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Safety Profile and Anti-Tumor Efficacy of VRN110755, a Highly Selective, Brain Penetrant EGFR Inhibitor for Patients with EGFR-Driven Non-Small Cell Lung Cancer

Phase 1/2 study of VRN110755

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06 Dec 2025

DECLARATION OF INTERESTS

- Honoraria (AstraZeneca, BMS, MSD, Lilly, Merck, ONO, Roche, TAKEDA,YUHAN, Amgen)
- Consultant or Advisor (AstraZeneca, BMS, ONO, Takeda, Lilly, Merck, MSD, Amgen, Novartis, Roche, YUHAN, Arcus, Pfizer, Daichi-Sankyo, Genexin, VORONOI)

EGFR activating mutation in non-small cell lung cancer (NSCLC)

- Approximately 25~30% of NSCLC patients harbor EGFR activating mutations.
- Third-generation EGFR TKIs are widely used as a standard of care for EGFR-mutant NSCLC, but on-target EGFR resistance mutations still arise.
- EGFR-C797S is one of the most common acquired resistant mechanisms against 3G EGFR TKI; however, there is no approved treatment available.
- CNS metastasis is associated with poor prognosis in EGFRm NSCLC, and 20% of patients treated with osimertinib develop CNS progression[1].
- VRN11 is a mutant-selective EGFR inhibitor characterized by high brain permeability.

[1]Wang C, Zhao K, Hu S, Dong W, Gong Y, Xie C. Clinical Outcomes of Afatinib Versus Osimertinib in Patients With Non-Small Cell Lung Cancer With Uncommon EGFR Mutations: A Pooled Analysis. Oncologist. 2023 Jun 2;28(6):e397-e405. doi: 10.1093/oncolo/oyad111. PMID: 37116899; PMCID: PMC10243768.

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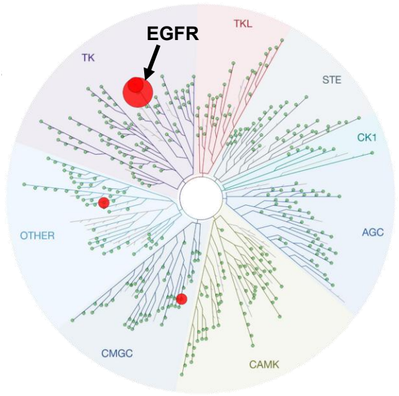
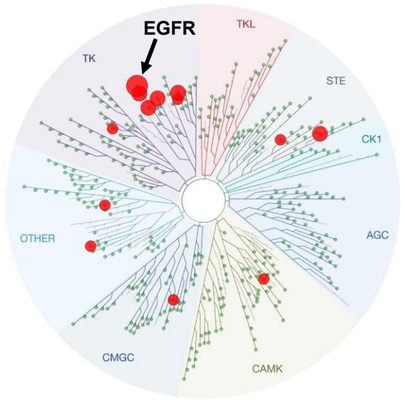
VRN110755, a selective EGFR inhibitor with activity against common, uncommon, and resistance mutations

Kinase Profiling

VRN110755



Osimertinib

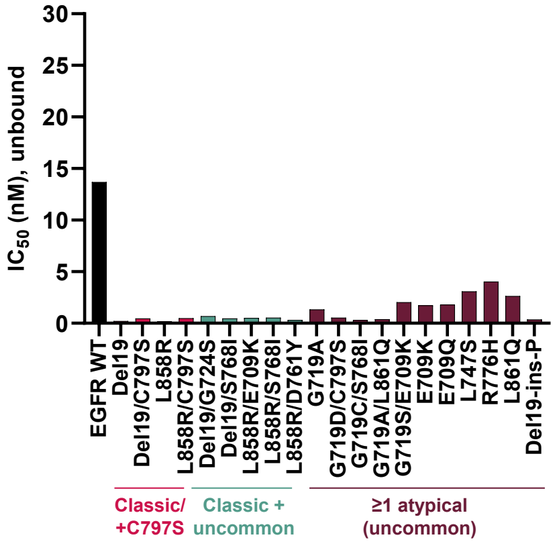


In vitro, catalytic inhibition potency

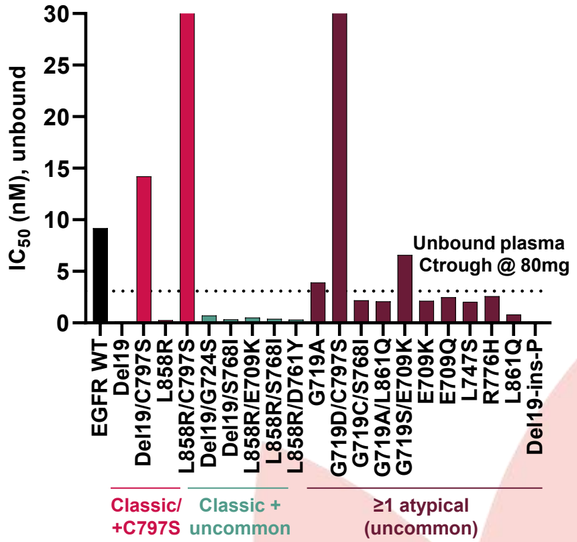
EGFR mutants Catalytic IC_{50} (nM)	Common	Common + Resistance		Uncommon		
	Del19	Del19-T790M	Del19-C797S	L861Q	G719S	L718Q
1G, Erlotinib	3.0	1,390	<1.0	<1.0	2.0	34.1
3G, Osimertinib	2.8	<1.0	240	<1.0	10.3	292
4G, VRN110755	2.4	7.1	<1.0	<1.0	<1.0	3.0

Cell proliferation inhibition in Ba/F3-EGFRm

VRN110755



Osimertinib



✓ **Plasma trough concentration of Osimertinib 80mg was <15X higher than mutant inhibition potency (IC_{50})**

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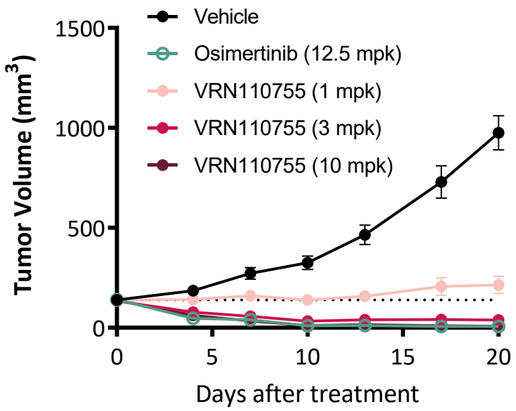
VRN110755, potent EGFRm inhibitor with high CNS activity in preclinical model

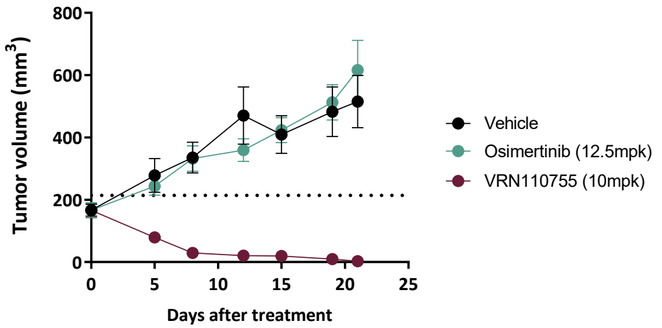
EGFR Common: Del19, Xenograft



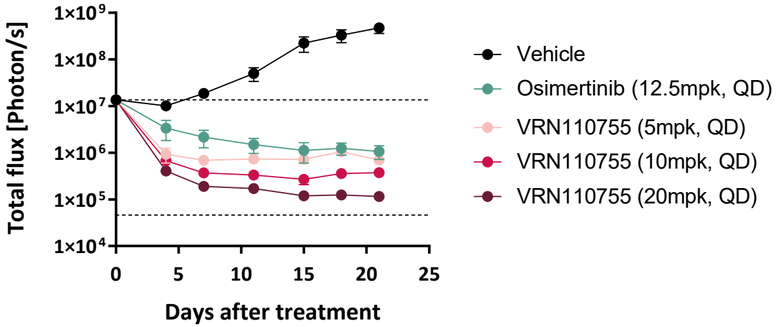
+ C797S

Brain

EGFR, Del19 + C797S, Xenograft

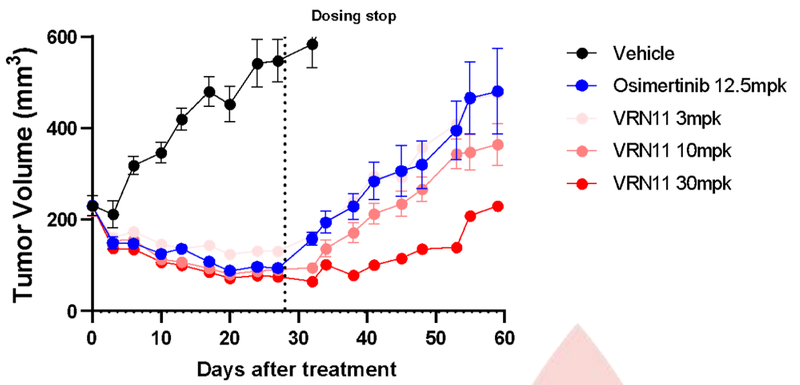


EGFR, Del19, Xenograft in Brain



	Mouse	Monkey
$K_{p,uu,brain}$	0.6	1.7
$K_{p,uu,csf}$	N.D.	2.6

EGFR Uncommon: G719A-S768I PDX



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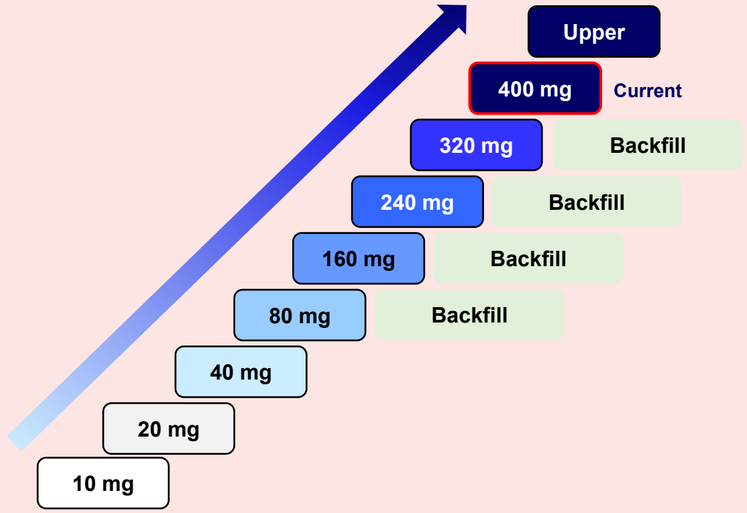
VRN110755-01 study design (Phase 1/2)_Monotherapy

Key Eligibility Criteria

- Age ≥ 18 years
- Diagnosis of advance (Stage IIIB/IV or recurrent) NSCLC, harboring EGFR mutation
- Measurable disease per RECIST v1.1
- Prior EGFR TKI treatment with disease progression
- ECOG 0-1
- Advanced NSCLC with EGFR mutation
- Without other driver mutations, e.g. KRAS G12X, cMET amp, etc
- Without EGFR/HER2 exon20 insertion mutation
- Asymptomatic brain metastasis can be enrolled

Dose escalation



Primary endpoints:
Maximal Tolerable Dose, Serious Adverse Events, DLT

Secondary endpoints:
Pharmacokinetics, Anti-tumor responses, ctDNA changes

Dose expansion

Cohort-1
Common EGFRm
Treatment naive

Cohort-2
Common EGFRm with CNS metastasis
TKI-naïve

Cohort-3
Common EGFRm with C797S after 1L
3rd Gen TKI (Osi, Laz, Ami+Laz)

Cohort-4
Atypical/uncommon EGFRm
TKI-naïve

Cohort-5
Atypical/uncommon EGFRm
One prior TKI (allow ≤ 1 prior systemic regimen)

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Patient and disease characteristics (10-400mg)

Characteristics	VRN110755 monotherapy (10 - 400mg QD), n = 56
Median age, years (range)	60 (45-87)
Sex, n (%)	
Male / Female	19 (34) / 37 (66)
ECOG PS, n (%)	
0 / 1	25 (45) / 31 (55)
Mutation ctDNA profiles at the baseline, n (%)	
Not detected or unknown EGFR mutation	**15 (27)**
EGFR Del19	**21 (36)**
EGFR L858R	**14 (25)**
EGFR Atypical mutations	**8 (14)**
EGFR C797S	**4 (7)**
EGFR T790M	7 (13)
TP53 mutations	32 (54)
CNS Metastasis, n (%)	
Brain	**29 (52)**
Leptomeningeal	**2 (4)**
None	27 (48)
Median number of prior systemic therapies, n (range)	3 (1-15)
Prior systemic chemo, including ADC, n (%)	42 (75)
Prior systemic TKI, n (%)	56 (100)
Osimertinib	27 (48)
Lazertinib	20 (36)
Afatinib	13 (23)
Dacomitinib	4 (7)
Gefitinib	13 (23)
Erlotinib	7 (13)

EGFR mutations were confirmed by Guardant360 at baseline. Atypical mutations include G719S, S768I, R776H, Del19-insertion. Data cut-off: Oct 30, 2025

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Summary of adverse events

TRAE, n (%)	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=3)	All (N=56)
Any grade	1 (33)	2 (50)	1 (33)	2 (17)	7 (54)	9 (64)	1 (25)	2 (67)	25 (45)
Grade 1	1 (33)	2 (50)	1 (33)	2 (17)	5 (38)	7 (50)	0 (0)	1 (33)	19 (34)
Grade 2	0 (0)	0 (0)	0 (0)	0 (0)	2 (15)	1 (7)	1 (25)	1 (33)	5 (9)
Grade 3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (7)	0 (0)	0 (0)	1 (2)
Dose limiting toxicity	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0

VRN110755, high Doses (80–400 mg QD, N = 46)		Grade 1	Grade 2	Grade 3	Any grade
Any treatment-related AE		33%	11%	2%	46%
EGFR-related	Diarrhea	9%	2%	-	11%
	Rash	11%	2%	-	13%
	Dry skin	7%	2%	-	9%
	Pruritus	2%	5%	-	7%
	Stomatitis	5%	-	-	5%
EGFR-unrelated	Decreased appetite	5%	-	-	5%
	Nausea	5%	2%	-	7%
	Fatigue	2%	-	-	2%
	Acute Kidney Injury	-	-	2%	2%
	ALT increased	5%	-	-	5%
	AST increased	5%	-	-	5%
Special interests	Interstitial lung disease*	-	-	-	-
	QT prolongation*	-	-	-	-
No dose discontinuation due to any treatment-related adverse event up to 400mg					

Data cut-off: Oct 30, 2025.

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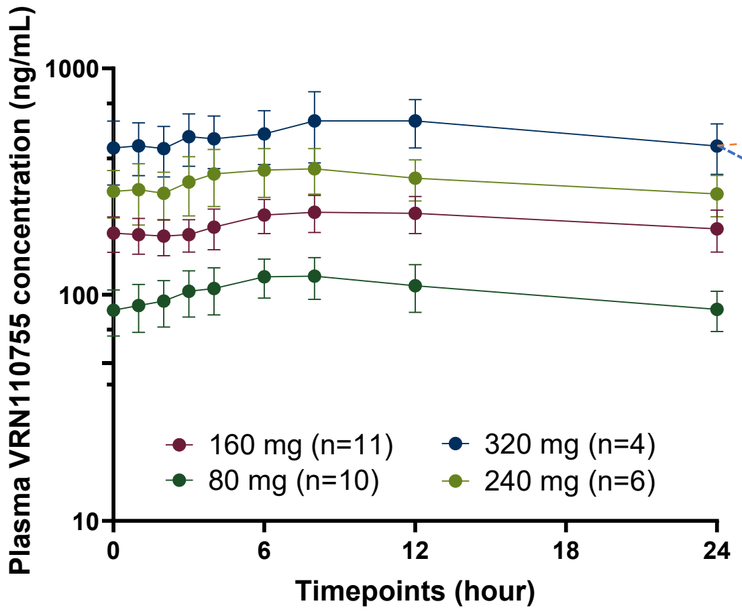
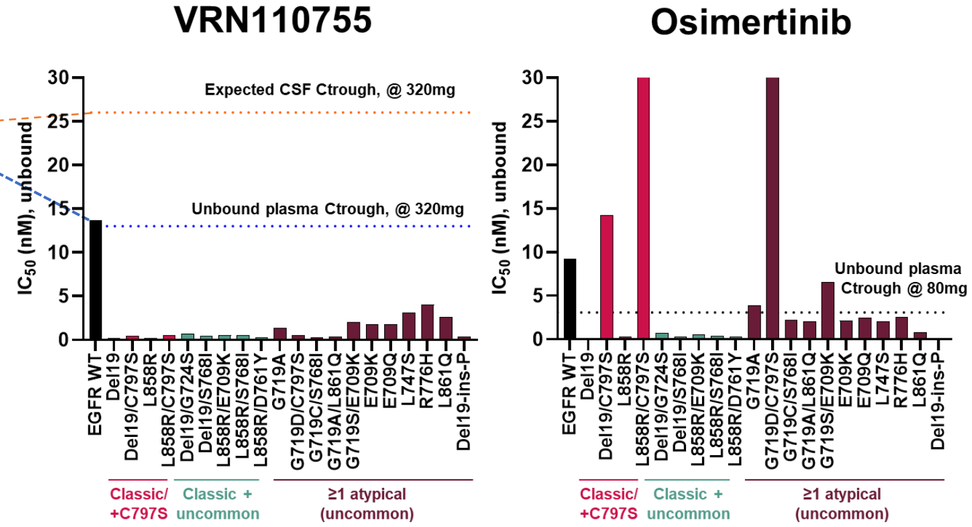
Pharmacokinetics and brain permeability

Pharmacokinetics of VRN110755 @ C1D15

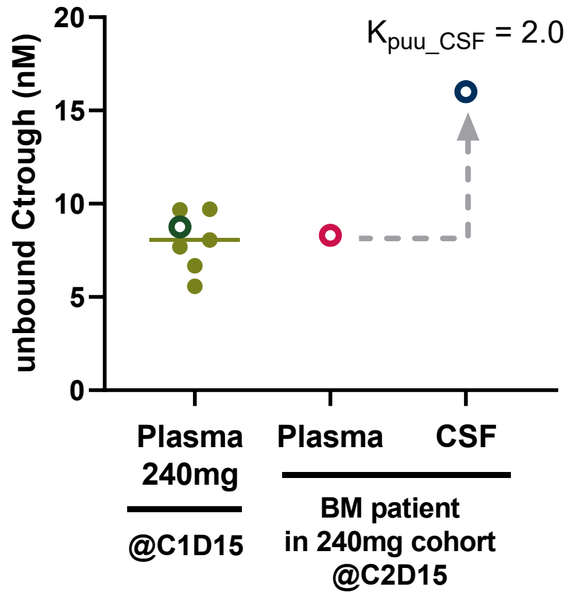


Cell proliferation inhibition in Ba/F3-EGFRm



- ✓ VRN110755 showed high brain permeability
- ✓ Plasma and CSF trough concentrations of VRN110755 320mg are >60X higher than mutant inhibition potency (IC_{50}), indicating superior target engagement to Osimertinib

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, 98.3% was used for calculation

[1]S Park, et al., 2024 J. Clinic. Oncology.

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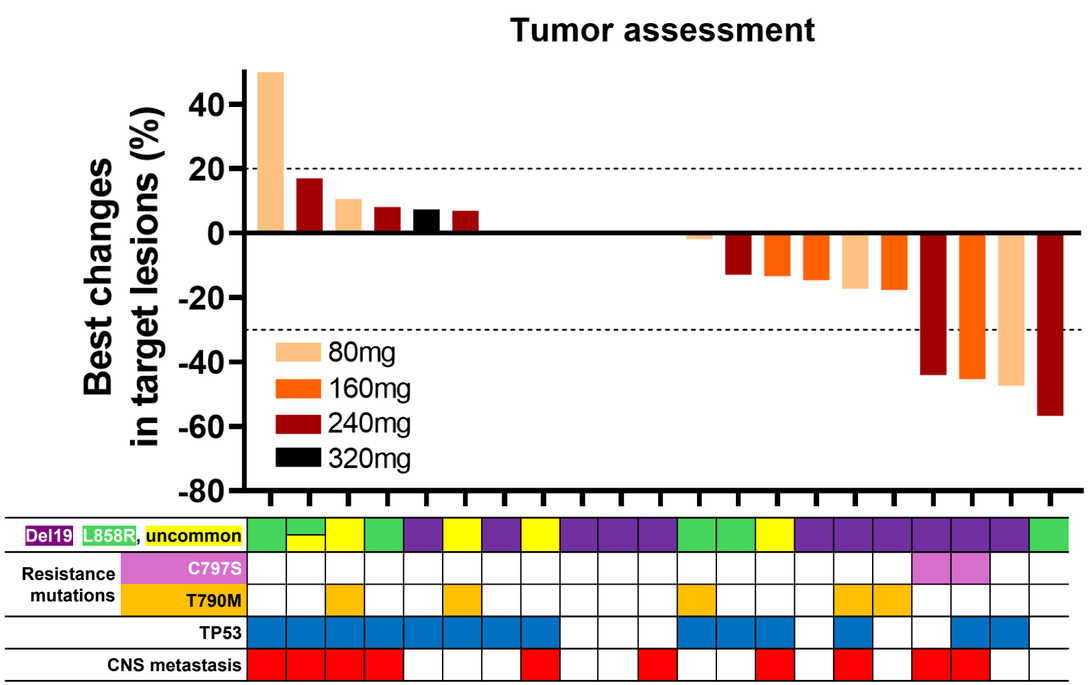
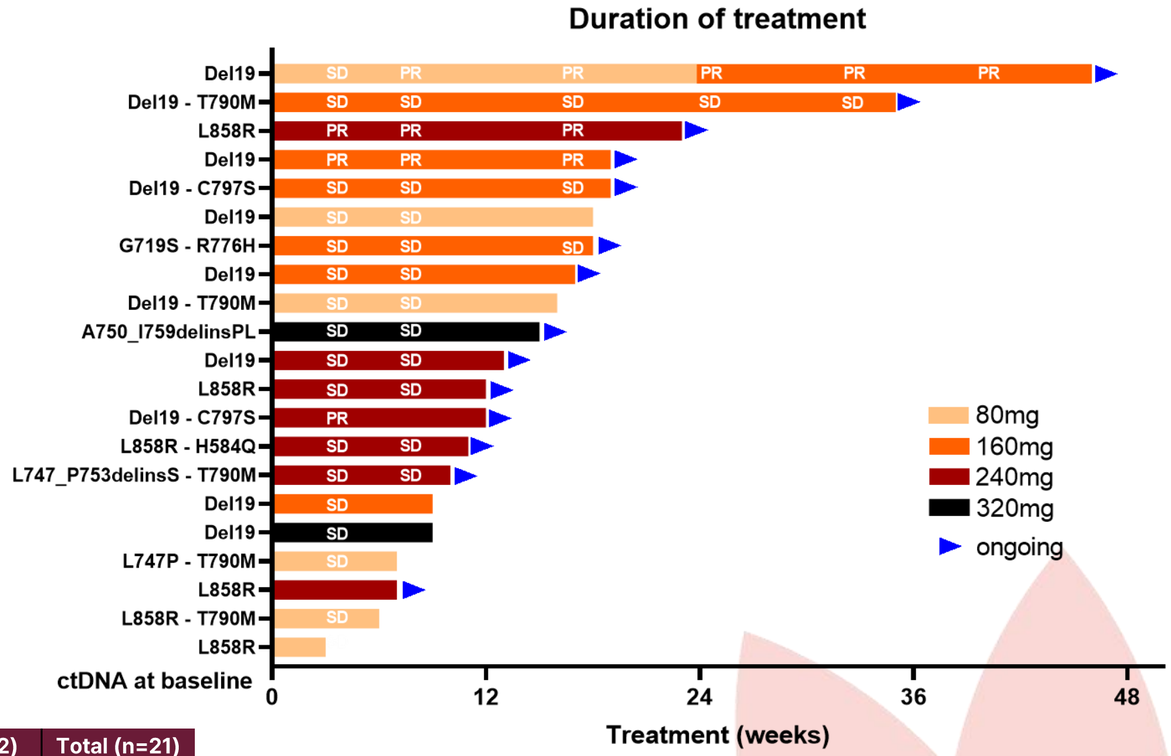
Promising anti-tumor efficacy in heavily pre-treated patients (N=21)

≥ 80mg (≥ 2, median 3 prior systemic therapies) and EGFRm ctDNA-positive at baseline





Tumor responses	80 mg (n=6)	160 mg (n=6)	240 mg (7)	320 mg (n=2)	Total (n=21)
Partial response (PR), N (%)	1 (17)	1 (20)	2 (29)	0 (0)	4 (19)
Stable disease (SD), N (%)	3 (50)	5 (80)	5 (71)	2 (100)	15 (71)
Progressive disease (PD), N (%)	2 (33)	0 (0)	0 (0)	0 (0)	2 (10)
Disease Control Rate (DCR), %	67	100	100	100	90
Overall Response Rate (ORR), %	17	20	29	0	19
Median Duration of Treatment, Weeks (range)	13 (3-NE)	16 (11-NE)	15 (6-NE)	11 (9-NE)	14 (3-NE)

- Efficacy evaluable patients: at least one tumor assessment with ≥ 1 cycle of treatment. Disease control rate: CR+PR+SD. ND: Not estimable
- Data cut-off: Oct 30, 2025.

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CNS progression in patients with and without CNS meta at baseline (N=37)

≥ 80mg and at least one tumor assessment

Efficacy evaluable patients	80 mg	160 mg	240 mg	320 mg	Total
All evaluable patients, N	9	12	13	3	37
CNS progression, n/N (%)	2/9 (22%)	**0/12 (0%)**	**0/13 (0%)**	**0/3 (0%)**	2/37 (5%)
CNS metastases at baseline, N	5	7	4	1	17
CNS progression, n/N (%)	2/5 (40%)	**0/7 (0%)**	**0/4 (0%)**	**0/1 (0%)**	2/17 (12%)
No CNS metastases at baseline, N	4	5	9	2	20
CNS progression, n/N (%)	**0/4 (0%)**	**0/5 (0%)**	**0/9 (0%)**	**0/2 (0%)**	**0/20 (0%)**

- Efficacy evaluable patients: at least one tumor assessment with ≥ 1 cycle of treatment.
- Brain and leptomeningeal metastases at baseline were confirmed by MRI.
- Disease control rate: CR+PR+SD.
- Data cut-off: Oct 30, 2025.

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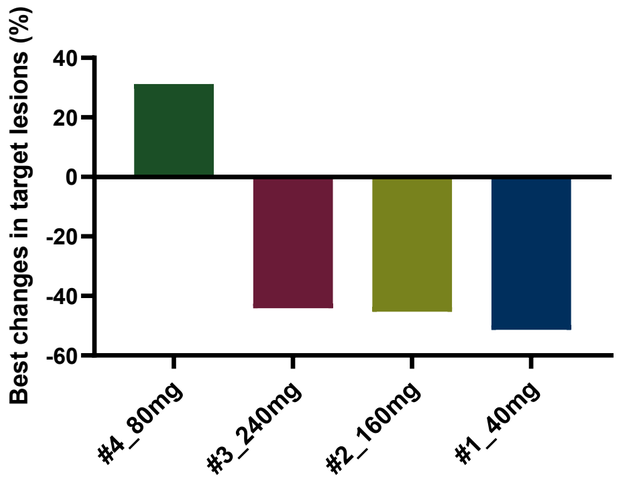
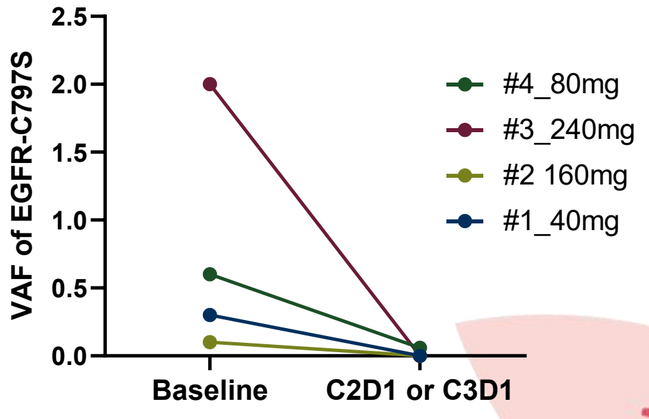
Clinical efficacy in patients with C797S-positive

Patient ID	Dose level	EGFR mutants	Prior TKIs	ctDNA clearance (C797S)	Best changes in Target lesions (%)	Brain lesion response	Best response
1	40 mg	L858R/C797S/R776H	Dacomitinib – Osimertinib	100%	-51.4	Response	PR
2	160 mg	Del19/C797S	Osimertinib	100%	-45.3	Response	PR
3	240 mg	Del19/C797S	Lazertinib Osimertinib	100%	-44.1	Response	PR
4	80 mg	Del19/C797S	Osimertinib	90%	31.2	Non-response	PD

Tumor assessment (C797S+ patients)



Molecular response (C797S+ patients)



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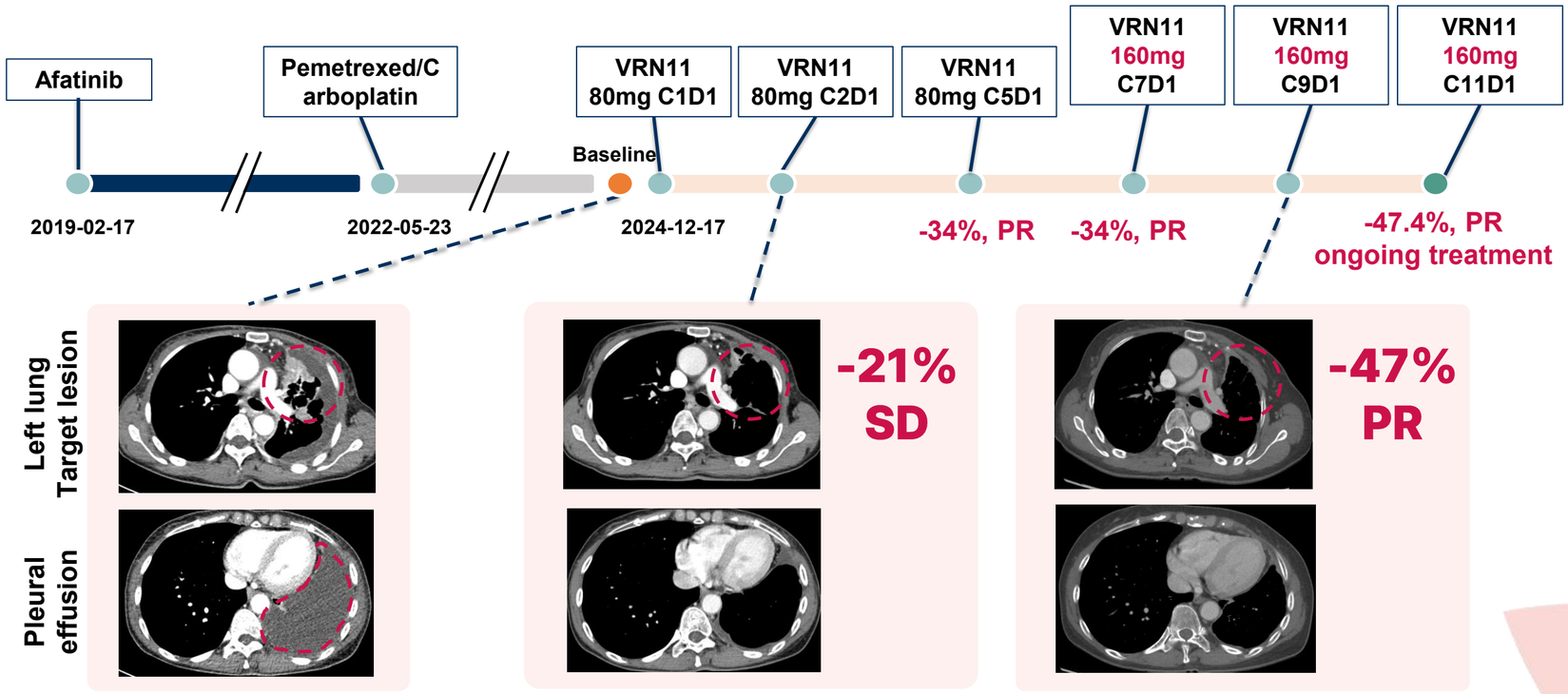
The EGFR common driver mutation progressed after EGFR TKI, without resistance mutations

Case Study at 80 mg cohort: 53 years old, female patient harboring EGFR Del19 progressed on Platinum, following Afatinib. Dose escalation to 160mg further reduced size of the tumor.



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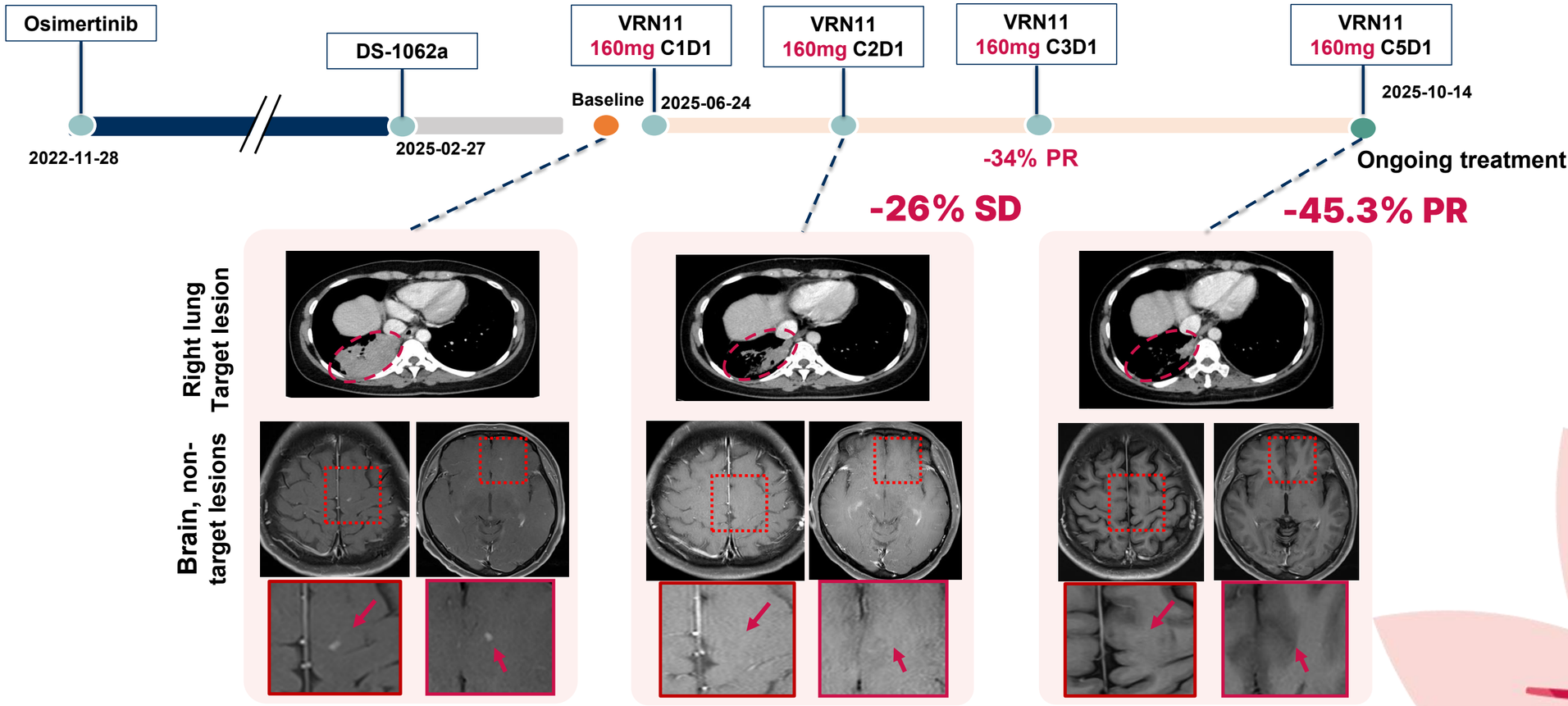
C797S-Positive patients with brain metastases

Case Study at 160 mg cohort: 47 years old female patient harboring EGFR Del19/C797S progressed on DS-1062a, following Osimertinib.



Brain non-target lesions had disappeared

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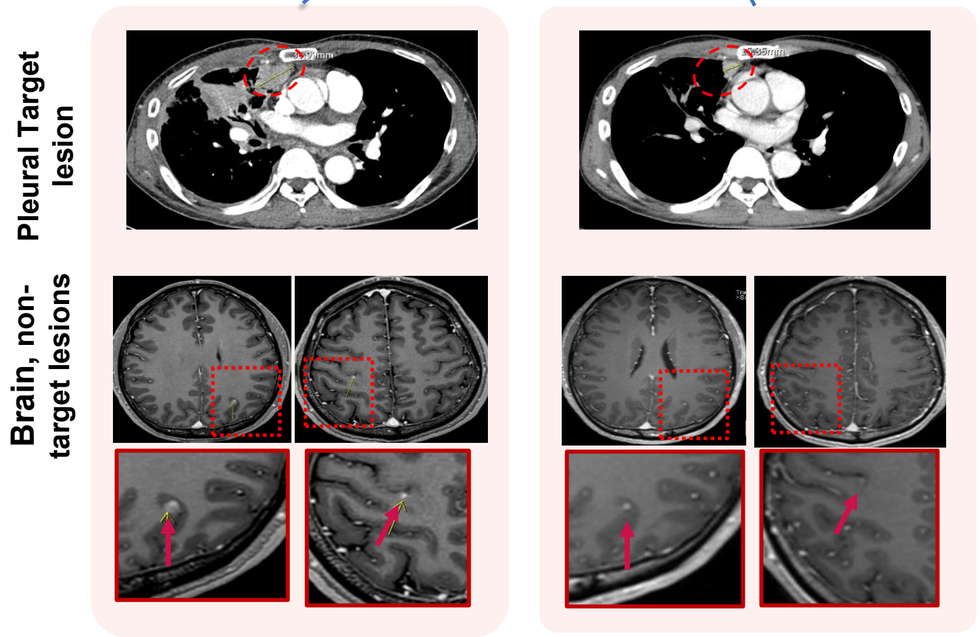
C797S-Positive patients with brain metastases

Case Study at 240 mg cohort: 55 years old male patient harboring EGFR Del19/C797S progressed on Osimertinib and previously discontinued from Lazertinib due to adverse event.



-44%
PR

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Conclusions

- VRN110755 demonstrates favorable pharmacokinetics and high CNS penetration, promising high target engagement (4x) compared to osimertinib
- The most common adverse events were diarrhea, skin rash, and dry skin, but mostly grade 1-2. No dose-limiting toxicity was observed up to 400mg
- Promising anti-tumor efficacy (ORR 19% and DCR 90%) was observed with VRN110755 treatment, ≥80mg in heavily pretreated patients (≥ 2, median 3 prior systemic therapies)
- Its robust activity in 3G TKI–resistant EGFR-mutant (C797S), together with high brain permeability and intracranial efficacy, supports VRN110755 as a potential best-in-class frontline EGFR inhibitor.

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Acknowledgements

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Thank You

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