VRN101099, a Covalent HER2 Inhibitor Driving HER2 Internalization, Demonstrates Early Clinical Activity and Synergy With HER2-Targeted Antibody and ADC Therapies

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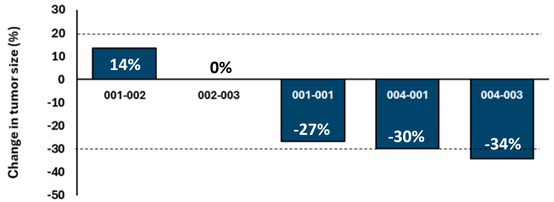
Background

- **Unmet Need**: Patients with HER2-positive breast cancer who progress after trastuzumab deruxtecan (T-DXd) have limited targeted treatment options.
- **Novel Mechanism**: VRN101099 is a covalent HER2 inhibitor designed to induce rapid HER2 internalization and degradation, distinct from other HER2 TKIs.
- **Mechanistic Advantages**:

1) Selectively and potently inhibits HER2 kinase catalytic activity.
2) Reduces HER2 surface expression and drive its internalization, unlike tucatinib, sevabertinib, and zongertinib.
3) Accelerates T-DXd internalization in HER2+ cells, including T-DXd–resistant models, potentially restoring ADC trafficking.

- **Monotherapy:** Early clinical data show meaningful activity in patients harboring HER2 activating mutations, previously treated with T-DXd, together with a favorable safety profile.
- **Combination Potential**: By enhancing HER2 internalization and augmenting ADC uptake, VRN101099 provides a strong scientific rationale for synergistic combination with HER2-directed antibodies and antibody–drug conjugates.

Clinical results



Patient	001-002	002-003	001-001	004-001	004-003
Dose (mg)	160	80	80	160	160
HER2 (historical IHC)	1+	2+	NA	1+	Negative
HER2 mt.	-	-	S310F	V777L	S310Y
Primary site	Salivary Gland	Gastric	Pancreas	Breast	Lung
Prior systemic Tx	0	2	3	7	3
Immediate prior regimen	-	Irinotecan Fluorouracil	Tucatinib Trastuzumab	T-DXd	T-DXd

Table 1. This ongoing open-label, dose-escalation study (NCT06806982) has completed DLT assessment for the 240 mg cohort. Among patients treated at 80 mg and 160 mg, clinically meaningful tumor shrinkage was observed across multiple HER2-positive solid tumors, including two patients who previously progressed on T-DXd. Data cut-off: Nov 21, 2025.

Case study

Case study : 160mg, HER2 V777L breast cancer

Cycle	Best response	Overall %	Note
C1D1	-	-	Treatment ongoing at Cycle 6 No dose reductions or interruptions
C3D1	SD	-24	
C5D1	SD	-30	

* Based on RECIST 1.1 criteria, the tumor size reduction rate was calculated to be 29.7%, which corresponds to stable disease (SD)

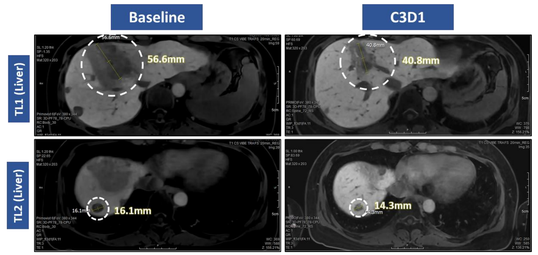


Figure 1. Case study of a patient with metastatic breast cancer harboring a HER2 V777L mutation. The patient had received 7 prior lines of systemic therapy, including T-DXd, and achieved -29.7% of tumor shrinkage with VRN101099 160 mg QD. Treatment remains ongoing at Cycle 6.
The figure is adapted from the poster presented at the AACR-NCI-EORTC Annual Meeting (2025).

Safety

Event (%)	VRN101099						Zongertinib	
	80mg (n=3)		160mg (n=5)		240mg (n=4)		120mg (n=75)	
	All	G ≥3	All	G ≥3	All	G ≥3	All	G ≥3
Any TRAE	33	-	40	-	50	-	97	17
Diarrhea	-	-	20	-	25	-	56	1
Rash	-	-	-	-	-	-	33	-
ALT increased	-	-	-	-	-	-	24	5
AST increased	-	-	20	-	-	-	21	8
Dry skin	-	-	-	-	25	-	15	-
Pruritus	-	-	-	-	-	-	13	-

Table 2. VRN101099 demonstrates a favorable safety profile across 80–240 mg, with no Grade ≥3 TRAEs. All-grade events were infrequent and primarily Grade 1–2, showing a more tolerable profile relative to Zongertinib (Beamion LUNG-1 study).

Preclinical in vitro results

VRN101099 mediated HER2 internalization / degradation

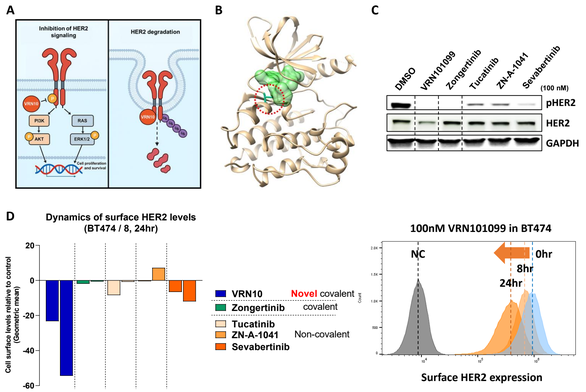


Figure 2. A. Scheme of HER2 dynamics mediated by VRN101099 B. Crystal structure of an engineered activating HER2 kinase domain mutant in complex with VRN101099. The covalent inhibitor occupies the ATP-binding pocket and forms a covalent bond with Cys809. C, D. Dynamics of cell surface HER2 expression in BT474 cells treated with various inhibitors. Cells were treated with 100 nM of the indicated HER2 TKIs. HER2 expression was subsequently analyzed by western blot (C) and flow cytometry (D).

T-DXd internalization in HER2+ cells

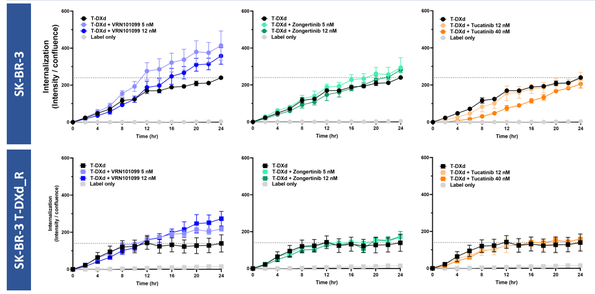
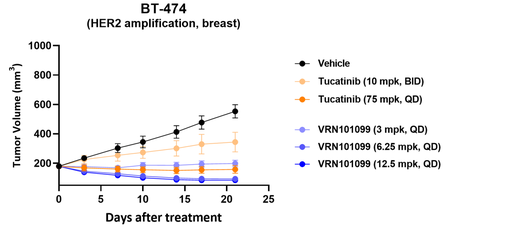


Figure 3. T-DXd internalization with or without HER2 TKIs in SK-BR-3 cells. Cells were treated with fluorescence labeled T-DXd (1 μg/ml) with or without indicated HER2 TKIs. The fluorescence signal was measured by Incucyte® Live-Cell Analysis System..

Preclinical in vivo results

Monotherapy



Combination with ADC or antibodies

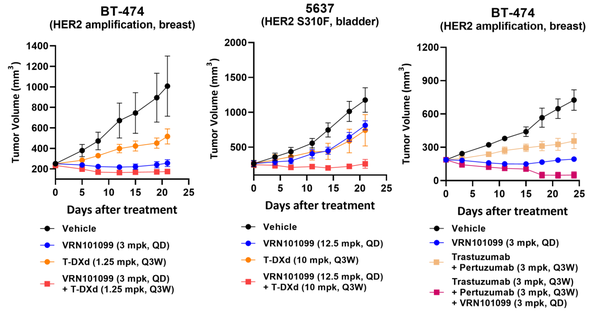


Figure 4. In vivo efficacy of VRN101099 in HER2-amplified BT-474 and HER2 S310F-mutant 5637 xenograft models. VRN101099 monotherapy demonstrated greater tumor growth inhibition than tucatinib, and combination with T-DXd or trastuzumab/pertuzumab produced a synergistic anti-tumor effect.

Conclusions

- VRN101099 demonstrates encouraging early clinical activity with a favorable safety profile, including tumor shrinkage in patients previously treated with T-DXd.
- Through covalent HER2 inhibition that drives HER2 internalization and degradation, VRN101099 shows strong monotherapy activity and synergistic efficacy when combined with HER2-directed antibodies or ADCs, supporting its potential across HER2-positive tumors.

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References

1. The VRN101099 clinical data has been adapted and updated from the poster presented at AACR-NCI-EORTC Annual Meeting (2025)
2. Jung, HR, et al. "Abstract LB284: VRN101099: A novel treatment option for HER2-driven cancer patients, overcoming T-DXd resistance and brain metastases." Cancer Research 85.8_Supplement_2 (2025): LB284-LB284.
3. Heymach, JV., et al. "Zongertinib in Previously Treated HER2-Mutant Non–Small-Cell Lung Cancer." New England Journal of Medicine 392.23 (2025): 2321-2333.
4. Son, J, et al. "A Novel HER2-Selective Kinase Inhibitor Is Effective in HER2 Mutant and Amplified Non–Small Cell Lung Cancer." Cancer research 82.8 (2022): 1633-1645.
5. A Study of VRN101099 in Patients With HER2-Positive Solid Tumors (NCT06806982)

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