Early Clinical Evidence of VRN110755: A Novel Brain-Penetrant EGFR TKI Active Across Common, Uncommon, and Resistance EGFR Mutations (REACH-EGFR)

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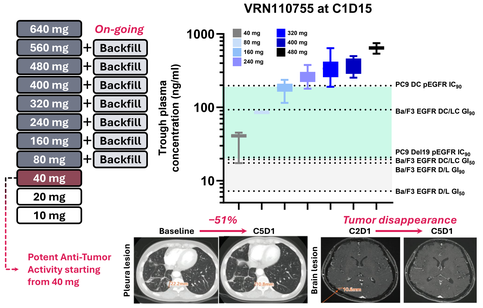
Introduction

Abstract

- VRN110755 (VRN11) is an orally available, highly selective EGFR tyrosine kinase inhibitor (TKI) designed to target a broad spectrum of EGFR mutations, including C797S.
- Based on safety and clinical activity, 320 mg was selected as the lower dose for randomized dose optimization against a higher dose (TBD).
- As of the October 9, 2026 data cut-off, safety is reported for all treated patients, focusing on the ≥ 160 mg subset, the lowest exposure attainable at 320 mg after two permitted reductions.

REACH-EGFR: Ongoing Phase Ia study

- Primary Endpoints: DLTs · AEs / SAEs
- Secondary Endpoints: PK · ctDNA · ORR · DoR · DCR · PFS · intracranial ORR



Demographics

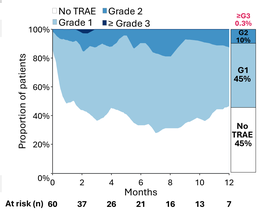
Characteristics	Enrolled patients (10-560 mg, N=82*)
Age, years	
Median (range)	61 (45–87)
<65 / ≥65	49 (59.8) / 33 (40.2)
Sex, n (%)	
Female / Male	53 (64.6) / 29 (35.4)
Race, n (%)	
Asian	80 (97.6)
White	1 (1.2)
Others	1 (1.2)
ECOG PS, n (%)	
0 / 1	28 (34.1) / 54 (65.9)
EGFR mutation† at baseline, n (%)	
Del19	33 (40.2)
L858R	24 (29.3)
T790M	9 (11.0)
C797X	15 (18.3)
Uncommon EGFR	10 (12.2)
EGFR amplification	8 (9.8)
EGFR not detected / Not reported	6 (7.3) / 13 (15.9)
Brain metastases at baseline, n (%)	
Yes	39 (47.6)
Measurable / Non-measurable	13 (15.9) / 26 (31.7)
No	43 (52.4)
Prior systemic regimens	
Median (range)	3 (1–10)
1	17 (20.7)
2	18 (22.0)
≥ 3	46 (56.1)
Not reported	1 (1.2)

*Patients administered ≥1 dose of VRN11 at any dose level.
†EGFR mutations are not mutually exclusive; Total percentages may exceed 100%. EGFR status was based on baseline Guardant360; if not confirmed, historical results were used (no subsequent therapy given for ≥2 cycles)

Safety and Long-term tolerability

Treatment-related adverse events**	Patients (10-560 mg, N=82) G1	G2	≥ G3	Total
Any	28 (34)	20 (24)	2 (2)	50 (61)
EGFR-related				
Diarrhea	11 (13)	3 (4)	0 (0)	14 (17)
Pruritus	9 (11)	4 (5)	0 (0)	13 (16)
Rash maculo-papular	9 (11)	2 (2)	0 (0)	11 (13)
Rash	5 (6)	4 (5)	0 (0)	9 (11)
Dermatitis acneiform	5 (6)	0 (0)	0 (0)	5 (6)
Dry skin	4 (5)	1 (1)	0 (0)	5 (6)
Paronychia	3 (4)	2 (2)	0 (0)	5 (6)
Stomatitis	5 (6)	0 (0)	0 (0)	5 (6)
Non-EGFR-related				
Nausea	9 (11)	1 (1)	0 (0)	10 (12)
AST increased	7 (9)	1 (1)	0 (0)	8 (10)
ALT increased	7 (9)	0 (0)	0 (0)	7 (9)
Special interests				
Lung-related	0 (0)	0 (0)	1 (1)	1 (1)
QT prolongation	3 (4)	0 (0)	0 (0)	3 (4)

Time-Course of Any Grade TRAE[a] in patients ≥ 160 mg (n=60)



**TRAEs occurring in ≥5% of patients and adverse events of special interest are shown.
[a]Proportion of patients on treatment at each point, by highest ongoing TRAE grade.
Right bar: pooled across all patients, % of on-treatment days by highest TRAE grade

- Most TRAEs were mild to moderate with known EGFR-related AEs (diarrhea and skin); no DLT during dose escalation, and no drug-related discontinuation was reported.
- Total 90% of treatment days were TRAE-free or G1 only, with no accumulation of high grade TRAEs in patients at ≥ 160 mg.

Preclinical Evidences

Target Engagement Ratio (TER)[b]

Systemic TER

	VRN11 320mg	Osimertinib 80mg	VRN11 ÷ Osimertinib
Common	56	14	~4x
+ C797S	22	< 1	140x
+ uncommon	20	9	2x
Uncommon	5	2	3x

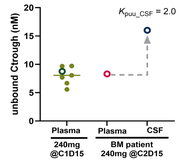
x 2.0 x 0.2

CNS TER

	VRN11 320mg	Osimertinib 80mg	VRN11 ÷ Osimertinib
Common	112	3	~40x

[b] Systemic TER = unbound $C_{trough,ss}$ ÷ unbound IC_{50}. CNS TER = human $K_{p,uu,CSF}$ × Systemic TER.

Brain Permeability in Human

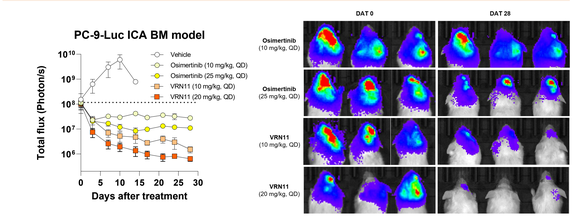


$K_{p,uu,CSF}$	VRN11	Osimertinib[f]
Mouse	2.3[c]	0.8
Monkey	2.7[d]	NA
Human	2.0[e]	0.2

[c] Mouse: in-house data
[d] Monkey: Chempartner,
[e] kindly provided by one patient treated with VRN11 240 mg
[f] Colclough N., et al. Clin Cancer Res. 2021;27:189–201
Human $K_{p,uu,CSF}$ values were applied to calculate CNS TER

- Estimated target engagement at 320 mg exceeded osimertinib 80 mg by ~4-fold for common and 2–3-fold for uncommon EGFR mutations, and ~40-fold in the CNS.

Intracranial activity: PC-9 Luc Intracranial Model

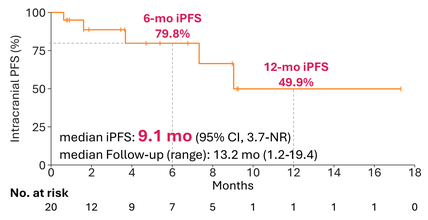


#Vehicle-treated mice euthanized due to ≥ 20% body weight loss
AUC-based human equivalent exposure: Osimertinib (10–25 mg/kg) ≈ Human 80 mg; VRN11 (10–20 mg/kg) ≈ Human 320 mg

- VRN11 10 mg/kg outperformed osimertinib 25 mg/kg
- Continued decline through day 28, while osimertinib plateaued

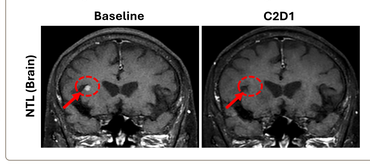
Clinical Results

Efficacy (1) Intracranial activity ; C797S-negative, ≥ 160 mg (n=20)[g]



Prior Lines, median (range)	**3 (1-9)**
Prior 3G EGFR TKI	17 (85.0%)
Intracranial Best overall response, n (%)	
CR	**4 (20.0)**
PR	0 (0.0)
SD	5 (25.0)
Non-CR/Non-PD	10 (50.0)
PD	1 (5.0)
NE	0 (0.0)
Confirmed iORR, n (%)	4 (20.0)
iDCR, n (%)	**19 (95.0)**

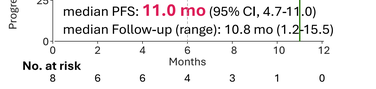
[g]Patients with CNS lesions at baseline and ≥1 post-baseline RANO-BM assessment. Median follow-up = time from first dose (C1D1) to data extract for all evaluable patients, regardless of progression, death or discontinuation.
In T790M-negative patients treated with osimertinib 80 mg, median iPFS was 3.5 months and the 6-mo iPFS rate was 31%[3]. [3]Eide IJZ, et al. Acta Oncol. 2021;60:1565–71.



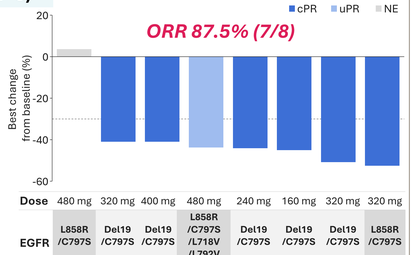
Case Report: intracranial CR within 4 weeks

- 71-year-old female · 400 mg · ECOG 1 · 3 prior lines including **osimertinib and lazertinib**
- Genomic alteration at entry: EGFR L858R, PIK3CA, two TP53
- Week 4: Intracranial CR and ~95% decrease in ctDNA VAF
- **Week 8: Confirmed systemic PR**

Efficacy (2) C797S-positive, ≥ 160 mg (n=8)[h]



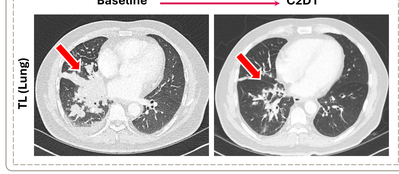
[h]Response-evaluable: patients with C797S treated at ≥ 160 mg and ≥ 1 post-baseline tumor assessment. Median follow-up = time from first dose (C1D1) to data extract for all evaluable patients, regardless of progression, death or discontinuation.



PEM, pemetrexed; GEM, gemcitabine; DTX, docetaxel; ABCP, atezolizumab + bevacizumab + carboplatin + pemetrexed; Red, third-generation EGFR TKI.

Case Report: C797S after osimertinib +savolitinib

- 63-year-old male · 480 mg · ECOG 0 · 6 prior lines
- **Resistance shifted from MET amp to C797S**
- EGFR VAF (entry): L858R 25.74%, C797S 25.36%, L718V 1.75%, L792V 0.42%
- All 4 target lesions decreased: 2 lung, 2 lymph node



Speed of response

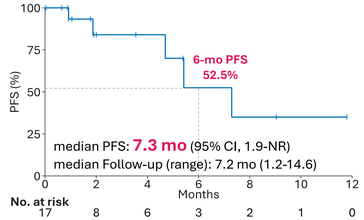
	Depth of Response	Time to Best Response
VRN11 ≥ 160 mg[i] (C797S-positive)	**-45.9%**	**26 days**
Osimertinib 80 mg[j] (T790M-positive)	**-43.7%**	**54 days**

- Driven by strong target engagement, deep response reached earlier with VRN11 than with osimertinib (26 days vs 54 days) in a later line setting (C797S-positive vs T790M-positive).

[i]Time from first dose to best response in C797S-positive patients who received ≥ 160 mg of VRN11 (1-cycle = 28 days)
[j]Oh DK, et al. PLoS One. 2019;14(1):e0210225, Data shown are for T790M-positive patients

Ongoing Phase 1/2 Design

Efficacy (3) C797S-negative, ≥ 320 mg (n=17)[k]



Prior lines, median (range)	**3 (1–9)**
Prior lines ≥3	10 (58.8%)
Prior 3G EGFR TKI	14 (82.4%)
Prior 1/2G EGFR TKI	11 (64.7%)
Prior chemotherapy	13 (76.5%)

[k] Response-evaluable: patients without C797S treated at ≥ 320 mg and ≥ 1 post-baseline tumor assessment. Median follow-up = time from first dose (C1D1) to data extract for all evaluable patients, regardless of progression, death or discontinuation.

- For reference, osimertinib in T790M-negative disease showed **2.8 months** (AURA phase 1; dose-ranging 20–240 mg, after prior EGFR TKI) and **4.1 months** (WJOG12819L; 80 mg, after 1st/2nd-generation EGFR TKI and platinum); cross-study comparisons, different populations— both references enrolled after 1st/2nd-generation TKI only.

Dose selection

✓ Low dose 320mg

High dose TBD

- Clinical activity was observed from ≥ 160 mg across all three settings — intracranial disease, C797S-positive disease, and C797S-negative disease after prior TKI.
- 320 mg was selected as the low dose because two permitted reductions from it still land at 160 mg, keeping every patient within the active range; no DLT occurred during dose escalation, so a higher dose is being evaluated against it.

Expansion cohorts

- All three results come almost entirely from patients who had already progressed on a third-generation EGFR TKI, whereas every osimertinib figure they are set against comes from patients treated after a first- or second-generation TKI only. In that harder setting, (1) suppression of EGFR-dependent disease lasted longer, (2) C797S-positive target lesions shrank faster than osimertinib achieves in its own T790M-positive population, and (3) intracranial PFS was longer — in line with an estimated target engagement ~4-fold over osimertinib 80 mg systemically and ~40-fold in the brain, and (4) achieved with no treatment-related discontinuation. Cohorts B and D open the first line.

Move to First Line (1L)

1L common EGFR
Treatment-naïve
Enrolling Cohort B

1L atypical EGFR
Treatment-naïve
Enrolling Cohort D

Overcome Resistance after 3G TKI

C797X
Common + C797X
Enrolling Cohort A

Combination
Post-3G TKI; BOIN design
Cohort G

CNS metastases
Lesion ≥ 5 mm and/or LM
Cohort E

Conclusions

- **Well tolerated:** TRAEs mostly G1–2 (any 61%, ≥ G3 2%); no DLT or treatment-related discontinuation.
- **C797S+, ≥ 160 mg:** 7/8 with > 40% target lesion reduction; median time to best response 26 days (osimertinib, T790M+: 54 days); mPFS 11.0 mo.
- **C797S−, CNS lesions, ≥ 160 mg** (n=20; 85% post-3G TKI): 6-/12-mo iPFS 79.8%/49.9% (osimertinib, T790M−, post-1·2G TKI: 31% at 6 mo).
- **C797S−, ≥ 320 mg** (n=17; 82% post-3G TKI): mPFS 7.3 mo (osimertinib, post-1·2G TKI: 2.8–4.1 mo).
- Activity, observed almost entirely after 3G TKI progression, is consistent with estimated target engagement ~4× (systemic) and ~40× (CNS; $Kp_{uu,CSF}$ 2.0 vs 0.22) that of osimertinib 80 mg.
- Cohorts B and D open the first line.

Disclosures
T.-Y. Yang: Advisory board/consulting fees: AbbVie, Amgen, AstraZeneca, Bayer, BeOne Medicines, Boehringer Ingelheim, Bristol Myers Squibb, Chugai, Daiichi Sankyo, Eli Lilly, GSK, Johnson & Johnson (Janssen), Lotus Pharmaceuticals, Merck KGaA, MSD, Novartis, Pfizer, Roche, Takeda. Travel/accommodation/registration support: AstraZeneca, Chugai, Pfizer, Roche.

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