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VRN101099: A novel treatment option for HER2-driven cancer patients, overcoming T-DXd resistance and brain metastases

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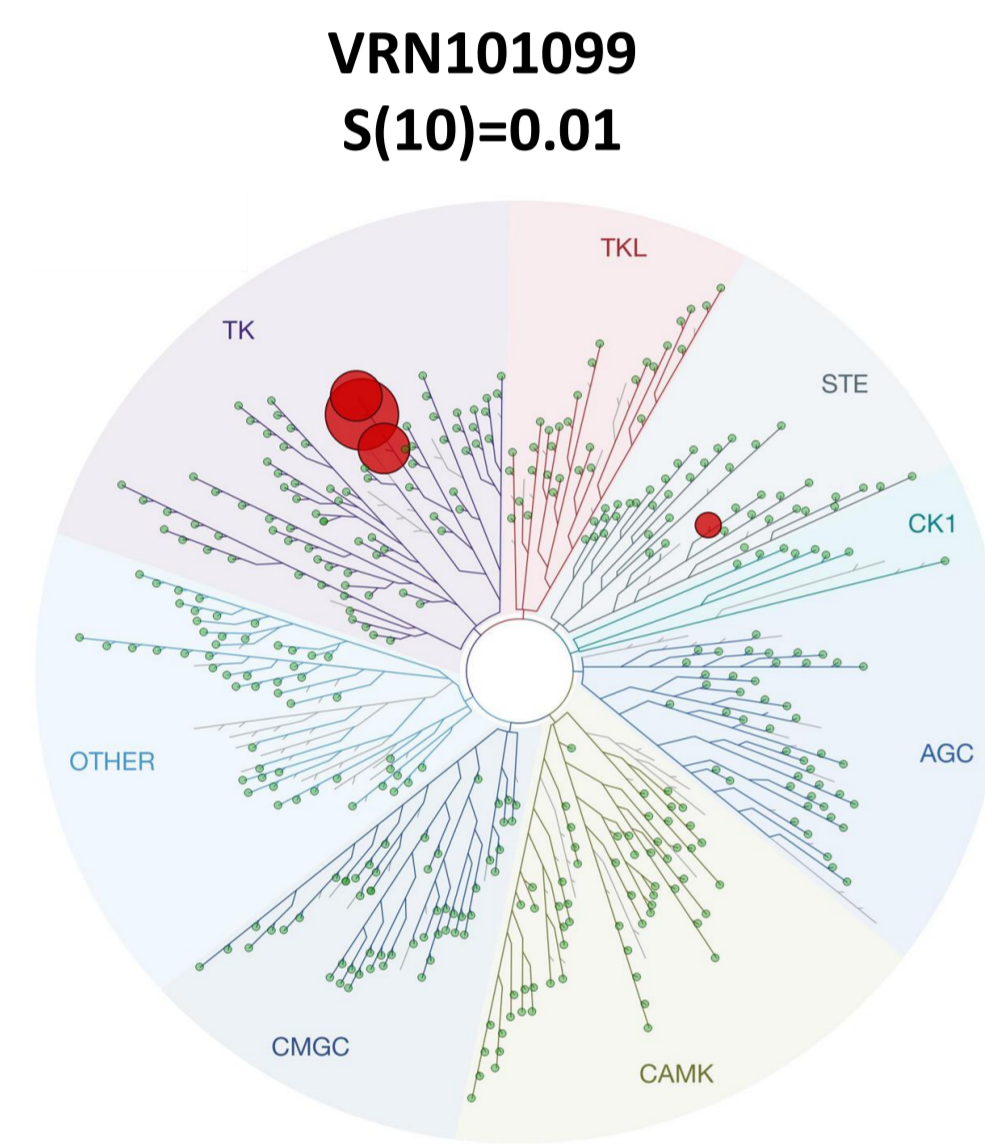
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Introduction

Many systemic therapeutic options for advanced metastatic HER2-positive breast cancer have been approved, including antibody-based therapies, chemotherapies, and tyrosine kinase inhibitors (TKIs). However, brain metastasis and acquired resistance are still major unmet medical needs for HER2-driven metastatic breast cancer and advanced solid cancers.

Kinase selectivity and catalytic inhibition potency



Kinase	Kinase profile	Enzyme
	activity (%)	IC ₅₀ (nM)
EGFR	0.0	77.1
HER2	0.4	4.51
HER2 V777L	N/A	0.95
HER2 P1170A	N/A	2.85
HER2 R896C	N/A	2.91
HER2 D769H	N/A	4.14
HER2 D769Y	N/A	21.6
HER4	0.5	5.76
MEK5	7.0	>10,000

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 (IC₅₀) was determined by HotSpot™.

Comprehensive activity against HER2-driven cancer cells including resistant to T-DXd

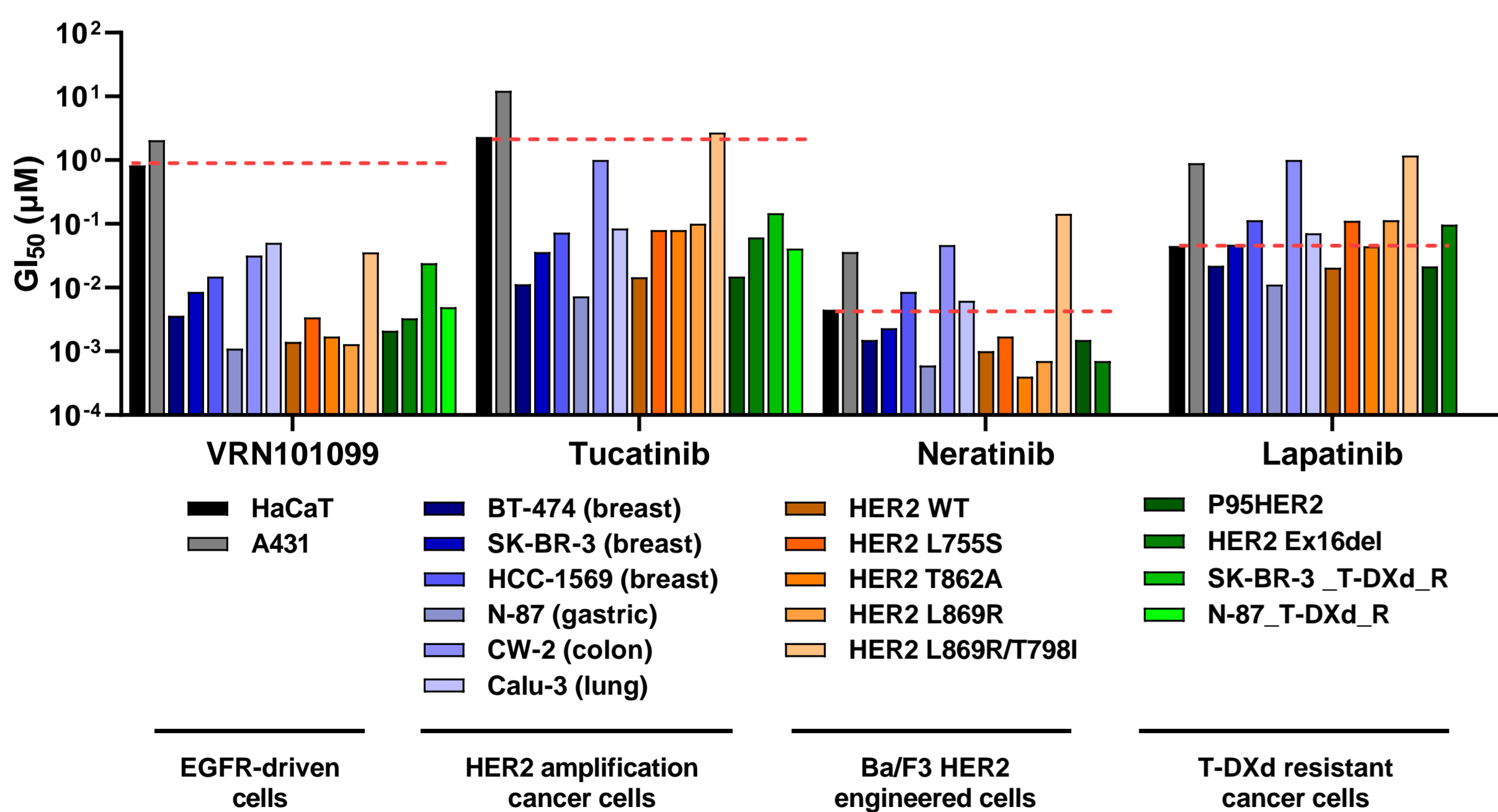


Figure 2. Growth inhibition of tumor cells, GI₅₀ values were determined via CellTiter-Glo assays. SK-BR-3_T-DXd_R cells were generated and tested in-house, while N-87_T-DXd_R cells were tested at WuXi AppTec.

Overcome T-DXd resistance mechanisms (1)

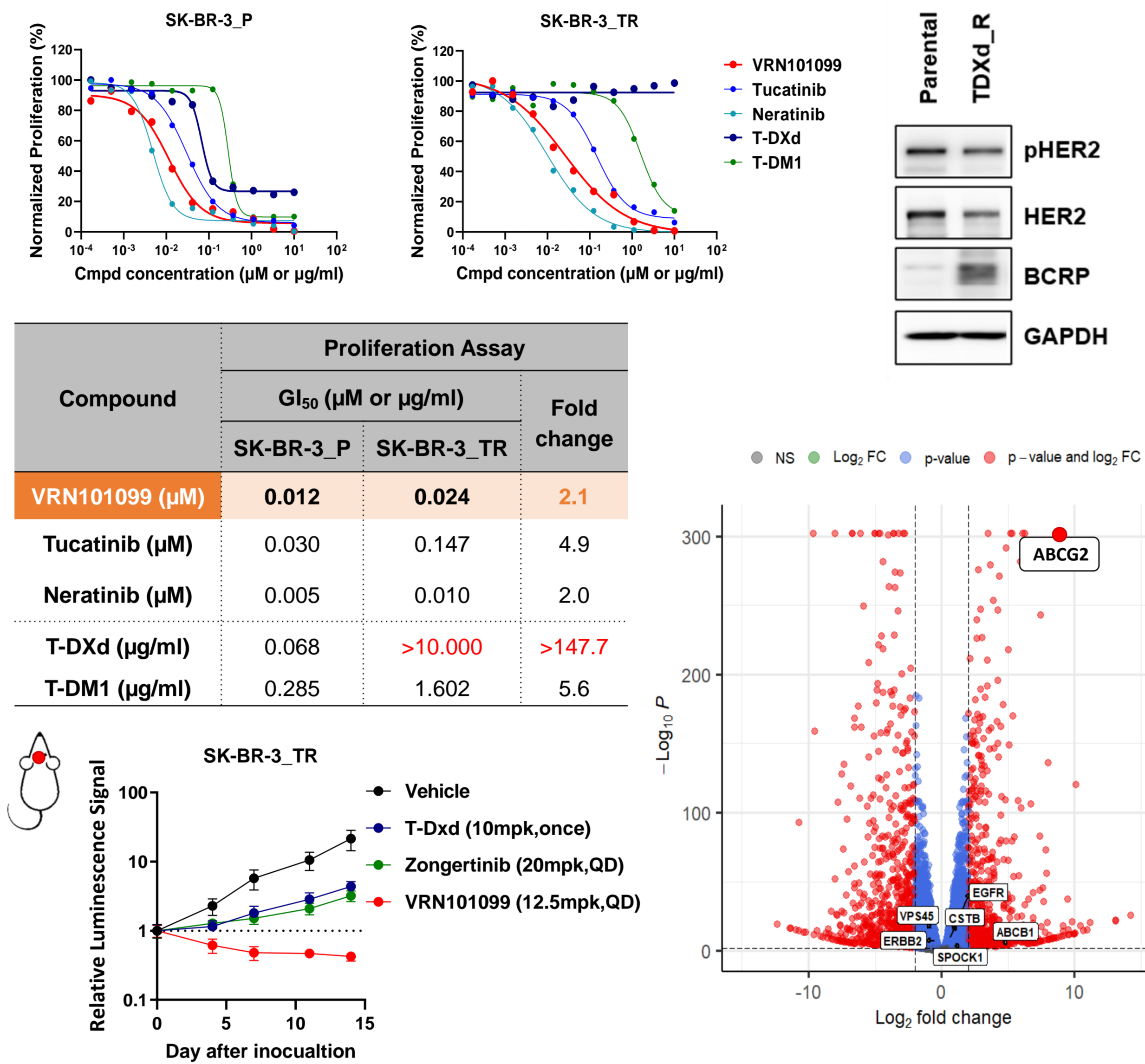


Figure 3. T-DXd-resistant (TR) SK-BR-3 cells were generated by long-term T-DXd treatment and characterized by downregulated HER2 and upregulated BCRP. VRN101099 showed superior efficacy both in SK-BR-3 parental (P) and TR intracranial model.

Overcome T-DXd resistance mechanisms (2)

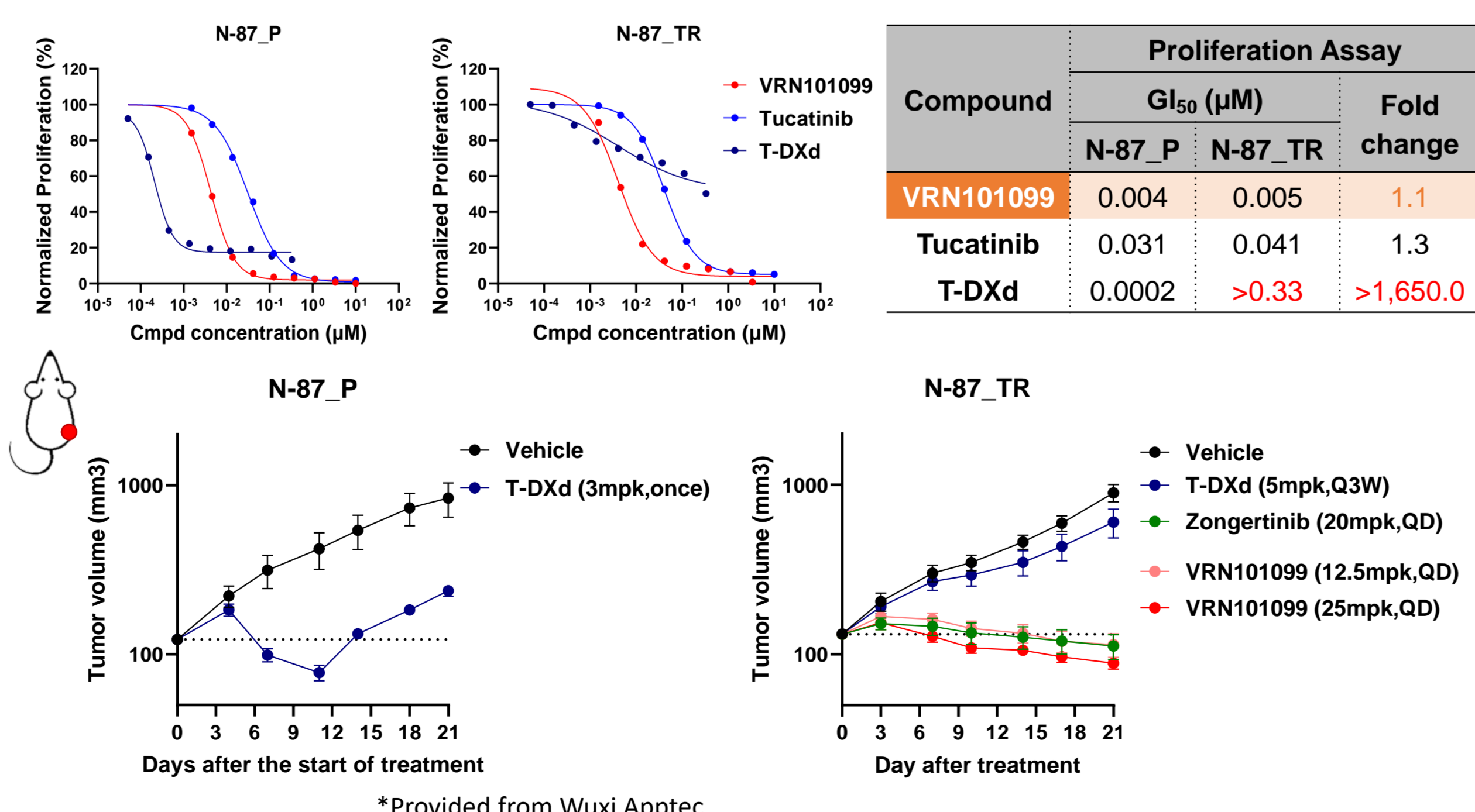


Figure 4. T-DXd-resistant N-87 cells were generated by Wuxi characterized by upregulated AKR1C1, a gene involved in drug metabolism. VRN101099 showed superior efficacy in N-87_T-DXd_R subcutaneous model.

Superior efficacy on HER2+ SC and IC xenograft models

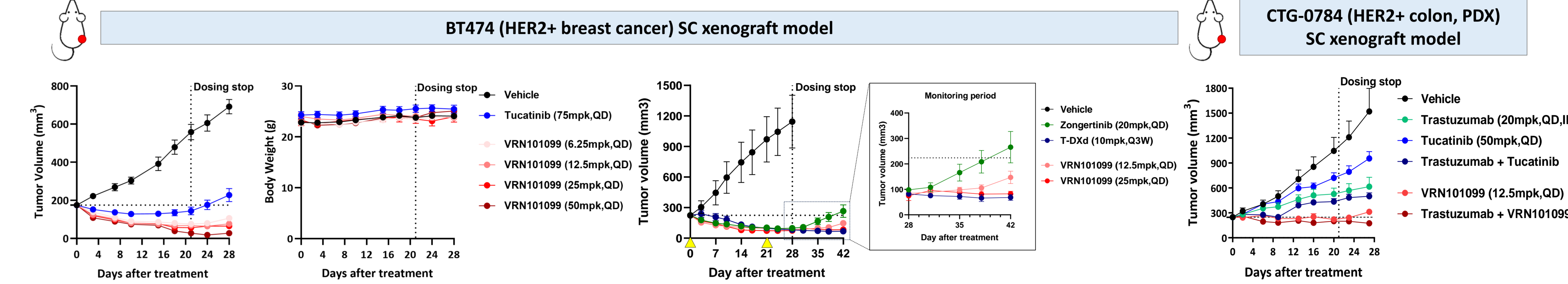


Figure 5. *in vivo* efficacy in HER2+ breast and colorectal cancer subcutaneous model

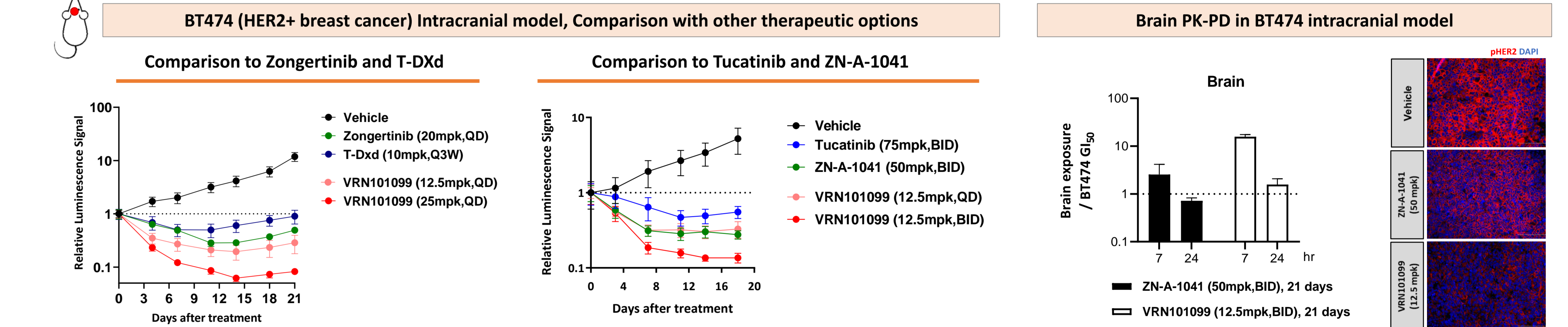


Figure 6. *in vivo* efficacy in the BT474 intracranial model. Brain PK was measured 21 days after the final dose. Immunostaining was performed 6hr after a single dose.

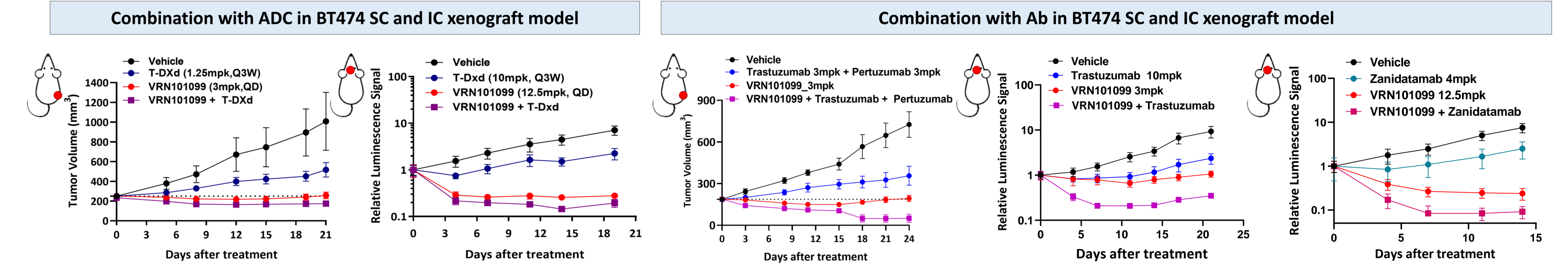
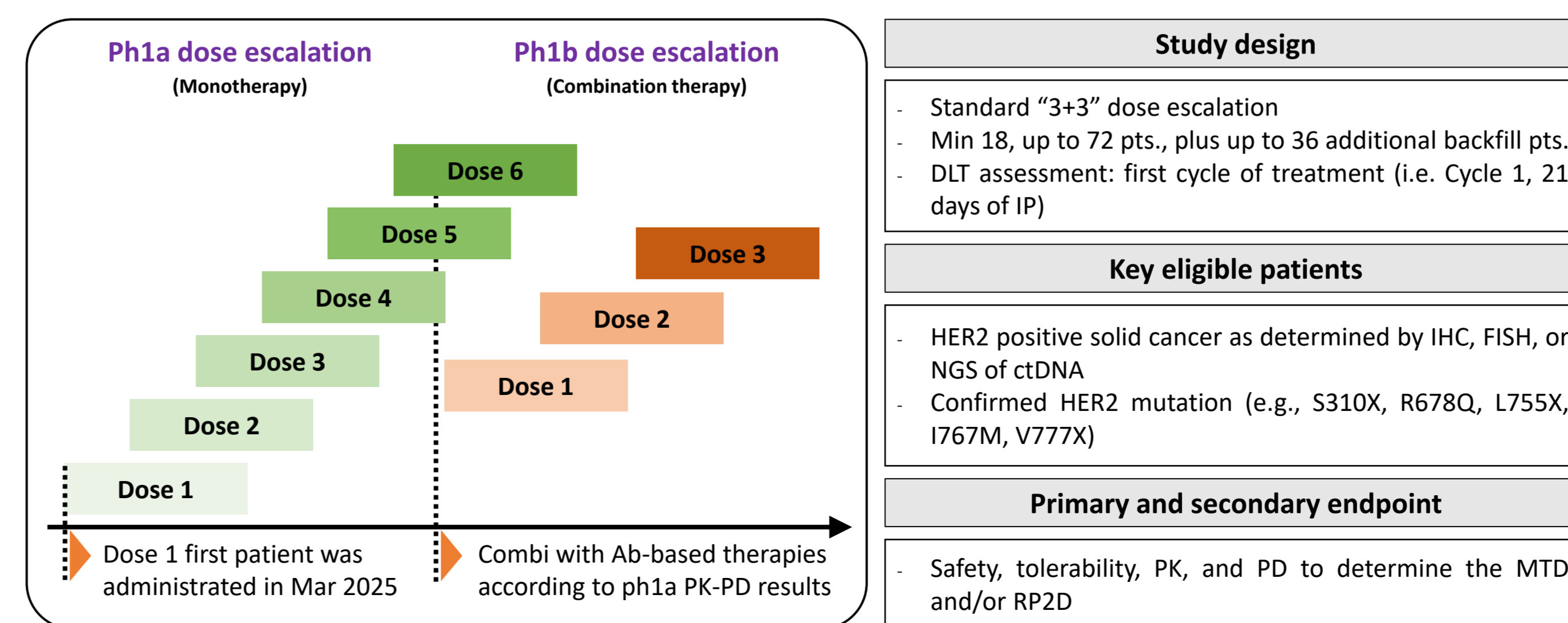


Figure 7. *in vivo* efficacy in BT474 model combination with T-DXd or HER2 targeted antibodies

Phase 1 study design



Conclusion

- VRN101099 is a promising HER2-selective TKI with a favorable profile including regarding potency, tolerability, and brain permeability.
- This identifies VRN101099 as a potential novel systemic treatment option for patients with HER2-driven cancers, particularly those with brain metastases or those who have progressed after or failed with T-DXd.
- The phase 1 dose-escalation study of VRN101099 in Korea and Australia has been approved and is evaluating its safety, tolerability, pharmacokinetics, and pharmacodynamics of VRN101099 to determine the recommended Phase 2 dose (RP2D).

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