VRN101099: a novel oral treatment option for patients with advanced solid tumors including brain metastasis driven by HER2 amplification or HER2-activating mutations even with T-DXd resistance

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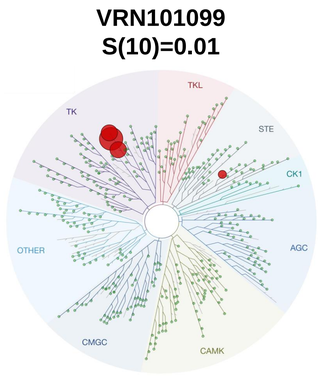
Introduction

Despite the efficacy of T-DXd, challenges such as brain metastasis and acquired resistance remain unmet medical needs in HER2-driven solid cancers. Various resistance mechanisms of T-DXd have been identified including p95HER2, exon16-deleted HER2, internalization defects, and payload-related resistance. Furthermore, a high incidence of metastasis and progression in the brain is still a challenge to the current standard of care. Thus, new therapeutic options need to overcome these challenges.

Highly selective and potent to HER2 and its variants



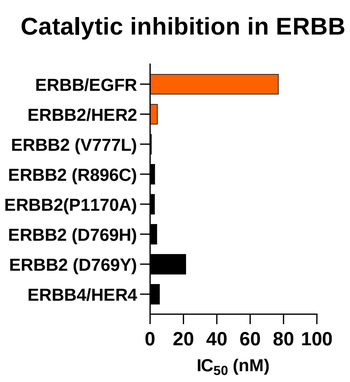
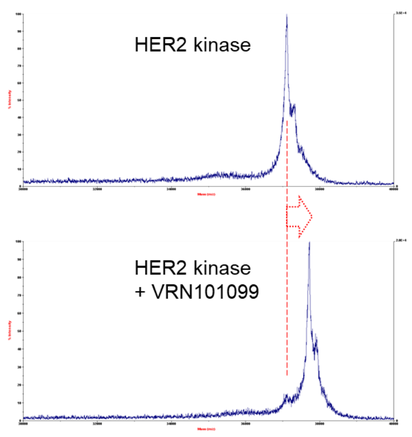
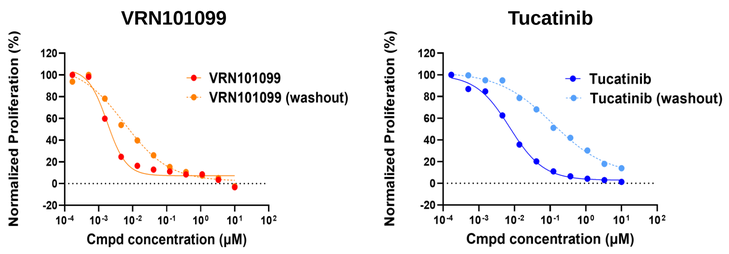


Figure 1. VRN101099 kinase selectivity was confirmed at 1 μM by KINOMEscan®. Kinome trees are marked with red circles indicating hits with less than 10% remaining binding capacity. Catalytic inhibition potency (IC_{50}) was determined by HotSpot™.

Retaining target potency by covalent bind to HER2

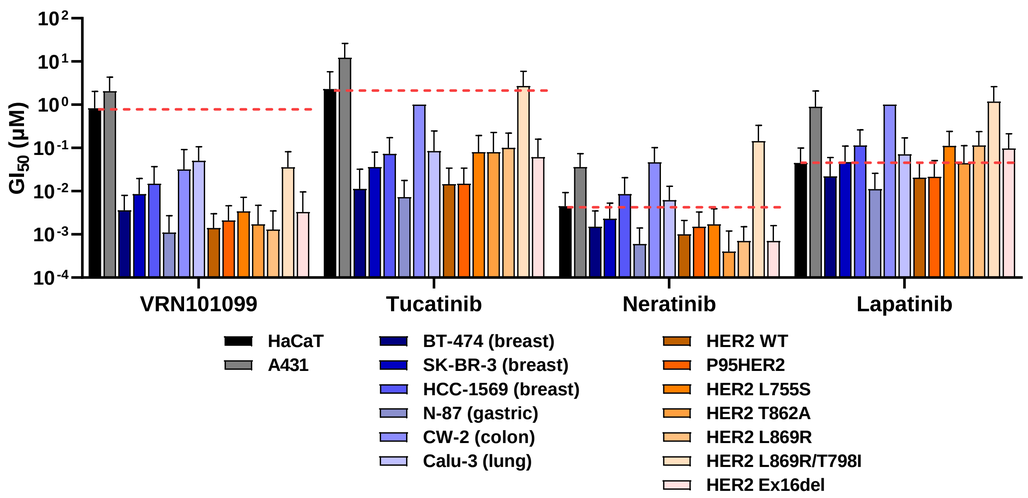




Compound	BT474 proliferation assay		
	GI_{50} (μM)		Fold change
	- Washout	+ Washout	
VRN101099	0.002	0.009	3.6
Tucatinib	0.009	0.193	21.9
Lapatinib	0.017	0.099	5.7
Neratinib	0.001	0.005	4.1

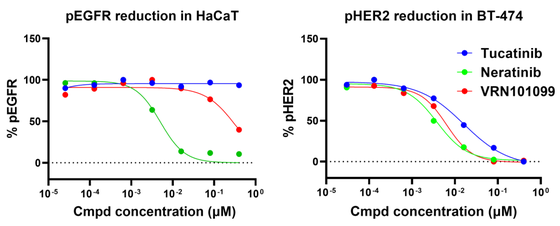
Figure 2. The covalent bond formation of VRN101099 was confirmed by MALDI-TOF analysis. Compounds were washed out after 24hr treatment to BT474 cells. VRN101099 remained high potency after wash-out, supporting longer resident time by covalent binding.

Potent HER2 inhibitor with wider selectivity over EGFR



	VRN101099	Tucatinib	Neratinib	Lapatinib
EGFR sparing (ratio to HaCaT GI_{50})	16~754	1~317	0~11	0~4

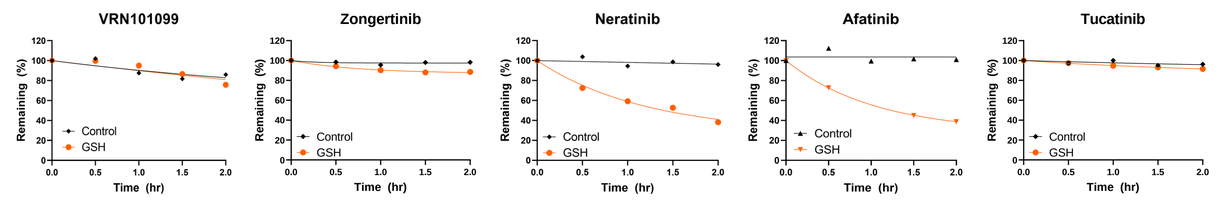
Figure 3. Growth inhibition of tumor cells, GI_{50} values were determined via CellTiter-Glo assays. As EGFR-dependent cells, HaCaT and A431 cells were used. For HER2 variants, Ba/F3-engineered cells were used.



Cmpd.	Class	pIC50 (μM)		Ratio
		HaCaT (pEGFR)	BT-474 (pHER2)	EGFR/HER2
VRN101099	Covalent	0.305	0.007	41.2
Neratinib	Covalent	0.005	0.007	0.7
Tucatinib	Non-covalent	N.A	0.027	N.A

Figure 4. Reduction of phosphorylated EGFR and HER2 by VRN101099, pIC_{50} were determined by In-Cell-Western via Odyssey CLx imaging system.

Less GSH reactivity anticipating less GSH depletion or cysteine modifications

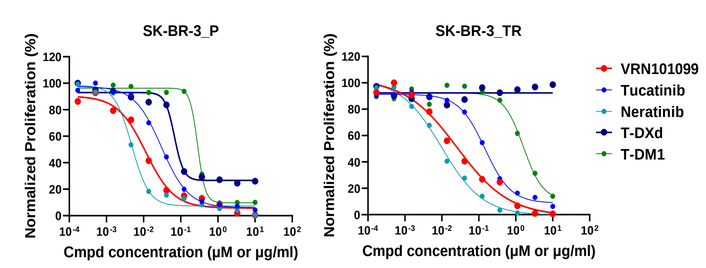


Type	Covalent HER2 specific				Covalent pan-ERBB				Non-covalent HER2 specific	
Half-life(hr)	VRN101099		Zongertinib		Neratinib		Afatinib		Tucatinib	
	k	$T_{1/2}$ (hr)	k	$T_{1/2}$ (hr)	k	$T_{1/2}$ (hr)	k	$T_{1/2}$ (hr)	k	$T_{1/2}$ (hr)
Control	0.105	*6.6	0.007	*96.3	0.026	*26.5	0.058	*12.0	0.020	*35.0
GSH	0.140	*4.9	0.085	*8.1	0.449	1.5	0.474	1.5	0.044	*15.6
GSH – control	0.035	19.8	0.078	8.9	0.423	1.6	0.416	1.7	0.025	28.2

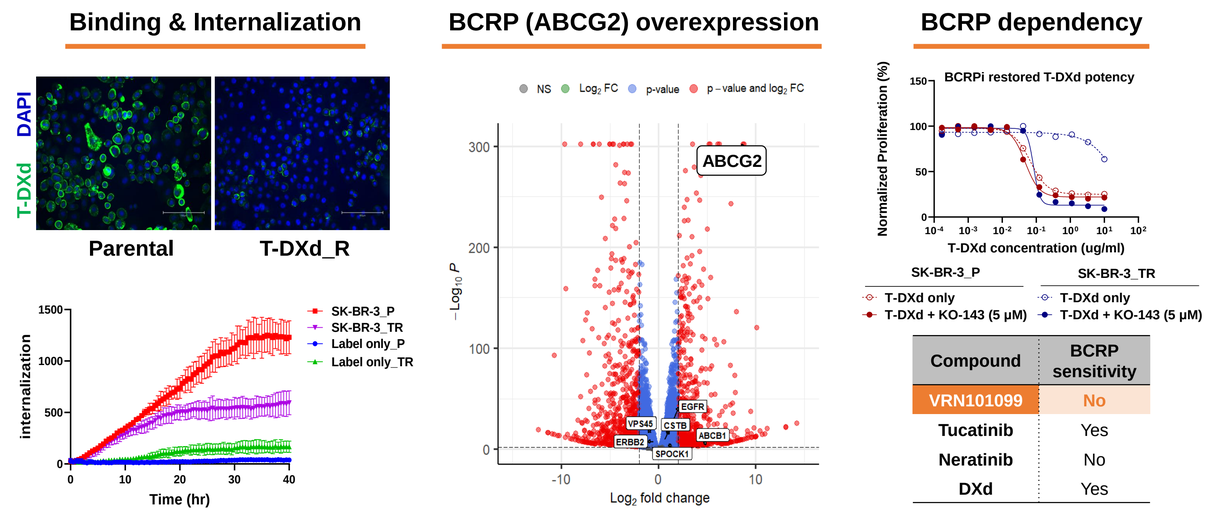
*Extrapolated value

Figure 5. Glutathione conjugation was confirmed at 2 μM compounds with 5 mM reduced GSH and determined by LCMS-based quantification

Overcome T-DXd resistant mechanisms



Compound	Proliferation Assay		
	GI_{50} (μM or μg/ml)		Fold change
	SK-BR-3_P	SK-BR-3_TR	
VRN101099 (μM)	0.012	0.024	2.1
Tucatinib (μM)	0.030	0.147	4.9
Neratinib (μM)	0.005	0.010	2.0
T-DXd (μg/ml)	0.068	>10.000	>147.7
T-DM1 (μg/ml)	0.285	1.602	5.6



Compound	BCRP sensitivity
VRN101099	No
Tucatinib	Yes
Neratinib	No
DXd	Yes

Figure 6. VRN101099 overcomes T-DXd resistance. T-DXd-resistant SK-BR-3 cells were generated by long-term T-DXd treatment and characterized by low T-DXd binding, low internalization, and overexpression of BCRP. BCRPi (KO-143) restored T-DXd potency, and VRN101099, a non-BCRP substrate, could overcome this resistance.

Superior efficacy on HER2+ SC and IC xenograft models

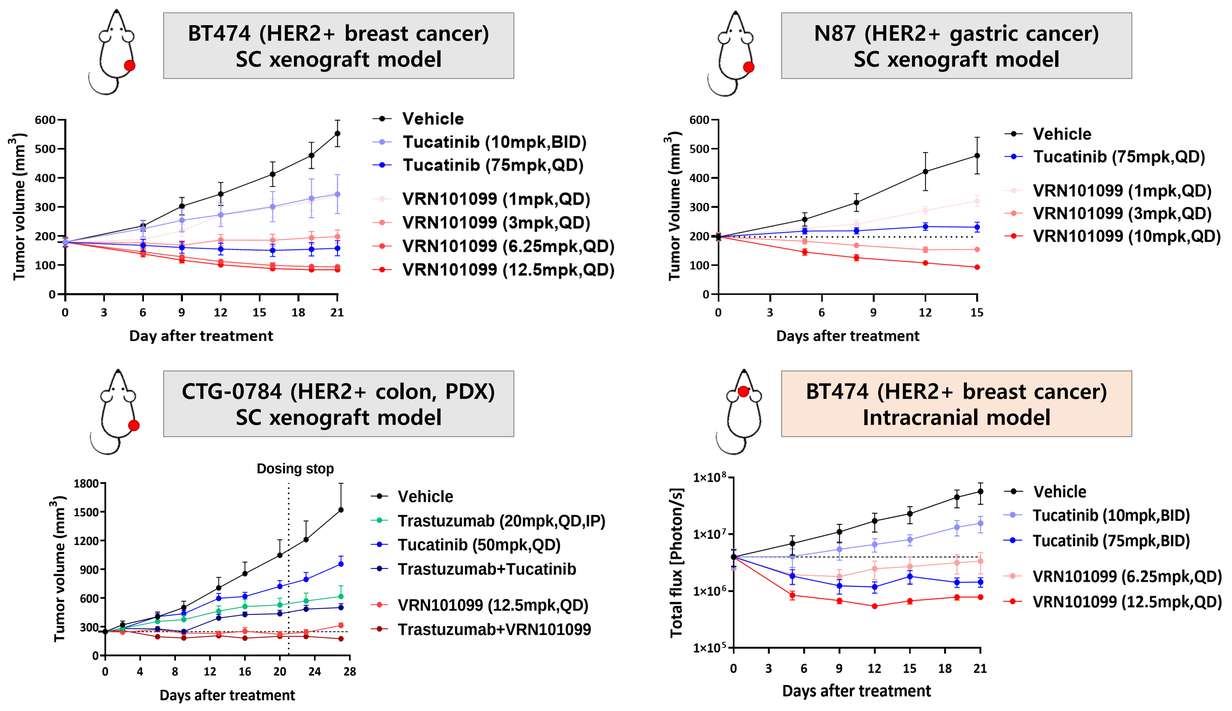
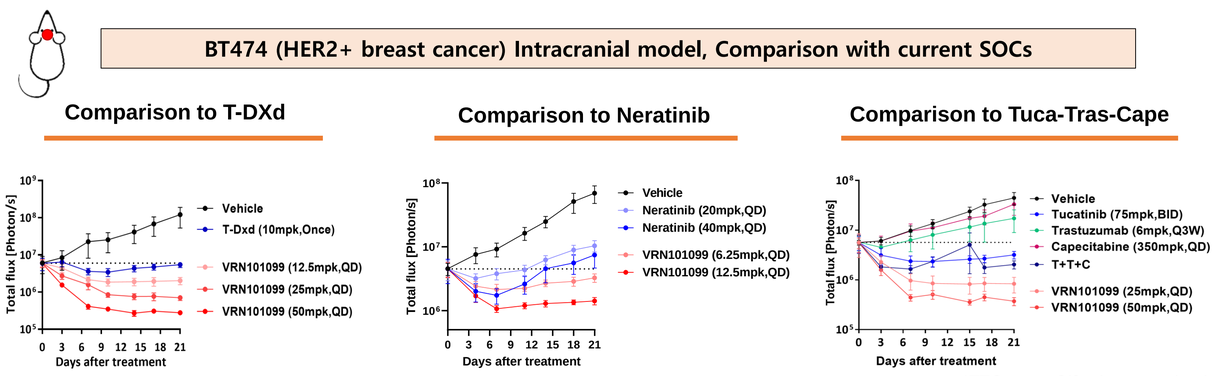


Figure 7. *in vivo* efficacy in breast, gastric and colon cancer xenograft



*TTC group 3/6 mice were dead

Figure 8. *in vivo* efficacy in BT474 intracranial model

Conclusion

- **VRN101099**
  - Competitive HER2 selective TKI offering a favorable profile regarding potency, tolerability, and brain permeability.
  - A novel systemic treatment option for patients with HER2-driven cancer, particularly with brain metastasis or who have progressed after or discontinued T-DXd.
  - The first-in-human study of VRN101099 is expected at the end of 2024.

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