A Phase 1, First-in-Human, Dose-Escalation Study of VRN101099, a Brain-Penetrant HER2 TKI, in Patients with Advanced HER2 Alteration Solid Tumors

#LB-A017

Hong-ryul Jung[1], Yeon Hee Park[3], Rasha Cosman[4], Christopher Steer[5], Jee Hung Kim[6], Jieun Lee[7], Seock-ah Im[8], Shuang Yin Zhang[2]

[1] Voronoi inc., Incheon, Korea Rep., [2] Voronoi-USA, Boston, MA, United States, [3] Samsung Medical Center, Seoul, Korea Rep., [4] St Vincent's Hospital Sydney, Darlinghurst, Australia, [5] Border Medical Oncology, East Albury , Australia, [6] Gangnam Severance Hospital, Seoul, Korea Rep., [7] Seoul St. Marys Hospital, Seoul, Korea Rep., [8] Seoul National University Hospital Seoul, Korea Rep.

BACKGROUND

HER2 gene amplification and activation mutations are major oncogenic drivers in solid tumors. in addition, the brain and bone are common metastatic sites which significantly increase mortality and impairing quality of life in breast and gastrointestinal cancers.

VRN101099, potent and highly selective covalent HER2 TKI, exhibited remarkable brain- and bone- penetrating capacity and superior anti-tumor efficacy in preclinical models compared to other TKIs and T-DXd, positioning it as a promising therapeutic candidate for HER2 alteration tumors, including those with brain and bone metastases.

VRN101099 also demonstrated inhibitory activity against the proliferation of various HER2-positive cancer cell lines and showed efficacy against multiple resistant analogues, including p95HER2, exon 16 deletion, and kinase domain mutations which are known as intrinsic and acquired resistance to approved HER2 targeted therapeutics.

The ongoing Phase 1, multicenter, open-label study evaluates VRN101099 as once-daily oral monotherapy using a standard 3+3 dose-escalation. (ClinicalTrials.gov Identifier: NCT06806982)

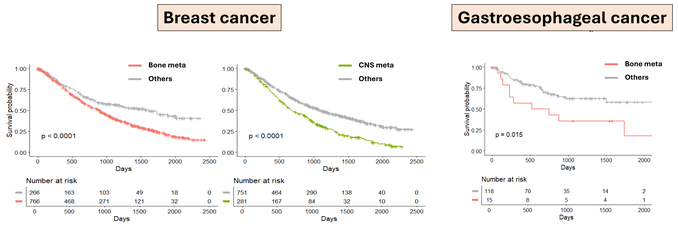


Figure 1. A comparison of overall survival in patients with breast cancer and gastrointestinal stromal tumor, with and without bone or CNS metastasis.

ELIGIBILITY CRITERIA

Key inclusion criteria

- Aged ≥ 18 years
- ECOG PS 0-1
- at least 1 evaluable lesion based on RECIST v1.1
- 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)
- Patients without any other treatment option, including the standard of care

Key exclusion criteria

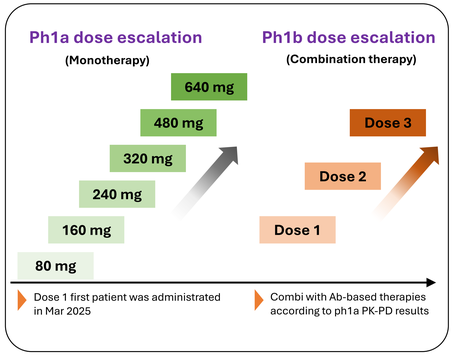
- EGFR/HER2 exon 20 mutation
- Received any anticancer drugs within 3 weeks
- Not recovered to NCI-CTCAE Grade ≤ 1
- CNS metastases or spinal cord compression that is associated with progressive neurological symptoms or requires increasing does of corticosteroids

STUDY DESIGN

Phase 1a/b dose escalation

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)

Phase 1b dose escalation
Standard "3+3" dose escalation
Will receive escalating doses of VRN101099, plus fixed doses of antibody-based therapies (e.g., T-DXd or Trastuzumab) in 21-day cycles
DLT assessment: first cycle of treatment (i.e. Cycle 1, 21 days of IP)



Key eligible patients
- HER2 positive solid cancer as determined by IHC, FISH, or NGS of ctDNA
- Or HER2 mutation (e.g., S310X, R678Q, L755X, I767M, V777X)

Primary endpoints
- Safety
- Tolerability
- Determine the MTD or RP2D

Secondary endpoints
- PK, PD
- ORR according to RECIST v1.1

EX VIVO PD ANALYSIS

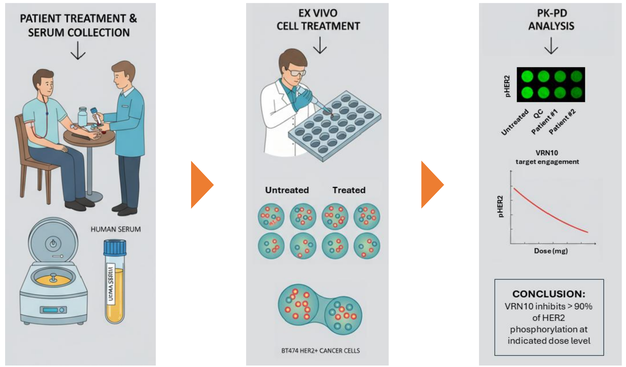
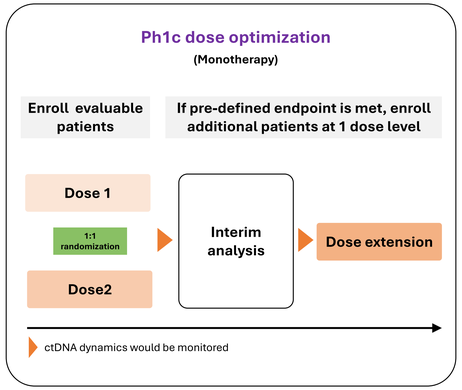


Figure 2. Scheme of ex vivo PD experiment

- Collect serum from patients who have taken the VRN101099
- Measure phospho HER2 inhibition through *ex vivo* assay
- Identify the optimal dose for either monotherapy or combination with Ab-based therapies

Phase 1c dose optimization

Phase 1c dose optimization
Will be randomized 1:1 to receive one of two VRN101099 dose levels
Recruit small population patients (10~20 pts.), with the potential expansion to 1 dose following an interim analysis

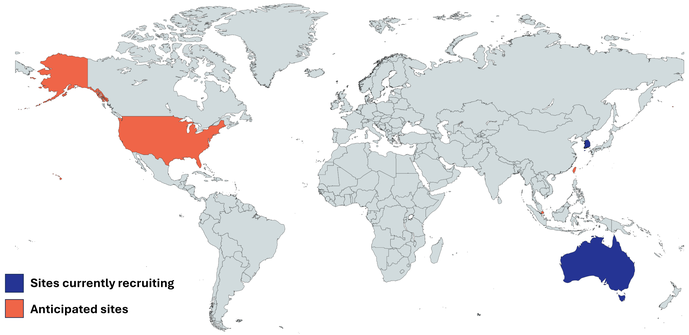


Key eligibility criteria
- Advanced solid tumors with activating HER2 mutations (e.g., S310F/Y, R678Q, L755X, I767M, V777X, etc.)
- Without other driver mutations, e.g., KRAS, BRAF, etc.

Primary endpoints
- ORR and intracranial ORR if brain metastatic lesions are present
- Incidence of AEs/SAEs

Secondary endpoints
- DOR, DCR, and PFS
- PK, ctDNA evaluation

STUDY LOCATIONS



REFERENCES

- Marra, A. et al., Nat Rev Clin Oncol. 2024 Mar;21(3):185–202
- Nguyen B. et al., Cell. 2022 Feb 3;185(3):563-575.e11
- Bose R. et al., Cancer Discov. 2013 Feb;3(2):224-37

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