REACH-EGFR: A Phase 1/2 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of VRN110755 in Patients with Epidermal Growth Factor Receptor (EGFR) Mutant Non-small Cell Lung Cancer (NSCLC)

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BACKGROUND

- Most patients with EGFR-mutant NSCLC develop acquired resistance to third-generation EGFR TKIs (e.g., osimertinib), including on-target EGFR C797S, and CNS progression remains a major clinical limitation, an ongoing unmet need.[1,2]
- VRN110755 is a brain-penetrant, highly potent, and mutant-selective EGFR inhibitor designed to spare wild-type EGFR while retaining activity across common drivers (Del19, L858R), C797S-mediated resistance (Del19/C797S, L858R/C797S), and several uncommon variants.
- Preclinically, VRN110755 shows sub-nanomolar potency against key EGFR mutants, >100-fold selectivity over wild-type EGFR, high brain exposure across species, and activity in intracranial tumor models.[3]

METHODS

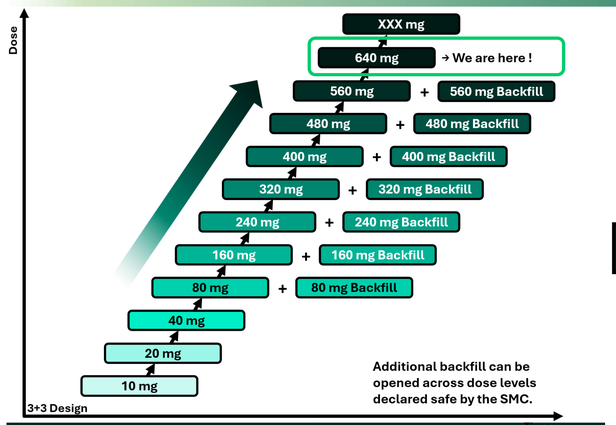
- This is a Phase 1/2 multicenter, open-label, dose-escalation, dose optimization and multi-cohort dose expansion clinical trial to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics (PK/PD), and antitumor activity of VRN110755, a highly selective oral epidermal growth factor receptor (EGFR) inhibitor, in patients with EGFR mutant non small cell lung cancer (NSCLC).

KEY OBJECTIVES/ENDPOINTS

Phase 1a	Phase 1b/2
Objectives	
• To evaluate the **safety and tolerability** of VRN110755 in patients with EGFR mutant NSCLC • To determine the maximum tolerated dose (MTD) of VRN110755 in Phase 1a of the study	• To evaluate the **safety and tolerability of VRN110755 in monotherapy** NSCLC patients with common or atypical EGFR mutations who progressed after prior therapies or were treatment-naïve • To evaluate the **safety and tolerability of VRN110755 in combination with platinum-based chemotherapy** in NSCLC patients with common EGFR mutations who progressed after prior therapies • To determine the **optimized recommended phase 2 dose (RP2D)** of VRN110755 monotherapy and in combination with platinum-based chemotherapy
Primary Endpoints	
• Incidence of DLTs • Incidence of adverse events (AEs)/serious AEs (SAEs)	• Incidence of AEs/SAEs • Incidence of DLTs (Cohort G, Cycle 1 only)
Secondary Endpoints	
• PK, ctDNA evaluation • ORR, DOR, DCR, PFS and intracranial ORR and PFS if brain metastatic lesions are present	• PK, ctDNA evaluation • ORR, DOR, DCR, PFS and OS (investigator and BICR); intracranial ORR/DCR/DOR/PFS per RANO-BM; LM response per RANO-LM (Cohort E)

REACH-EGFR(NCT07699328): STUDY DESIGN

Phase 1a: Dose Escalation



Dose Levels	Number of Patients Enrolled (including backfill cohorts)
Dose level 1 / 10mg QD	3
Dose level 2 / 20mg QD	4
Dose level 3 / 40mg QD	3
Dose level 4 / 80mg QD	12
Dose level 5 / 160mg QD	13
Dose level 6 / 240mg QD	14
Dose level 7 / 320mg QD	9
Dose level 8 / 400mg QD	9
Dose level 9 / 480mg QD	6
Dose level 10 / 560mg QD	3
Total*	**72**

*Data cut-off: 03Sep2026

Establish monotherapy RD1 and RD2

Phase 1b: Dose Expansion and Optimization — Phase 2

Cohort A [RD1 and RD2: up to 10 each]
- Common EGFR mutation, with C797X
- Progressed after one or more 3rd generation(3G) TKI-containing regimens, with no prior non-3G TKI therapy

Cohort B [RD1 and RD2: up to 10 each]
- Common EGFR mutation
- **Treatment-naïve**

Cohort C [RD1 and RD2: up to 10 each]
- Atypical/Uncommon EGFR mutation
- Progressed after one prior TKI (allows ≤ 1 prior systemic regimen)

Cohort D [RD1 and RD2: up to 10 each]
- Atypical/Uncommon EGFR mutation
- **Treatment-naïve**

Cohort E [RD1 and RD2: up to 10 each]
- Common EGFR mutation
- With **at least one CNS lesion** ≥5 mm in longest diameter **and/or leptomeningeal involvement**
- Progressed after one or more 3G TKI-containing regimens, with no prior non-3G TKI therapy

Cohort F (Optimization; N=40)
- Atypical/Uncommon EGFR mutation
- **Treatment-naïve**

→ R 1:1 → RD2 (N=20), RD1 (N=20) → **Select Mono-therapy RP2D**

Cohort G (N~27)
VRN110755 + Pemetrexed/Carboplatin
- BOIN design; Start dose = RD1-1
- Common EGFR mutation;
- Progressed after one or more 3G TKI-containing regimens, with no prior non-3G TKI therapy.
- Ended last chemo ≥ 12 months prior to C1D1

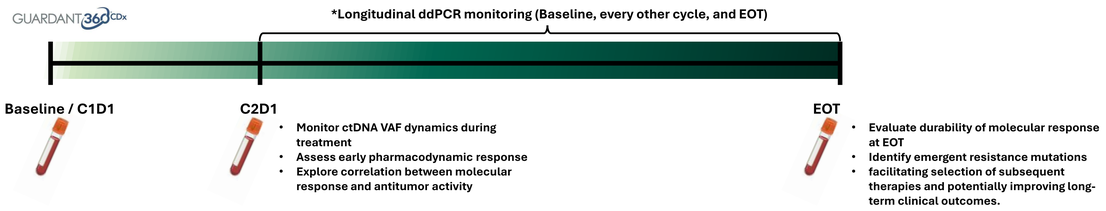
→ **Establish cRD1 and cRD2 for combination**

Cohort H (Optimization)
VRN110755 + Pemetrexed/Carboplatin
- Common EGFR mut;
- Progressed after only one 3G TKI-containing regimen, with no prior non-3G TKI therapy.
- Ended last chemo ≥ 12 months prior to C1D1

→ R 1:1 → cRD2 (N=20), cRD1 (N=20) → **Select Combination RP2D**

RD: Recommended Dose; cRD: Recommended Dose for Combination

PD ANALYSIS PLAN



Pharmacodynamic (PD) assessments are planned through liquid biopsy, which will enable the non-invasive monitoring of circulating tumor DNA (ctDNA) dynamics at Baseline, C2D1, and at the end of treatment (EOT). Sequential ctDNA measurements during the study will provide insights into treatment response, mutation clearance, and potential mechanisms of resistance.
*Additional longitudinal ddPCR assessments will be conducted as an exploratory analysis.

Global Study Footprint (Expanding)

11 Countries Across APAC, Europe, and North America

- Asia-Pacific
  - South Korea, Taiwan, Australia, Hong Kong, Malaysia, Singapore, Thailand
- North America
  - United States, Canada
- Europe
  - France, Spain

Spanning 11 countries across 3 continents, with ongoing global expansion to enhance patient enrollment

REFERENCES & ACKNOWLEDGEMENTS

1. Kim S, et al. Cancer Res. 2025;85(8 Suppl 2):CT136.
2. Ahn MJ, et al. Mol Cancer Ther. 2025;24(10 Suppl):A093.
3. Kim S, et al. Cancer Res. 2025;85(8 Suppl 2):CT136

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