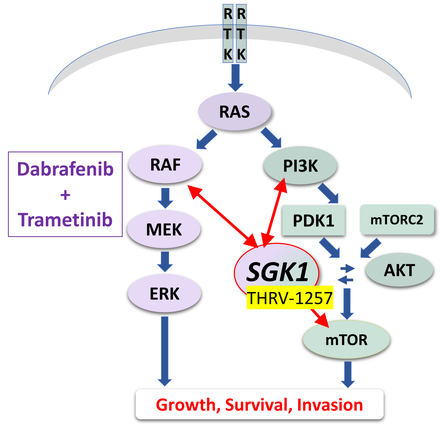


Figure 1: Schematic of RAS/MAPK and PI3K/AKT/mTOR signaling and role of SGK1. SGK1 is involved in maintaining RAS/MAPK and PI3K/AKT/mTOR signaling when these pathways are inhibited. BRAF inhibitor dabrafenib and MEK inhibitor trametinib are shown. RTK: receptor tyrosine kinase.

TESTING OF NOVEL SGK1 INHIBITORS IN ATC CELL LINES

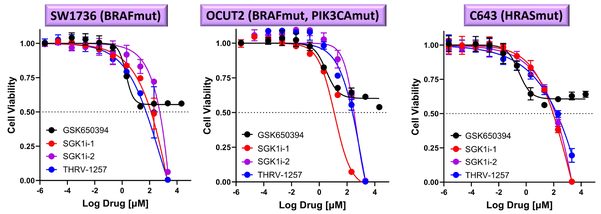
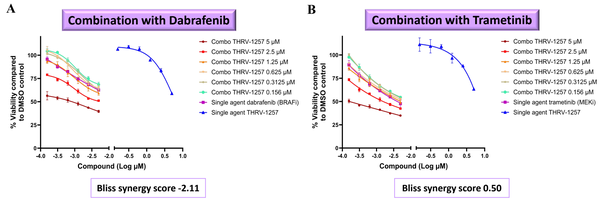


Figure 2: Three SGK1 inhibitors (SGK1i-1, 2 and THRV-1257) were compared to the commercially available SGK1 inhibitor GSK650394 in three ATC cell lines with BRAF or RAS activating mutations. SGKi-1, 2 and THRV-1257 achieved greater inhibition of proliferation than GSK650394.

COMBINATIONS OF THRV-1257 WITH RAF AND MEK INHIBITORS



Summary of Bliss Synergy Scores

Inhibitor(s) combined with THRV-1257 (target)	SW1736 (BRAF V600E)	8305c (BRAF V600E)
Naporafenib/ dabrafenib (RAF)	2.39	-2.11
Selumetinib/trametinib (MEK)	3.41	0.50
Dabrafenib + trametinib (RAF + MEK)	NT	-3.03

Bliss Scores
< -10 = antagonist
-10 to 10 = additive
> 10 = synergistic

Figure 3: THRV-1257 increases the activity of RAF and MEK pathway inhibitors. A) and **B):** THRV-1257 shows additive activity when used in combination with the BRAF inhibitor dabrafenib or MEK inhibitor trametinib in the 8305c ATC cell line. **C)** The triple combination of THRV-1257 + dabrafenib + trametinib also showed additivity in this cell line. BOTTOM: summary table of additive Bliss synergy scores between THRV-1257 and different RAF and MEK inhibitors in two BRAF V600E mutant ATC cell lines.

DEEP AND SUSTAINED TUMOR REGRESSION WHEN THRV-1257 IS COMBINED WITH DABRAFENIB (D) + TRAMETINIB (T)

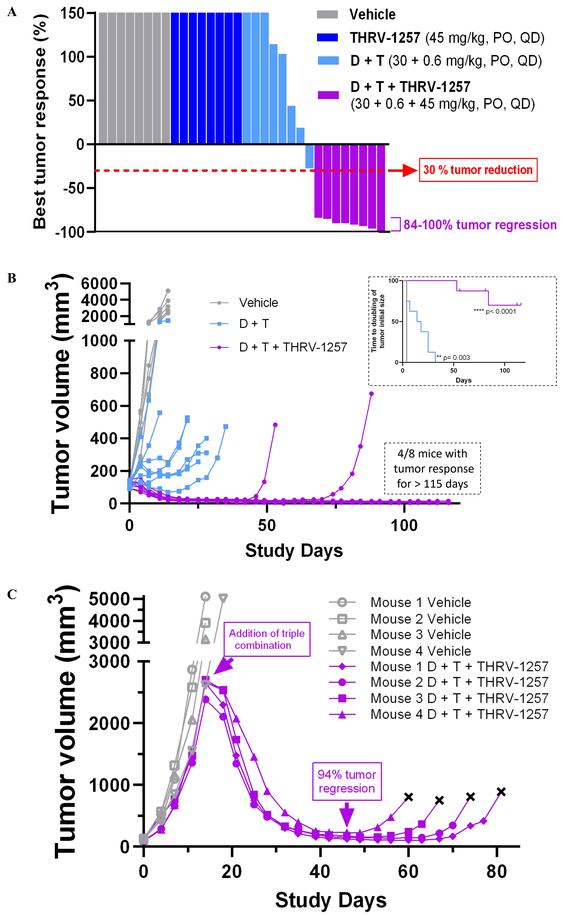


Figure 4: A) Best tumor responses over the course of the treatment in the 8305c ATC BRAF V600E mutant xenograft model. **B)** Combination of THRV-1257 with D + T results in sustained tumor regression >115 days with a significant overall survival (p<0.0001, inset). **C)** Tumor regression was also observed in tumors with an initial tumor size > 2,000 mm^3. Treatments were well tolerated with no weight loss for the study duration (not shown).

THRV-1257 REVERSES RESISTANCE TO DABRAFENIB + TRAMETINIB

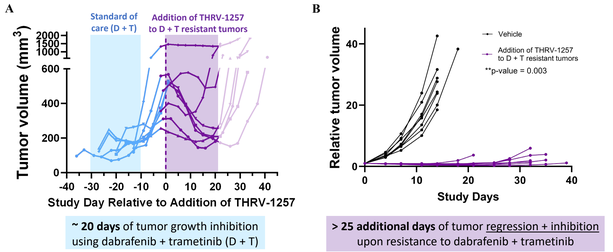


Figure 5: A) Addition of THRV-1257 to tumors resistant to D + T resulted in tumor regression and increased mouse survival (p=0.02, not shown). X-axis is centered on the day THRV-1257 was added. Prior treatment responses with D + T are shown in blue, and in purple after addition of THRV-1257. **B)** Activity of THRV-1257 in the D + T resistant tumors compared to the vehicle-treated group (N=8 each, p = 0.003). Tumor volumes were normalized to Day 0 (vehicle) and day of THRV-1257 addition, respectively.

THRV-1257 MAINTAINS LOSS OF S6 PHOSPHORYLATION FOLLOWING MAPK PATHWAY REACTIVATION

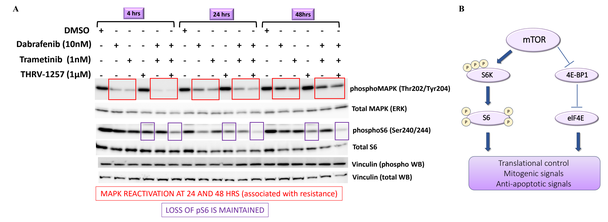


Figure 6: Prolonged incubation with BRAF and MEK inhibitors reactivates the MAPK pathway, which is associated with resistance to the treatment. **A)** THRV-1257 inhibits the phosphorylation of ribosomal protein S6 (pS6), which is maintained by THRV-1257 following MAPK pathway reactivation at 24 and 48 hours. **B)** S6 is involved in translation regulation and mitogenic signaling. Further characterization of the mechanism of cell cycle arrest and tumor regression are underway.

CONCLUSIONS

- THRV-1257 promotes a robust tumor regression and overcomes resistance when added to the standard of care dabrafenib + trametinib.
- These results supports the clinical evaluation of THRV-1257 in ATC patients with a BRAF V600E mutation.
- THRV-1257 is scheduled to start Phase 1 clinical trials in Q1 2024 (TRIFEKTA study).

REFERENCES: [1]Orlacchio et al. 2017, [2]Labit et al. SABCS 2022