P3.237 Quantitative Prediction of Progression-Free Survival (PFS) From Early Tumor Response in Non-Small Cell Lung Cancer

Changwon Kim[1], Kun Jong Lee[1], Kyungho Lee[1], Youngyi Lee[1], Donghyun Park[1], Hongryul Jung[1], Kwangwoo Hwang[1], Jae Han Choi[1], M-J. Ahn[2*], Sunghwan Kim[1*]
[1]Voronoi, Inc., Incheon/KR ,[2]Hanyang University Medical Center, Hanyang University School of Medicine, Seoul/KR , *Corresponding author

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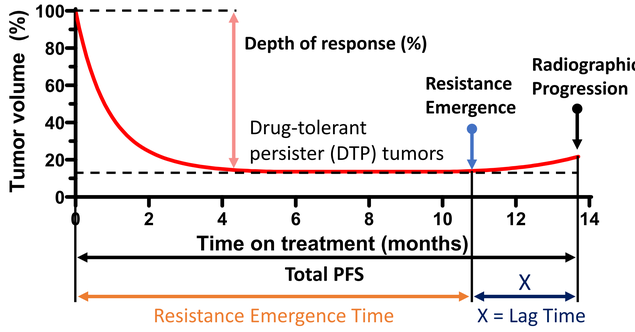
Introduction

Progression-free survival (PFS) reflects both anti-tumor activity and durability of disease control in oncogene-driven non-small cell lung cancer (NSCLC). However, predicting clinical PFS prior to pivotal trials remains challenging. Depth of tumor response and breadth of resistance mechanism coverage are key determinants of PFS that generally improve across TKI generations. We developed a clinical outcomes model incorporating these parameters and applied it to estimate the expected PFS of VRN110755, a mutant-selective, CNS-penetrant EGFR TKI currently in Phase 1a/b evaluation, in EGFR-mutant NSCLC.

Concept of PFS Prediction Model

Conceptual Tumor Response Model



PFS = X + Resistance Emergence Time = X + C_{Target}* Prediction Score

Prediction Score = **Weighted Resistance Coverage Score ($\sum P_i/\sum P_i S_i$)**
P = Clinical prevalence, S = Survival rate
i = T790M, C797S, brain met, Others
/ **Remaining Tumor Volume (%)**
Response rate is converted to volume change

Remaining tumor volume derived from relative best response

Gefitinib[1] (Reference point)
median best response = -49.9%
Remaining tumor volume = 12.6%

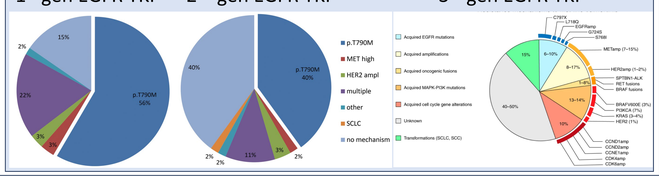
Dacomitinib[1]
median best response = -58.2%
Remaining tumor volume = 7.3%

Gefitinib/Erlotinib[2]
Relative best response = -49.9%
Remaining tumor volume = 12.6%

Osimertinib[2]
Relative best response = -56.5%
Remaining tumor volume = 8.2%

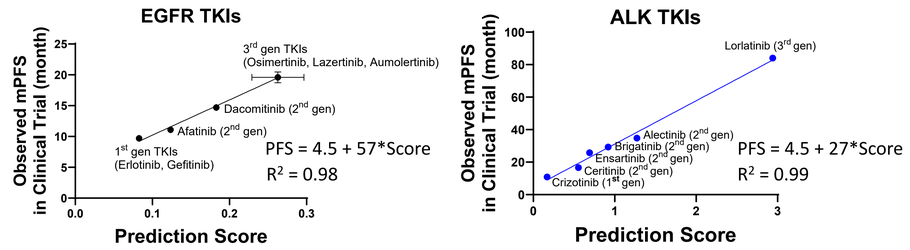
Distribution of acquired resistance mechanisms

1st gen EGFR TKI[3] 2nd gen EGFR TKI[3] 3rd gen EGFR TKI[4]



Result 1. PFS Prediction Score vs. Observed PFS

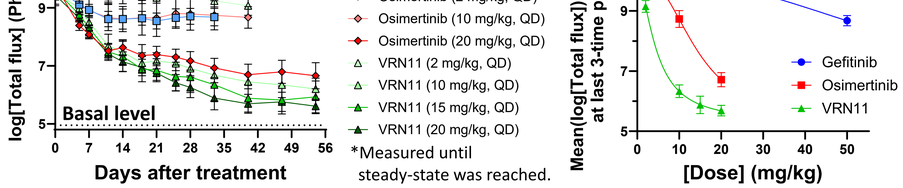
Prediction Score Strongly Correlates with 1L PFS Across EGFR and ALK TKIs



- Prediction scores calculated for EGFR and ALK TKIs were linearly correlated with observed PFS.
- Both models estimated X(Lag time) at 4.5 months, consistent with clinical observations[5].
- The framework was then used to independently predict the best response and PFS of VRN11 using two complementary approaches.

Result 2. Preclinical Data-Based PFS Prediction

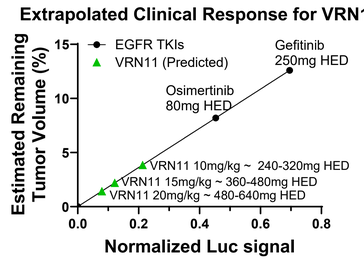
VRN11 Demonstrated Superior Antitumor Efficacy in the PC-9-Luc CDX Model



- A PC-9-Luc CDX study demonstrated dose-dependent reductions in bioluminescence signals.
- The relationship between steady-state bioluminescence signal and drug concentration was used to translate the preclinical tumor response into an estimated clinical best response for VRN11.

Preclinical Translation Predicts Deeper Response and Prolonged PFS for VRN11

Extrapolated Clinical Response for VRN11



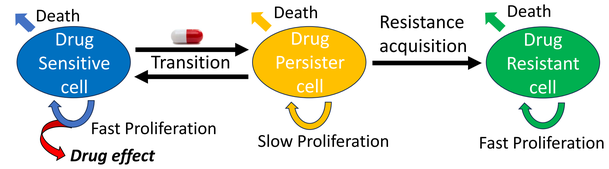
Prediction Results Table

Preclinical dose (HED)	Remaining Tumor volume (%)	Best response (% shrinkage)	PFS (month)
VRN11 10mg/kg (240-320mg)	3.9	-66.2	~30
VRN11 15mg/kg (360-480mg)	2.2	-72.0	~48
VRN11 20mg/kg (480-640mg)	1.4	-75.7	~72

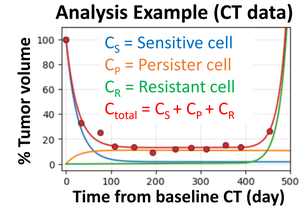
- Mouse exposures associated with the observed tumor responses were mapped to corresponding human doses based on PK data from the PC-9-Luc CDX study and clinical PK data.
- The resulting response estimates predicted deeper clinical responses and longer PFS for VRN11 than for approved third-generation EGFR TKIs at clinically relevant exposures.

Result 3. Model & Clinical Data-Based PFS Prediction

Tumor Response Model Framework



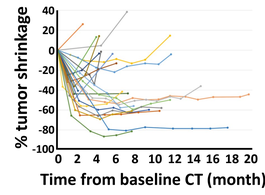
Analysis Example (CT data)



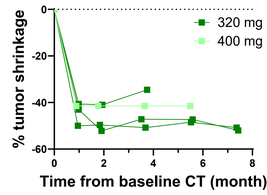
- The model is based on transitions among drug-sensitive, persister, and resistant cell populations.
- An example fit to longitudinal tumor measurements from computed tomography (CT) scans shows the inferred population dynamics of each state during treatment.

Higher Model-Estimated Drug Effect for VRN11

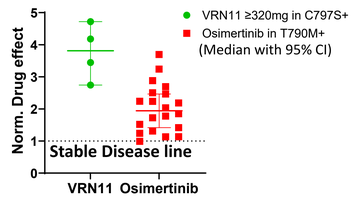
Osimertinib in T790M+ patients[6]



VRN11 ≥320mg in C797S+ patients



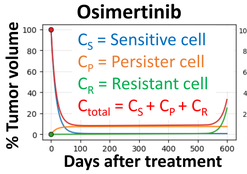
Comparison of Drug Effects in biomarker+ patients



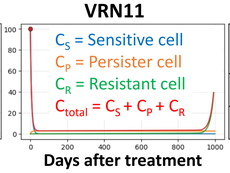
- Drug effects were estimated by fitting the model to longitudinal tumor response data from biomarker-positive patients and subsequently normalized for comparison between VRN11 and Osimertinib.

VRN11 Is Predicted to Outperform Approved third-generation EGFR TKIs

Osimertinib



VRN11



Modeling Results Table

	Remaining Tumor volume (%)	Best response (% shrinkage)	PFS (month)
Osimertinib*	8.2*	-56.5*	**~19***
VRN11(~320mg)	2.8	-69.5	**~32**

*Reference: published Osimertinib clinical outcomes.[2]

- The osimertinib-calibrated model was applied to VRN11 using VRN11-specific drug-effect and resistance-acquisition parameters.
- Predicted tumor response and PFS aligned with the independent preclinical prediction, with further efficacy gains possible as dose escalation continues.

Key Conclusions & Discussion

Key Conclusions

- The tumor-response model consistently recapitulated clinical 1L PFS across approved EGFR and ALK TKIs, supporting its translational relevance.
- Two independent predictive approaches converged on the same conclusion: **VRN11 is predicted to achieve deeper tumor responses and longer first-line PFS than approved third-generation EGFR TKIs.**

Discussion

- The deep tumor response observed with VRN11 may reflect multiple pharmacologic advantages, including efficient tissue penetration, favorable efflux properties, and robust target engagement.
- As dose escalation is ongoing, PFS may exceed current predictions at higher doses, particularly if higher target engagement extends coverage against resistance mechanisms not captured by the model.
- Clinical collaborations are ongoing to validate and refine the model using individual patient-level data.

References

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Artificial Intelligence (AI) Use Disclaimer

- Claude (Anthropic) was used to assist with coding and debugging of the analysis code.
- ChatGPT (OpenAI) was used for English-language editing.
- All analytical methods, outputs, and scientific interpretations were reviewed and validated by the authors.

Contact info: won5379@voronoi.io (C. KIM)
sunghwan@voronoi.io (S. KIM)