



Early Clinical Anti-tumor Activity of VRN101099 Across Diverse HER2-altered Solid Tumors

LUMIN-HER2(NCT06806982): Phase 1 Study in HER2-Driven Advanced Solid Tumors

Y.H. Park¹, S.Y. Rha², S-A. Im³, J.H. Youk³, R. Cosman⁴, C. Steer⁵, J.H. Kim⁶, J.H. Kim⁷, K.H. Jung⁸, J.L. Lee⁹, J.Y. Park¹⁰, S.Y. Zhang¹¹

¹Department of Haemato-Oncology, Department of Medicine, Samsung Medical Center (SMC) - Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, ²Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea, ³Seoul National University Hospital, Seoul National University College of Medicine, Cancer Research Institute, Seoul National University, Seoul, Republic of Korea, ⁴The Kinghorn Cancer Centre, St. Vincent's Hospital, Sydney, Garvan Institute of Medical Research, University of New South Wales, Australia, ⁵Border Medical Oncology, Albury Wodonga Regional Cancer Centre, Albury, Australia, ⁶Division of Medical Oncology, Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, ⁷Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, ⁸Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, ⁹Division of Medical oncology, Department of Internal Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, ¹⁰Department of Medical Science, Voronoi Inc., Incheon, Republic of Korea, ¹¹Department of Medical Oncology, Voronoi USA, Waltham, United States of America

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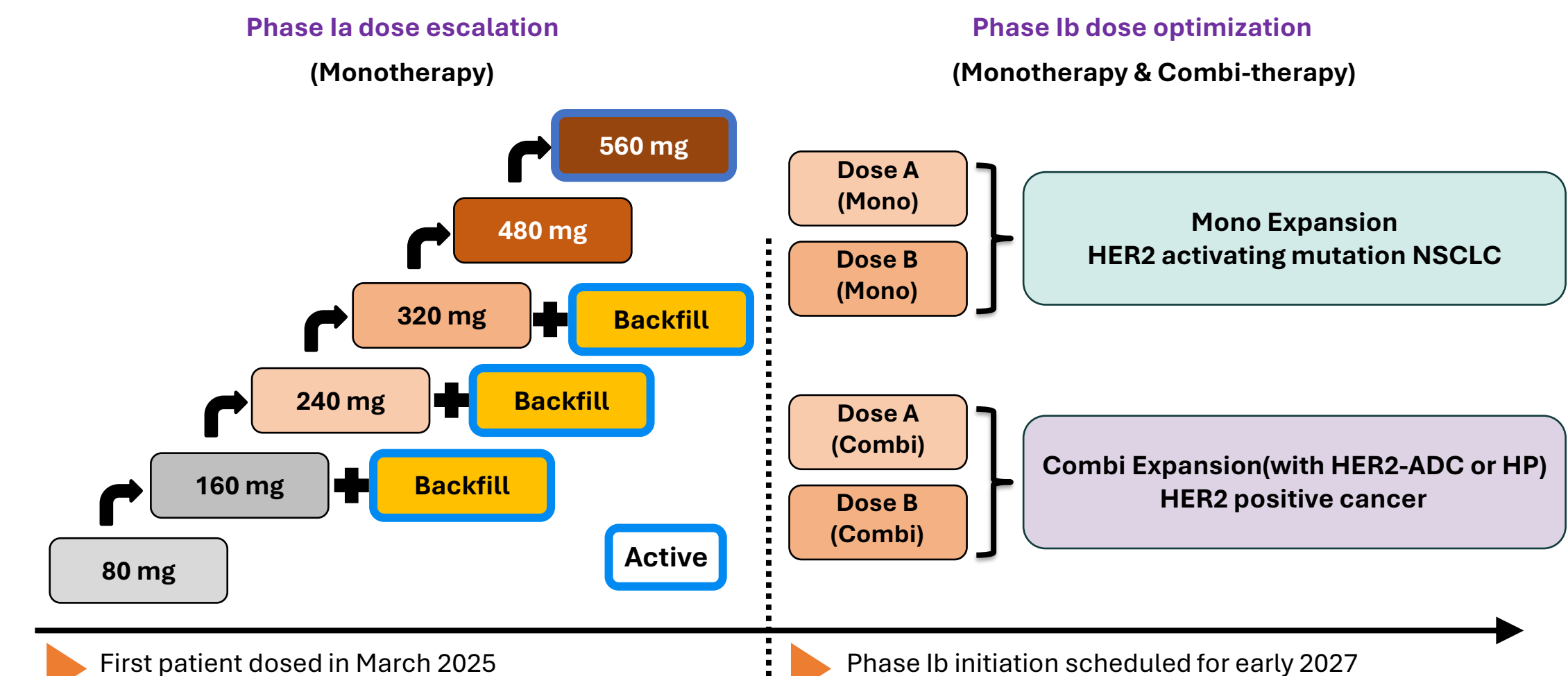
Background

- HER2 alterations comprise amplification/overexpression (HER2-positive disease) and activating mutations, arising within the tyrosine kinase domain (TKD; exon 20 insertions, L755) and outside it (extracellular S310F/Y, transmembrane V659/S653). CNS progression is a frequent and poorly addressed failure mode across these HER2-driven tumors.
- VRN101099 (VRN10) is an oral, once-daily, brain-penetrant covalent HER2 TKI binding an open-state activation loop conformation, promoting HER2 internalization and degradation. It is selective over wild-type EGFR, is not a BCRP substrate, and retains preclinical activity in T-DXd-resistant and intracranial models.
- Here we report Phase 1a safety, exposure-response and early activity across TKD and non-TKD HER2-mutant and HER2-positive solid tumors (LUMIN-HER2, NCT06806982).

Trial design

Phase I study design

- Standard “3 + 3” dose escalation
- 18 to 30 pts in dose escalation, plus up to 72 backfill pts (up to 102 pts in total)
- 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 1a 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 **no 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)
- ORR, DOR, DCR, PFS, and TTP per RECIST v1.1

Exploratory endpoints

- PD (Pharmacodynamics): ctDNA, pHER2
- Intracranial ORR per RANO-BM

- 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+

Disclosures
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Demographics

Characteristics	VRN101099 N=50, (80–480 mg)
Median age, years (range)	63 (35–82)
Sex, n (%)	
Male / Female	26 (52%) / 24 (48%)
Race, n (%)	
Asian / White	40 (80%) / 10 (20%)
ECOG PS, n (%)	
0 / 1	30 (60%) / 20 (40%)
HER2 aberration*, n (%)	
HER2 positive / mutation	21 (42%) / 16 (32%)
Primary tumor site	
Breast	11 (22%)
Gastrointestinal†	13 (26%)
Hepatobiliary‡	7 (14%)
Lung	4 (8%)
others§	15 (30%)
CNS metastasis, n (%)	
Yes / No	10 (20%) / 40 (80%)
Median No. prior systemic therapies, n (range)	3 (0–11)
Prior HER2 Abs	24 (48%)
Prior HER2 ADC, n (%)	26 (52%)
Prior HER2 TKIs, n (%)	7 (14%)

* Patients with HER2 IHC 1+, IHC 2+/ISH–, or NGS amplification only were excluded. One patient with both HER2 positivity and a HER2 mutation was included in both subgroups.
† Stomach, colon, esophageal, and jejunal cancer;‡ Biliary tract (ampulla of Vater, common bile duct, gallbladder) and pancreatic cancer;§ Salivary gland, head and neck, sinonasal, gynecologic (ovarian, cervical, endometrial, uterine carcinosarcoma), renal, urothelial, and skin cancer.

Exposure-Response correlation

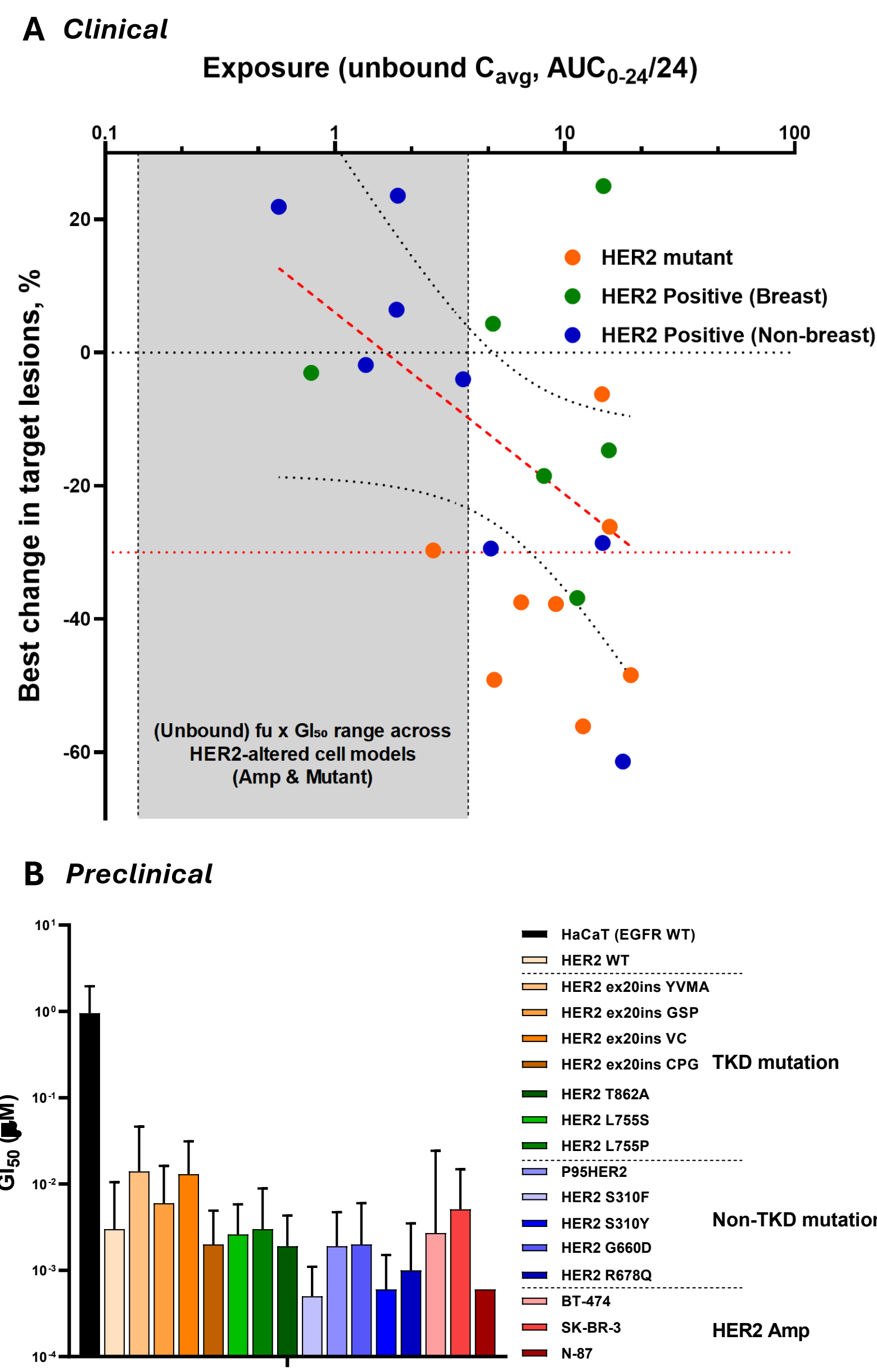


Figure 2. Exposure-response relationship of VRN101099.

(A) VRN101099 exposure (unbound C_{avg} , $AUC_{0-24}/24$) versus best change in target lesion size. Higher exposure was associated with greater tumor shrinkage, and shrinkage occurred when exposure exceeded the $fu \times Gl_{50}$ range (shaded) of HER2-altered cell lines. (B) In vitro Gl_{50} across HER2-altered cell lines.

Clinical results

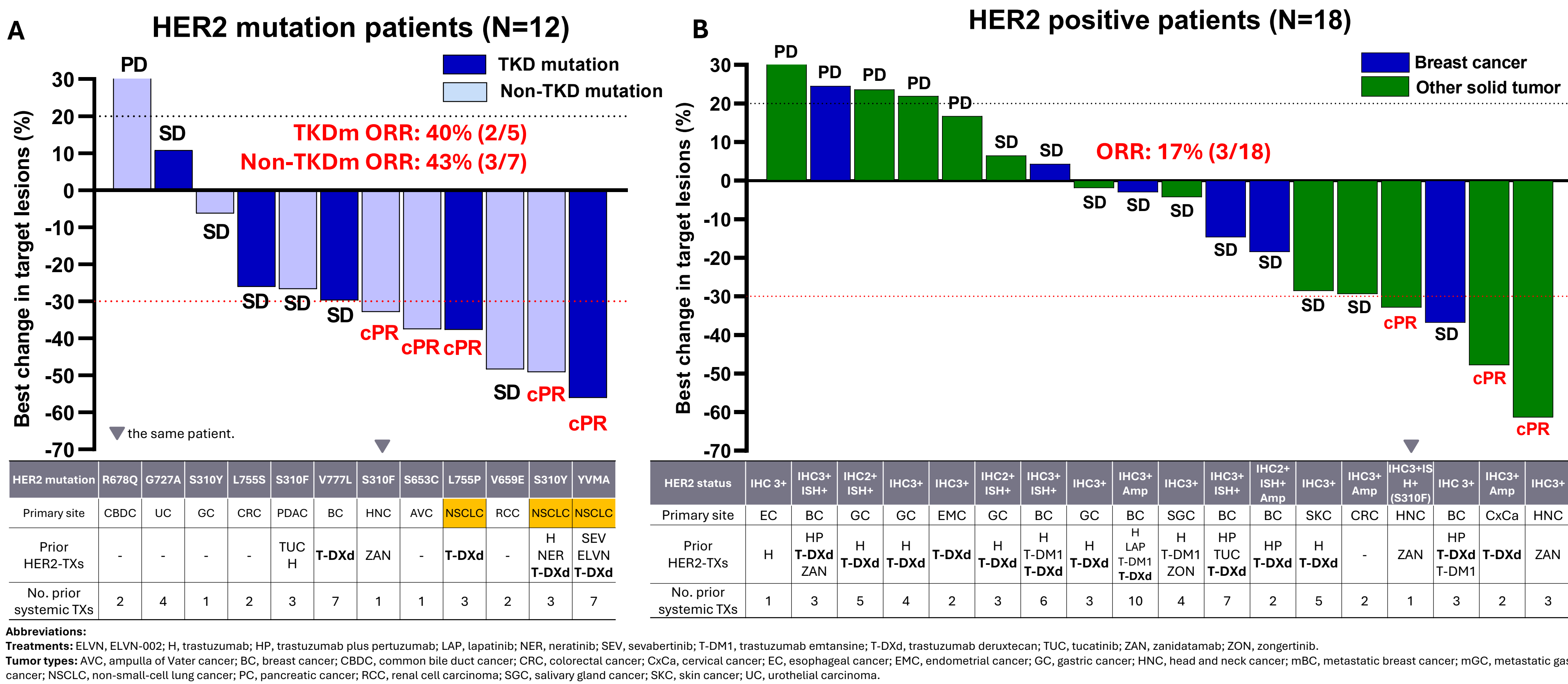


Figure 1. Best percentage change from baseline in target lesion size with VRN101099 monotherapy.

Evaluable patients had at least one post-baseline tumor assessment. (A) HER2m tumors: responses occurred in both TKD (PR, 2/5) and non-TKD (PR, 3/7) mutations. (B) HER2-positive tumors (BC and other solid tumors): most patients had received prior HER2-targeted therapy, yet tumor shrinkage was observed despite heavy pretreatment.

VRN101099 induced HER2 internalization

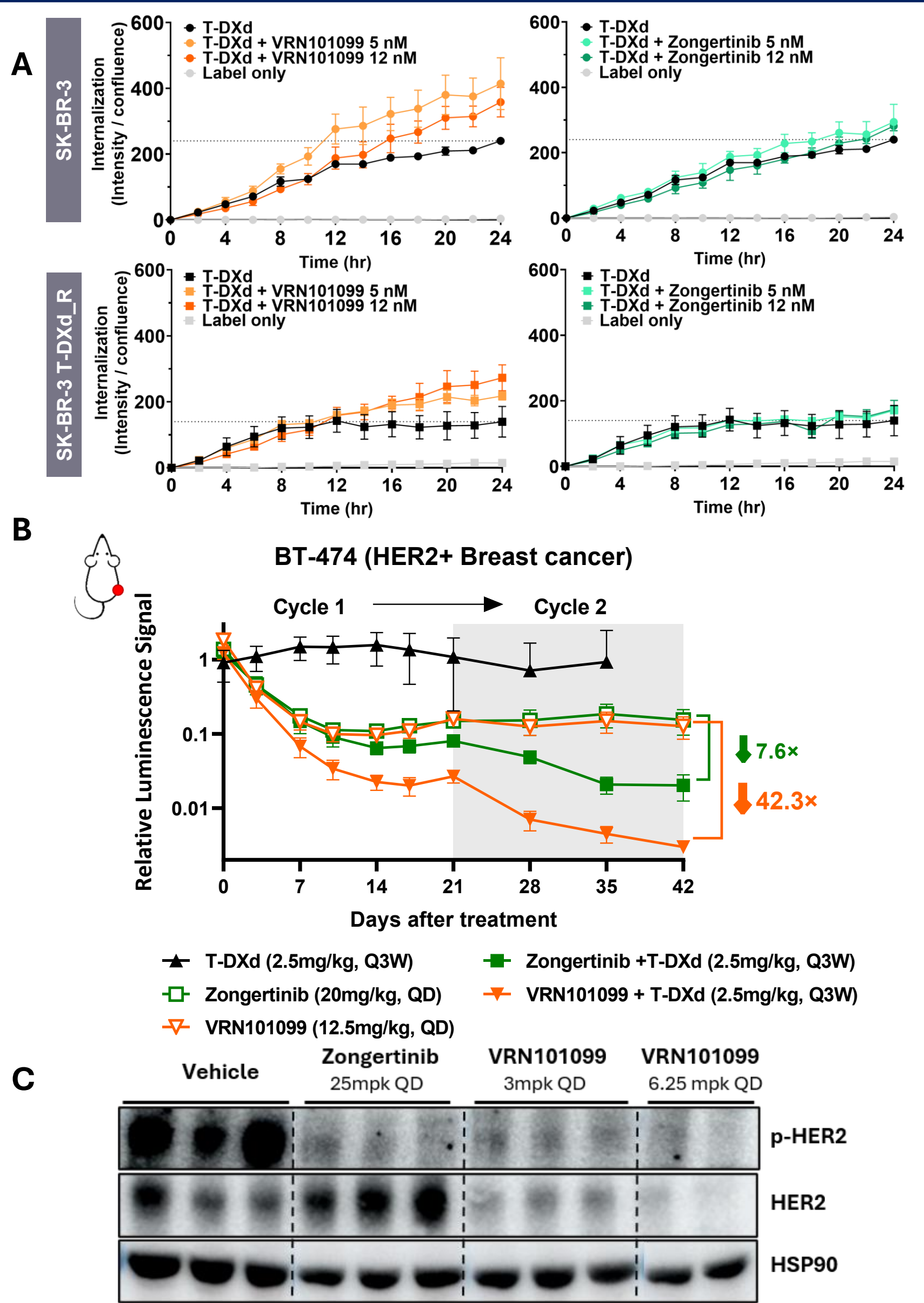
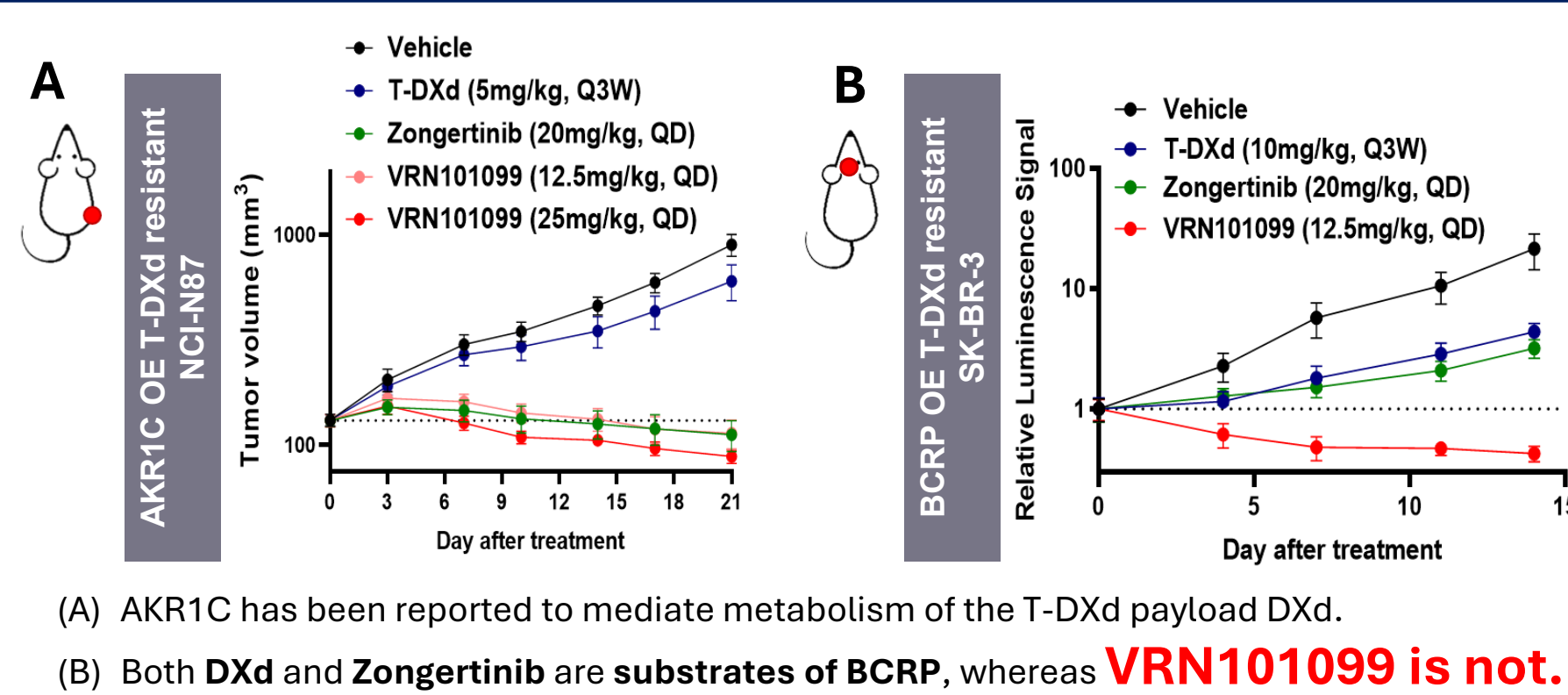


Figure 3. Enhanced activity of VRN101099 in combination with T-DXd.

(A) VRN101099 promoted HER2 internalization, enhancing T-DXd uptake vs. zongertinib (Incucyte). (B) VRN101099 + T-DXd induced greater tumor regression than zongertinib + T-DXd in HER2+ BT-474 xenografts. (C) In vivo tumor HER2 degradation by VRN101099 (PD analysis; 6 h post-dose, Day 5). Together, these data suggest that VRN101099-induced HER2 internalization enhances T-DXd uptake, contributing to the improved combination efficacy.

T-DXd resistance model



(A) AKR1C has been reported to mediate metabolism of the T-DXd payload Dxd.

(B) Both Dxd and Zongertinib are substrates of BCRP, whereas **VRN101099 is not**.

Figure 4. VRN101099 retains antitumor activity in T-DXd-resistant models.

(A) Mice bearing AKR1C overexpressing(OE), T-DXd-resistant NCI-N87 xenografts were treated with vehicle, T-DXd, zongertinib, or VRN101099, and tumor volume was measured over 21 days. (B) Mice bearing BCRP-overexpressing, T-DXd-resistant SK-BR-3 tumors were treated as in (A), and tumor burden was monitored by bioluminescence imaging over 14 days. Data are mean ± SEM.

CNS activity in intracranial models

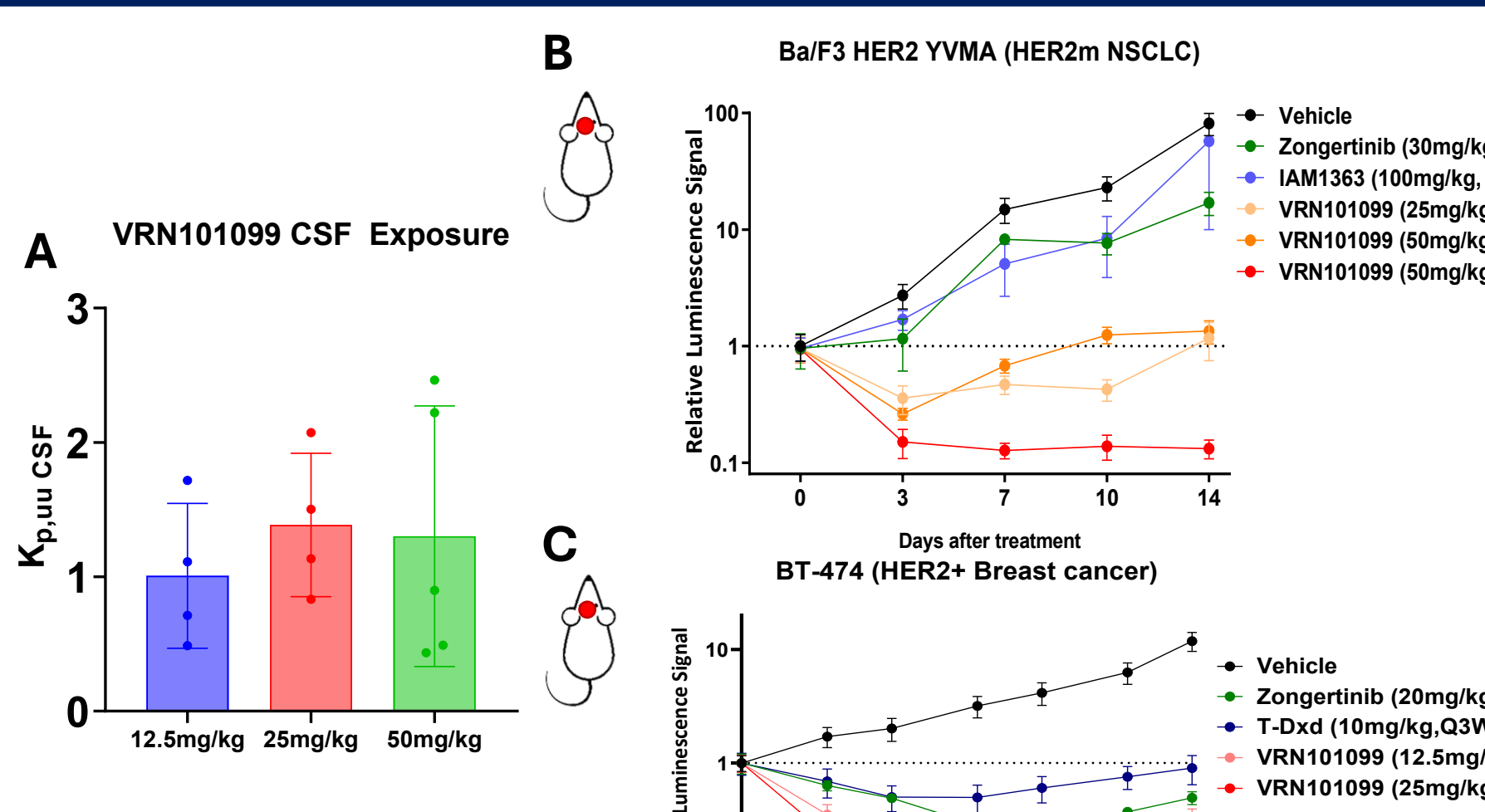


Figure 5. CNS penetration and intracranial activity of VRN101099.

(A) VRN101099 $K_{p,uu,CSF}$ in mouse. (B) Greater activity versus HER2 TKIs in intracranial Ba/F3 HER2 YVMA model (HER2m NSCLC). (C) Greater activity versus zongertinib and T-DXd in intracranial BT-474 model (HER2+ BC).

Safety

- Overall, the safety profile was **tolerable** and **manageable** across all dose levels.
- Diarrhea was effectively managed with loperamide administered on an as-needed basis upon symptom onset.
- Escalation to 560 mg is ongoing, with MTD not yet reached.

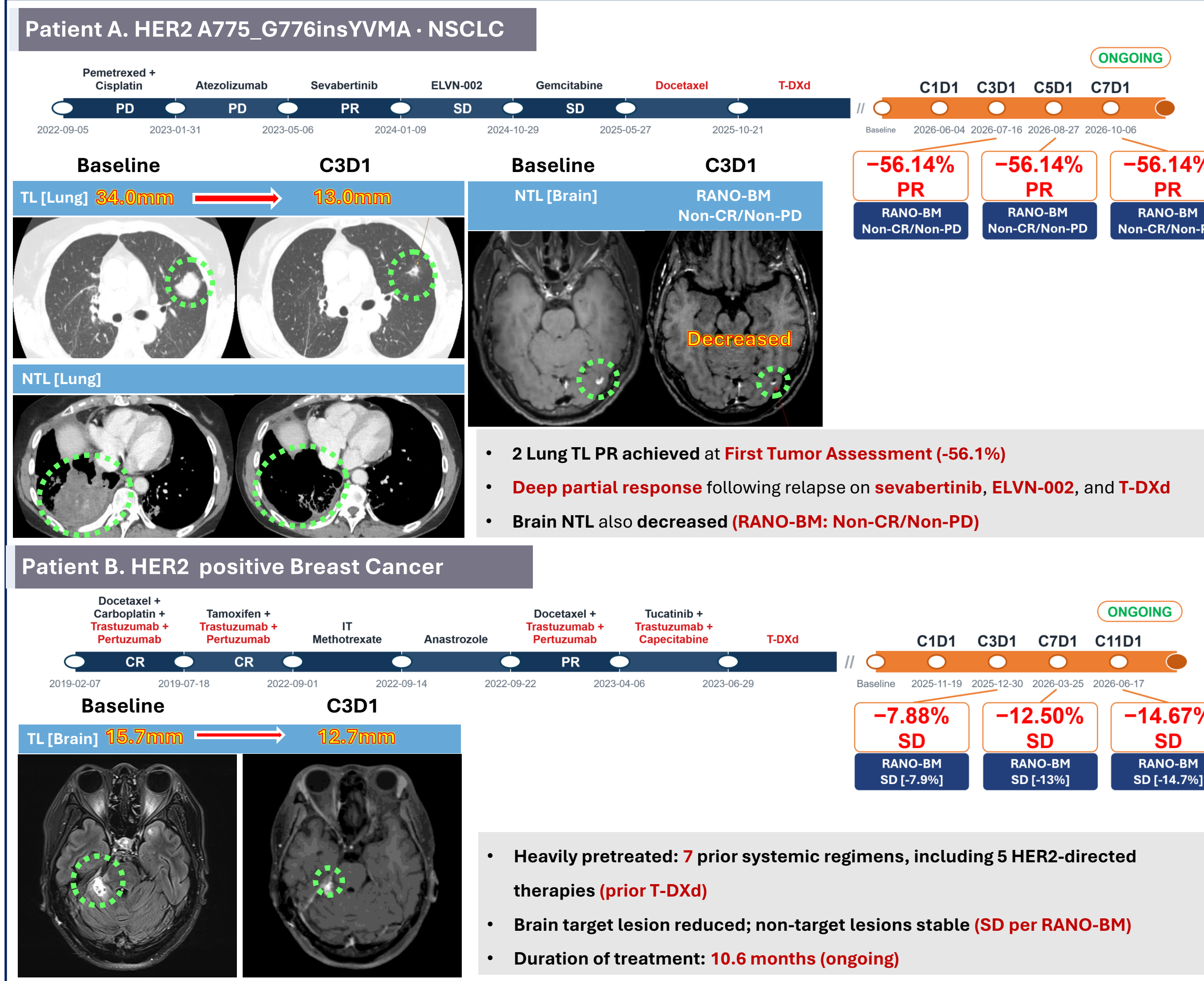
TRAEs occurring in ≥5% of patients are shown.

TRAE	VRN101099, 80-480mg (N=50)	
	All	≥ Grade 3
Any	38 (76%)	3 (6%)
Diarrhea	26 (52%)	2 (4%)
Nausea	16 (32%)	0
Vomiting	6 (12%)	0
Decreased appetite	3 (6%)	0
Rash	4 (8%)	0
Fatigue	3 (6%)	0
Stomatitis	3 (6%)	0

Patients (%)

Grade 1, Grade 2, ≥ Grade 3

Intracranial response case study



Conclusion

- Partial responses occurred in both TKD (2/5) and non-TKD (3/7) HER2-mutant tumors, Non-TKD mutation which lack an approved HER2 TKI.
- Activity was observed despite prior T-DXd, received by 17 of 30 evaluable patients (Phase 1b-eligible population), and favorable brain penetration and CNS activity.
- VRN10 was tolerable at 80–480 mg (any TRAE 76%, ≥ G3 6%); MTD was not reached.
- Escalation continues to define the RP2D for the planned Phase 1b monotherapy and combination cohorts.

Contact: ahm@voronoi.io (BD) y-zhang@voronoi.io (CMO)