Preclinical and clinical activity of VRN101099, Novel Covalent HER2 TKI for HER2-Positive/Mutant Metastatic Solid Tumors

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#LB-C020

Background

HER2 alterations, including gene amplification and activating mutations, are oncogenic drivers across multiple solid tumors such as breast, lung, gastric, and colorectal cancers. Despite advances with HER2-targeted therapies, resistance and limited brain penetration remain major challenges.

VRN101099 is an oral, potent, and highly selective HER2 tyrosine kinase inhibitor with demonstrated brain permeability and favorable preclinical safety. In preclinical models, VRN101099 inhibited proliferation of HER2-driven tumor cells and induced apoptosis through MAPK and AKT–mTOR pathway inhibition.

Here, we report findings from a phase 1, open-label, dose-escalation study assessing the safety, pharmacokinetics, and preliminary efficacy of VRN101099 in patients with HER2-driven solid tumors (NCT06806982).

Clinical studies

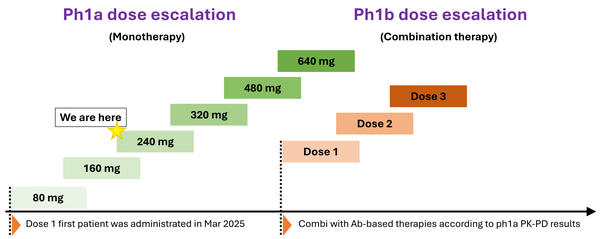
Phase 1a dose escalation

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)

Current 240mg cohort ongoing, no DLT up to 160 mg



Key eligible patients

- HER2-positive or mutated cancer as determined by IHC, ISH, or NGS
  Either (A) HER2-positive solid tumors (IHC 1+, 2+, 3+, or ISH+) (B) HER2 driver or resistant mutation (such as S310X, R678Q, L755X, I767M, V777X)

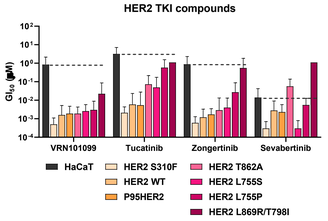
Primary endpoints

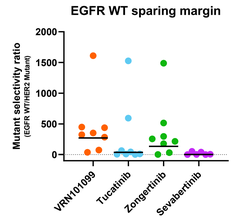
- Safety
- Tolerability
- PK, and PD to determine the MTD or RP2D

Preclinical Studies

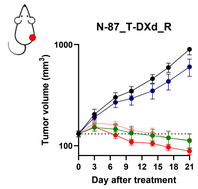
Kinase selectivity by KINOMEscan

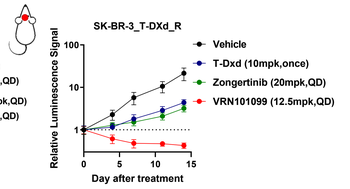
Growth inhibition of HER2 altered Ba/F3 engineered cells



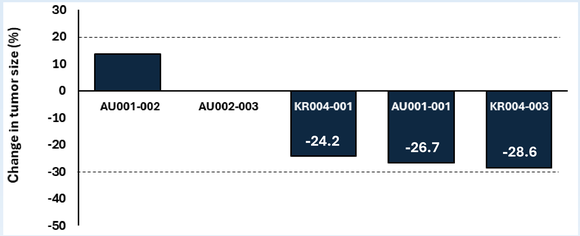


Efficacy of T-DXd resistance in vivo models





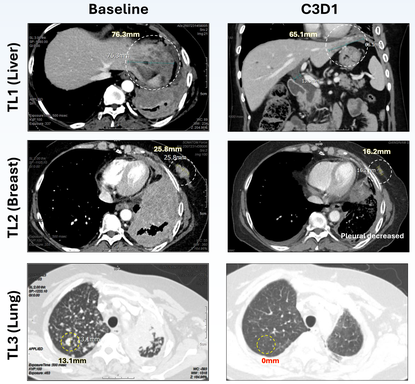
Efficacy data



Patient	AU001-002	AU002-003	KR004-001	AU001-001	KR004-003
Dose (mg)	160	80	160	80	160
HER2 amplification	1+	2+	1+	3+	Negative
HER2 mutation	-	-	V777L	S310F	S310Y
Primary site	Salivary Gland	Gastric	Breast	Pancreas	Lung
Prior systemic Tx	0	2	7	3	3
Last prescription	-	Irinotecan Fluorouracil	T-DXd	Tucatinib Trastuzumab	T-DXd

KR004-003: 160 mg, HER2 S310Y lung cancer

Cycle	Best response	Overall %	Note
C1D1	-	-	TL3 (lung) complete remission
C3D1	SD	-28.6	Cycle 4 ongoing

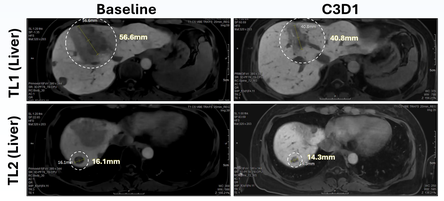


AU001-001: 80 mg, HER2 S310F pancreatic cancer

Cycle	Best response	Overall %
C1D1	-	-
C3D1	SD	-26.7

KR004-001: 160mg, HER2 V777L breast cancer

Cycle	Best response	Overall %	Note
C1D1	-	-	Cycle 5 ongoing
C3D1	SD	-24.2	



Safety

TRAEs in the VRN101099 80 mg and 160 mg cohorts

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

*A single case of diarrhea occurred and resolved within one week.

Conclusions

- VRN101099 monotherapy demonstrates preliminary antitumor activity with a manageable safety profile in patients with HER2-driven solid tumors.
- Preclinical and early clinical data suggest CNS activity, supporting further evaluation in patients with brain metastases.
- The favorable safety and brain-penetrant profile of VRN101099 support future combination and tumor-specific expansion studies.

References

1. Heymach JV, et al., HER2-Selective tyrosine kinase inhibitor, zongertinib (BI 1810631), in patients with advanced/metastatic solid tumors with HER2 alterations: a phase Ia dose-escalation study. Journal of Clinical Oncology. 2025 Apr 10;43(11):1337-47.
2. Heymach JV, et al., Zongertinib in Previously Treated HER2-Mutant Non–Small-Cell Lung Cancer. New England Journal of Medicine. 2025 Jun 19;392(23):2321-33.

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