The TEAD autopalmitoylation inhibitor VT3989 improves efficacy and increases durability of efficacy of osimertinib in preclinical EGFR mutant tumor models

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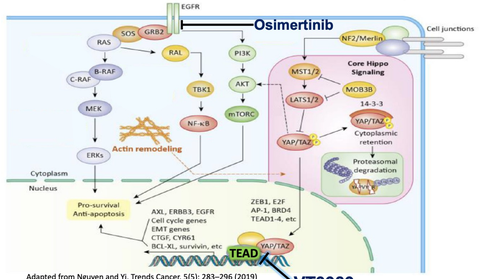
Introduction

The Hippo-YAP/TAZ pathway is involved in the regulation of cell proliferation, survival, and cell migration. The major effectors of the Hippo pathway are the TEAD transcription factors, which become transcriptionally activated upon YAP/TAZ binding. Genetic alterations of pathway components have been reported in a variety of human malignancies, resulting in YAP/TAZ constitutive nuclear localization and TEAD activation. The TEAD transcription factors have been shown to autopalmitoylate, and palmitoylation is required for its interaction with YAP/TAZ and hence activation of transcriptional activity. We have identified potent, selective, and orally available small molecule compounds that directly interact with TEAD and block its autopalmitoylation (Tang et al, 2021, Mol Cancer Ther. 20(6):986-998)[1]. These TEAD inhibitors disrupt YAP/TAZ-TEAD protein interaction, suppress TEAD transcriptional activity, and selectively block proliferation of NF2-deficient mesothelioma *in vitro* and inhibit NF2 mutant xenograft tumor growth *in vivo*.

Nuclear YAP accumulation and functional requirement have also been linked to resistance to targeted therapies and cancer relapse in BRAF-mutant, KRAS-mutant, EGFR-mutant, and ALK-rearranged non–small cell lung cancers (NSCLC).[2-6] Hence, as TEAD transcription factors are the main drivers for YAP/TAZ recruitment to chromatin, we evaluated the effect of our TEAD inhibitor VT3989, currently in clinical testing, on emerging drug tolerant persistent cancer cells and drug resistance during EGFR-tyrosine kinase inhibitor osimertinib treatment in combination studies.



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

Selectivity for *NF2* deficient mesothelioma confirms hypothesis of specific VT3989 inhibition of TEAD transcription activity

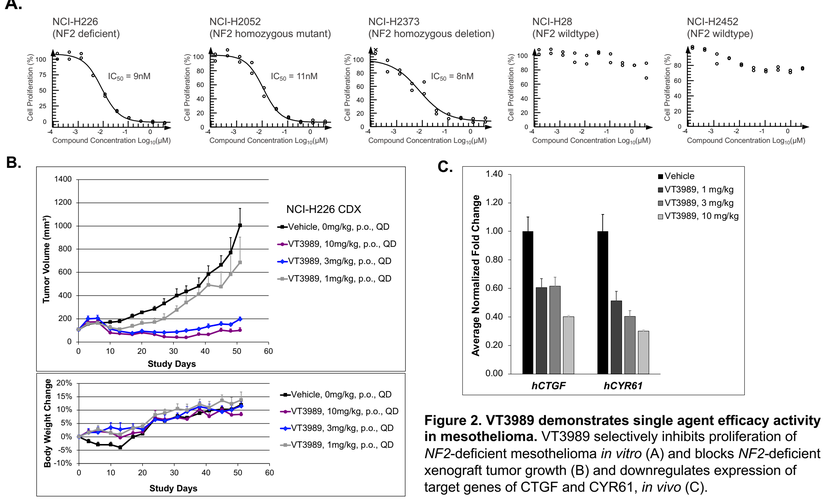


Figure 2. VT3989 demonstrates single agent efficacy activity in mesothelioma. VT3989 selectively inhibits proliferation of *NF2*-deficient mesothelioma *in vitro* (A) and blocks *NF2*-deficient xenograft tumor growth (B) and downregulates expression of target genes of CTGF and CYR61, *in vivo* (C).

VT3989 and osimertinib show strong synergy in patient-derived EGFR mutant NSCLC models

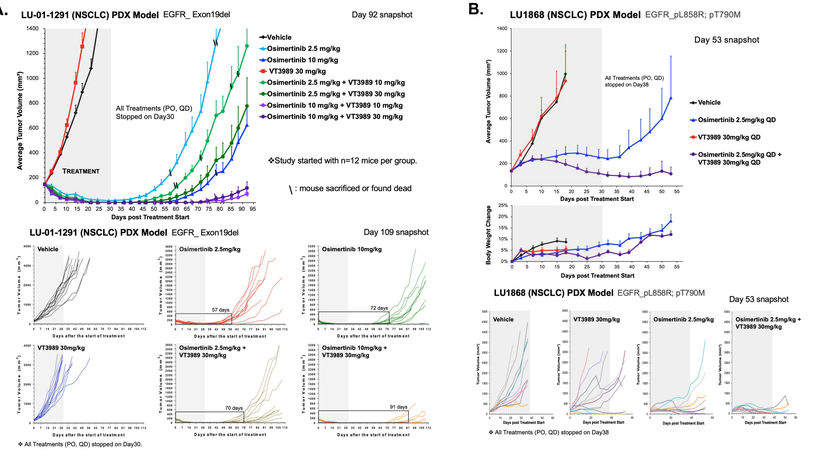


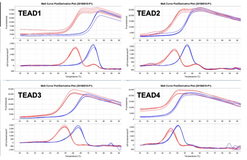
Figure 3. VT3989 and osimertinib combination shows synergy in EGFR mutant NSCLC PDX Models. Efficacy studies in (A) LU-01-1291 and (B) LU1868 PDX models demonstrate strong combination synergy and that the addition of VT3989 significantly delays tumor regrowth, enhancing durability of osimertinib anti-tumor efficacy.

VT3989 is a TEAD autopalmitoylation inhibitor

A.

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

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



B.

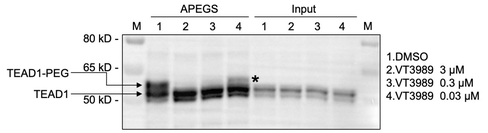
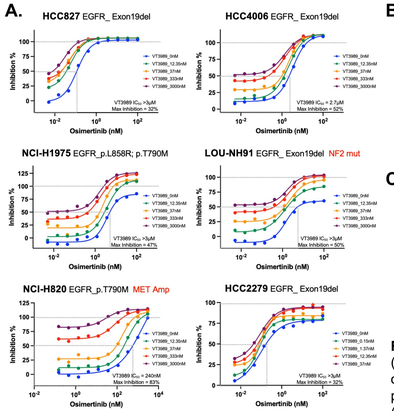
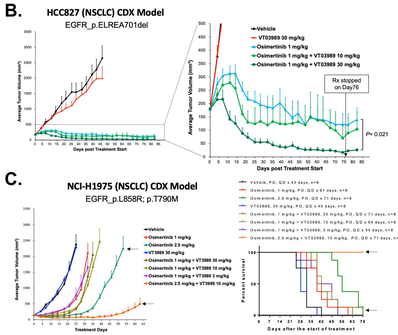


Figure 1. VT3989 is a TEAD autopalmitoylation inhibitor. (A) YAP reporter assay and thermal shift assays show that VT3989 suppresses TEAD transcriptional activity and directly interacts with TEAD proteins. (B) Acyl-PEGyl Exchange Gel-Shift (APEGS) Assay: VT3989 blocks palmitoylation of endogenous TEAD1 in NCI-H2373 mesothelioma cells..

VT3989 and osimertinib show strong synergy in EGFR mutant NSCLC cell lines *in vitro* and in CDX models *in vivo* – *significantly delay tumor regrowth*





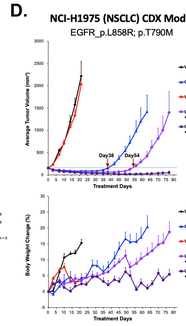


Figure 3. VT3989 and osimertinib combination shows synergy in EGFR mutant NSCLC. (A) *In vitro* matrix combination testing in 5-7day cell proliferation CTG assays. Only selected concentrations of VT3989 are shown. CI <0.1 was observed. (B) Comparison between osimertinib single agent (1 mg/kg, po, QD, daily) and combination with VT3989 (10 mg/kg or 30 mg/kg, po, QD, daily) in HCC827 CDX model. (C, D) Efficacy studies in NCI-H1975 CDX model.

Summary

- We have identified a potent and selective TEAD autopalmitoylation inhibitor VT3989.
- VT3989 selectively inhibits human *NF2*-deficient mesothelioma cell proliferation *in vitro and* blocks growth of *NF2*-deficient NCI-H226 xenograft tumors in mice at MED of 3mg/kg QD without adverse body weight effect.
- VT3989 exhibits strong synergy with EGFR inhibitor osimertinib in inhibiting proliferation of several EGFR mutant NSCLC cell lines. VT3989 shows significant combination effect with osimertinib in blocking tumor growth in NSCLC CDX models (HCC827 and NCI-H1975), even in the HCC827 model that is already very sensitive to osimertinib. Combination of VT3989 and osimertinib extends the median survival time and significantly increases the life span of NCI-H1975-tumor bearing mice compared to osimertinib monotherapy.
- Combination of VT3989 and osimertinib shows strong synergy in blocking tumor regrowth in human patient-derived xenograft models of EGFR mutant NSCLC. TEAD inhibition significantly delays the re-emergence of tumor mass after osimertinib treatment resulted in non-palpable tumors, providing evidence for the presence of osimertinib tolerant persister cells that are YAP-TEAD dependent.
- VT104, another Vivace TEAD palmitoylation inhibitor, has been demonstrated to suppress osimertinib tolerant persister cells and residual disease in lung cancer in combination studies (Haderk *et al.* 2021.)[7]

References

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