Safety and Antitumor Activity of VRN110755, a Brain-Penetrant, Selective EGFR Inhibitor, in Patients With EGFR-Driven Non–Small Cell Lung Cancer (REACH-EGFR)

#8623

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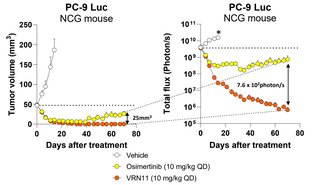
BACKGROUND

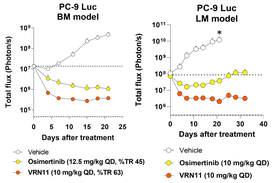
- Third-generation EGFR tyrosine kinase inhibitors (TKIs) have improved outcomes in EGFR-mutant non–small cell lung cancer (NSCLC). Despite the clinical benefit of osimertinib, insufficient target engagement may limit the depth of response to approximately 50%, and suboptimal brain penetration remains associated with CNS progression in approximately 30% of patients despite treatment.
- In addition, acquired resistance mediated by EGFR C797S mutations after third-generation EGFR TKI therapy remains an important unmet medical need.
- VRN110755 (VRN11) is an orally available, highly selective EGFR inhibitor designed to target a broad spectrum of EGFR mutations, including C797S, and has demonstrated robust brain penetration in preclinical models.

Broad *in vivo* efficacy across EGFR common mutant CDX model

Subcutaneous CDX model



Intracranial (BM or LM) CDX model

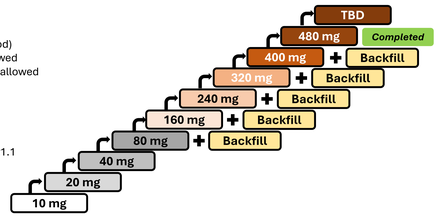


- In luciferin-based bioluminescence imaging, **residual tumor signals were detected in the osimertinib-treated group but were absent in the VRN110755-treated group**, suggesting deeper tumor suppression.
- In brain metastasis (BM) and leptomeningeal metastasis (LM) *in vivo* models, **VRN110755 showed stronger inhibition of CNS tumor growth than osimertinib.**

STUDY DESIGN

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

- 3+3 dose-escalating design
- 35 patients backfill above 80 mg
- 28-day cycle (DLT evaluation period)
- Intra-patient dose escalation allowed
- Stable and asymptomatic BM/LM allowed



Key Inclusion criteria

- Age ≥18 years
- Presence of EGFR mutation
- Measurable disease per RECIST v1.1
- Prior EGFR TKI treatment with disease progression
- ECOG PS 0–1

Primary endpoint

- Incidence of DLTs
- Incidence of adverse events (AEs)/serious AEs (SAEs)

Secondary endpoint

- PK, ctDNA evaluation
- ORR, DOR, DCR, PFS, and intracranial ORR if brain metastatic lesions are present
- PFS2 (PFS after next line of treatment) per RECIST v1.1 by investigator assessment
- Patient-reported outcomes

- Key objectives - determine the RP2D of VRN110755, safety, PK, and antitumor activity per RECIST v1.1
- Safety was assessed in all patients who received at least one dose of the study drug
- Efficacy was analyzed in EGFR-mutant NSCLC, including those harboring C797S resistance mutations

Patients' characteristics

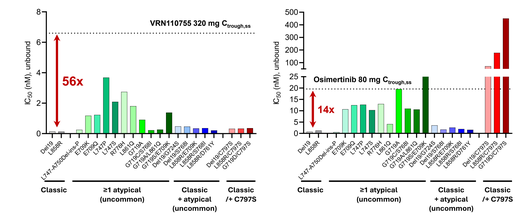
Characteristics	VRN110755 monotherapy (10 - 480mg daily), n = 65
Median age, years (range)	60 (45-87)
Sex, n (%)	
Male / Female	22 (34) / 43 (66)
Race, n (%)	
Asian	64 (98)
White	1 (2)
ECOG PS, n (%)	
0 / 1	28 (43) / 37 (57)
CNS metastasis baseline, n (%)	
BM	28 (43)
BM + LM	3 (5)
No BM	34 (52)
Mutation type, n (%)	
Classic	29 (45)
Classic + C797S	7 (11)
Classic + T790M	6 (9)
Atypical	5 (8)
Atypical + T790M	1 (2)
Not detected	17 (26)
Median No. of prior systemic therapies (range)	3 (1-10)

- EGFR mutations were confirmed by Guardant360 at baseline. Del19 insertion (e.g., A750_I759 delinsPL, Del19 insP, L747_A750 delinsP, L747P_P753 delinS) was considered as a classic mutant.
- Data cutoff date was March 12, 2026

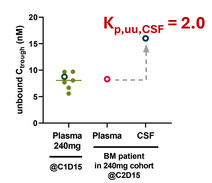
RESULTS

Preclinical/clinical evidence of potent activity on BM/LM in EGFR mutant NSCLC

In Vitro Target Engagement in Ba/F3-engineered Cell Lines



Brain Permeability in human



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

$K_{p,uu,csf}$ of osimertinib in human has been reported, 0.22[1]

*A representative human PPB, 98.9 % was used for calculation.

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

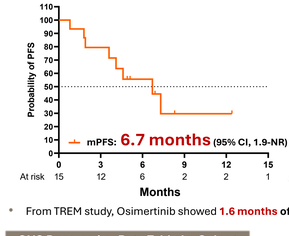
	VRN11 320mg	Osimertinib 80mg	VRN11 / Osimertinib
Classic	112	2.8	40x

- 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**, which was more than four-fold higher than that of osimertinib.

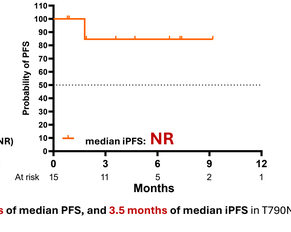
Potent CNS disease control in EGFR mutant NSCLC patients with BM/LM

PFS/iPFS in Patients with Baseline BM (≥160 mg, C797S^{neg})

1) Progression-Free Survival (PFS) (n=15)



2) Intracranial Progression-Free Survival (iPFS) (n=15)



- From TREM study, Osimertinib showed **1.6 months of median PFS, and 3.5 months of median iPFS** in T790M^{neg} group[2-3]

CNS Progression Rate Table by Cohort

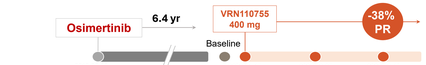
Efficacy evaluable patients	160 mg	240 mg	320 mg	400 mg	480 mg	Total
All evaluable patients, N	12	14	6	5	2	39
CNS progression, n/N (%)	1/12 (8%)	2/14 (14%)	1/6 (17%)	0/5 (0%)	0/2 (0%)	4/39 (10%)
CNS metastases at baseline, N	7	5	2	4	0	18
CNS progression, n/N (%)	1/7 (14%)	0/5 (0%)	1/2 (50%)	0/4 (0%)	0/0 (0%)	2/18 (11%)
No CNS metastases at baseline, N	5	9	4	1	2	21
CNS progression, n/N (%)	0/5 (0%)	2/9 (22%)	0/4 (0%)	0/1 (0%)	0/2 (0%)	2/21 (10%)
Median Duration of Treatment (Weeks)	24	19	16	13	7	18

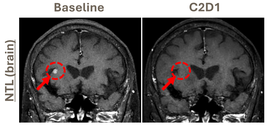
- Efficacy evaluable patients: at least one tumor assessment with ≥ 1 cycle of treatment.
- Brain and leptomeningeal metastases at baseline were confirmed by MRI.

- **2 of 5 brain non-target lesions (NTL) were absent at the first tumor assessment** (Osimertinib-treated patient with EGFR del19/C797S In 320 mg cohort).
- **Complete response of brain NTL was observed in 3 patients** (baseline BM pts in the 160–480 mg dose cohorts (n=18)).

Representative Cases of Robust CNS Activity

1) 400 mg: 71 yr-male with EGFR L858R NSCLC

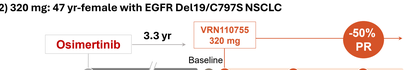


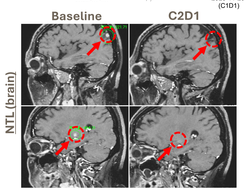


Baseline and Treatment History
- Lung and brain metastasis
- Prior EGFR TKI: **Osimertinib, Lazertinib**

VRN110755 treatment
- Lung target lesion: **38% tumor reduction**
- **Brain NTL: absent**
- Overall best response: **PR**

2) 320 mg: 47 yr-female with EGFR Del19/C797S NSCLC



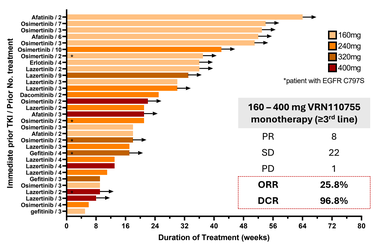


Baseline and Treatment History
- Lung, Brain, Bone metastasis
- Disease progression **after osimertinib**

VRN110755 treatment
- Lung target lesion: **50% tumor reduction**
- **Two brain NTLs were absent** at first TA
- Baseline ctDNA of EGFR mutation cleared
- Overall best response: **PR**

Potent anti-tumor activity on heavily pretreated EGFR mutant NSCLC

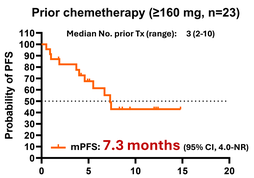
Swimming Plot (≥160 mg, ≥3rd line)



160 – 400 mg VRN110755 monotherapy (≥3rd line)	
PR	8
SD	22
PD	1
ORR	**25.8%**
DCR	**96.8%**

Prior chemotherapy-treated subgroup analysis

Prior chemetherapy (≥160 mg, n=23)



Prior EGFR TKI	
Gefitinib	22%
Erlotinib	13%
Afatinib	30%
Dacomitinib	4%
Osimertinib	48%
Lazertinib	35%

- Osimertinib showed **4.07 months of median PFS** in T790M-negative group progressed after treatment with first- or second-generation EGFR TKIs and platinum-based chemotherapy in phase II study (WJOG12819L)[4]

Representative Case in heavily-treated patient

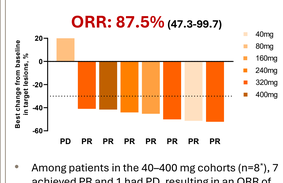
240 mg : 68 yr-male with EGFR L858R NSCLC

Baseline and Treatment History
- Metastatic site: Lung, Lymph node
- had received **10 prior lines of therapy**, including erlotinib and **osimertinib.**

VRN11 treatment
- Target lesions showed a sustained decrease over time, reaching **a 70% reduction** at C11D1 (Lymph node: **17.4 → 5.6mm**/Lung target lesion: **18.9 → 4.7mm**).
- Baseline ctDNA of EGFR L858R mutation also decreased (**VAF 5.7 → 0.06%**)

Clinical Activity in EGFR C797S-resistant mutation NSCLC

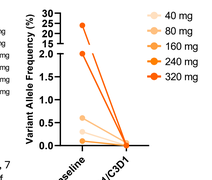
Best Response in Target Lesion Size



- Among patients in the 40–400 mg cohorts (n=8*), 7 achieved PR and 1 had PD, resulting in an ORR of 87.5% (95% CI, 47.3–99.7; exact binomial method).

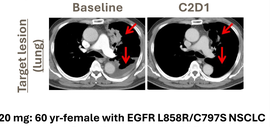
*For patients with C797S undetected on screening ctDNA, inclusion required tumor tissue NGS confirmation of C797S within 3 months prior to C1D1

ctDNA (C797S) VAF dynamics

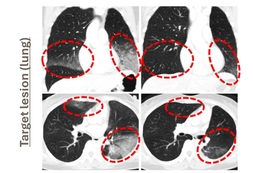


Representative Cases of Systemic Control

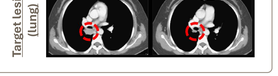
320 mg: 63 yr-male with EGFR Del19/C797S NSCLC



320 mg: 60 yr-female with EGFR L858R/C797S NSCLC

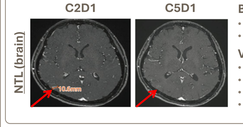


320 mg: 47 yr-female with EGFR Del19/C797S NSCLC



Representative Case of CNS Disease Control

40 mg: 52 yr-female with EGFR L858R/R776H/C797S NSCLC



Baseline and Treatment History
- Lung, brain, and pleural metastasis
- Two prior systemic treatments including **osimertinib**

VRN110755 treatment
- 40mg QD, 19 weeks
- Pleural target lesion: **46% tumor reduction**
- **Brain lesion: tumor disappearance**
- Overall best response: **PR**

Favorable safety profile in EGFR mutant NSCLC patients

Compound	VRN110755, high Doses (80–480 mg QD, N = 55)				Osimertinib (80 mg QD, N=201)[5]			
Median No. of prior systemic therapies (range)	3 (1-10)				2 (1-11)			
Treatment-related adverse events	**Grade 1**	**Grade 2**	**≥ Grade 3**	**Any grade**	**Grade 1**	**Grade 2**	**≥ Grade 3**	**Any grade**
Any treatment-related AE	**40%**	**24%**	**2%***	**68%**	***NR*** **	***NR***	**15%**	**92%**
EGFR-Related Diarrhea	9%	4%	-	13%	37%	5%	<1%	43%
EGFR-Related Rash	18%	4%	-	22%	33%	6%	<1%	40%
EGFR-Related Dry skin	9%	4%	-	13%	28%	3%	0%	31%
EGFR-Related Pruritus	11%	4%	-	16%	10%	3%	0%	13%
EGFR-Related Stomatitis	5%	-	-	5%	10%	3%	0%	13%
Non-EGFR-Related Decreased appetite	5%	-	-	5%	8%	1%	<1%	10%
Non-EGFR-Related Nausea	11%	-	-	11%	9%	1%	<1%	11%
Special interests Interstitial lung disease (ILD)	-	-	-	**0%**	1%		3%	**4%**
Special interests QT prolongation	-	-	-	**0%**	1%	<1%		**2%**

*One patient experienced Grade 3 acute kidney injury; the event was reversible, and no recurrent cases were observed in other treated patients.
**NR, not reported; Grade1/2 breakdown for overall TRAE not reported in source.

- **No DLTs were observed**, and the MTD and RP2D have not yet been determined.
- **No patients experienced drug-related adverse events leading to treatment discontinuation.**
- **No treatment-related clinically meaningful QT prolongation or ILD was observed.**
- Any drug-related adverse event leading to dose reduction was observed in 4 patients (6%).
- Any drug-related adverse event leading to dose interruption was observed in 8 patients (13%).

CONCLUSIONS

- VRN110755 demonstrated clinical CNS disease control consistent with its potent preclinical target inhibition and favorable brain penetration.
- Robust antitumor activity was observed in C797S-positive patients, along with a high disease control rate in C797S-negative patients.
- VRN110755 showed a favorable safety profile, with fewer EGFR-related toxicities, no ILD or QT prolongation, and no permanent treatment discontinuations.

References

1. Park S, et al. Phase II efficacy and safety of 80 mg osimertinib in patients with leptomeningeal metastases associated with EGFR mutation-positive non-small cell lung cancer (BLOSSOM). J Clin Oncol. 2024;42(23):2747–2756.
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