#P3.247

VRN110755, a Mutant-Selective CNS-Penetrant EGFR TKI, Demonstrates Superior Antitumor Activity over Osimertinib in EGFR-Mutant NSCLC Models

Youngyi Lee, Hong-ryul Jung, Donghyun Park, Songyee Han, Sangho Jeon, Yeonsil Kim, Somi Lee, Sunghwan Kim, Daekwon Kim

Voronoi Inc., Yeonsu-gu, Incheon, South Korea

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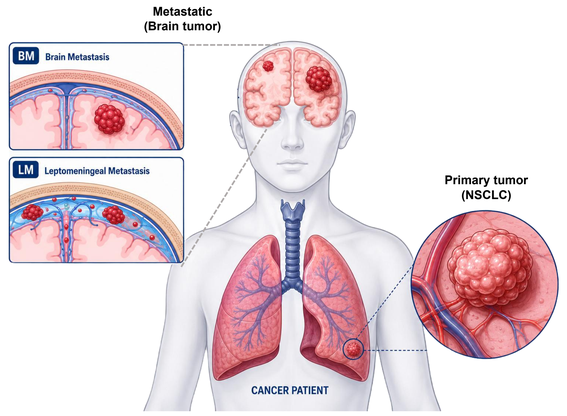
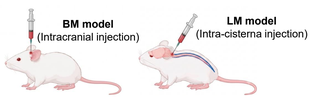
INTRODUCTION

- Third-generation EGFR tyrosine kinase inhibitors (TKIs) have improved progression-free survival (PFS) and overall survival (OS) in patients with EGFR-mutant non–small cell lung cancer (NSCLC)
- However, their clinical utility is limited by dose-dependent ERBB-mediated toxicities, including rash and diarrhea.
- Furthermore, although osimertinib demonstrates intracranial activity, patients with brain metastasis (BM) continue to experience shorter PFS than those without CNS disease, indicating a need for agents with enhanced CNS penetration.
- VRN110755 (VRN11) is a novel mutant-selective, brain-penetrant EGFR TKI designed to increase target engagement against mutant EGFR while minimizing the inhibition of wild-type (WT) ERBB family members.
- Here we evaluated the preclinical efficacy and CNS penetration of VRN110755 compared with osimertinib in EGFR-mutant NSCLC models.



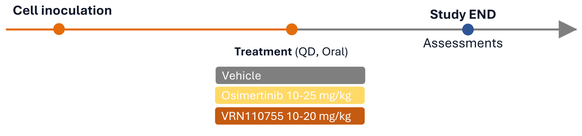
METHODS

In vivo model



Measurements

Endpoints included TGI, TR
Bioluminescence imaging
Clinical signs
Survival



In vitro	• EGFR selectivity assessed in engineered Ba/F3 cells.
In vivo Efficacy	• Antitumor efficacy evaluated in SC, BM, and LM PC9 (EGFR Ex19del) xenograft models.
CNS PK	• Brain penetration assessed by brain-to-plasma ratio and unbound plasma-to-CSF partitioning. • PK/PD correlation performed using preclinical and clinical PK datasets.
CNS PD	• H&E and immunofluorescence images of brain sections encompassing the ventricular region. • Quantitative analysis confirmed a statistically significant reduction in pEGFR positive cells.

Contact ahn@voronoi.io (BD)
y.zhang@voronoi.io (CMO)

DISCUSSION AND CONCLUSION

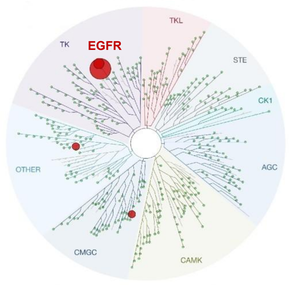
Key Findings and Conclusion

- VRN110755 is a potent, next-generation, mutant-selective EGFR TKI that demonstrates a wider therapeutic window with respect to WT ERBB family inhibition and enhanced CNS penetration compared with osimertinib in preclinical models.
- Its greater intracranial efficacy in BM and LM models, combined with deeper tumor responses in SC xenografts, positions VRN110755 as a promising candidate for the treatment of EGFR-mutant NSCLC, particularly in patients with CNS disease.
- These findings provide a preclinical rationale for the ongoing and future clinical evaluation of VRN110755.

VRN110755 is a potent and selective in EGFR NSCLC

Kinase selectivity

VRN110755



***In vitro* target engagement**

Target engagement ratio (TER)

	VRN11 320mg	Osimertinib 80mg	VRN11 / Osimertinib
Classic	56	14	4x
Classic + C797S	22	< 1	140x
Classic + Atypical	20	9	2x
Atypical	5	2	3x

x 2.0 x 0.2

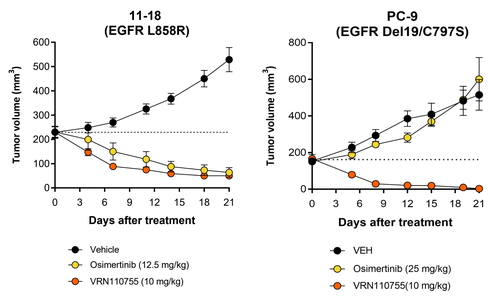
Target engagement ratio (TER); Brain

	VRN11 320mg	Osimertinib 80mg	VRN11 / Osimertinib
Classic	112	2.8	40x

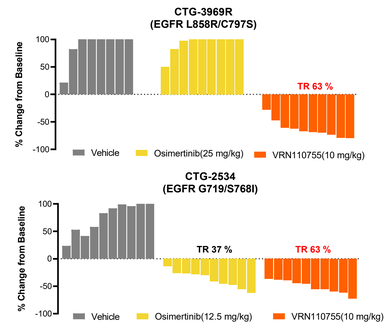
- VRN110755 demonstrated substantially enhanced target engagement against common EGFR mutations at the 320 mg dose level, **including Del19 and L858R, achieving approximately 56-fold target engagement.**

Pre-clinical antitumor activity in EGFR-mutation NSCLC

Cell Line-Derived Xenograft (CDX)

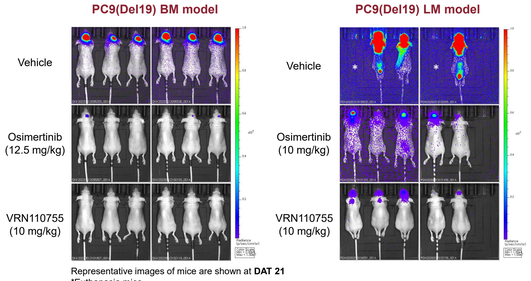


Patient-Derived Xenograft (PDX)



- VRN110755 led to marked tumor regression in EGFR-mutant CDX and PDX models, demonstrating strong activity across a broad range of EGFR mutation.

In vivo efficacy in Intracranial Metastasis models (LM & BM)

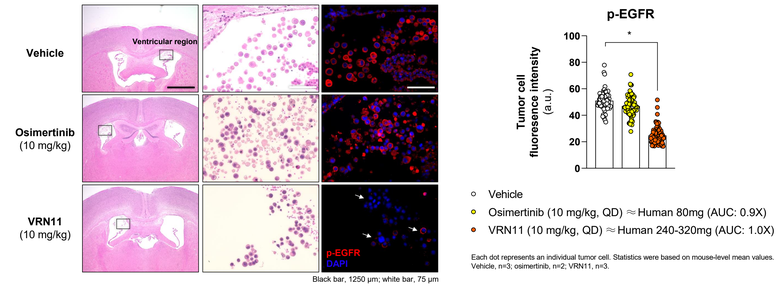


Representative images of mice are shown at **DAT 21**
*Euthanasia mice

- **Treatment with VRN110755 demonstrates outstanding CNS activity** in brain metastasis (BM) and leptomeningeal metastasis (LM) *in vivo* models.
- VRN110755 achieved **100% survival,** whereas vehicle and osimertinib treated mice exhibited rapid disease progression and mortality.

CNS target engagement

PC9(Del19) LM model (Single dose at 24 hr)

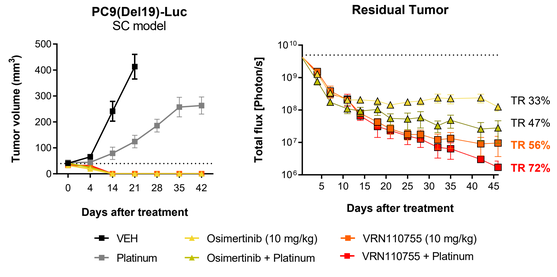


Each dot represents an individual tumor cell. Statistics were based on mouse-level mean values. Vehicle, n=3; osimertinib, n=2; VRN11, n=3.

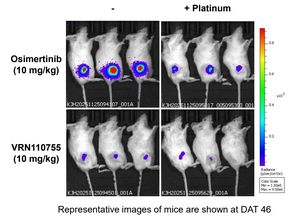
Black bar, 1250 μm; white bar, 75 μm

- Significant reduction of **pEGFR** levels within tumor cells located in the ventricular region, a key site associated with CSF flow, supports effective CNS target engagement by VRN110755.

Antitumor activity in the PC9(Del19) SC Xenograft model with Chemotherapy



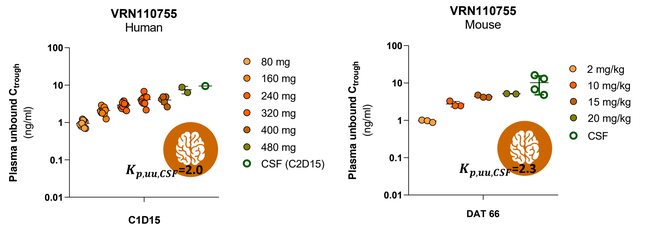
***Platinum chemotherapy** consisted of carboplatin (60 mg/kg, IP, QW) plus pemetrexed (100 mg/kg, IP, QW).



Representative images of mice are shown at DAT 46

- VRN110755 showed deeper tumor regression than osimertinib alone or with carboplatin/pemetrexed, with further enhancement when combined with chemotherapy.

Preclinical to clinical evidence of potent activity in EGFR mutant NSCLC



*$K_{p,uu,csf}$ was calculated using PPB value of 98.9% (Human) and 98.84% (Mouse). Human data were obtained from BM patient in the 240 mg cohort at C2D15; Mouse data were obtained 4 hr after single 10 mg/kg dose.

- Human C1D15 exposure at 240-320 mg was comparable to that achieved at efficacious repeat dose of 10 mg/kg in mice.
- Consistent $K_{p,uu,csf}$ across mouse, monkey, and human supports robust CNS delivery and strengthens the translational relevance of the observed target engagement and antitumor efficacy.

VRN11 Brain permeability

	$K_{p,uu,brain}$	$K_{p,uu,csf}$
Mouse	0.2	**2.3**
Monkey	1.7	**2.6**
Human	*N.A.*	**2.0***

$K_{p,uu,csf}$ of osimertinib in human has been reported, 0.22

P3.237 Quantitative Prediction of Progression-Free Survival (PFS) From Early Tumor Response in Non-Small Cell Lung Cancer

Changwon Kim[1], Kun Jong Lee[1], Kyungho Lee[1], Youngyi Lee[1], Donghyun Park[1], Hongryul Jung[1], Kwangwoo Hwang[1], Jae Han Choi[1], M-J. Ahn[2*], Sunghwan Kim[1*]
[1]Voronoi, Inc., Incheon/KR ,[2]Hanyang University Medical Center, Hanyang University School of Medicine, Seoul/KR , *Corresponding author

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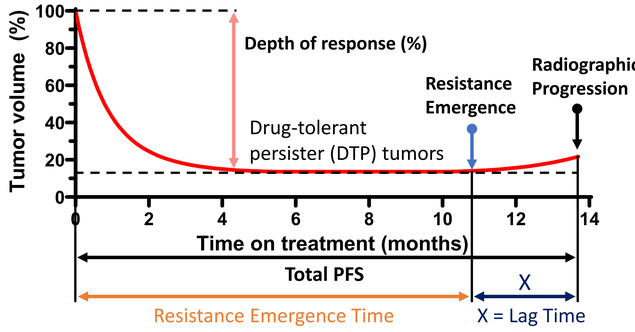
Introduction

Progression-free survival (PFS) reflects both anti-tumor activity and durability of disease control in oncogene-driven non-small cell lung cancer (NSCLC). However, predicting clinical PFS prior to pivotal trials remains challenging. Depth of tumor response and breadth of resistance mechanism coverage are key determinants of PFS that generally improve across TKI generations. We developed a clinical outcomes model incorporating these parameters and applied it to estimate the expected PFS of VRN110755, a mutant-selective, CNS-penetrant EGFR TKI currently in Phase 1a/b evaluation, in EGFR-mutant NSCLC.

Concept of PFS Prediction Model

Conceptual Tumor Response Model



PFS = X + Resistance Emergence Time = X + C_{Target}* Prediction Score

Prediction Score = **Weighted Resistance Coverage Score ($\sum P_i/\sum P_i S_i$)**
P = Clinical prevalence, S = Survival rate
i = T790M, C797S, brain met, Others
/ **Remaining Tumor Volume (%)**
Response rate is converted to volume change

Remaining tumor volume derived from relative best response

Gefitinib[1] (Reference point)
median best response = -49.9%
Remaining tumor volume = 12.6%

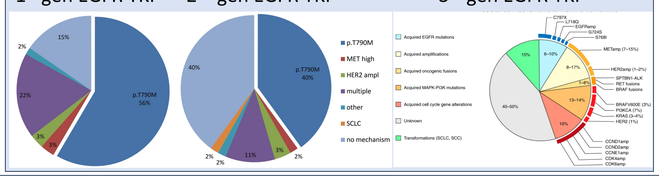
Dacomitinib[1]
median best response = -58.2%
Remaining tumor volume = 7.3%

Gefitinib/Erlotinib[2]
Relative best response = -49.9%
Remaining tumor volume = 12.6%

Osimertinib[2]
Relative best response = -56.5%
Remaining tumor volume = 8.2%

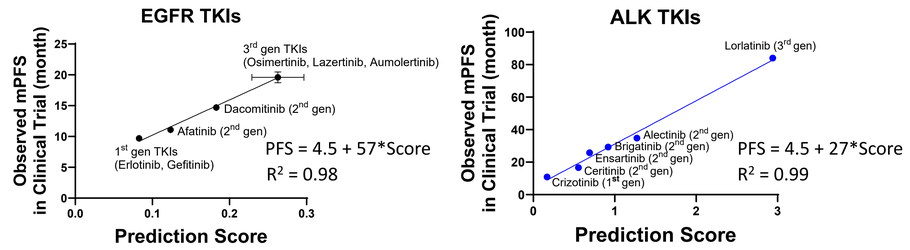
Distribution of acquired resistance mechanisms

1st gen EGFR TKI[3] 2nd gen EGFR TKI[3] 3rd gen EGFR TKI[4]



Result 1. PFS Prediction Score vs. Observed PFS

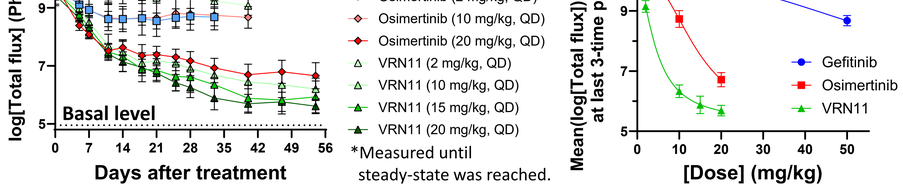
Prediction Score Strongly Correlates with 1L PFS Across EGFR and ALK TKIs



- Prediction scores calculated for EGFR and ALK TKIs were linearly correlated with observed PFS.
- Both models estimated X(Lag time) at 4.5 months, consistent with clinical observations[5].
- The framework was then used to independently predict the best response and PFS of VRN11 using two complementary approaches.

Result 2. Preclinical Data-Based PFS Prediction

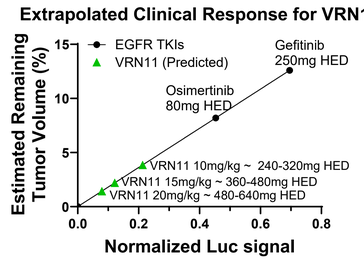
VRN11 Demonstrated Superior Antitumor Efficacy in the PC-9-Luc CDX Model



- A PC-9-Luc CDX study demonstrated dose-dependent reductions in bioluminescence signals.
- The relationship between steady-state bioluminescence signal and drug concentration was used to translate the preclinical tumor response into an estimated clinical best response for VRN11.

Preclinical Translation Predicts Deeper Response and Prolonged PFS for VRN11

Extrapolated Clinical Response for VRN11



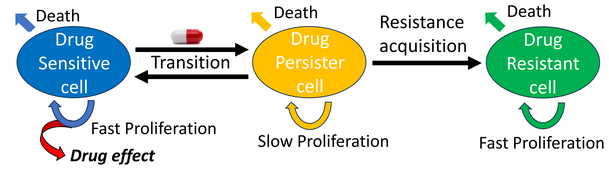
Prediction Results Table

Preclinical dose (HED)	Remaining Tumor volume (%)	Best response (% shrinkage)	PFS (month)
VRN11 10mg/kg (240-320mg)	3.9	-66.2	~30
VRN11 15mg/kg (360-480mg)	2.2	-72.0	~48
VRN11 20mg/kg (480-640mg)	1.4	-75.7	~72

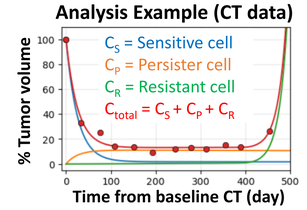
- Mouse exposures associated with the observed tumor responses were mapped to corresponding human doses based on PK data from the PC-9-Luc CDX study and clinical PK data.
- The resulting response estimates predicted deeper clinical responses and longer PFS for VRN11 than for approved third-generation EGFR TKIs at clinically relevant exposures.

Result 3. Model & Clinical Data-Based PFS Prediction

Tumor Response Model Framework



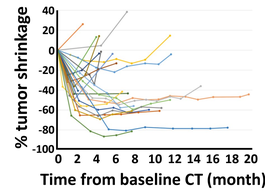
Analysis Example (CT data)



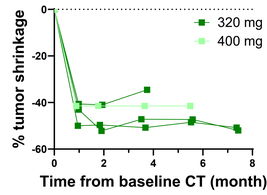
- The model is based on transitions among drug-sensitive, persister, and resistant cell populations.
- An example fit to longitudinal tumor measurements from computed tomography (CT) scans shows the inferred population dynamics of each state during treatment.

Higher Model-Estimated Drug Effect for VRN11

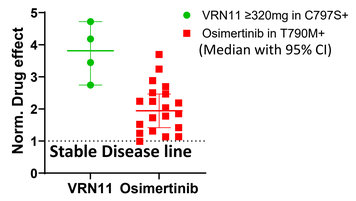
Osimertinib in T790M+ patients[6]



VRN11 ≥320mg in C797S+ patients



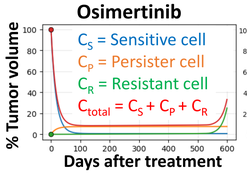
Comparison of Drug Effects in biomarker+ patients



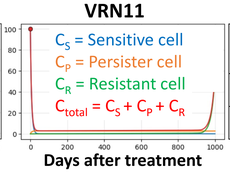
- Drug effects were estimated by fitting the model to longitudinal tumor response data from biomarker-positive patients and subsequently normalized for comparison between VRN11 and Osimertinib.

VRN11 Is Predicted to Outperform Approved third-generation EGFR TKIs

Osimertinib



VRN11



Modeling Results Table

	Remaining Tumor volume (%)	Best response (% shrinkage)	PFS (month)
Osimertinib*	8.2*	-56.5*	**~19***
VRN11(~320mg)	2.8	-69.5	**~32**

*Reference: published Osimertinib clinical outcomes.[2]

- The osimertinib-calibrated model was applied to VRN11 using VRN11-specific drug-effect and resistance-acquisition parameters.
- Predicted tumor response and PFS aligned with the independent preclinical prediction, with further efficacy gains possible as dose escalation continues.

Key Conclusions & Discussion

Key Conclusions

- The tumor-response model consistently recapitulated clinical 1L PFS across approved EGFR and ALK TKIs, supporting its translational relevance.
- Two independent predictive approaches converged on the same conclusion: **VRN11 is predicted to achieve deeper tumor responses and longer first-line PFS than approved third-generation EGFR TKIs.**

Discussion

- The deep tumor response observed with VRN11 may reflect multiple pharmacologic advantages, including efficient tissue penetration, favorable efflux properties, and robust target engagement.
- As dose escalation is ongoing, PFS may exceed current predictions at higher doses, particularly if higher target engagement extends coverage against resistance mechanisms not captured by the model.
- Clinical collaborations are ongoing to validate and refine the model using individual patient-level data.

References

1. Mok TS, et al. Dacomitinib versus gefitinib in EGFR-mutated NSCLC (ARCHER 1050). *Lancet Oncol.* 2017.
2. Soria JC, et al. Osimertinib in untreated EGFR-mutated advanced NSCLC. *N Engl J Med*. 2018.
3. Wagener-Ryczek S, et al. Acquired resistance to reversible versus irreversible EGFR TKIs. *BMC Cancer.* 2020.
4. Leonetti A, et al. Resistance mechanisms to osimertinib in EGFR-mutated NSCLC. *Br J Cancer.* 2019.
5. Herbst RS, et al. Molecular residual disease analysis of adjuvant osimertinib. *Nat Med.* 2025.
6. Cho JH, et al. Osimertinib in T790M-positive NSCLC: efficacy and resistance profile. *PLoS One.* 2019.

Artificial Intelligence (AI) Use Disclaimer

- Claude (Anthropic) was used to assist with coding and debugging of the analysis code.
- ChatGPT (OpenAI) was used for English-language editing.
- All analytical methods, outputs, and scientific interpretations were reviewed and validated by the authors.

Contact info: won5379@voronoi.io (C. KIM)
sunghwan@voronoi.io (S. KIM)

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)

***M-J. Ahn*[1]**, K.H. Lee[2], M.H. Hong[3], H.R. Kim[3], C-C. Lin[4], B.Y. Shim[5], T-Y. Yang[6], C-H. Chiu[7], Y.J. Kim[8], S. Sukumaran[9], Y-H. Luo[10], S. Arulananda[11], M. Li[12], H-R. Jung[13], S.Y. Zhang[14]

[1]Hanyang University, Seoul/KR, [2]Chungbuk National University Hospital, Cheongju/KR, [3]Yonsei Cancer Center, Severance Hospital, Seoul/KR, [4]National Taiwan University Hospital, Taipei/TW, [5]St. Vincent´s Hospital, Seoul/KR, [6]TaichungVeterans General Hospital, Taichung/TW, [7]Taipei Medical University Hospital, Taipei/TW, [8]Seoul National University, Bundang Hospital, Seoul National University College of Medicine, Seongnam/KR, [9]Southern Oncology Clinical ResearchUnit (SOCRU), Adelaide/AU, [10]Taipei Veterans General Hospital, Taipei/TW, [11]Monash Medical Centre, Clayton/AU, [12]The Chinese University of Hong Kong, Hong Kong China/HK, [13]Voronoi, Inc., Incheon/KR, Voronoi USA, Inc.,Boston/MA/USA

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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

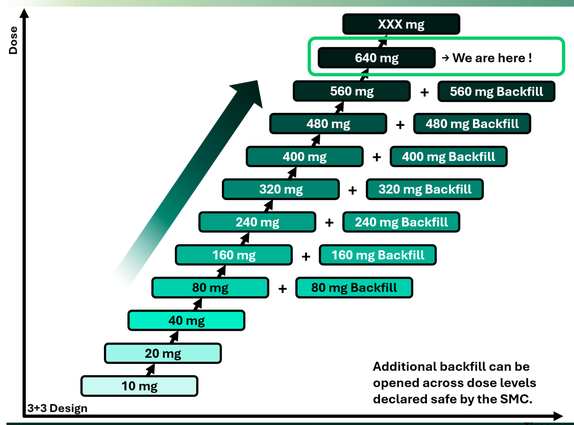
- This is a Phase 1/2 multicenter, open-label, dose-escalation, dose optimization and multi-cohort dose expansion clinical trial to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics (PK/PD), and antitumor activity of VRN110755, a highly selective oral epidermal growth factor receptor (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

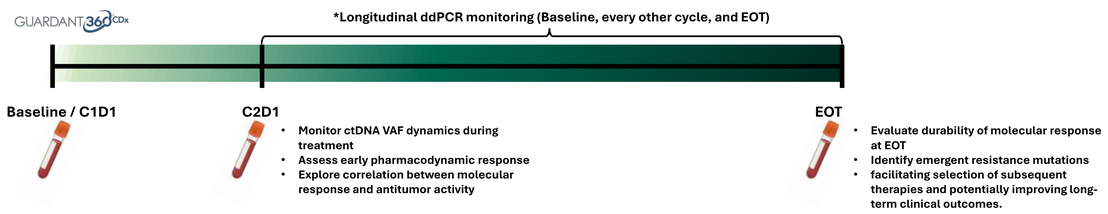
→ **Establish cRD1 and cRD2 for combination**

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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