



VRN110755: a Next-Generation Non-Covalent EGFR Tyrosine Kinase Inhibitor for EGFR-Mutated NSCLC

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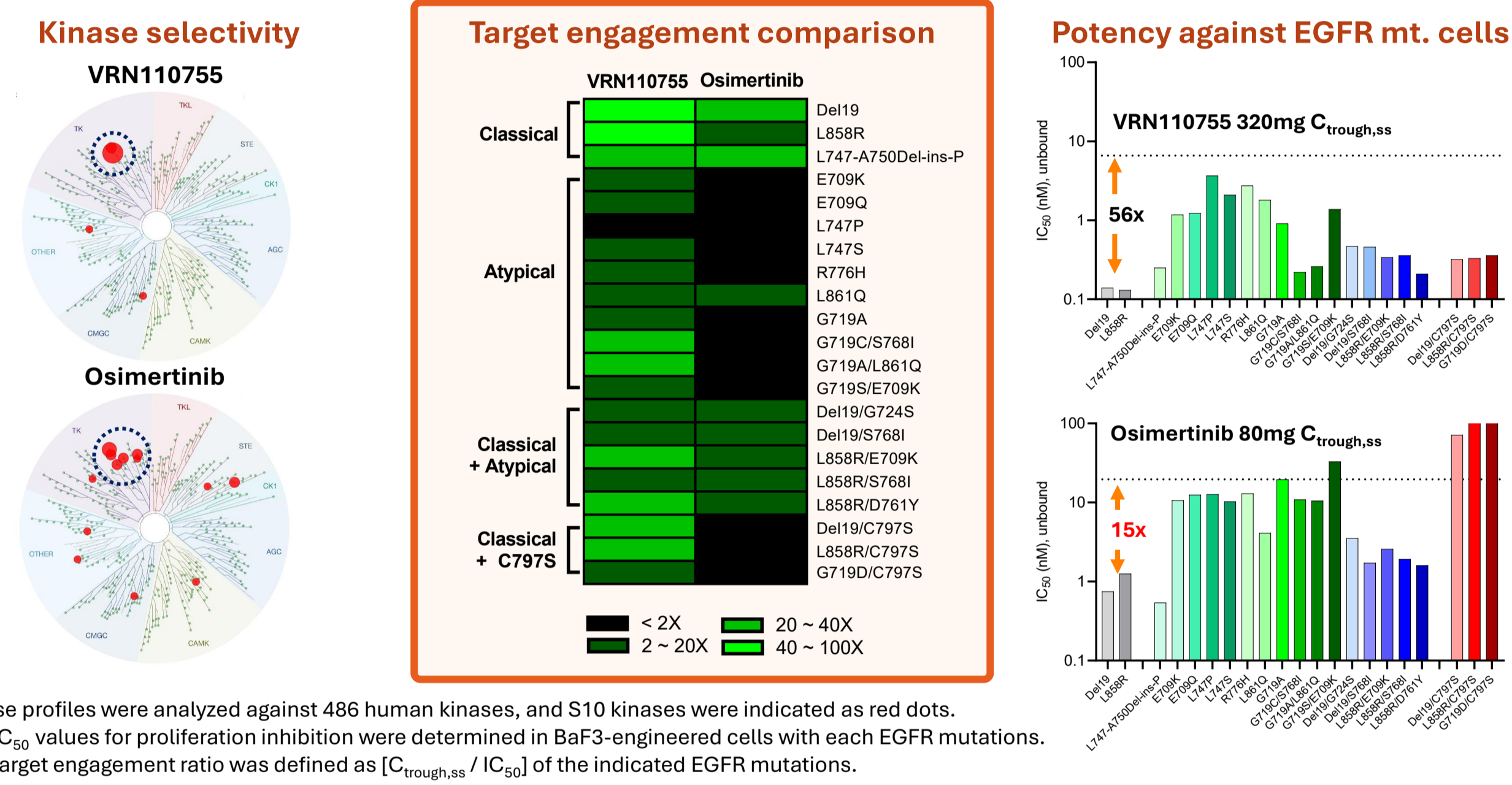
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BACKGROUND

- EGFR oncogenic mutations account for approximately 15%–20% of NSCLC in Western populations and up to 50% in Asian populations. Despite the availability of third-generation EGFR TKIs, substantial unmet need remains, particularly in the setting of acquired C797S resistance and CNS metastases.
- VRN110755 is a potent, brain-penetrant EGFR inhibitor designed to selectively target EGFR oncogenic mutations over EGFR wild-type and other kinases. VRN110755 shows activity against common and uncommon EGFR driver mutations, including acquired C797S resistance following osimertinib treatment.
- In preclinical models, VRN110755 demonstrates robust systemic and intracranial antitumor activity, with a pharmacokinetic and safety profile supporting once-daily oral dosing.
- This Phase 1a study evaluates the safety, tolerability, pharmacokinetics, and preliminary antitumor activity of VRN110755 in patients with EGFR-mutant NSCLC, including those with C797S-mediated resistance.

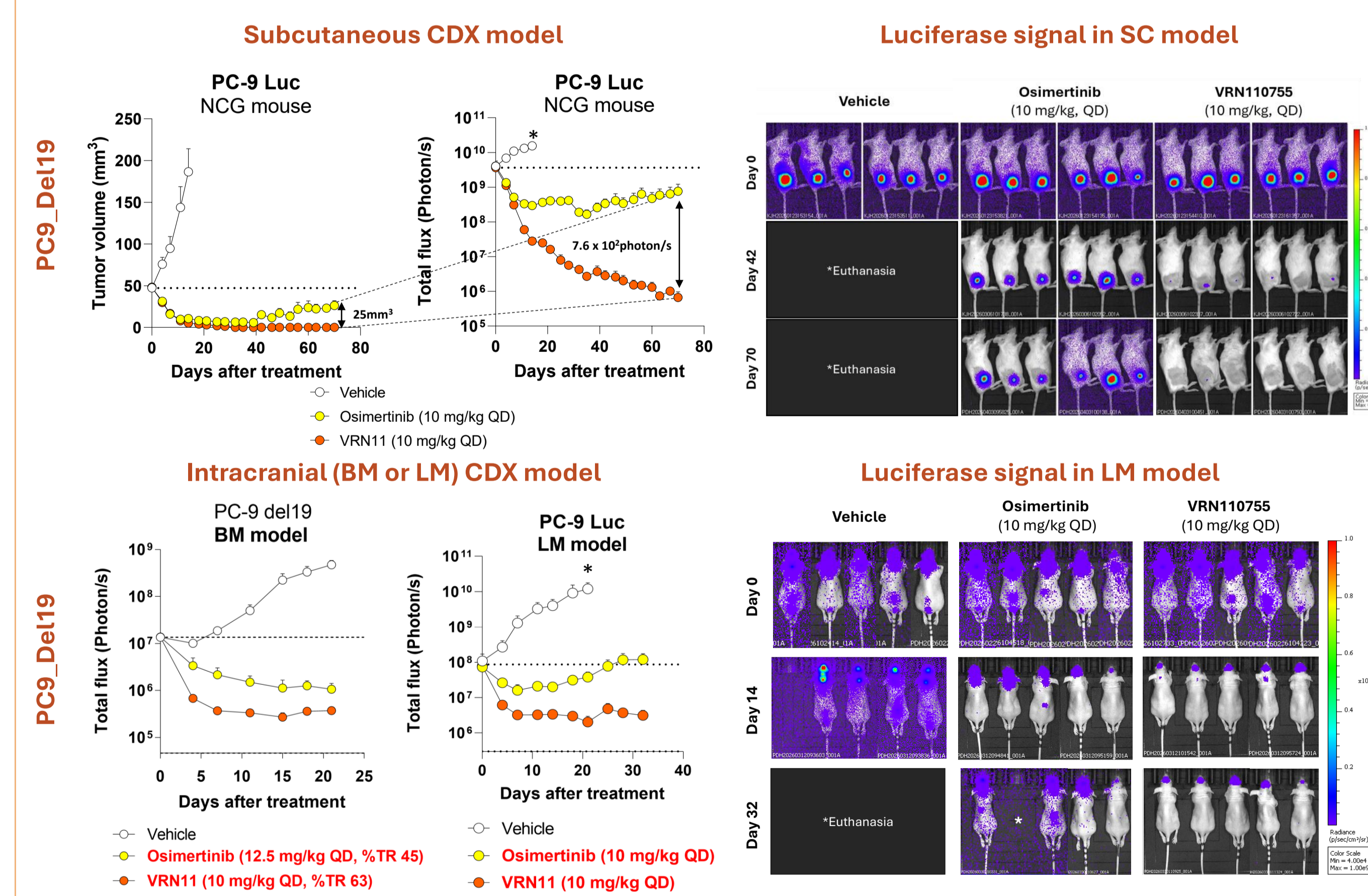
PRECLINICAL STUDIES

Robust target engagement across classical/atypical/C797S-resistant EGFR mutant cell models

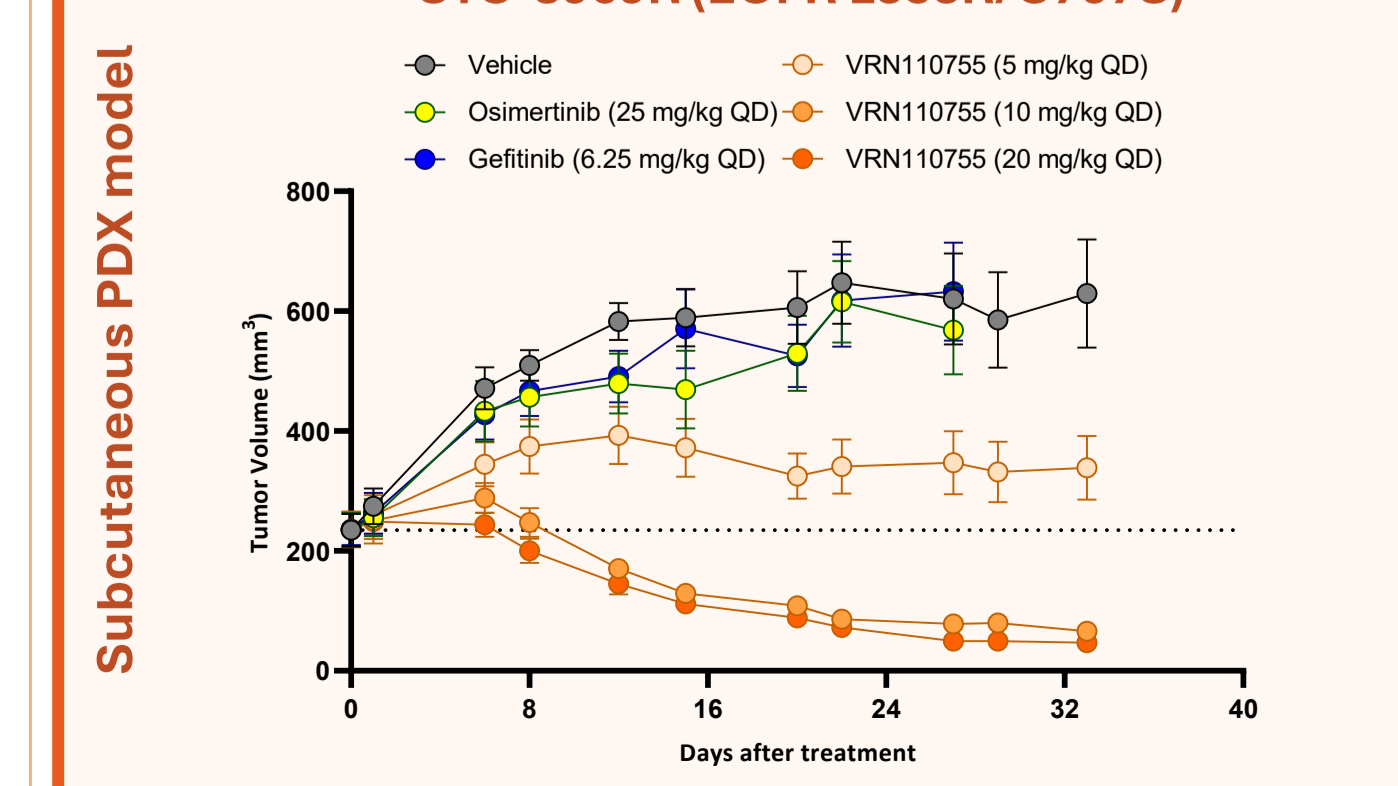


Potent systemic and intracranial activity of VRN110755

: Surpassing the insufficient target engagement of osimertinib



Subcutaneous PDX model



- VRN110755 exhibited superior antitumor efficacy compared to first- and third-generation EGFR inhibitors, including erlotinib and osimertinib, in both EGFR Del19 subcutaneous and intracranial CDX models.
- VRN110755 demonstrated marked antitumor activity compared to gefitinib and osimertinib in the L858R/C797S PDX model.

CLINICAL RESULTS

REACH-EGFR: Ongoing First-in-Human Study in EGFR-Mutated NSCLC

Phase I study design

- 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

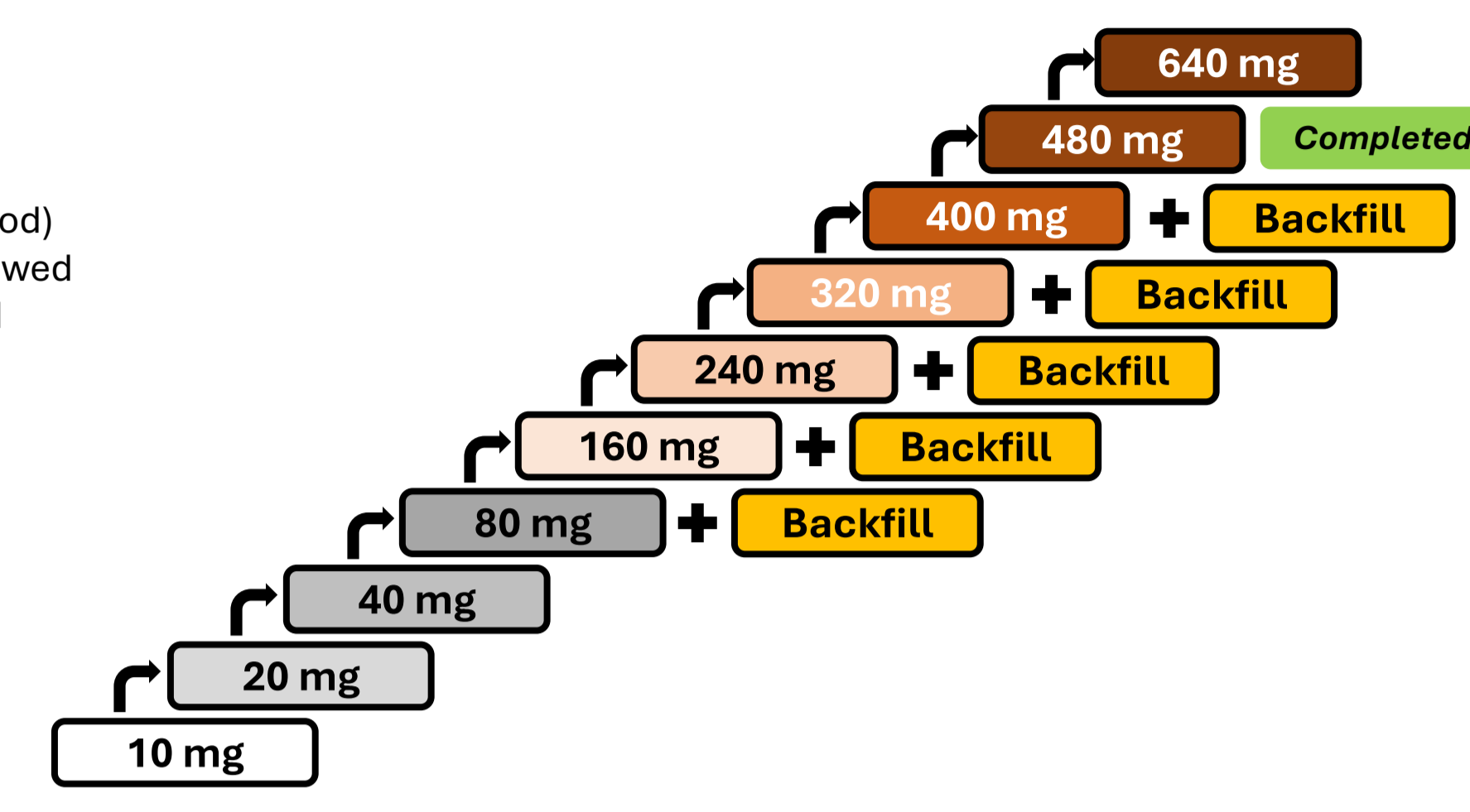
Primary endpoint

- 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
- Data cutoff date was March 12, 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



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 number of prior systemic therapies (range)	3 (1-15)

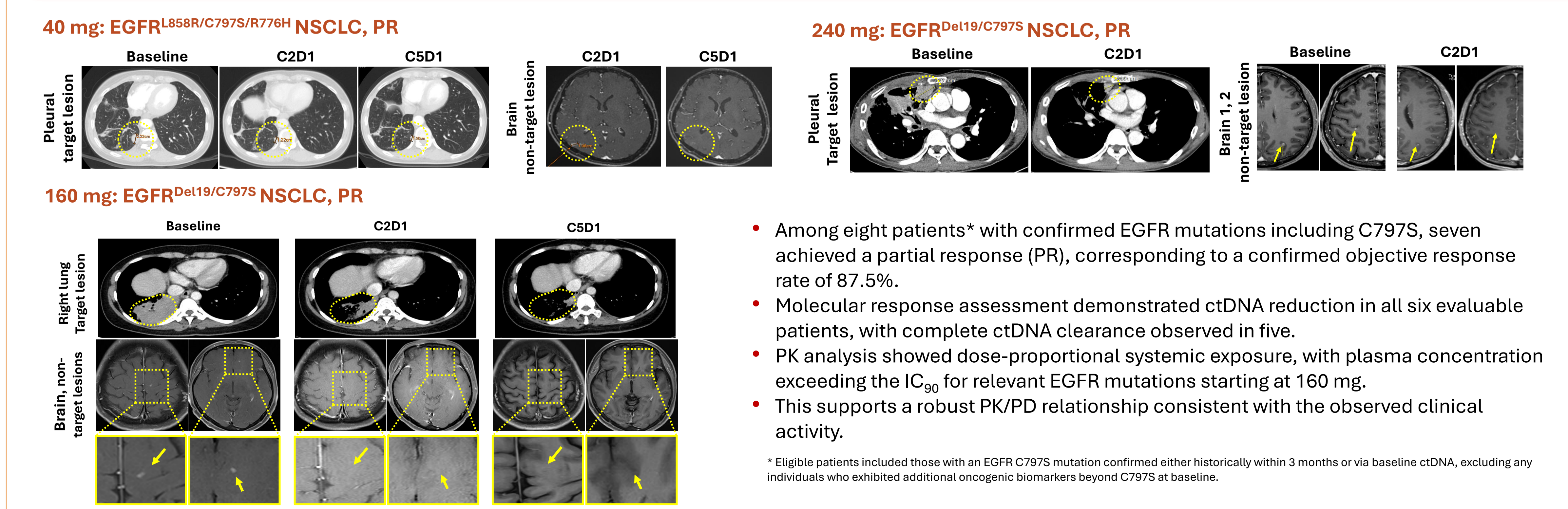
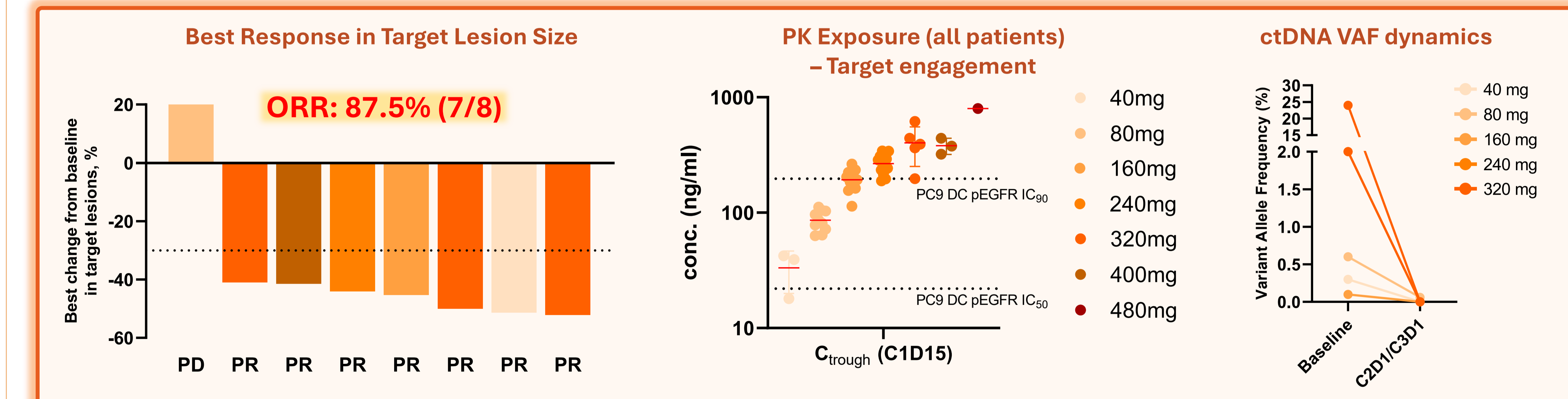
* EGFR mutations were confirmed by the Guardant360 at baseline. Del19 insertions (e.g., A750_L759 delinsPL, Del19 insP, L747_A750 delinsP, L747P_P753 delinsS) were considered as classic mutations.

Clinical molecular and exposure-response evidence of activity in EGFR C797S-mutant NSCLC

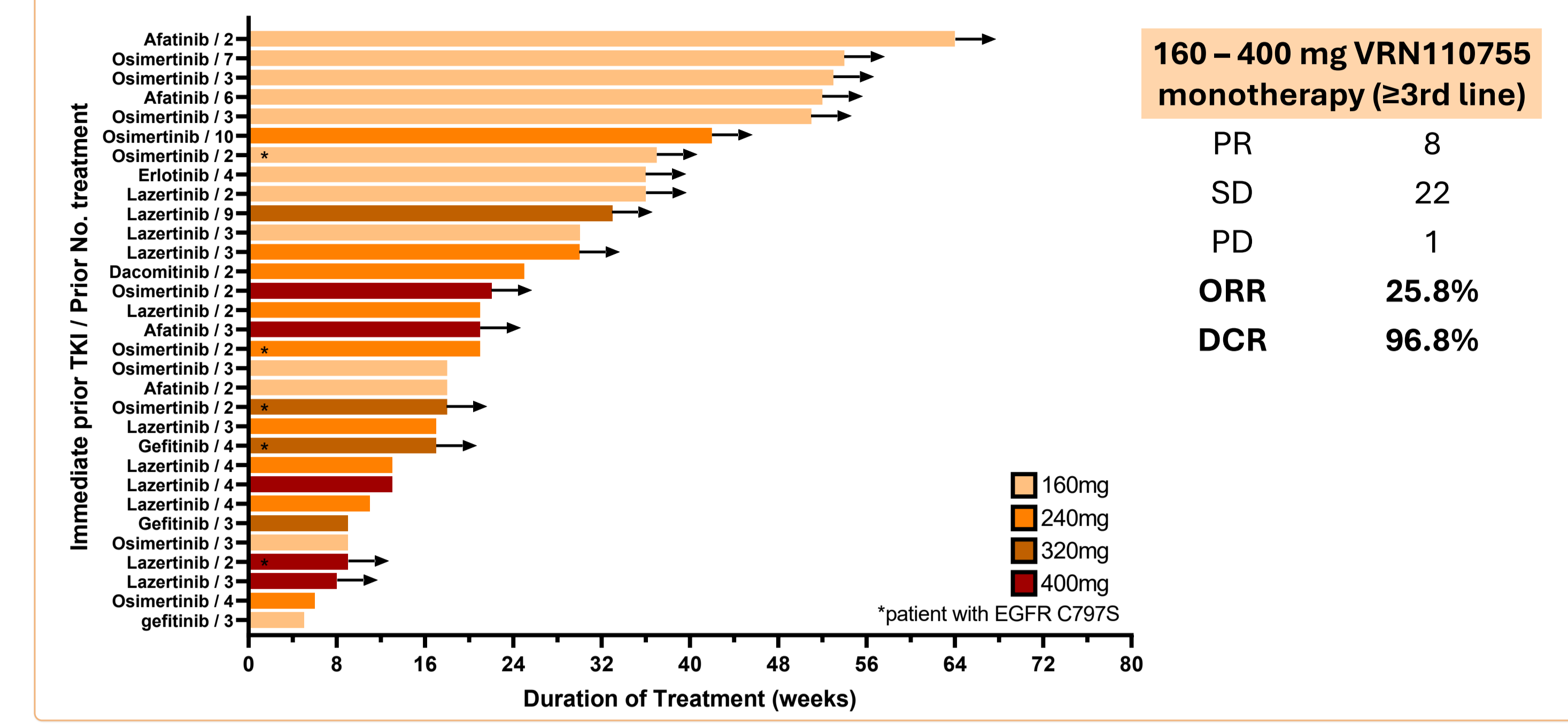
Dose	EGFR mutation	Prior TKI Treatment	Best % on Overall	Best Response	Observed responses in C797S-mutant NSCLC (across separate early clinical datasets)															
40mg	L858R - C797S - R776H	Dacomitinib → Osimertinib	-51.4	PR	<table border="1"> <thead> <tr> <th>Best response</th> <th>Phase 1 VRN110755 (n=8)</th> <th>Phase 2 Silevertinib (BDTX-1535) (n=9)</th> </tr> </thead> <tbody> <tr> <td>PR</td> <td>7 (87.5%)</td> <td>4 (44.4%)</td> </tr> <tr> <td>SD</td> <td>0</td> <td>5 (55.5%)</td> </tr> <tr> <td>PD</td> <td>1 (12.5%)</td> <td>0</td> </tr> <tr> <td>ORR</td> <td>87.5%</td> <td>44.4%</td> </tr> </tbody> </table>	Best response	Phase 1 VRN110755 (n=8)	Phase 2 Silevertinib (BDTX-1535) (n=9)	PR	7 (87.5%)	4 (44.4%)	SD	0	5 (55.5%)	PD	1 (12.5%)	0	ORR	87.5%	44.4%
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80mg	Del19 - C797S**	Osimertinib	-42.6	PD																
160mg	Del19 - C797S	Osimertinib	-45.3	PR																
240mg	Del19 - C797S	Lazertinib → Osimertinib	-44.1	PR																
320mg	Del19 - C797S	Osimertinib	-41.0	PR																
320mg	L858R - C797S*	Afatinib → Gefitinib	-52.2	PR																
320mg	Del19 - C797S	Osimertinib	-50.0	PR																
400mg	Del19 - C797S*	Afatinib → Lazertinib	-41.5	PR																

* In cases where C797S was not detected in baseline ctDNA, inclusion was based on tumor tissue NGS confirmation within 3 months prior to C1D1.
** Intracranial response by RANO-BM without extracranial target lesion.

* External dataset adapted from publicly available Black Diamond Therapeutics materials, August 7, 2025.



Overall duration of treatment in heavily pretreated EGFR mutant NSCLC patients

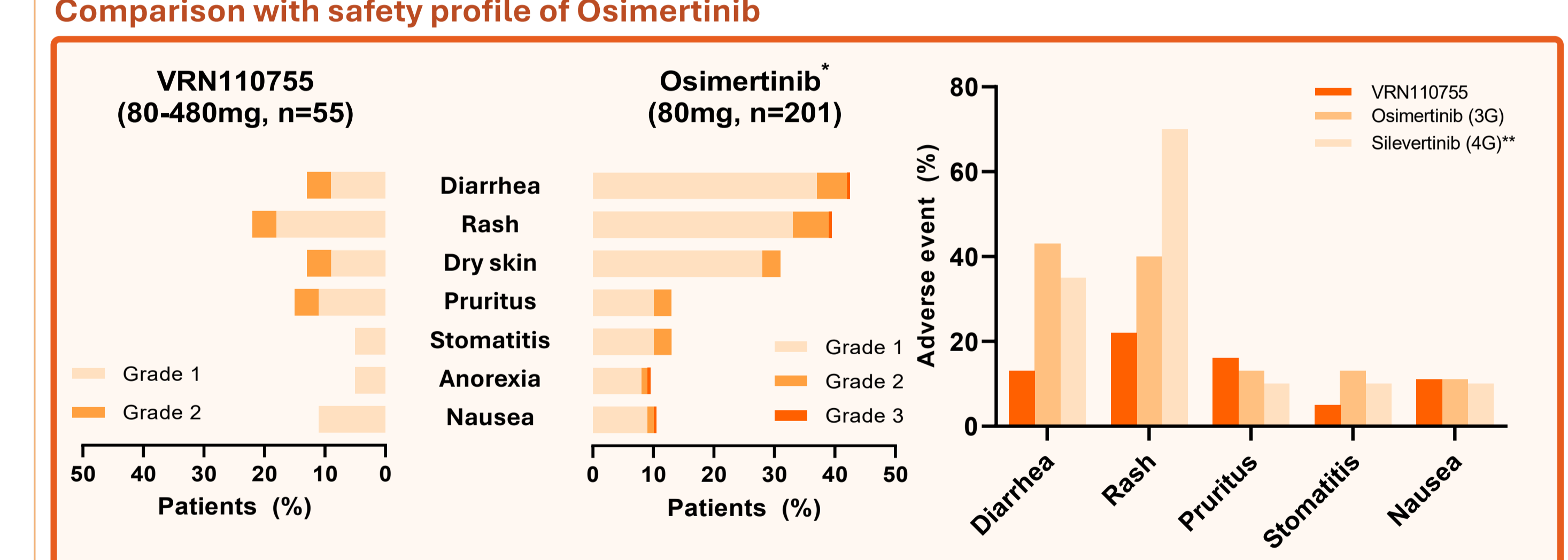


Favorable safety profile in EGFR mutant NSCLC patients

Adverse events of VRN110755 monotherapy

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=7)	400 mg (N=5)	480 mg (N=4)	All (N=65)
Any grade	1 (33)	2 (50)	1 (33)	3 (25)	7 (54)	12 (86)	4 (57)	5 (100)	4 (100)	39 (60)
Grade 1	1 (33)	2 (50)	1 (33)	3 (25)	5 (38)	7 (50)	3 (43)	2 (40)	1 (25)	25 (38)
Grade 2	0 (0)	0 (0)	0 (0)	0 (0)	2 (15)	4 (29)	1 (14)	3 (60)	3 (75)	13 (20)
Grade 3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (7)*	0 (0)	0 (0)	0 (0)	1 (2)
DLT	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

* One patient experienced Grade 3 acute kidney injury; the event was reversible, and no recurrent cases were observed in other treated patients.
* 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%).
* No patients experienced drug-related adverse events leading to treatment discontinuation.
* No treatment-related clinically meaningful QT prolongation or ILD was observed.



* Osimertinib safety profiles adapted from AURA phase 2 extension
** Median DoT: Silevertinib: 4.3m, VRN110755: 4m

- No dose-limiting toxicities (DLTs) were observed with VRN110755 at doses up to 480 mg.
- VRN110755 showed an overall favorable safety profile, comparing favorably with approved Osimertinib and other fourth-generation EGFR TKIs.
- Notably, no cases of interstitial lung disease (ILD) or QT prolongation were observed in patients treated with VRN110755.

CONCLUSIONS

- VRN110755 demonstrates encouraging preliminary antitumor activity in patients with EGFR-mutant NSCLC, including those with C797S mutations, with tumor shrinkage and objective responses observed in the current dataset.
- VRN110755 maintains a favorable safety profile at doses up to 480 mg once daily, with no DLTs observed and MTD not yet reached as of the current data cutoff.
- The study is ongoing, and these data support continued dose optimization and Phase 1b expansion in multiple cohorts.

References

- Jänne PA, et al., AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. *New England Journal of Medicine*. 2015 Apr 30; 372(18): 1689-99.
- Black Diamond Therapeutics, Inc. Corporate presentation. August 7, 2025.
- Yang JCH, et al., Osimertinib in pretreated T790M-positive advanced non-small-cell lung cancer: AURA study phase II extension component. *Journal of Clinical Oncology*, 2017 Feb 21; 35:1288-96

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