VRN110755, a CNS-penetrant EGFR inhibitor, demonstrates clinical activity in EGFR-mutant NSCLC, including C797S and brain metastases, with a favorable safety profile

[1]Myung-Ju Ahn, [2]Ki Hyeong Lee, [3]Chia-Chi Lin, [4]Byoung-Yong Shim, [5]Min Hee Hong, [5]Hye Ryun Kim, [6]Yu Jung Kim, [7]Jen-Yu Hung, and *[8]Shuang Yin Zhang

[1]Department of Medicine, Samsung Medical Center (SMC) - Sungkyunkwan University School of Medicine, Seoul, Korea, Rep. [2]Internal Medicine Department, Chungbuk National University Hospital, Cheongju, Korea, Rep. [3]Department of Oncology, NTUH - National Taiwan University Hospital, Taipei City, Taiwan. [4]Department of Medical Oncology, The Catholic University of Korea - St. Vincent's Hospital, Suwon, Korea, Rep. [5]Department of Internal Medicine, Yonsei Cancer Center, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea, Rep. [6]Department of Internal Medicine, SNUBH - Seoul National University Bundang Hospital, Seongnam, Korea, Rep. [7]Division of Pulmonary and Critical Medicine, Kaohsiung Medical University Hospital, Kaohsiung City, Taiwan. [8]Voronoi-USA, Boston, MA, United States

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Background

- EGFR oncogenic mutations in ~15% to 20% of NSCLC in Western populations and up to 50% in Asian population. Following third-generation EGFR TKI therapy, resistant mutations, C797S, and brain metastasis are major unmet medical needs.
- VRN110755 is a potent, brain-penetrant EGFR inhibitor with high selectivity against EGFR oncogenic mutations over EGFR wild-type and other human kinases, promising favorable safety profile. It is highly active against EGFR common, uncommon driver mutants and osimertinib-resistant (C797S) mutant. Preclinical studies show robust systemic and intracranial antitumor activities, superior to osimertinib, with favorable safety and PK supporting once-daily oral dosing.
- This Phase 1 study (VRN110755-01) evaluates safety, tolerability, pharmacokinetics, and preliminary efficacy of VRN110755 in patients with EGFR-mutant NSCLC, including C797S resistance.

Study design

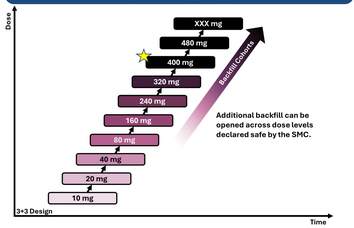
Phase 1a Eligibility

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

Phase 1a Design

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

Phase 1a/b Escalation and Expansion (10 – 320 mg daily)



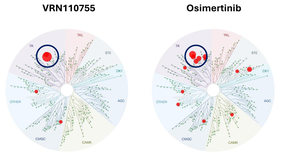
- Key objectives - determine the RP2D of VRN110755, safety, PK, and antitumor activity per RECIST v1.1
- Data cutoff date was October 14, 2025
- Safety was assessed in all patients who received at least one dose of the study drug
- Efficacy was analyzed in EGFR-mutant NSCLC, including those harboring C797S resistance mutations

Patient and disease characteristics

Characteristics	VRN110755 monotherapy (10 - 400mg daily), n = 54
Median age, years (range)	60 (45-87)
Sex, n (%)	
Male / Female	18 (33) / 36 (67)
Race, n (%)	
Asian	54 (100)
ECOG PS, n (%)	
0 / 1	24 (44) / 30 (56)
Mutation type, n (%)	
Classic	26 (48)
Classic + C797S	4 (7)
Classic + Atypical	1 (2)
Atypical	7 (13)
Median number of prior systemic therapies (range)	3 (1-15)

EGFR mutations were confirmed by Guardant360 at baseline. Del19 insertion (e.g., A750_I759delinsPL) was considered as an atypical mutant.

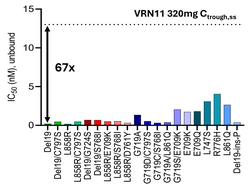
Preclinical studies

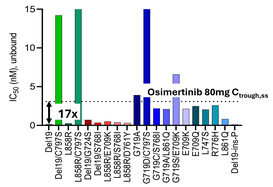


Target engagement ratio

EGFR mutations	VRN110755 320mg	Osimertinib 80mg	VRN11 /Osimertinib
Classic	67	17	4x
Classic + C797S	27	< 1	180x
Classic + Atypical	26	8	3x
Atypical	15	4	4x

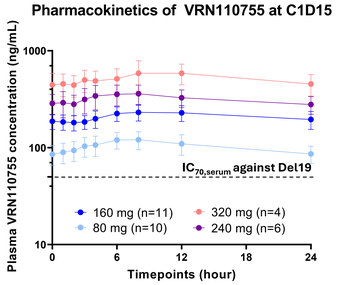
Target engagement ratio was determined with [$C_{trough,ss}$ / IC_{50} of the indicated EGFR mutations]

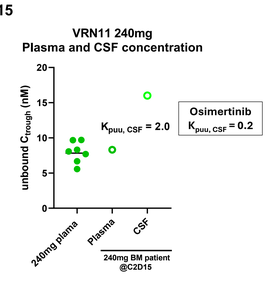




- Kinase profiles were analyzed against 486 human kinases, and S10 kinases were indicated as a red dot.
- IC_{50} (proliferation inhibition) values against each mutant were determined based on BaF3-engineered cells. Black dot lines indicate C_{trough} free drug concentrations in humans.

Pharmacokinetics





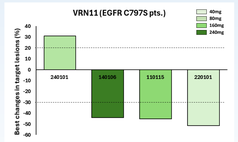
- Dose-proportional exposure was observed in humans.
- From 80 mg, VRN110755 maintains plasma concentration above IC_{70} against EGFR-Del19 in 100% human serum for 24 hours.
- Average half-life of VRN110755 was around 50 hours.
- $K_{puu,\ CSF}$ measured in 1 patient who received 240 mg
- Osimertinib $K_{puu,\ CSF}$ were adapted from BLOSSOM (JCO 2024)

Efficacy

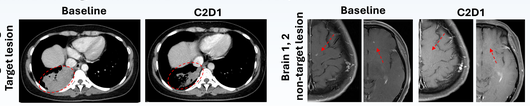
C797S-Positive Patients with Brain Metastases

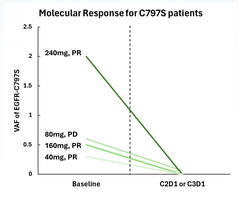
Patient ID	Dose level	EGFR mutants	Prior TKIs	ctDNA clearance (C797S)	Best changes in Target lesions (%)	Brain lesion	Best response
1	40 mg	L858R/C797S/R776H	Dacomitinib – Osimertinib	100%	-51.4	Disappeared (non-target)	PR
2	160 mg	Del19/C797S	Osimertinib	100%	-45.3	Disappeared (non-target)	PR
3	240 mg	Del19/C797S	Lazertinib Osimertinib	100%	-44.1	Decreased (non-target)	PR
4	80 mg	Del19/C797S	Osimertinib	80%	31.2	Increased (target)	PD

Patient 1: 40 mg, Patient with EGFR$^{L858R/C797S/R776H}$ NSCLC, PR

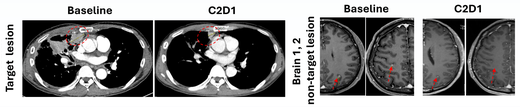


Patient 2: 160 mg, Patient with EGFR$^{Del19/C797S}$ NSCLC, PR

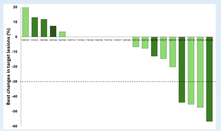


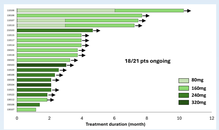


Patient 3: 240 mg, Patient with EGFR$^{Del19/C797S}$ NSCLC, PR



EGFR Driver-Positive Patients, 3rd line





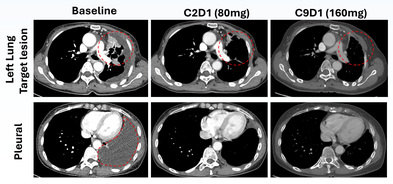
Response to treatment (n=21)	
Response	No (%)
CR	0 (0%)
PR	4 (19.0%)
SD	16 (76.2%)
PD	1 (4.8%)
not evaluable	0 (0.0%)
ORR	19.0%
DCR*	95.2%

*All BM/LM patients (11/11) are ongoing treatment

Response to treatment (n=55)	
Response	No (%)
CR	0 (0%)
PR	16 (29.1%)
SD	16 (29.1%)
PD	18 (32.7%)
not evaluable	5 (9.1%)
ORR	29.1%
DCR	58.2%

Osimertinib A phase II study (WJOG12819L)

80 -160 mg (intra-patient dose escalation, EGFR^{Del19}, PR (> 10 months)



Safety

Safety of VRN110755 monotherapy

	10 mg (N=3)	20 mg (N=4)	40 mg (N=3)	80 mg (N=12)	160 mg (N=13)	240 mg (N=14)	320 mg (N=4)	400 mg (N=1)	All (N=54)
Any grade TRAE, n (%)	1 (33)	2 (50)	1 (33)	2 (17)	7 (54)	8 (58)	1 (25)	0(0)	22 (41)
Grade 1 TRAE, n (%)	1 (33)	2 (50)	1 (33)	2 (17)	5 (38)	6 (43)	1 (25)	0(0)	19 (35)
Grade 2 TRAE, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	2 (15)	1 (7)	0 (0)	0(0)	3 (6)
Grade 3 TRAE, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0(0)	0 (0)
DLT or TR-SAE, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0(0)	0 (0)

*2 of grade 2 pruritus and 1 of grade 2 gastritis resolved without dose reduction or interruption of the drug

Adverse events of VRN110755 monotherapy (≥ 160mg) in comparison to Osimertinib 80 mg

Event (%)	VRN110755 (160-400mg, n=34)		osimertinib (80mg, n=279)	
	All	Grade ≥3	All	Grade ≥3
EGFR on target tox.				
Diarrhea	9	-	49	2
Rash	18	-	54	1
Dry skin	9	-	33	<1
Paronychia	-	-	33	<1
Stomatitis	6	-	25	<1
Pruritus	6	-	15	-
EGFR off target tox.				
Anemia	-	-	12	1
QT prolongation	-	-	10	2
ILD/Pneumonitis	-	-	4	2

* Osimertinib safety profiles adapted from FLAURA (NEJM 2019)

VRN110755 statistics (160-320mg, n=33)

- Median time on treatment was 9 weeks
- No DLTs were observed
- 0 (0%) patients required VRN110755 dose hold due to TRAEs
- 0 (0%) patients dose reduced VRN110755 due to TRAEs
- 0 (0%) permanently discontinued VRN110755 due to TRAEs

Conclusions

- VRN110755 demonstrates clinical activity in EGFR-mutant NSCLC, including C797S and CNS lesions.
- Favorable safety profile up to 320 mg; MTD not reached.
- Pharmacokinetic data confirm CNS penetration.
- Phase 2 expansion is planned.

References

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