VRN110755, a new therapeutic option for EGFR mutation-driven NSCLC with brain metastasis or first-line osimertinib-resistant EGFR mutations

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Introduction

- The NCCN recommends osimertinib as 1st line therapy for patients with metastatic non-small cell lung cancer (NSCLC) harboring EGFR-activating mutation, Del19 or L858R.
- Despite recent advances, there are still unmet medical needs.
  - First is the acquired resistant EGFR mutations, like C797S, the most frequent resistant mutation to Osimertinib.
  - Second is the rare EGFR mutations, generally classified as P-loop and αC-helix compressing (PACC), resistant to Osimertinib. Afatinib has been used for these mutations but has poor tolerability due to low margin against wild-type EGFR.
  - Lastly, although osimertinib has shown promising results in patients with brain metastases (BM), BM patients with intrinsic and acquired osimertinib-resistant EGFR mutations are left with no treatment options.

Table 1. Unmet Medical Needs in EGFR mutant NSCLCs

EGFR mutation NSCLC	Unmet medical needs
1L Osimertinib resistance	No approved drug yet for C797S
Brain metastasis	Limited therapeutic effect of Osimertinib in brain metastasis patients
Uncommon mutations	Afatinib is only approved but with poor tolerability

Kinase selectivity and catalytic inhibition potency

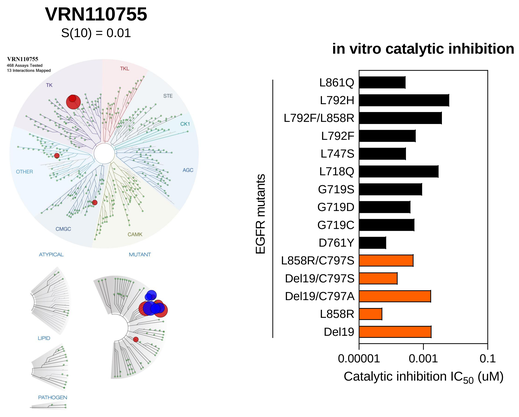


Figure 1. VRN110755 kinase selectivity was confirmed at 100 nM by KINOMEscan®. Kinome trees are marked with red circles indicating top 10% hit. The blue circles indicate EGFR mutations including del19, L858R, G719C/S and L861Q. Catalytic inhibition potency (IC_{50}) was obtained through HotSpot™.

Unique scaffold without risk of hyperglycemia by IR/IGF1R inhibition

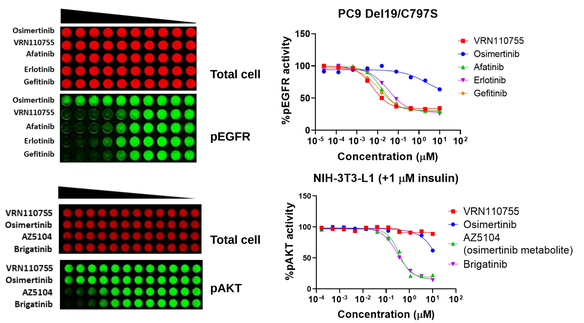


Figure 2. Phospho-EGFR and phospho-AKT1 IC_{50} were determined via in-cell Western. In order to assess potential hyperglycemia induced by IR/IGF1R inhibition, pAKT was quantified in NIH-3T3-L1 cells treated with insulin.

Higher cellular potency against EGFR mutants than WT EGFR

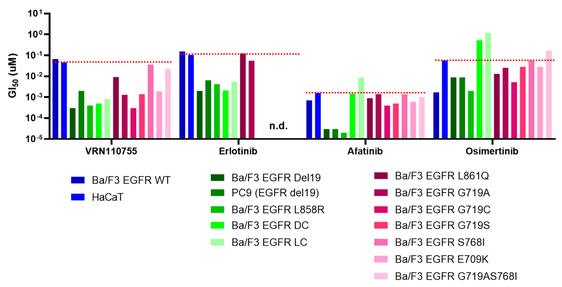
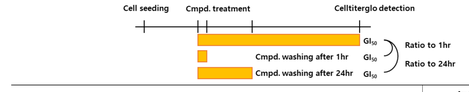


Figure 3. Cell proliferation inhibition, GI_{50} were determined via CellTiter-Glo assays; DC is del19/C797S; LC is L858R/C797S; n.d. is not determined.

Long residence time in cancer cells



			Relative GI_{50} in PC9 cells (EGFR Del19)			Intracellular concentration (ng/ml)*	
			No washout	Washout after 1hr	Washout after 24hr	PC9 (Del19)	11-18 (L858R)
1st Gen	reversible	Erlotinib	1	38.2	20.7	2	2
	reversible	Gefitinib	1	22.9	6.4	n.d.	n.d.
2nd Gen	irreversible	Afatinib	1	16.8	1.9	n.d.	n.d.
3rd Gen	irreversible	Osimertinib	1	7.6	3	600	560
	irreversible	Lazertinib	1	7.5	3	n.d.	n.d.
Novel	reversible	VRN110755	1	4.3	1.9	460	650

Figure 4. Intracellular concentration was determined after incubating 1 μM compounds for 24hr followed by washing; n.d. is not determined.

Tumor regression efficacy in subcutaneous models and intracranial BM models of osimertinib-resistant EGFR C797S

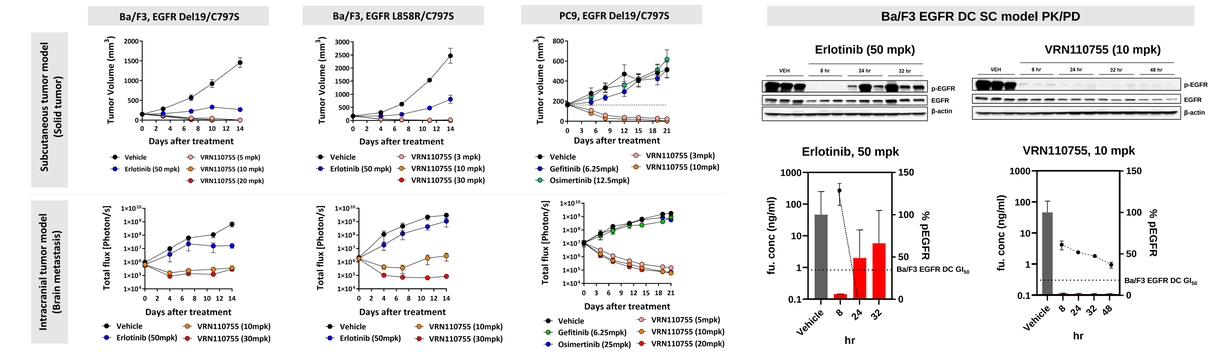


Figure 5. In vivo anti-tumor activities were determined in subcutaneous and intracranial mouse models with engineered Ba/F3 cells or NSCLC cells expressing EGFR mutants. At the time after oral dosing, tumor tissue and plasma were collected for PK/PD studies; DC is del19/C797S; LC is L858R/C797S

Comparison to osimertinib in intracranial BM model of PC9 (EGFR del19)

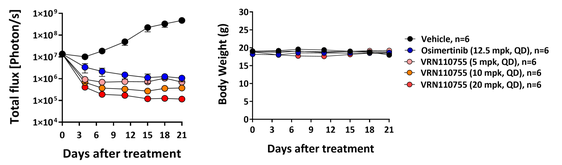


Figure 6. VRN110755 showed superior efficacy to osimertinib in PC9 CDX intracranial BM model.

Comparison with osimertinib and afatinib in PDX (CTG-2534) of EGFR rare mutations, G719C/S768I

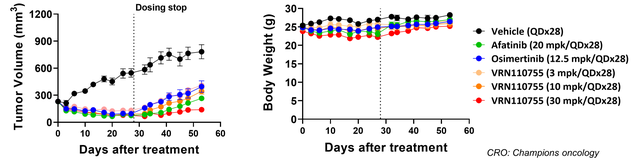


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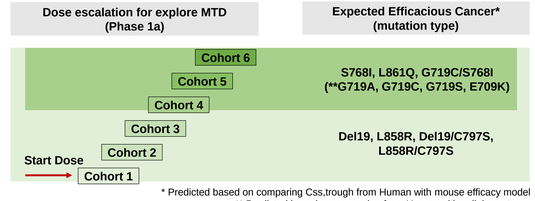
Figure 7. VRN110755 showed comparable efficacy to osimertinib and afatinib in PDX model of EGFR rare mutations, G719C/S768I.

Good brain penetrant PK profile

		Osimertinib	VRN110755
Mouse	BP ratio	0.28[1]	5.7
	$K_{p,uu,brain}$	0.3[1]	0.4~1.6[4]
Rat	BP ratio	6.1[2]	8
	$K_{p,uu,brain}$	0.2[2]	-
Dog	BP ratio	-	21.8
Monkey	BP ratio	4.2[2]	29.4
	$K_{p,uu,brain}$	-	2.5
Human	BP ratio	1.8[3]	-
Transporters	Substrate inhibition	MDR1, BCRP[2]	No substrate MDR1

[1]DOI: 10.1124/dmd.118.084210
[2]DOI: 10.1158/1078-0432.CCR-19-1871
[3]DOI: 10.1177/0271678X19843776
[4] $f_{u,plasma}$ difference depending on mouse strains

Target occupancy expected from low dose cohorts



* Predicted based on comparing Css,trough from Human with mouse efficacy model
** Predicted based on comparing from Human with cellular potency

Figure 8. EGFR mutation types anticipated to show favorable efficacy in respective clinical cohorts are presented.

Conclusion

- Nonclinical data of VRN110755 showed anti-tumor efficacy against EGFR common mutations (Del19 and L858R), uncommon, and resistance mutants for 1st-line osimertinib (C797S) in both subcutaneous and intracranial in vivo models, with enough therapeutic window.
- VRN110755 can be considered a potential treatment option for EGFR mutation-driven NSCLC patients with brain metastasis or 1st-line osimertinib-resistant EGFR mutations NSCLC.
- The first-in-human study will be initiated in 2023.

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