P3.280: Early Clinical Outcomes of VRN101099 in ERBB2-Mutated Advanced Non-Small Cell Lung Cancer: a Case Series from a Phase 1a Study

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INTRODUCTION

Backgrounds

- HER2-activating mutations occur in ~ 2–3% of solid tumors[1] and are associated with poor prognosis and frequent brain metastases in NSCLC[2].
- Recently approved HER2 TKIs, zongertinib and sevabertinib, have demonstrated clinical activity in HER2-mutant NSCLC, particularly against kinase domain mutations[3].
- VRN101099 is a covalent, CNS-penetrant, HER2 selective TKI with a distinct **degradation mechanism** (P3.240) active across HER2 domains and tumor types.
- Here we report early clinical activity across HER2 mutation domains and tumor types in the first HER2-mutant patients from the Phase 1a study (NCT06806982).

Methods

- Ten HER2-mutant patients had ≥1 post-baseline tumor assessment as of 2 September 2026. Patients A-D (most mature follow-up) and Patient E (an additional NSCLC case) are presented here.
- Patients received dose ranging from 80 to 480 mg with tumor assessment every 2 cycles according to RECIST v1.1 and for safety per CTCAE v5.0.

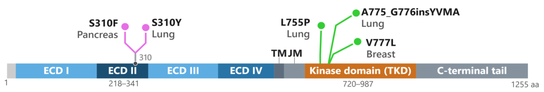


FIGURE 1. Map of Identified HER2 Mutations

Patient Characteristics

	Patient A	Patient B	Patient C	Patient D	Patient E
Age/Sex	56/F	60/M	46/F	72/M	62/F
ECOG	0	1	0	0	0
Dose (mg)	160	320	160	80	240
HER2 mutation	S310Y	L755P	V777L	S310F	A775_G776ins YVMA
HER2 domain	ECD	TKD	TKD	ECD	TKD
Primary site	Lung	Lung	Breast	Pancreas	Lung
Metastatic site	Lymph Nodes, Brain, LT.PLEURAL	Lymph Nodes, Bone, Brain, Pleural seeding	Liver, Lung, Pleura	Gastric, Lymph node	Lung, Lymph Nodes, Brain
Prior HER2 Tx	trastuzumab, neratinib, T-DXd	T-DXd	T-DXd	trastuzumab, tucatinib	sevabertinib, ELVN-002, T-DXd
Prior Systemic Tx	3	3	7	3	7

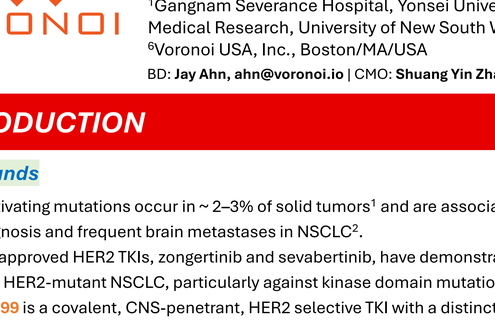
ECD, Extracellular Domain; TKD, Tyrosine Kinase Domain

- Enrolled patients carried HER2 mutations in the **extracellular domain (ECD; S310Y, S310F)** and **kinase domain (L755P, V777L, A775_G776insYVMA)** in **lung**, **breast**, and **pancreas**.
- Heavily pretreated (median of 3 prior systemic therapies) with prior exposure to HER2-directed therapies: **4/5 post T-DXd**, **3/5 post-HER2 TKI (neratinib, tucatinib)**.
- **3/5 had baseline brain metastases.**

CLINICAL CASES

Patient A — 56 Female · 160 mg · HER2 S310Y · Lung Cancer

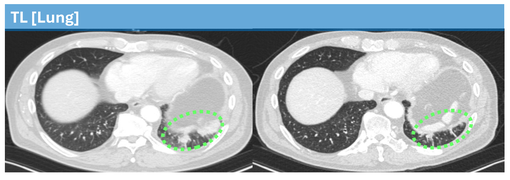
pembrolizumab+pemetrexed+cisplatin **SD** → **trastuzumab+neratinib** **SD** → **T-DXd** **SD** → **VRN101099** **PR**



- **Prior therapies**, including T-DXd, all reached **only stable disease**
- Achieved PR at C5D1 with continued response by **-49.1% at C14D1**
- **Overall PR** with **sequential CR in TLs**; **Lung at C3D1** and **Breast at C14D1**

Patient B — 60 Male · 320 mg · HER2 L755P · Lung Cancer

MEDI5752(anti-PD-1xCTLA-4 bispecific antibody)+pemetrexed+carboplatin **SD** → pembrolizumab+pemetrexed+carboplatin **PD** → **T-DXd** **PR** → **VRN101099** **PR**



- **PR maintained** with **VRN101099** following prior **T-DXd (17 months)**
- **Overall PR with -35.8%** tumor reduction in 2 Lung TL at C5D1
- **G3 diarrhea resolved** within a week via anti-diarrheal regimen

Patient C — 46 Female · 160 mg · HER2 V777L · Breast Cancer

palbociclib+letrozole **PR** → fulvestrant **Unknown** → fulvestrant+alpelisib **PD** → everolimus+exemestane **SD** → capecitabine **PR** → paclitaxel **PR** → **T-DXd** **PR** → **VRN101099** **SD**

- Anti-Tumor activity in **heavily pre-treated** setting **(≥7 prior Tx)**
- Tumor response by RECIST v1.1: **SD (-29.7%** in **Liver** TL at C5D1)
- Discontinued due to **non-TL PD**

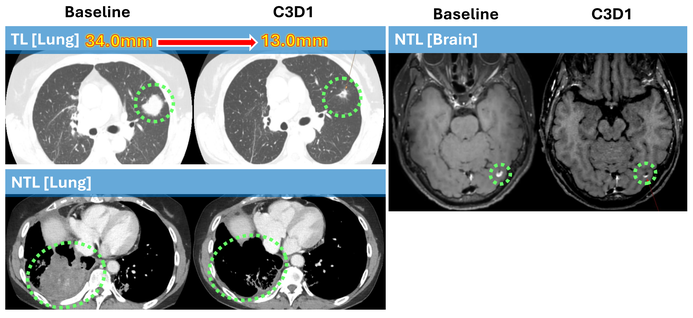
Patient D — 72 Male · 80 mg · HER2 S310F · Pancreatic Cancer

FOLFIRINOX **Unknown** → nab-paclitaxel+gemcitabine **Unknown** → **trastuzumab+tucatinib** **SD** → **VRN101099** **SD**

- Tumor response by RECIST v1.1: SD (**-26.7%** shrinkage in **Stomach at C3D1**)
- Tx interrupted for ~3 weeks due to underlying disease
- Discontinued to **subject withdrawal**

Patient E — 62 Female · 240 mg · HER2 A775_G776insYVMA · Lung Cancer

pemetrexed+cisplatin **PD** → atezolizumab **PD** → sevabertinib **PR** → ELVN-002(HER2 TKI) **SD** → gemcitabine **SD** → docetaxel **PD** → **T-DXd** **PR** → **VRN101099** **PR**



- **2 Lung TL PR achieved** at **first tumor assessment of -56.1%)**
- **Deep partial response** following relapse on **sevabertinib**, **ELVN-002**, and **T-DXd**
- **Brain NTL also decreased**

CLINICAL & MOLECULAR OUTCOME

Depth of Response

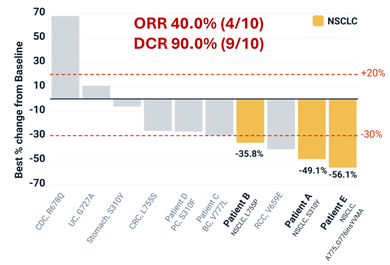


FIGURE 2: Anti-Tumor Activity of VRN101099 in Patients with Diverse HER2-Mutated Cancers

Anti-tumor activity of VRN101099 extended beyond the kinase domain to include extracellular domain mutations and diverse histology. Among 10 response-evaluable HER2-mutant patients, ORR was 40.0% and DCR was 90.0%.

CDC, Gallbladder carcinoma; UC, Urothelial Carcinoma; CRC, Colorectal Cancer; PC, Pancreatic Cancer; BC, Breast Cancer; NSCLC, Non-Small Cell Lung Cancer; RCC, Renal Cell Carcinoma

Safety

TRAEs (n=47)	VRN101099, 80-480 mg	
	All	≥Grade 3
Any	70%	6%
Diarrhea	45%	4%
Nausea	34%	-
Rash	9%	-
Dry skin	2%	-
Pruritus	4%	-
AST increased	2%	2%
ALT increased	4%	2%

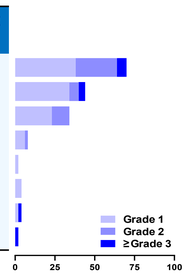
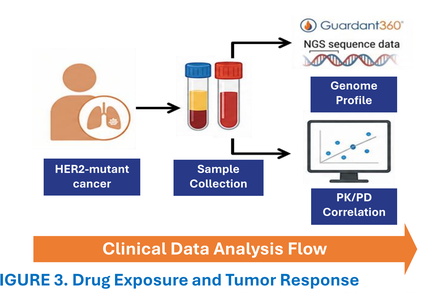


Table 1: Safety Profile of VRN101099

As of the data cutoff, 47 patients were evaluable in the dose-escalation study (80-480 mg). VRN101099 demonstrated a favorable safety profiles with ≥Grade 3 events limited to 6%. Observed TRAEs were expected and readily managed with standard supportive care.

Exposure-Response Relationship



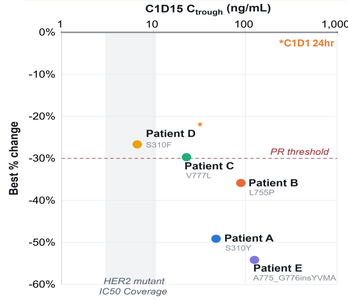


FIGURE 3. Drug Exposure and Tumor Response

Exploratory analysis included baseline plasma ctDNA profiling (Guardant360) and serial pharmacokinetic sampling during VRN101099 treatment. Tumor shrinkage was correlated with higher drug exposure levels.

Genetic Profiling and Durability

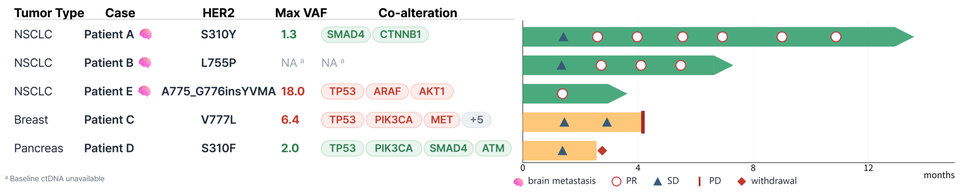


FIGURE 4. Genomic Context, Response, and Treatment Duration

Durable PRs occurred in NSCLC patients with baseline brain metastases carrying both extracellular (S310Y) and kinase domain (L755P, A775_G776insYVMA) mutations regardless of co-occurring genetic alterations and high variant allele fraction .

SUMMARY

EFFICACY

Of 10 patients with HER2 activating mutations, 3 NSCLC patients with brain metastases showed efficacy. Despite heavy treatment history including T-DXd exposure just prior to enrollment, all three achieved PR with decreased intracranial non-target lesions.

COVERAGE

Antitumor activity extends across the mutation and tumor spectrum. VRN101099 exposure translated into tumor reduction from NSCLC to breast (TKD mutation) and pancreatic (ECD mutation) cancers.

NEXT STEPS

A Phase 1b expansion is planned with cohorts stratified by HER2 status (HER2-mutant NSCLC and HER2-positive solid tumors), including combinations with other HER2-directed agents.

Reference: [1] Adesoye T, et al. Clinical Cancer Research. 2026 [2] Zhang Q, et al. Lung Cancer. 2025 [3] Heymach JV, et al. N Engl J Med. 2025; FDA, Nov 2025 (sevabertinib).

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.

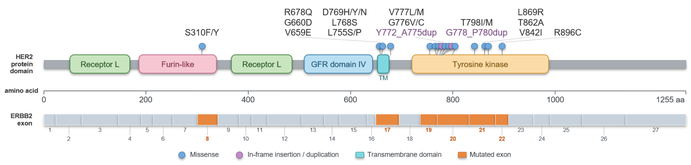


Figure 1. Activating mutations of HER2 (ERBB2).

Open-State Targeting and Protein Degradation

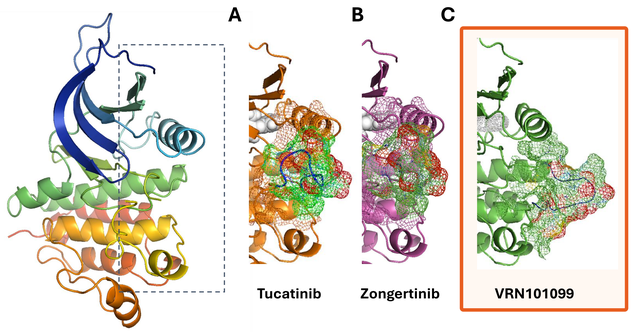


Figure 2. VRN101099: a unique open-state activation loop.

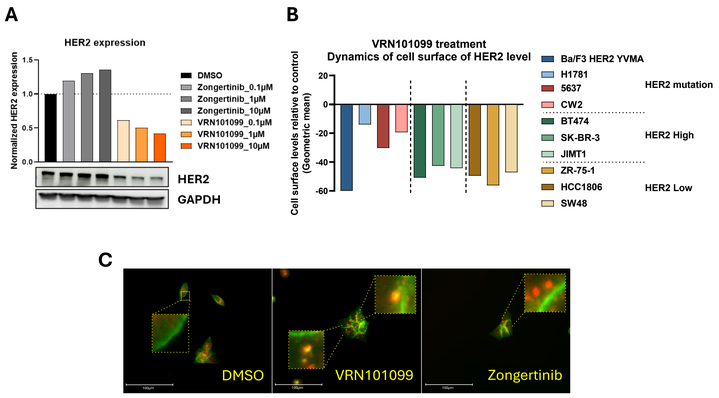


Figure 3. (A) VRN10 dose-dependently reduced total HER2 level in BT-474 cells (100% serum). (B) FACS confirmed reduced surface expression of HER2 in both HER2-amplified and mutant models. (C) IF demonstrated HER2 internalization via HER2/EEA1 co-localization.

Potent Cellular Activity of VRN101099

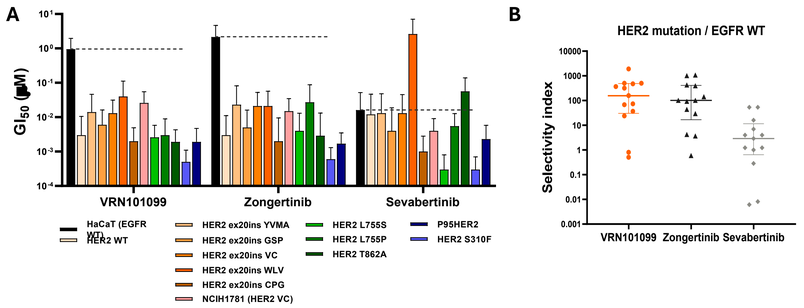


Figure 3. VRN10 activity and selectivity. (A) VRN10 dose-dependently inhibits growth of HER2 mutation Ba/F3 models. (B) Superior selectivity index of VRN10 (HER2 mutant vs. EGFR WT) compared to other HER2 TKIs.

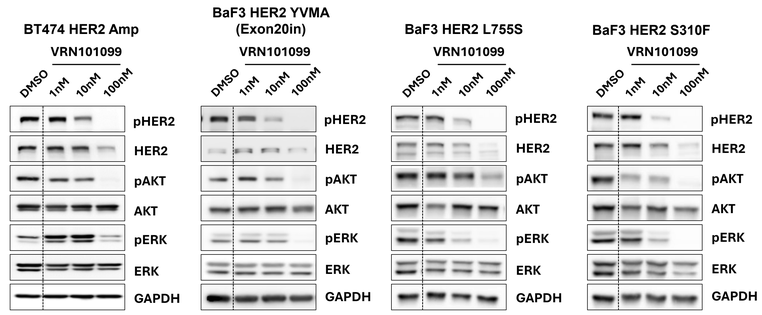
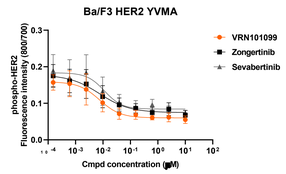


Figure 4. Response of ERBB2 and downstream signaling to VRN10 in ERBB2-altered cancer cells. Similar HER2 signaling inhibition was observed at 1–100nM in HER2-amplified BT474 and Ba/F3 cells expressing HER2 YVMA, L755S, or S310F.



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

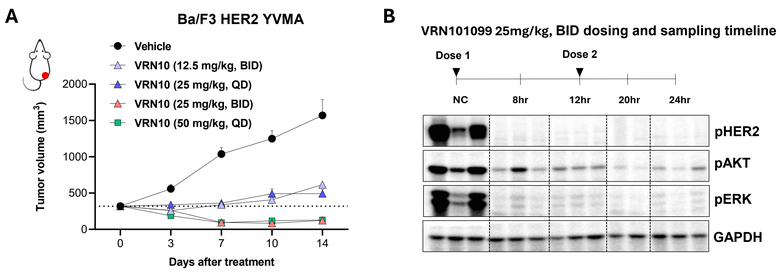


Figure 6. (A) Potent tumor regression efficacy of VRN10 in Ba/F3 HER2 YVMA-bearing mice. (B) Sustained target inhibition, showing prolonged suppression of pHER2 up to 24 hours.

Intracranial efficacy and CNS activity of VRN101099

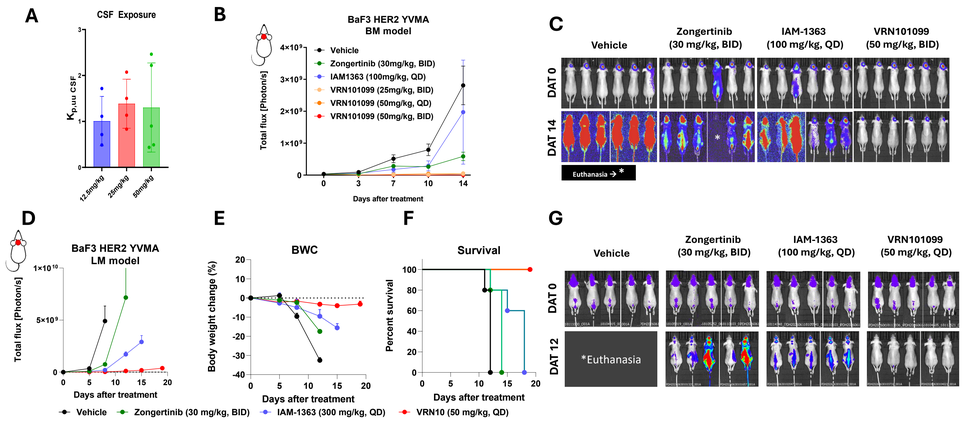
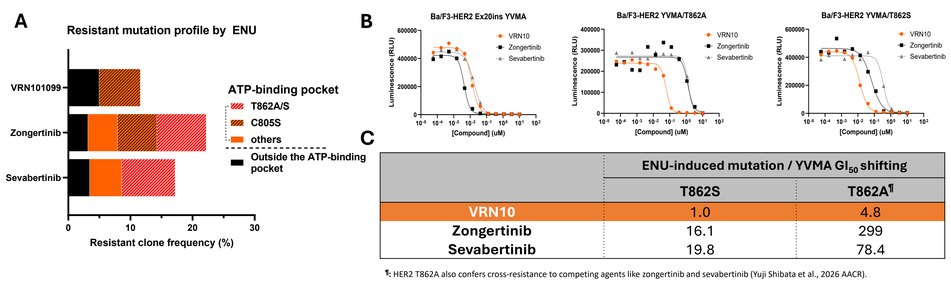


Figure 7. VRN10 brain penetrance and in vivo CNS efficacy. (A) $K_{p,uu,CSF}$ of VRN10. (B) In vivo efficacy in a brain metastasis (BM) model. (C) Mouse imaging data of the BM model. (D) In vivo efficacy in a leptomeningeal metastasis (LM) model. (E) Body weight changes of mice in the LM model over the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

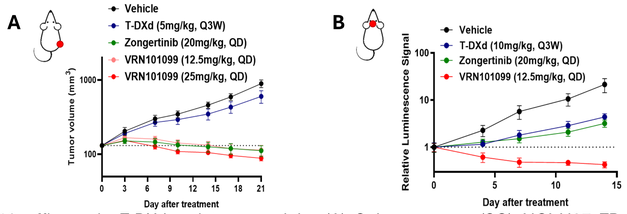


Figure 9. VRN10 efficacy in T-DXd-resistant models. (A) Subcutaneous (SC) NCI-N87_TR anti-tumor activity. (B) Intracranial SK-BR-3_TR CNS activity.

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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