Phase Ia Study of VRN101099, a Brain-Penetrant, Highly Selective Covalent HER2 Inhibitor, in HER2-Positive or HER2-Mutant Advanced Solid Tumors

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

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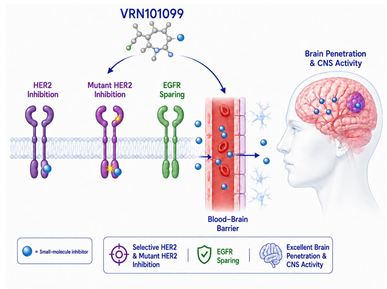
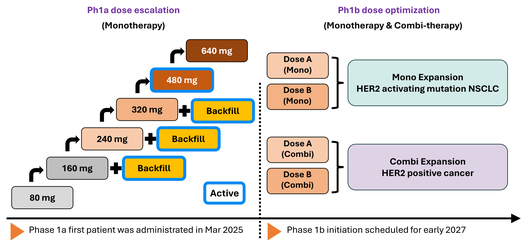
Background

Despite advances in HER2-targeted therapies, including trastuzumab deruxtecan (T-DXd), unmet needs remain for patients with HER2-driven solid tumors who develop treatment resistance, particularly those with central nervous system (CNS) metastases. VRN101099 (VRN10) is an orally bioavailable, brain-penetrant covalent HER2 inhibitor that irreversibly inhibits HER2 and induces receptor internalization and degradation. It is currently being evaluated in an ongoing Phase 1a **dose-escalation** study, with dose escalation ongoing at the **480 mg** dose level.



Phase I study design

- Standard "3+3" dose escalation
- Minimum of 18 and up to 72 pts, plus up to 36 additional backfill pts
- DLT assessment: first cycle of treatment (i.e. Cycle 1, 21 days of IP)
- **Phase 1b Monotherapy** (dose optimization and expansion): HER2 activating mutation NSCLC, **Phase 1b combination**(dose finding and expansion): HER2 positive solid tumors.



Phase Ia dose escalation key eligible patients

- Age ≥18 years with **HER2-altered solid tumors** (confirmed by IHC 1+/2+/3+, FISH/ISH, or NGS of tissue/ctDNA)
- HER2 positive **mBC** or **mGC** with PD after prior anti-HER2 therapy
- Other HER2-altered solid tumors with **not approved HER2-targeted SoC**, progressed on all available therapies
- **NSCLC** with HER2-activating mutations after prior **HER2 TKI** or **ADC**.

Primary endpoints

- Safety
- Tolerability
- Determine the MTD or RP2D

Secondary endpoints

- PK (Pharmacokinetics), PD (Pharmacodynamics)
- ORR according to RECIST v1.1

- Key objectives - determine the RP2D of VRN101099, safety, PK, and antitumor activity per RECIST v1.1
- Data cutoff on May 12, 2026.
- Safety was assessed in all patients who received at least one dose of the study drug
- mBC, metastatic breast cancer; mGC, metastatic gastric cancer; NSCLC, non-small-cell lung cancer.
- HER2-positive: IHC 3+ or IHC 2+/ISH+

Clinical Results

Patients' characteristics (N=35)

Characteristics	VRN10 monotherapy, N=35 (80–320 mg)
Median age, years (range)	63 (37-82)
Sex, n (%)	
Male / Female	17 (49%) / 18 (51%)
Race, n (%)	
Asian / White	26 (74%) / 9 (26%)
ECOG PS, n (%)	
0 / 1	23 (66%) / 12 (34%)
HER2 aberration, n (%)	
HER2 positive / mutation	**18 (51%) / 7 (20%)**
Primary tumor site	
Breast	11 (31%)
Gastrointestinal†	10 (29%)
Hepatobiliary‡	3 (9%)
Lung	2 (6%)
others§	9 (26%)
CNS Metastasis, n (%)	
Yes / No	**7 (20%) / 28 (80%)**
Median No. prior systemic therapies, n (range)	3 (0 - 13)
Prior HER2 Abs / ADC, n (%)	21 (60%) / 20 (57%)
Prior HER2 TKIs, n (%)	6 (17%)

- † Includes stomach, esophagus, colon, jejunum, and pancreas; ‡ includes ampullary, gallbladder ducts, and liver (near gallbladder); § includes salivary gland, skin, ovary, urothelial carcinoma, renal, and uterine tumors.

Efficacy Evaluable Patients (N=26)

All / HER2 positive or HER2 mutations		
	All (N=26)	HER2 positive / mutation (N=19)
CR	0	0
PR	4 (15%)	4 (21%)
SD	14 (54%)	10 (53%)
PD	8 (31%)	5 (26%)
ORR	4 (15%)	**4 (21%)**
DCR	18 (69%)	**14 (74%)**

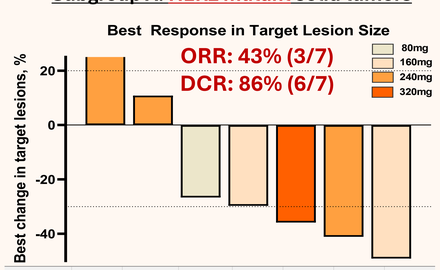
- Analysis sets: Safety, all dosed patients (N=35); response-evaluable, patients with ≥1 post-baseline tumor assessment (N=26).
- Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, CR+PR; DCR,

CNS control in BM patients	
	Baseline BM (N=6†); Assessed (N=4)
Intracranial DCR, n (%)	**3 /4 (75%)**
Patients with target lesion	1 intra SD with tumor reduction, 1 intra PD
Patients with non-target lesion	2 Non-CR/non-PD (1 with reduction)
mDOT	3.0 months (range, 1.6-9.4) 3/4 (75%) ongoing

- †Among 6 patients with baseline BM, 4 patients had at least one post-baseline intracranial tumor assessment; one discontinued treatment prior to the first intracranial assessment, and one had not yet reached the first intracranial assessment.
- mDOT: median duration of treatment.

Subgroup A: HER2 mutant solid tumors

Best Response in Target Lesion Size

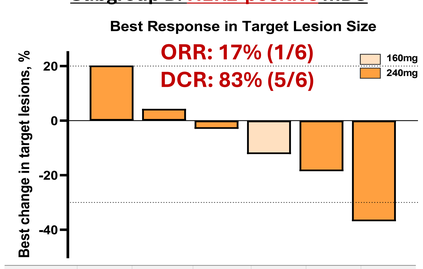


Patient #	007-002	009-004	001-001	004-001	009-006	008-001	004-003
HER2 (status)	R678Q	G727A	S310F	V777L	L755P	V659E	S310Y
Primary tumor site	Bladder	Urothelial	Pancreas	Breast	Lung	Renal	Lung
No. prior Systemic Tx	2	4	3	7	3	2	3
Prior HER2 TKI	N	N	**Y**	N	N	N	**Y**
Prior T-DXd	N	N	N	**Y**	**Y**	N	**Y**

- S310F / S310Y: Extracellular domain, V659E: Transmembrane domain , R678Q: Juxtamembrane domain, G727A / L755P / V777L: Kinase domain

Subgroup B: HER2-positive mBC

Best Response in Target Lesion Size

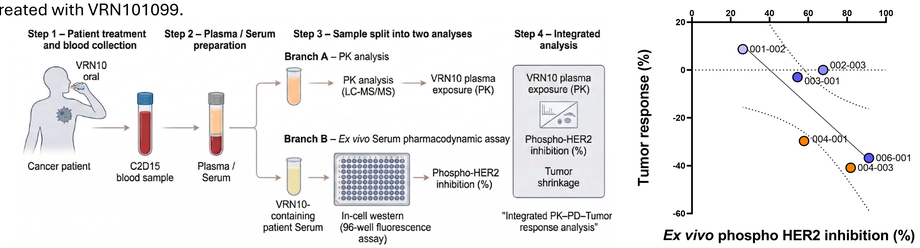


Patient #	005-001	006-003	003-001	005-002	003-003	006-001
HER2 (status)	IHC 3+	IHC 2+ ISH+	IHC 3+	IHC 3+	IHC 2+ ISH+	IHC 3+
Primary tumor site	Breast	Breast	Breast	Breast	Breast	Breast
No. prior Systemic Tx	3	6	10	8	2	3
Prior HER2 TKI	N	N	Y	Y	N	N
Prior T-DXd	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**

- KR005-002 Target lesion: Brain

Tumor response - *Ex vivo* pHER2 inhibition correlation

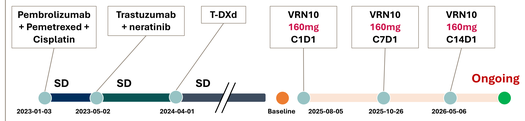
- *Ex vivo* phospho-HER2 IC_{50} was assessed, and tumor response correlated with *ex vivo* phospho-HER2 inhibition in patients treated with VRN101099.



Case Study

004-003 (160 mg) : HER2 S310Y lung adenocarcinoma

56 years old female patient harboring HER2 S310Y progressed on T-DXd

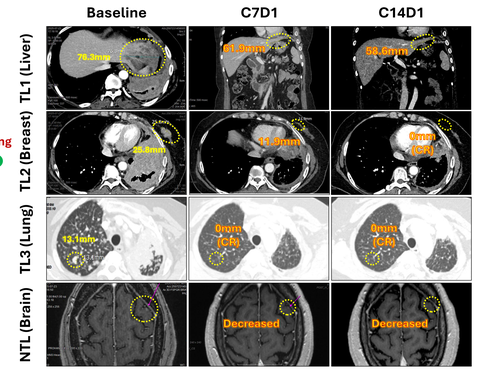


Baseline and Treatment History

- Metastatic site: Lung, lymph nodes, brain
- Disease progression after **T-DXd** treatment (~1yr)

VRN10 treatment

- **Best response: PR**
- **CR** was achieved in **2 target lesions**: lung at C3D1 and breast at C14D1
- **Brain non-target lesion(NTL) was decreased**
- Duration of treatment: **10 months (Ongoing)**



005-002 (160 mg) : HER2 positive Breast cancer

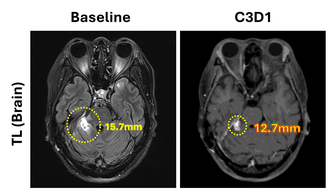
37 years old female patient with HER2-positive disease who progressed on T-DXd and had CNS metastases

Baseline and Treatment History

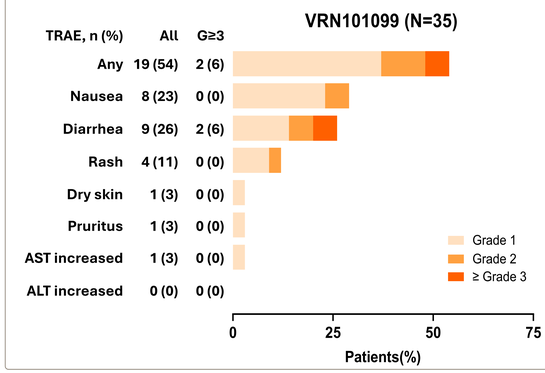
- **Metastatic site: Brain**
- Early HER2 therapy + surgery (Complete resection of primary tumor)
- Radiation + **Systemic HER2 targeted therapy multiple lines**
- Tucatinib -> **T-DXd** -> Progression

VRN10 treatment

- **Best response: SD**
- **Reduction in Brain target** lesions and non-target lesion was stable
- Duration of treatment: **6 months (Ongoing)**



Safety



- Overall, the safety profile was **tolerable** and **manageable** across all dose levels.
- One drug-related Grade 1 AST increased was observed in a one patient at 160 mg; notably, no hepatotoxicity was reported at higher dose levels.
- Diarrhea was effectively managed with loperamide administered on an as-needed basis upon symptom onset.
- Escalation to 480 mg is ongoing, with MTD not reached and RP2D determination ongoing.

Abbreviations: adverse event; TRAE; AE, adverse event; AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferase.

- Combined term, includes rash, rash maculopapular, exfoliative rash.

Conclusion

- VRN101099 was **tolerated** across evaluated dose levels and demonstrated encouraging antitumor activity in **heavily pretreated** HER2-driven solid tumors.
- VRN101099 induced **overall tumor shrinkage** in patients with **HER2 mutations**. In HER2-positive breast cancer, a favorable disease control rate (DCR) was observed, even in patients previously treated with T-DXd.
- Among the 4 patients evaluable for CNS response in the VRN101099 study, 3 patients had **well-controlled CNS disease**.
- These findings support continued dose escalation and expansion to define the RP2D and further characterize the therapeutic potential of VRN101099. (Clinical trial information: NCT06806982)

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