VT3989, a clinical TEAD palmitoylation inhibitor, enhances the efficacy and durability of multiple targeted therapies of the MAPK and PI3K/AKT/mTOR pathways

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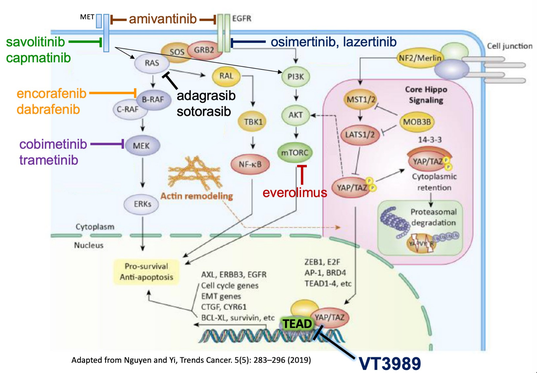
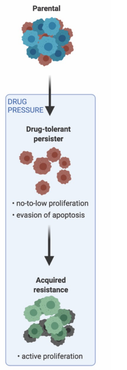
Poster #B088

Background

- TEAD transcription factors are the major effectors of the Hippo-YAP/TAZ-TEAD pathway involved in the regulation of cell proliferation, survival, and cell migration.
- TEAD auto-palmitoylation has been shown to be required for TEAD interaction with coactivator YAP/TAZ and hence activation of transcriptional activity.
- There are multiple reports that YAP/TEAD activation provides the essential survival signal in drug-tolerant persister/dormant cells in cancer in response to treatment with targeted therapies, leading to drug resistance and cancer relapse in *BRAF*-mutant, *KRAS*-mutant, *EGFR*-mutant, and *ALK*-rearranged non–small cell lung cancers (NSCLC).
- VT3989, with similar biological activity *in vitro* and *in vivo* as the potent small molecule TEAD auto-palmitoylation inhibitors reported (Tang *et al*, 2021, *Mol Cancer Ther.* 20(6):986-998), disrupts YAP/TAZ-TEAD protein interaction, suppresses TEAD transcriptional activity, and selectively blocks proliferation of *NF2*-deficient mesothelioma *in vitro* and inhibit *NF2* mutant xenograft tumor growth *in vivo*.
- VT3989, currently in clinical testing, was evaluated for effect on emerging drug tolerant persister/dominant cancer cells and drug resistance.



Adapted from Nguyen and Yi, Trends Cancer. 5(5): 283–296 (2019)



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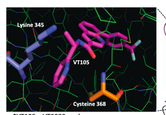
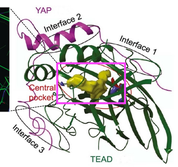


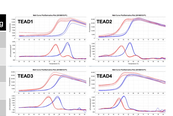
*VT105 = VT3989 analog

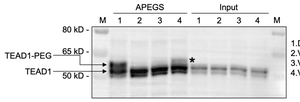


Tang et al., *Mol Cancer Ther*, 2021
Chan et al., *Nat Chem Biol*, 2016
Noland et al., *Structure*, 2016
Pobatti et al., *Structure*, 2015

Compound ID	VT3989	Inactive Analog
YAP IC_{50} (nM)	4.9	>3uM
TEAD1 ΔTm (°C)	11.6	0.2
TEAD2 ΔTm (°C)	8.8	0.5
TEAD3 ΔTm (°C)	8.5	0.2
TEAD4 ΔTm (°C)	4.6	0.2

YAP IC_{50} = YAP Reporter Assay IC_{50}





- Palmitoylation of a conserved cysteine is required for TEAD interaction with YAP. The palmitate is buried in a central pocket in the YAP-binding domain of TEAD.

➢ **VT3989 and other Vivace TEAD inhibitors occupy the palmitate pocket in TEAD, inhibiting auto-palmitoylation and thereby inhibiting transcription function of YAP-TEAD.**

Summary and Conclusions

- **VT3989 enhances the efficacy and durability of response to clinically approved EGFR inhibitors (osimertinib, lazertinib), MET inhibitors (savolitinib, capmatinib), EGFR-MET bispecific antibody (amivantamab), KRAS-G12C inhibitors (sotorasib, adagrasib), BRAF inhibitors (encorafenib, dabrafenib), MEK inhibitors (trametinib, cobimetinib), and mTOR inhibitor (everolimus).**
- **With the addition of VT3989, combination anti-tumor effect was observed and/or tumor regrowth was delayed compared to targeted therapies alone. The persister cell mechanism seems to work in a very broad range of combinations, and the broad range of combination agents suggests a fundamental role for YAP-TEAD in the development of resistance to targeted therapy.**
- **In addition to Hippo-YAP/TAZ-TEAD pathway driven cancers, such as mesothelioma, where VT3989 can show monotherapy efficacy, future VT3989 clinical studies will include combination therapy with approved targeted therapies to enhance the efficacy and durability of treatment.**

Combination with EGFR small molecule inhibitors in EGFR mutant NSCLC models

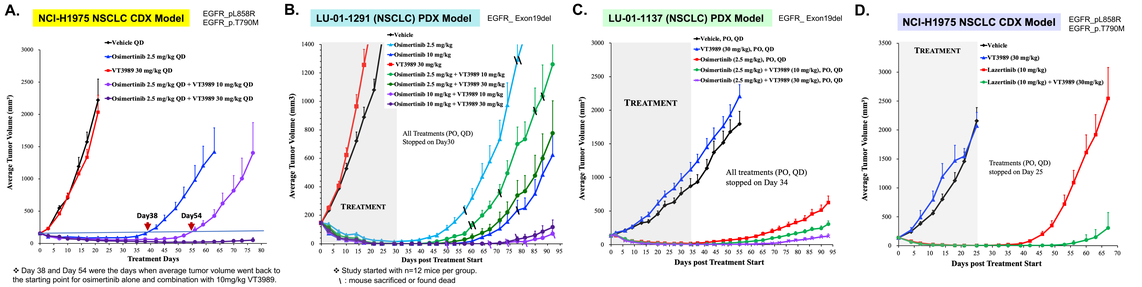


Figure 1. VT3989 and EGFR small molecule inhibitor combination studies *in vivo*
EGFR inhibitor, osimertinib (A, B, and C) or lazertinib (D) was combined with VT3989 in EGFR mutant NSCLC CDX models (A and D) and PDX models (B and C). Treatments (>75 days) were continuous throughout the entire study in the study shown in (A). Treatments in the studies shown in (B, C, and D) were stopped at the indicated time points. Tumor volumes were measured throughout the studies to monitor tumor regrowth.VT3989 shows strong synergy in combination with EGFR inhibitors and significantly delay the tumor regrowth in combination.

Combination with KRAS-G12C inhibitor

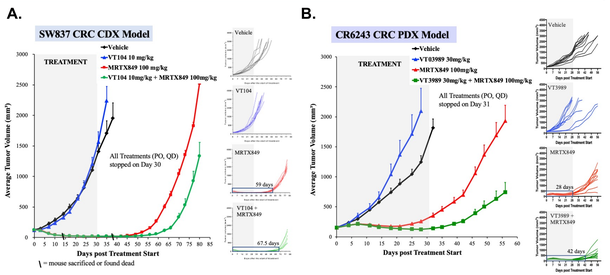


Figure 3. TEAD and KRAS-G12C small molecule inhibitor combination studies
KRAS-G12C inhibitor, MRTX869 (adagrasib), was combined with TEAD inhibitors, VT104 (A) or VT3989 (B) in KRAS-G12C CRC models. Treatments in the studies were stopped at the indicated time points. Tumor volumes were measured throughout the studies to monitor tumor regrowth.

Combination with BRAF / MEK inhibitors

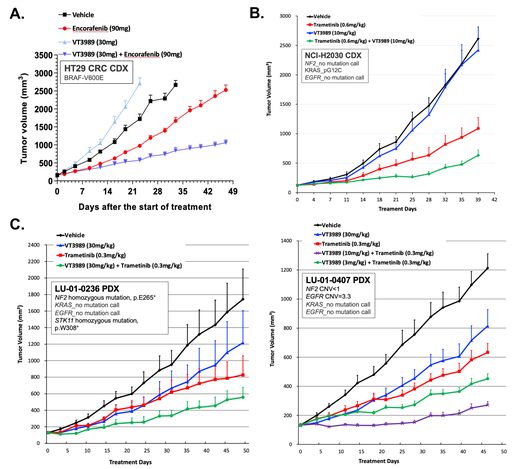


Figure 4. VT3989 and BRAF / MEK small molecule inhibitors combination studies
(A) VT3989 shows strong synergy with BRAF inhibitor encorafenib in HT29 CRC CDX model. (B and C) VT3989 shows combination effect with trametinib in NSCLC CDX (B) and NSCLC PDX models (C). All treatments were PO, QD throughout the studies.

Combination with EGFR-MET bispecific antibody +/- EGFR small molecule inhibitor

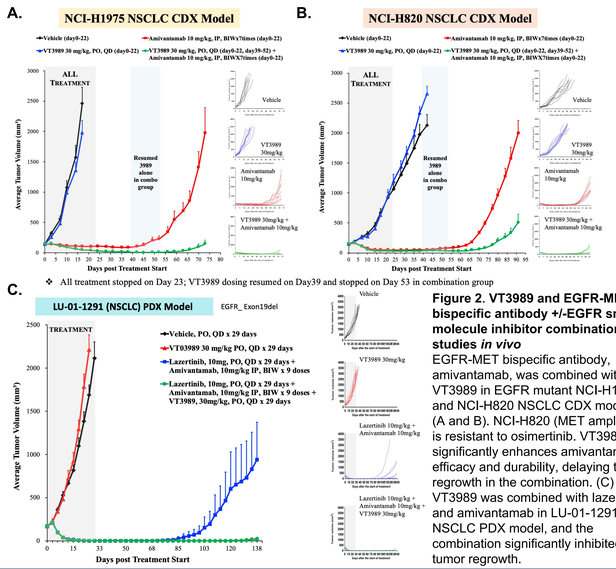


Figure 2. VT3989 and EGFR-MET bispecific antibody +/-EGFR small molecule inhibitor combination studies *in vivo*
EGFR-MET bispecific antibody, amivantamab, was combined with VT3989 in EGFR mutant NCI-H1975 and NCI-H820 NSCLC CDX models (A and B). NCI-H820 (MET amplified) is resistant to osimertinib. VT3989 significantly enhances amivantamab efficacy and durability, delaying tumor regrowth in the combination. (C) VT3989 was combined with lazertinib and amivantamab in LU-01-1291 NSCLC PDX model, and the combination significantly inhibited tumor regrowth.

Combination with MET small molecule inhibitor

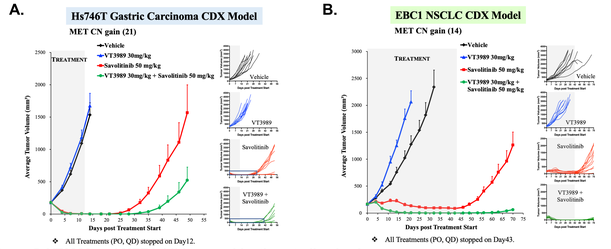


Figure 5. VT3989 and MET inhibitor combination studies *in vivo*
MET inhibitor, savolitinib, was combined with VT3989 in MET amplified CDX models. VT3989 significantly enhances savolitinib efficacy and durability, delaying tumor regrowth in the combination.

Combination with mTOR small molecule inhibitor

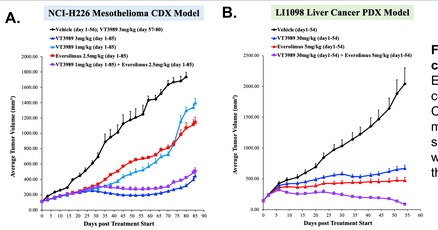


Figure 6. VT3989 and mTOR inhibitor combination studies in vivo
Everolimus mTOR inhibitor was combined with VT3989 in mesothelioma CDX model (A) and liver cancer PDX model (B). VT3989 shows strong synergy with everolimus. Treatments were administered continuously throughout the entire studies.

REFERENCE:

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