Mechanistic and Early Clinical Characterization of VRN101099, a Selective HER2 inhibitor with Receptor Degradation Activity

LUMIN-HER2 (Phase 1 Study in HER2-Driven Advanced Solid Tumors)

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#LB365

Introduction

- VRN101099 is a selective covalent HER2 inhibitor that induces rapid HER2 internalization and lysosomal degradation.
- VRN101099 reduces cell-surface HER2 and enhances uptake of HER2-directed antibody–drug conjugates.
- In combination with trastuzumab, VRN101099 enhances HER2 pathway inhibition and antitumor activity.
- These data support further clinical development of VRN101099 as both a monotherapy and in combination with HER2-directed therapies.

MoA of VRN101099: HER2 Inhibition & Internalization

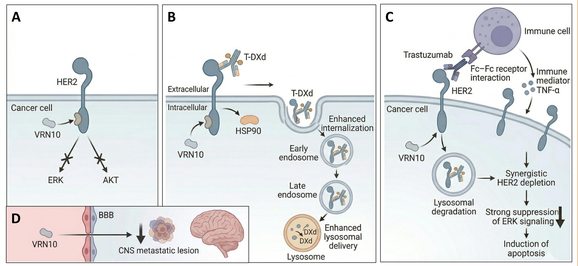

Figure 1. (A) Signaling inhibition: VRN101099 suppresses HER2 downstream pathways, including AKT and ERK, thereby inhibiting cell proliferation and survival.
(B) Internalization & payload enhancement: VRN101099 promotes HER2 internalization, enhancing T-DXd–mediated payload delivery and the bystander effect.
(C) Synergistic HER2 depletion and apoptosis: Interplay between VRN101099, trastuzumab, and immune cells enhances HER2 reduction, leading to stronger ERK suppression and tumor cell apoptosis.
(D) Brain penetration: VRN101099 efficiently crosses the BBB, enabling HER2 pathway inhibition in the brain.

VRN101099: A Unique Open-State Activation Loop

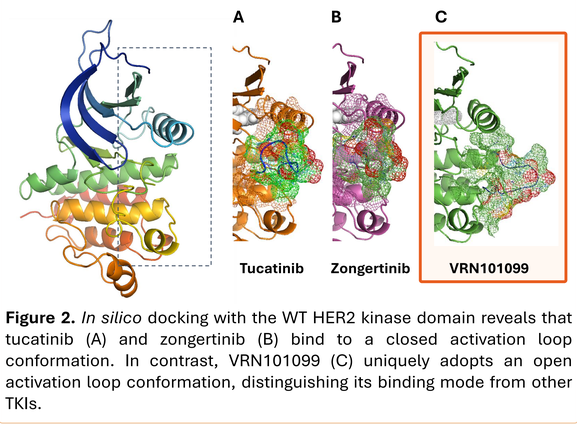

Figure 2. *In silico* docking with the WT HER2 kinase domain reveals that tucatinib (A) and zongertinib (B) bind to a closed activation loop conformation. In contrast, VRN101099 (C) uniquely adopts an open activation loop conformation, distinguishing its binding mode from other TKIs.

VRN101099 mediated HER2 degradation

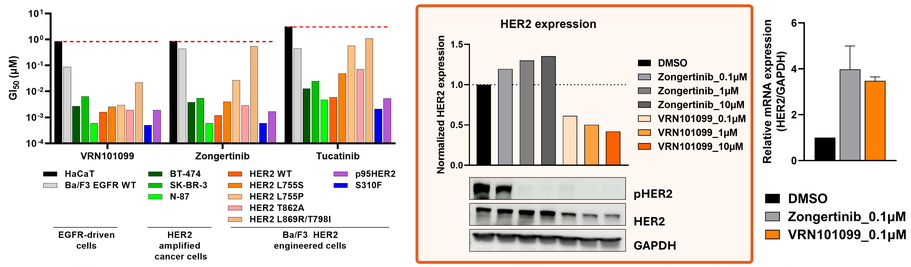

Figure 3. GI_{50} values were evaluated across HER2-amplified and HER2-mutant models, including T-DXd–resistant cell lines. In BT-474 cells, VRN101099 showed dose-dependent reductions in total HER2 protein in 100% human serum, whereas HER2 mRNA levels were increased following treatment with either VRN101099 or zongertinib.

HER2 internalization and lysosomal HER2 degradation via HSP90 dissociation

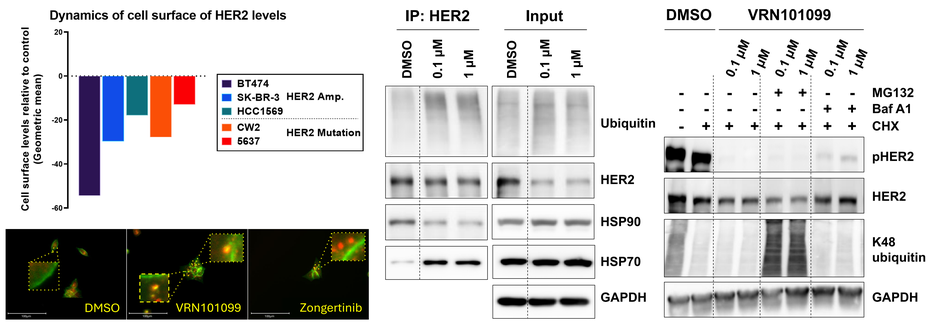

Figure 4. FACS analysis confirmed reduced surface HER2, while IF microscopy showed co-localization of HER2 (green) and EEA1 (red). This degradation process involves HER2 ubiquitination and a chaperone switch (HSP90→HSP70) as validated by the restoration of HER2 levels upon treatment with lysosomal acidification inhibitor.

Combination with Trastuzumab deruxtecan

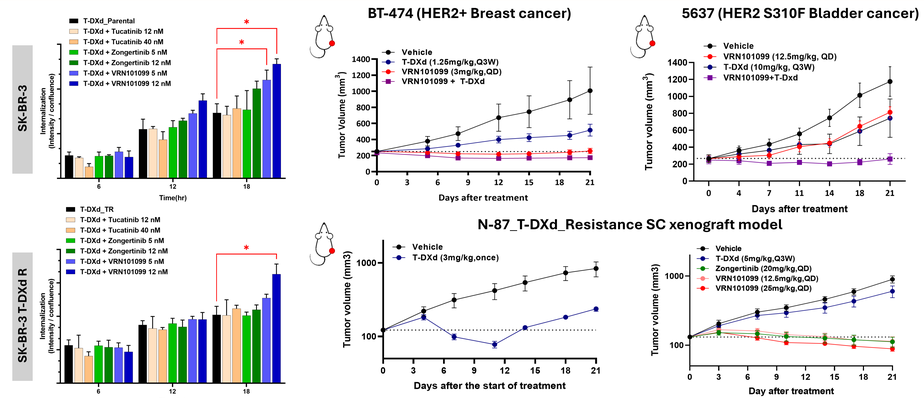

Figure 5. VRN101099 + T-DXd increased internalization vs. zongertinib + T-DXd and showed synergistic tumor inhibition in HER2+ and HER2-mutant xenografts, including T-DXd–resistant models (*p < 0.05 vs. control).

Combination with Trastuzumab

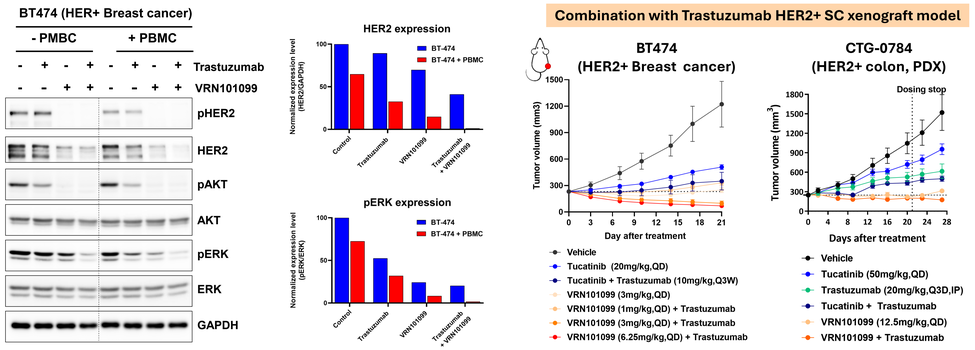

Figure 6. Synergistic antitumor activity of VRN101099 in combination with trastuzumab. This synergistically suppresses HER2 signaling and protein levels via post-translational degradation. VRN101099 achieved superior *in vivo* efficacy compared to tucatinib in both HER2-amplified CDX and PDX models .

Potent CNS Antitumor Activity

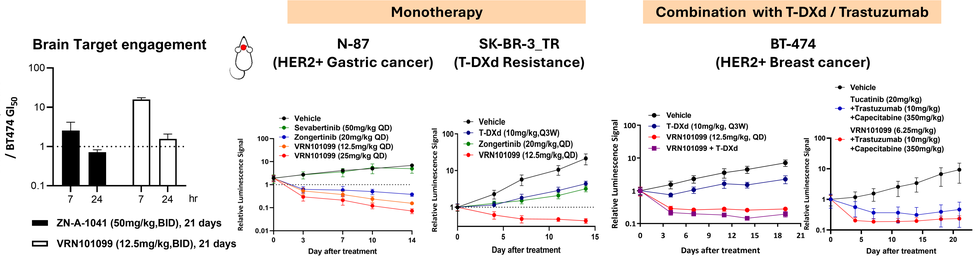

Figure 7. VRN101099 shows sustained brain target engagement for 24 hours, and synergistic antitumor activity was observed with VRN101099 alone and in combination with T-DXd/Trastuzumab in HER2+ and T-DXd–resistant *in vivo* models.

Tumor response - *Ex vivo* pHER2 inhibition correlation

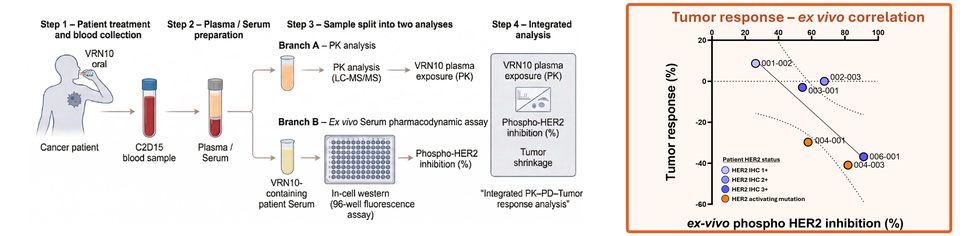

Figure 8. *Ex vivo* phospho-HER2 IC50 was assessed, and tumor response correlated with *ex-vivo* phospho-HER2 inhibition in patients treated with VRN101099.

Conclusions

- Mechanism: VRN101099 is a selective covalent HER2 inhibitor inducing HER2 internalization and degradation.
- Preclinical: Active in T-DXd-resistant models and shows CNS antitumor activity in preclinical models.
- Combination: Enhances HER2-directed therapies; *ex vivo* pHER2 inhibition correlates with tumor response.
- Clinical: Ongoing Phase 1 (3+3) study evaluating safety, PK/PD, and antitumor activity to determine MTD/RP2D.

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