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Safety, Pharmacokinetics, and Preliminary Antitumor Activity of VRN110755 in EGFR Mutant NSCLC

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Disclosure

- Honoraria: AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, BMS, MSD, Lilly, Merck, Roche, TAKEDA, YUHAN, Amgen
- Consultant or Advisor: AstraZeneca, Boehringer Ingelheim, BMS, Daiichi Sankyo, ONO, Takeda, Merck, MSD, Johnson & Johnson, Amgen, Novartis, Roche, YUHAN, Pfizer, AimedBio, Genexin, VORONOI, DaeWoong, Dong-A, BioNTech

REACH-EGFR: Ongoing First-in-Human Phase I study

Key eligibility

- At least 1 measurable lesion based on RECIST Version 1.1.
- EGFR mutation profile determined by liquid biopsy or pre-existing tumor biopsy result.
- Any EGFR activating mutations including Del19, L858R, C797S, and uncommon or complex mutations.

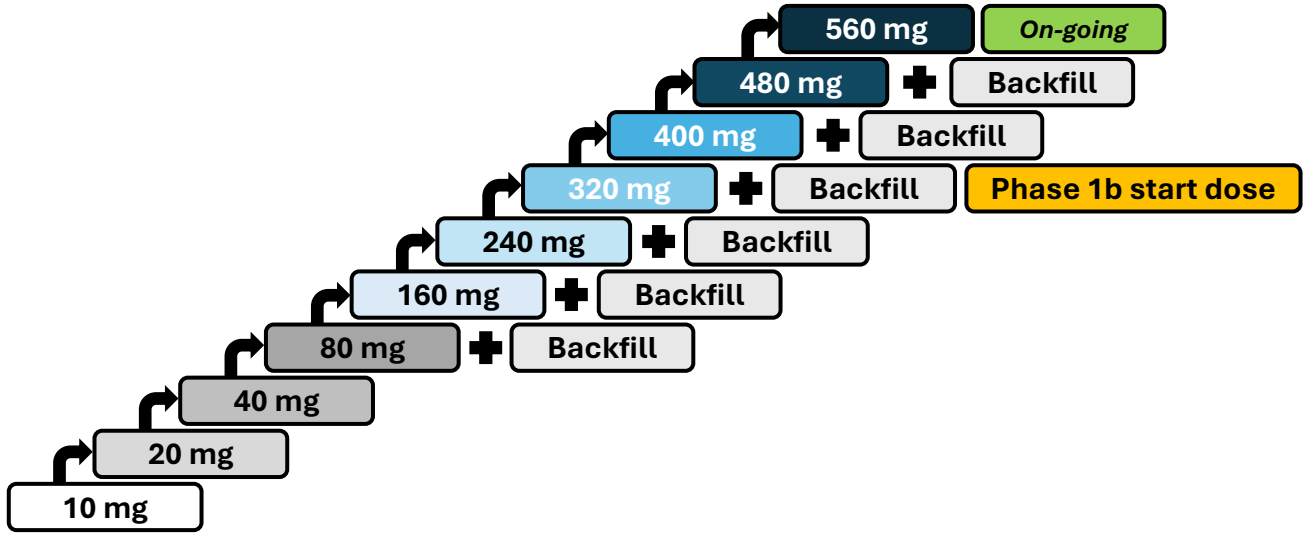
Objectives of Phase 1a study

Primary objectives

- Safety and tolerability of VRN110755 in patients with EGFR mutant NSCLC
- To determine the maximum tolerated dose (MTD)

Secondary objectives

- Pharmacokinetic profile of VRN110755
- Pharmacodynamic profile of VRN110755
- Preliminary antitumor effect of VRN110755



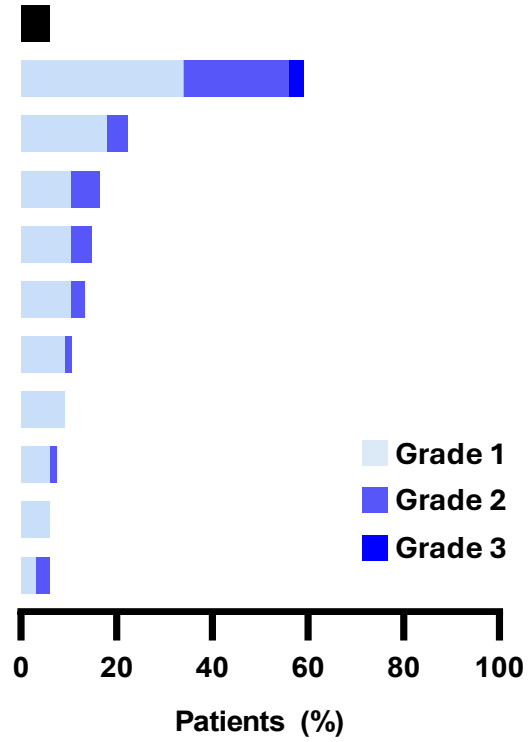
Characteristics	VRN110755 monotherapy (10 – 480 mg daily), n = 67
Median age, years (range)	60 (45-87)
Sex, n (%)	
Male / Female	22 (33) / 45 (67)
Race, n (%)	
Asian	66 (99)
White	1 (1)
ECOG PS, n (%)	
0 / 1	28 (42) / 39 (58)
CNS metastasis baseline, n (%)	
BM	29 (43)
BM + LM	3 (4)
No BM	35 (52)
Mutation type, n (%)	
Classic	30 (45)
Classic + C797S	7 (10)
Classic + T790M	6 (9)
Atypical	5 (7)
Atypical + T790M	1 (1)
Not detected	18 (27)
Prior EGFR TKI, n (%)	
Osimertinib	37 (55)
Lazertinib	24 (36)
Afatinib	16 (24)
Dacomitinib	4 (6)
Gefitinib	14 (21)
Erlotinib	10 (15)
Median No. of prior systemic therapies (range)	3 (1-10)

BM, brain metastasis; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; LM, leptomeningeal metastasis; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; RECIST version 1.1, Response Evaluation Criteria in Solid Tumors version 1.1. Data cut-off date: July 02, 2026

Safety Profile

- The MTD has not been identified, with no DLTs observed.
- TRAEs were reported in 60% of patients, including ≥ Grade 3 TRAEs in 3%.
- TRAE leading to dose reduction occurred in 4 (6%) patients.
- There was no TRAE leading to permanent discontinuation.
- Most treatment-related adverse events were mild and consistent with the expected on-target toxicity profile of EGFR inhibition.
- Rash was the most common, occurring in 22% of patients.

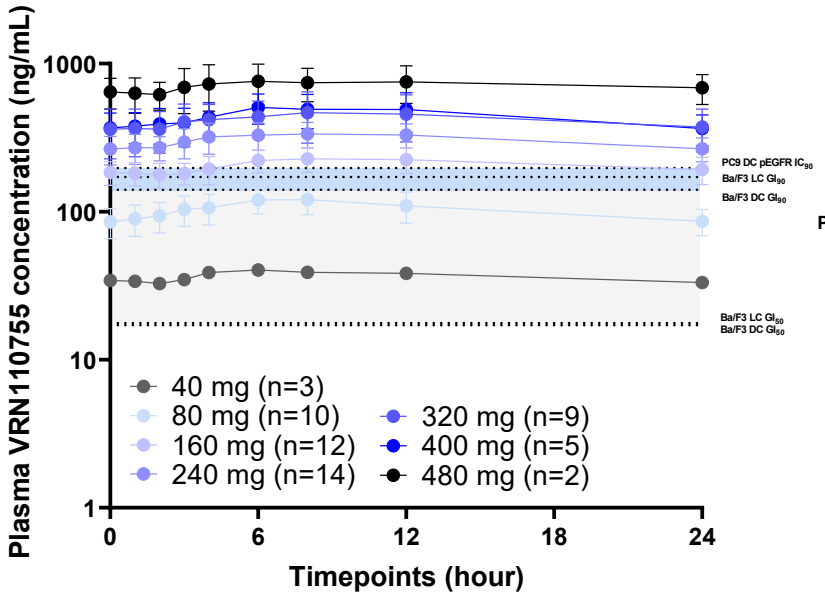
VRN110755 10 – 480 mg n=67	Treatment-Related Adverse Events (> 5%)	
	Any Grade	≥ Grade 3
Discontinuation	0%	
Dose reduction	6%	
Any AE	60%	3%
Rash	22%	-
Pruritus	16%	-
Diarrhea	15%	-
Dry skin	13%	-
AST increase	10%	-
ALT increase	9%	-
Nausea	8%	-
Anorexia	6%	-
Paronychia	6%	-



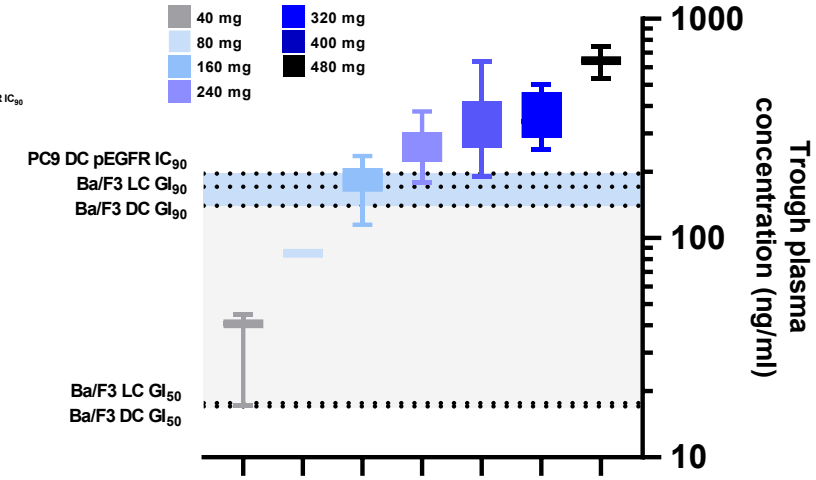
AE, adverse event; EGFR, epidermal growth factor receptor; MTD, maximum tolerated dose; TRAE, treatment-related adverse event.

Pharmacokinetics

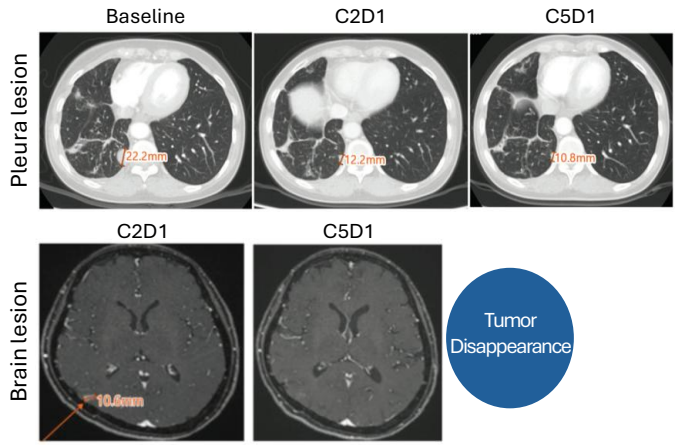
Pharmacokinetics of VRN110755 at C1D15



VRN110755 (C1D15)



40 mg cohort: EGFR$^{L858R/C797S/R776H}$

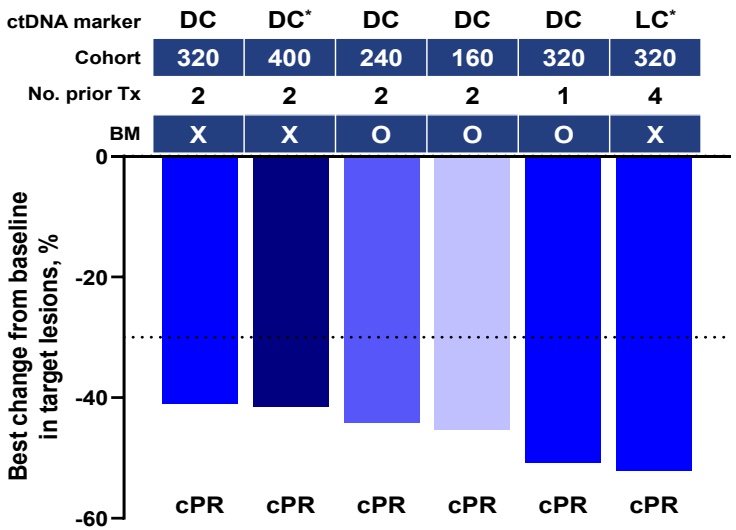


- Plasma exposure to VRN110755 increased in a dose-dependent manner.
- At 40 mg, systemic exposure exceeded the GI_{50} values in both the Ba/F3 DC and LC models, supporting for the clinical activity observed at this dose: a patient harboring a C797S mutation showed PR of the target lesion and disappearance of the brain lesion.
- At doses ≥160 mg, systemic exposures exceeded the pEGFR IC_{90} in PC9 DC cells and the GI_{90} in Ba/F3 DC and LC cells, and partial responses were observed in all C797S-positive patients.

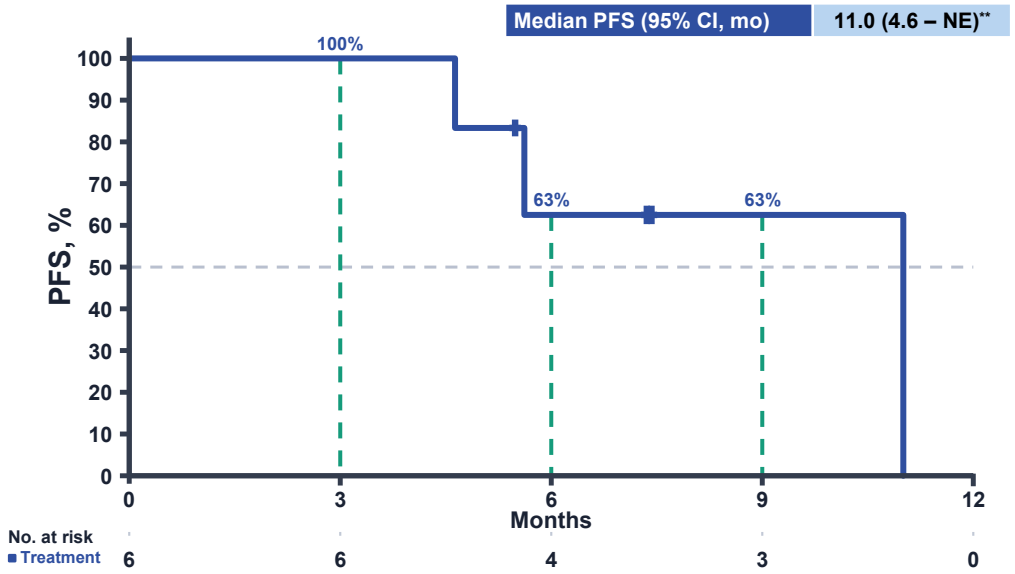
C1D15, Cycle 1 Day 15; DC, Del19/C797S; EGFR, epidermal growth factor receptor; GI50, 50% growth inhibitory concentration; GI90, 90% growth inhibitory concentration; IC90, 90% inhibitory concentration; LC, L858R/C797S.

Efficacy in Patients with C797S Mutation (treated ≥ 160mg, n=6)

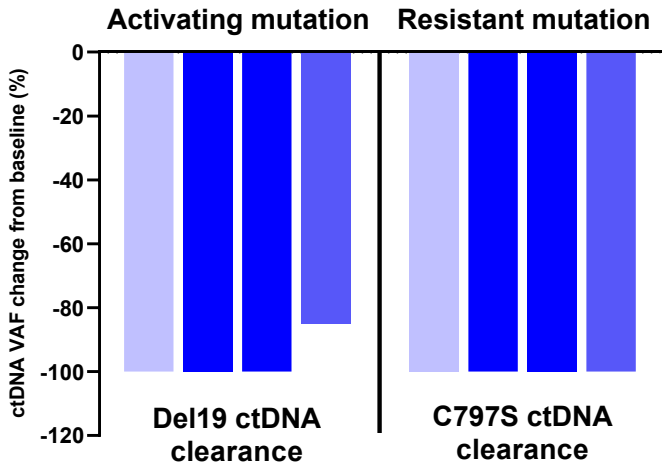
Best Response



Progression-Free Survival



ctDNA Clearance

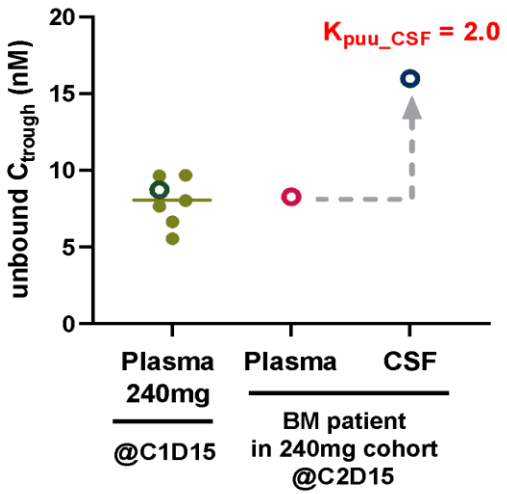


- Among six patients harboring C797S mutations who received doses ≥160 mg, the ORR was 100% (6/6), and all patients achieved tumor reductions of >40% from baseline.
- C797S ctDNA clearance was observed in all patients, with concurrent clearance of Del19 ctDNA in three patients.

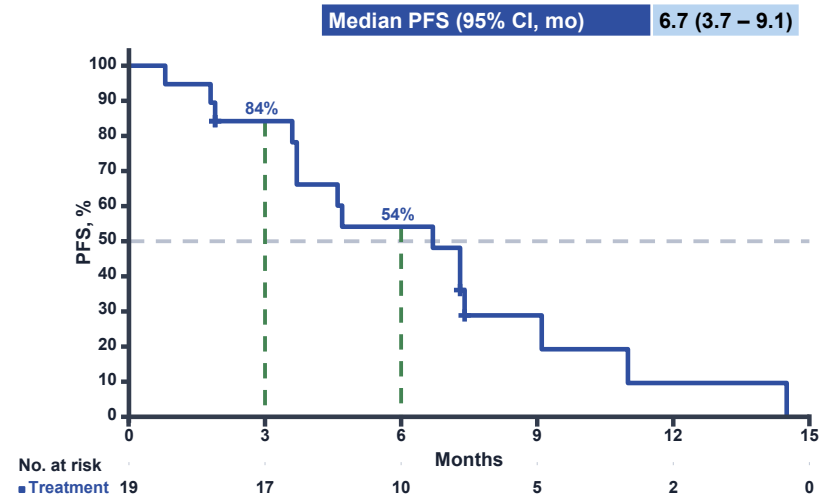
BM, brain metastasis; cPR, confirmed partial response; ctDNA, circulating tumor DNA; mo, months; NE, not estimable; ORR, objective response rate; PFS, progression-free survival; Tx, treatment; uPR, unconfirmed partial response.
* Patients with C797S undetected on screening ctDNA, pre-biomarker for inclusion required tumor tissue NGS confirmation of C797S within 3 months prior to C1D1.
** Preliminary data as of July 02, 2026; n=6, 3 PFS events. Median PFS estimate is not mature and subject to change with longer follow-up.

Efficacy in Patients with Baseline BM (treated ≥ 160mg, n=19)

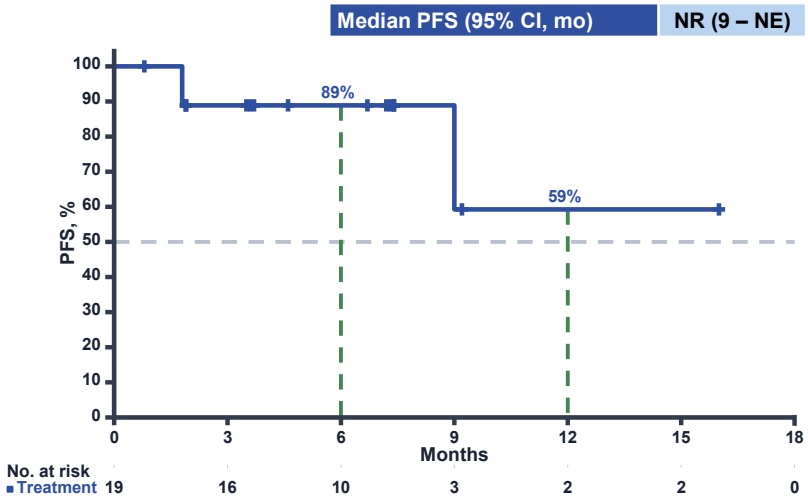
Brain Penetration



Progression-Free Survival



Intracranial PFS



Intracranial best response by RANO-BM

Base CNS lesion	Measurable	Non-measurable	Total
Patients, n	5	14	19
CR, n	0	4	4 (21%)
PR, n	0	-	0 (0%)
SD, n	5	-	15 (79%)
Non-CR/Non-PD, n	-	10	
PD, n	0	0	0 (0%)
Disease control, n	5	14	19 (100%)

- VRN110755 demonstrated high brain penetration and robust target engagement.
- Among the 45 patients treated at doses of 160 – 480 mg, 19 had brain metastases at baseline.
- Among patients with baseline BM, median PFS was 6.7 months, whereas median iPFS was not reached.
- The intracranial disease control rate was 100% including 4 CR (21%, 4/19).

BM, brain metastasis; CNS, central nervous system; CR, complete response; iPFS, intracranial progression-free survival; Non-CR/Non-PD, non-complete response/non-progressive disease; PFS, progression-free survival.

Conclusions

REACH-EGFR phase 1a study demonstrated

- Most common side effects were skin rash and EGFR-related on-target toxicity but 3% of Grade ≥3 adverse events.
- No DLT up to 480mg and a favorable and manageable safety profile.
- At doses ≥160 mg, preliminary but promising clinical activity was observed in C797S-mutant disease, including an ORR of 100% (6/6), tumor reductions of ≥40% in all patients, a median PFS of 11.0 months, and marked ctDNA reductions in all four evaluable patients.
- At doses ≥160mg in patients baseline brain metastasis, 100% of disease control rate with 4 CR and intracranial PFS was not reached, suggesting high penetration to the CNS.
- Collectively, these findings support further clinical development in patients with EGFR-mutant NSCLC.

CNS, central nervous system; CR, complete response; ctDNA, circulating tumor DNA; DLT, dose-limiting toxicity; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival.

Further Study Plan

Phase 1b/2 Expansion

Monotherapy

Cohort A
Common EGFR mut. With C797S

Cohort B
Common EGFR mut.
Treatment-naïve

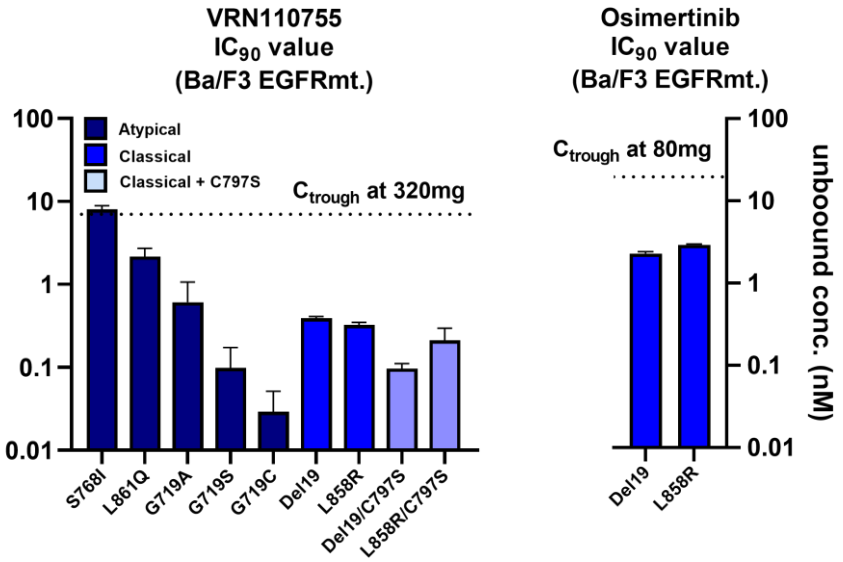
Cohort C
Atypical/uncommon EGFR mut.
One prior TKI (allow 1 ≤ prior systemic regimen)

Cohort D
Atypical/uncommon EGFR mut.
TKI-naïve

Cohort E
Common EGFR mut. With CNS
Progressed after 3rd gen TKI

Dose selection rationale

- **Low dose** (320 mg, QD; n=20)
- **High dose** (TBD, QD; n=20)



TE : Systemic (C_{trough}/IC_{90})	VRN110755	osimertinib
Del19	18x	9x
L858R	22x	7x

200% $K_{p,uu,CSF}$ 22% $K_{p,uu,CSF}$

TE : CNS (C_{trough}/IC_{90})	VRN110755	osimertinib
Del19	36x	2x
L858R	43x	1x

Combination Therapy (dose escalation)

Cohort G
VRN110755 with SOC chemotherapy
Any EGFR mut. after 3G TKI

- Dose 3
- Dose 2
- Dose 1

C1D15, Cycle 1 Day 15; IC_{90}, 90% inhibitory concentration; QD, once daily; SOC, standard of care; TBD, to be determined; TE, target engagement; TKI, tyrosine kinase inhibitor.

Acknowledgments

We sincerely thank:

- All study participants and their families and caregivers
- Investigators, physicians, nurses, and clinical staff who contributed to patient care and study conduct
- Study-site personnel and staff who contributed to data collection and analysis

For More Information on VRN110755, Please Visit Our Poster

1) **Poster #P2.352: VRN110755 phase 1b/2 trial in progress (Mon Sep 14, 10:30 AM)**

   A Phase 1/2 Study of VRN110755 in Patients with Epidermal Growth Factor Receptor (EGFR) Mutant Non-small Cell Lung Cancer (NSCLC).

2) **Poster #P3.247: VRN110755 pre-clinical results (Tue Sep 15, 9:30 AM)**

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

3) **Poster #P3.237: VRN110755 PFS prediction modeling (Tue Sep 15, 9:30 AM)**

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