Comparing AI Protein-Compound Modeling and Real-World Clinical Outcomes of TKI Response in Uncommon *EGFR*-Mutated NSCLC

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Background: In non-small cell lung cancer (NSCLC), uncommon *EGFR* mutations include classical-like, T790M-like, exon 20 loop insertion, and P-loop aC-helix compressing (PACC). TKI sensitivity to these atypical subtypes is poorly characterized. Boltz-2 is an AI model predicting 3D protein structure and compound binding affinity. We evaluate clinical, structural, and drug affinity outcomes using retrospective patient data and *in-silico* modeling of atypical *EGFR* mutation subtypes treated with afatinib and osimertinib.

Methods: We reviewed patients with advanced atypical *EGFR*-mutated NSCLC (n=36) from our cancer center. Median time to treatment failure (mTTF) was defined as months between EGFR-TKI initiation and systemic treatment change or death. We performed *in-silico* 3D structure and EGFR-TKI affinity binding analysis of select atypical *EGFR* mutations using Boltz-2 on the Rowan platform. Binding probability (BP) is the predicted chance of ligand binding on a scale of poor to excellent (0 – 1.0). Predicted pIC_{50} (negative log half-maximal inhibitory concentration) assesses the degree of affinity binding reported in $-\log10(IC_{50}$ in M).

Results: We identified 26 patients with atypical point mutation, 7 with Exon 18 alteration, and 3 with Exon 19 insertion. In patients with PACC mutations, mTTF on osimertinib and afatinib were 6.77 and 5.73 months, respectively. In this group, patients with brain metastasis had worse afatinib mTTF than those without (4.07 vs 6.80 months). Three patients with compound G719X/L861Q mutation had an osimertinib TTF of >13 months. Patients with exon 19 insertion had an osimertinib TTF of 8.7, 13.3, and 19.6 months. For a reference simulation, we modeled *EGFR* exon 19 deletion (BP 0.90, pIC_{50} 8.06) and L858R (BP 0.86, pIC_{50} 7.86) with osimertinib (Table). G719S/L861Q had higher predicted binding affinities to both osimertinib (BP 0.79, pIC_{50} 7.66) and afatinib (BP 0.83, pIC_{50} 7.97) compared to solitary G719S (BP 0.76, pIC_{50} 7.62). Of atypical mutations, exon18delinsD had the highest osimertinib BP (0.89), while G719S had the highest afatinib BP (0.86).

Conclusion: There is a diversity of clinical TKI responses and simulated affinities by the Boltz-2 model in atypical *EGFR*-mutated NSCLC. Despite high simulated affinities of PACC mutations with afatinib, patients with brain metastasis were observed to have poor responses, which may be related to limited CNS efficacy. Compound G719X/L861Q had prolonged osimertinib responses, correlating with higher affinity measures than solitary G719X. Our proof-of concept study demonstrates that Boltz-2 is a promising predictive tool for drug-protein modeling. Confirmatory in-vitro testing is warranted.

EGFR Mutation	Confidence Score	Binding Probability Osi	IC50 Value	Binding Probability Afatinib	IC50 Value
L861Q	0.784	0.848	7.961	0.710	7.691
G719S	0.782	0.755	7.620	0.860	8.205
S768I	0.786	0.876	7.980	0.762	7.889
G719S/L861Q	0.779	0.791	7.664	0.826	7.967
G719S/S768I	0.784	0.847	7.727	0.835	8.107
Exon18delinsD	0.776	0.894	8.124	0.802	8.076
Exon19ins	0.779	0.881	7.805	0.828	8.061
Exon19del	0.781	0.902	8.059	0.918	8.492
L858R	0.761	0.863	7.860	0.797	8.062
Exon19del/C797S	0.780	0.553	6.508	0.796	7.749
Exon19del/T790M	0.789	0.889	7.901	0.774	7.696

Table: An analysis of *EGFR* mutation modeling and TKI binding probability using Boltz-2 model. Confidence score is the overall quality of a model's structure prediction from 0 to 1. Binding probability (BP) is the predicted chance of ligand binding on a scale of poor to excellent (0 – 1.0). Predicted pIC50 (negative log half-maximal inhibitory concentration) assesses the degree of affinity binding reported in $-\log10(IC_{50}$ in M).