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, with YAP/TAZ constitutive nuclear localization and TEAD activation. The TEAD transcription factors have been shown to autopalmitoylate and palmitoylation is required for their interaction with TEAD and for their autopalmitoylation. Tang et al. (2021, Mol Cancer Ther 20:986-996) showed that YAP/TAZ disrupts TEAD-TEAD protein interaction, suppress TEAD transcriptional activity, and selectively blocks proliferation of NF2-deficient mesothelioma in vitro and inhibits 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). (1) 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/ALK kinase inhibitor osimertinib treatment in combination studies.

We have identified a potent and selective TEAD autopalmitoylation inhibitor VT3989.

VT3989 and osimertinib combination shows strong synergy in patient-derived EGFR mutant NSCLC models.

We tested VT3989 and osimertinib combination in both in vitro and in vivo models and found significant synergy in blocking tumor regrowth in both mesothelioma and NSCLC models.

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

Figure 1. VT3989 is a TEAD autopalmitoylation inhibitor. (A) YAP reporter assay and immunoblot confirm that VT3989 suppresses TEAD transcriptional activity in A549 cells. (B) APEGS assay: VT3989 blocks palmitoylation of endogenous TEAD1 in NCI-H2373 mesothelioma cells.

Figure 2. VT3989 demonstrates single agent efficacy activity in mesothelioma. VT3989 selectively inhibits proliferation of NF2-deficient mesotheliomas in vivo (A) and blocks NF2-deficient xenograft tumor growth (B) and downregulates expression of target genes of CTGF and CYR61 (C) in vivo (p<0.05).

Figure 3. VT3989 and osimertinib show strong synergy in vitro and in CDX models in vivo – significantly delay tumor regrowth.

Figure 4. VT3989 and osimertinib combination shows strong synergy in EGFR mutant NSCLC models. (A) In vitro matrix combination testing in 5-day cell proliferation CTG assays. Only selected combinations of VT3989 and osimertinib were observed. (B) Comparison between osimertinib single agent (1 µM, po. od. daily) and combination with VT3989 (10 µg/ml) or 30 µg/ml po. od. daily in HCC827 CDX model. (C) Efficacy studies in NCI-H1975 CDX model.

Figure 5. VT3989 and osimertinib combination shows synergy in EGFR mutant NSCLC PDX models. Efficacy studies in (A) LU-03-1291 (left) and (B) LU-1966 PDX models demonstrate strong combination synergy and that the addition of VT3989 significantly delays tumor regrowth, enhancing durability of osimertinib anti-tumor efficacy.

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-H2373 xenograft tumors in mice at MED of 3mg/kg 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 NIC-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 NIC-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 transiently delays the recurrence of tumor mass after osimertinib treatment resulted in non-palpable tumors, providing evidence for the presence of osimertinib tolerant persister cells that are VT3989 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.)

References


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