P3.12: VRN101099: A Potential Best-in-Class HER2 TKI with strong potency against HER2 ex20ins and BBB penetration.

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Introduction

- HER2 mutations (found in 2–4% of NSCLC) are predominantly exon 20 insertions with a high risk of CNS metastasis.
- Despite approved HER2 therapies, critical unmet needs remain for durable intracranial efficacy and overcoming T-DXd resistance.
- VRN101099 is a novel covalent HER2-selective TKI that potently inhibits ex20ins variants while sparing wild-type EGFR to minimize toxicity.
- Here, we present its preclinical characteristics, highlighting differentiated binding that induces target degradation, sustained brain exposure, and robust antitumor efficacy.

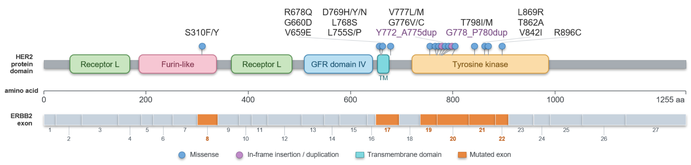


Figure 1. Activating mutations of HER2 (ERBB2).

Open-State Targeting and Protein Degradation

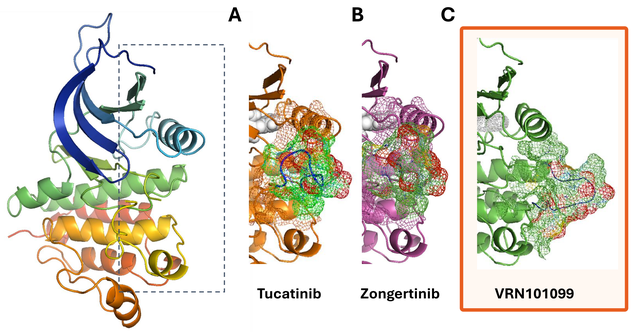


Figure 2. VRN101099: a unique open-state activation loop.

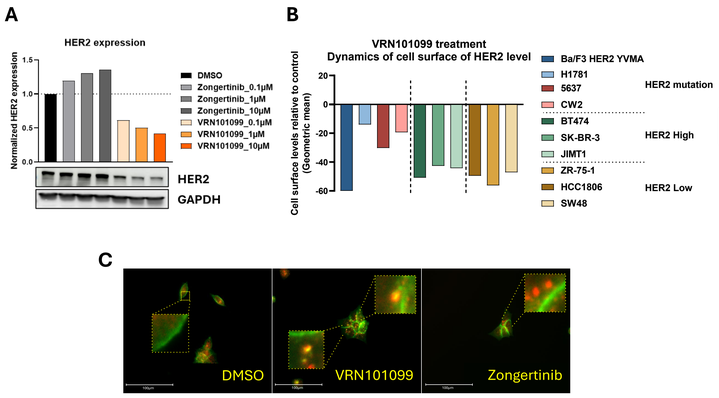


Figure 3. (A) VRN10 dose-dependently reduced total HER2 level in BT-474 cells (100% serum). (B) FACS confirmed reduced surface expression of HER2 in both HER2-amplified and mutant models. (C) IF demonstrated HER2 internalization via HER2/EEA1 co-localization.

Potent Cellular Activity of VRN101099

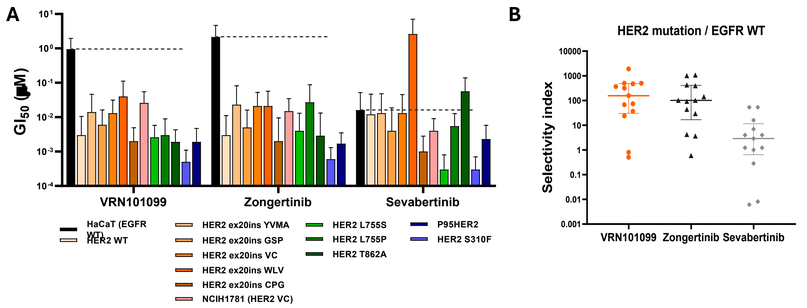


Figure 3. VRN10 activity and selectivity. (A) VRN10 dose-dependently inhibits growth of HER2 mutation Ba/F3 models. (B) Superior selectivity index of VRN10 (HER2 mutant vs. EGFR WT) compared to other HER2 TKIs.

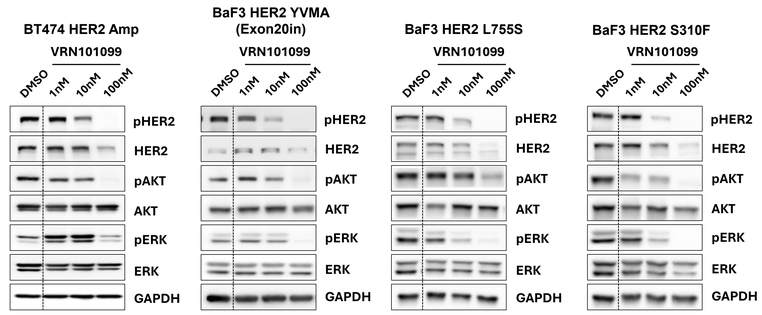
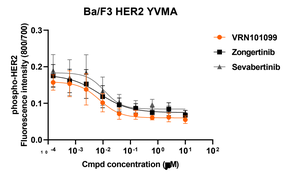


Figure 4. Response of ERBB2 and downstream signaling to VRN10 in ERBB2-altered cancer cells. Similar HER2 signaling inhibition was observed at 1–100nM in HER2-amplified BT474 and Ba/F3 cells expressing HER2 YVMA, L755S, or S310F.



Compound	HER2 YVMA ICW pHER2
	IC_{50} (μM)
VRN101099	0.007
Zongertinib	0.010
Sevabertinib	0.014

Figure 5. In-Cell Western analysis revealed that VRN10 exhibits superior pHER2 inhibition compared to zongertinib and sevabertinib in Ba/F3 cells expressing the HER2 ex20ins YVMA mutation. The experiment was performed in triplicate

In vivo anti-tumor efficacy in the HER2 ex20ins YVMA model

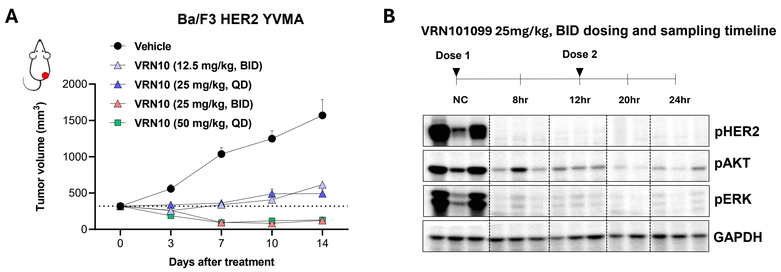


Figure 6. (A) Potent tumor regression efficacy of VRN10 in Ba/F3 HER2 YVMA-bearing mice. (B) Sustained target inhibition, showing prolonged suppression of pHER2 up to 24 hours.

Intracranial efficacy and CNS activity of VRN101099

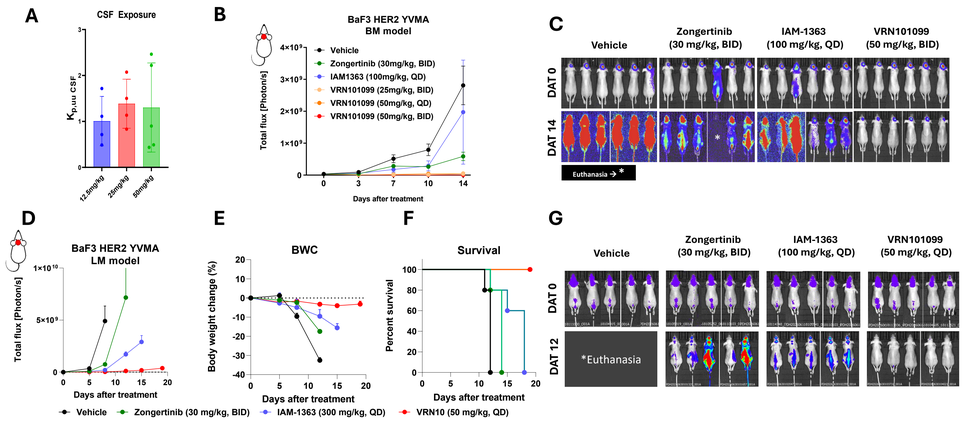
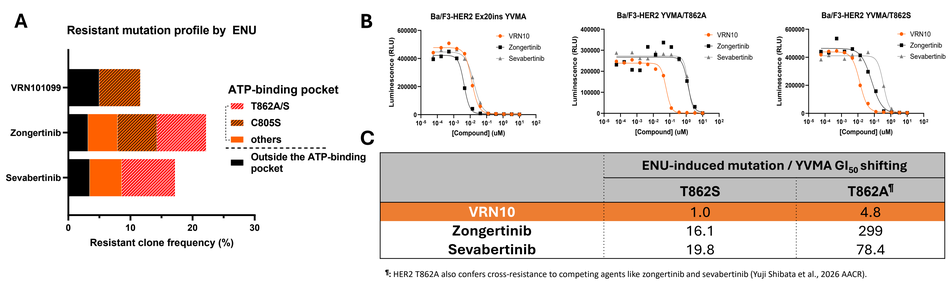


Figure 7. VRN10 brain penetrance and in vivo CNS efficacy. (A) $K_{p,uu,CSF}$ of VRN10. (B) In vivo efficacy in a brain metastasis (BM) model. (C) Mouse imaging data of the BM model. (D) In vivo efficacy in a leptomeningeal metastasis (LM) model. (E) Body weight changes of mice in the LM model over the experimental period. (F) Kaplan-Meier survival curves of mice in the LM model. (G) Mouse imaging data of the LM model.

Evaluation of resistance in ENU-induced mutants



C

	ENU-induced mutation / YVMA GI_{50} shifting	
	T862S	T862A¶
VRN10	1.0	4.8
Zongertinib	16.1	299
Sevabertinib	19.8	78.4

¶: HER2 T862A also confers cross-resistance to competing agents like zongertinib and sevabertinib (Yuji Shibata et al., 2026 AACR).

Figure 8. (A) ENU-induced drug-resistant mutation profiles.(B) GI_{50} values in YVMA and YVMA with secondary mutations (YVMA+mutation) (n = 3).(C) Fold changes of GI_{50} shifts in YVMA mutation models.

In vivo anti-tumor efficacy in T-DXd resistance model

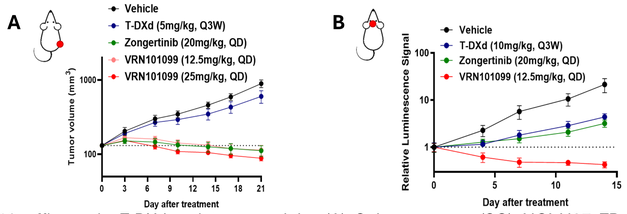


Figure 9. VRN10 efficacy in T-DXd-resistant models. (A) Subcutaneous (SC) NCI-N87_TR anti-tumor activity. (B) Intracranial SK-BR-3_TR CNS activity.

Conclusion

- **HER2 ex20ins Efficacy:** Excellent cellular and in vivo antitumor activity in HER2 ex20ins models.
- **Superior CNS Activity:** Enhanced intracranial efficacy compared to competitor drugs.
- **Reduced Mutation Liability:** Fewer ENU-induced resistance mutations than other HER2 TKIs, notably within the ATP pocket.
- **Overcoming Resistance:** Maintained robust efficacy in T-DXd-resistant models.
- **Future Plan:** Phase 1b dose optimization planned for HER2-mutant NSCLC.

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