#P3.247

# VRN110755, a Mutant-Selective CNS-Penetrant EGFR TKI, Demonstrates Superior Antitumor Activity over Osimertinib in EGFR-Mutant NSCLC Models

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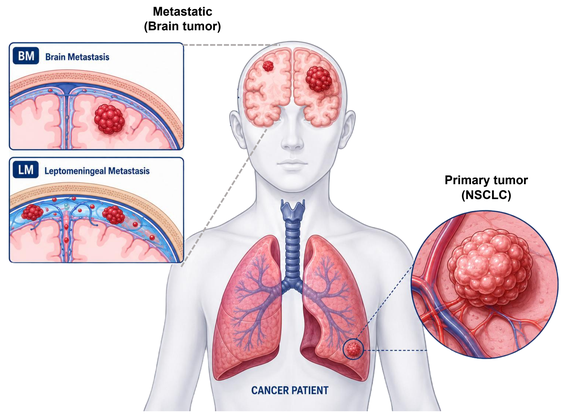
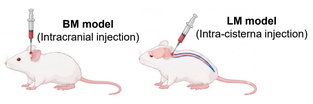
## INTRODUCTION

- Third-generation EGFR tyrosine kinase inhibitors (TKIs) have improved progression-free survival (PFS) and overall survival (OS) in patients with EGFR-mutant non–small cell lung cancer (NSCLC)
- However, their clinical utility is limited by dose-dependent ERBB-mediated toxicities, including rash and diarrhea.
- Furthermore, although osimertinib demonstrates intracranial activity, patients with brain metastasis (BM) continue to experience shorter PFS than those without CNS disease, indicating a need for agents with enhanced CNS penetration.
- VRN110755 (VRN11) is a novel mutant-selective, brain-penetrant EGFR TKI designed to increase target engagement against mutant EGFR while minimizing the inhibition of wild-type (WT) ERBB family members.
- Here we evaluated the preclinical efficacy and CNS penetration of VRN110755 compared with osimertinib in EGFR-mutant NSCLC models.



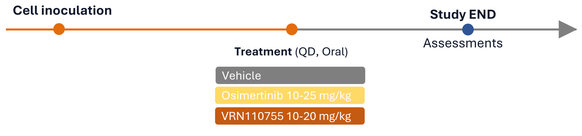

## METHODS

**In vivo model**




**Measurements**

Endpoints included TGI, TR
Bioluminescence imaging
Clinical signs
Survival




| | |
|---|---|
| **In vitro** | • EGFR selectivity assessed in engineered Ba/F3 cells. |
| **In vivo Efficacy** | • Antitumor efficacy evaluated in SC, BM, and LM PC9 (EGFR Ex19del) xenograft models. |
| **CNS PK** | • Brain penetration assessed by brain-to-plasma ratio and unbound plasma-to-CSF partitioning.<br>• PK/PD correlation performed using preclinical and clinical PK datasets. |
| **CNS PD** | • H&E and immunofluorescence images of brain sections encompassing the ventricular region.<br>• Quantitative analysis confirmed a statistically significant reduction in pEGFR positive cells. |

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## DISCUSSION AND CONCLUSION

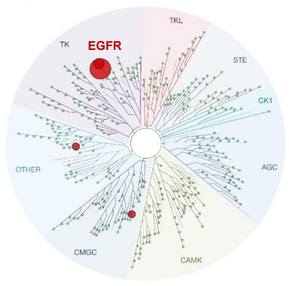
### Key Findings and Conclusion

- VRN110755 is a potent, next-generation, mutant-selective EGFR TKI that demonstrates a wider therapeutic window with respect to WT ERBB family inhibition and enhanced CNS penetration compared with osimertinib in preclinical models.
- Its greater intracranial efficacy in BM and LM models, combined with deeper tumor responses in SC xenografts, positions VRN110755 as a promising candidate for the treatment of EGFR-mutant NSCLC, particularly in patients with CNS disease.
- These findings provide a preclinical rationale for the ongoing and future clinical evaluation of VRN110755.

### VRN110755 is a potent and selective in EGFR NSCLC

**Kinase selectivity**

**VRN110755**




***In vitro* target engagement**

**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

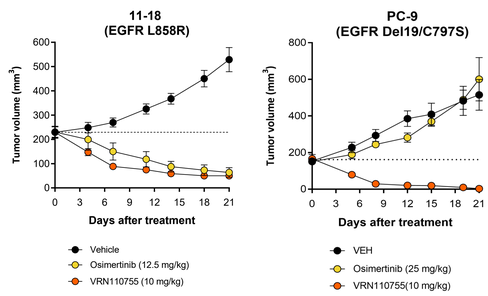
**Target engagement ratio (TER); Brain**

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

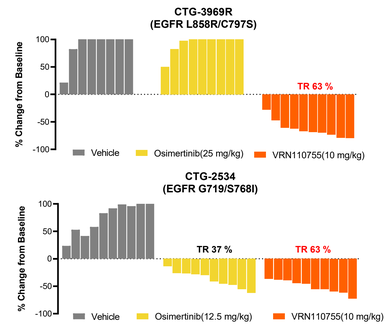
- VRN110755 demonstrated substantially enhanced target engagement against common EGFR mutations at the 320 mg dose level, **including Del19 and L858R, achieving approximately 56-fold target engagement.**

### Pre-clinical antitumor activity in EGFR-mutation NSCLC

**Cell Line-Derived Xenograft (CDX)**

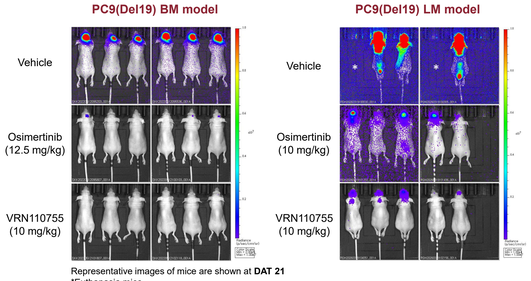



**Patient-Derived Xenograft (PDX)**




- VRN110755 led to marked tumor regression in EGFR-mutant CDX and PDX models, demonstrating strong activity across a broad range of EGFR mutation.

### In vivo efficacy in Intracranial Metastasis models (LM & BM)

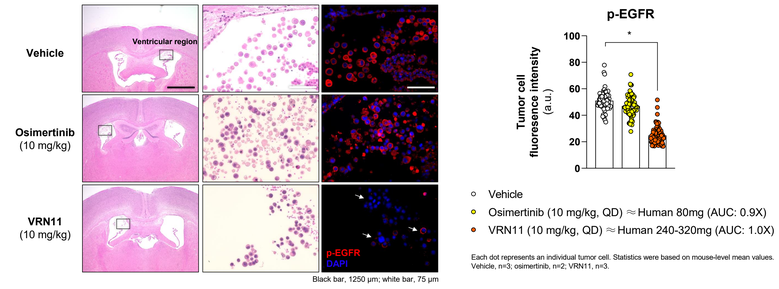



Representative images of mice are shown at **DAT 21**
*Euthanasia mice

- **Treatment with VRN110755 demonstrates outstanding CNS activity** in brain metastasis (BM) and leptomeningeal metastasis (LM) *in vivo* models.
- VRN110755 achieved **100% survival,** whereas vehicle and osimertinib treated mice exhibited rapid disease progression and mortality.

### CNS target engagement

**PC9(Del19) LM model (Single dose at 24 hr)**

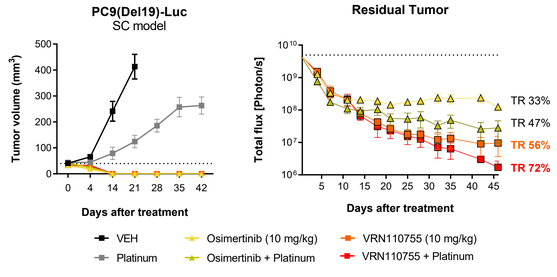



Each dot represents an individual tumor cell. Statistics were based on mouse-level mean values. Vehicle, n=3; osimertinib, n=2; VRN11, n=3.

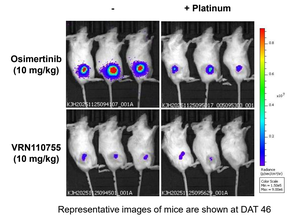
Black bar, 1250 μm; white bar, 75 μm

- Significant reduction of **pEGFR** levels within tumor cells located in the ventricular region, a key site associated with CSF flow, supports effective CNS target engagement by VRN110755.

### Antitumor activity in the PC9(Del19) SC Xenograft model with Chemotherapy



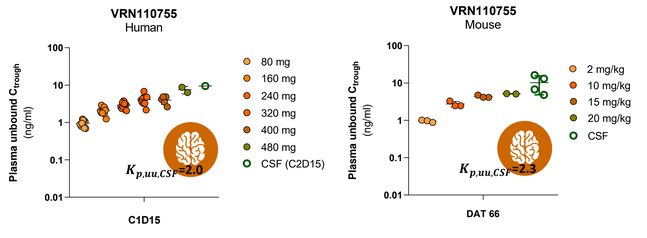

***Platinum chemotherapy** consisted of carboplatin (60 mg/kg, IP, QW) plus pemetrexed (100 mg/kg, IP, QW).




Representative images of mice are shown at DAT 46

- VRN110755 showed deeper tumor regression than osimertinib alone or with carboplatin/pemetrexed, with further enhancement when combined with chemotherapy.

### Preclinical to clinical evidence of potent activity in EGFR mutant NSCLC




*$K_{p,uu,csf}$ was calculated using PPB value of 98.9% (Human) and 98.84% (Mouse). Human data were obtained from BM patient in the 240 mg cohort at C2D15; Mouse data were obtained 4 hr after single 10 mg/kg dose.

- Human C1D15 exposure at 240-320 mg was comparable to that achieved at efficacious repeat dose of 10 mg/kg in mice.
- Consistent $K_{p,uu,csf}$ across mouse, monkey, and human supports robust CNS delivery and strengthens the translational relevance of the observed target engagement and antitumor efficacy.

**VRN11 Brain permeability**

| | $K_{p,uu,brain}$ | $K_{p,uu,csf}$ |
|---|---|---|
| **Mouse** | 0.2 | **2.3** |
| **Monkey** | 1.7 | **2.6** |
| **Human** | *N.A.* | **2.0*** |

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