

A mechanistic framework for interpretation and prediction of the PKPD/anti-tumour activity relationship for irreversible Tyrosine Kinase Inhibitors targeting EGFR Exon20Ins mutation

Adriana Savoca⁽¹⁾, Diana Zindel⁽²⁾, Radek Polanski⁽³⁾, Demetrios Kostomiris⁽⁴⁾, Mohammad Pirmoradian⁽⁵⁾, Aisha M. Swaih⁽⁶⁾, Sara Talbot⁽⁶⁾, Nicolas Floc'h⁽⁶⁾, Poppy Winlow⁽²⁾ Clare Thomson⁽⁷⁾, William McCoull⁽⁷⁾

(1) Clinical Pharmacology and Quantitative Pharmacology, Clinical Pharmacology and Safety Sciences, R&D, AstraZeneca, Cambridge Biomedical Campus, Cambridge CB2 0AA, United Kingdom, (2) Mechanistic Biology and Profiling, Discovery Sciences, R&D, AstraZeneca, Cambridge Biomedical Campus, Cambridge CB2 0AA, United Kingdom, (3) Clinical Trial Transparency, R&D Clinical Science, AstraZeneca, 02-676 Warsaw, Poland, (4) Mechanistic and Structural Biology, Discovery Sciences, R&D, AstraZeneca, Waltham, USA, (5) Biomarker, Discovery and Development, Translational Science and Experimental Medicine, R&D, AstraZeneca, SE-431 83 Gothenburg, Sweden, (6) Bioscience, Oncology OTD, AstraZeneca, Cambridge Biomedical Campus, Cambridge CB2 0AA, United Kingdom, (7) Chemistry, Oncology OTD AstraZeneca, Cambridge Biomedical Campus, Cambridge CB2 0AA, United Kingdom

Highlights & Introduction

- EGFR Exon20 insertions (Exon20Ins) are the third most common EGFR activating mutation in non-small cell lung cancer after the canonical single point L858R mutation in Exon21 and deletions in Exon19 [1].
- Because EGFR Exon20Ins patients are generally less sensitive to traditional EGFR Tyrosine Kinase Inhibitors (TKIs) [2], this target is of clinical interest as shown by recent approvals of the bispecific antibody amivantamab [3].
- We aimed at building a modelling framework for PK/PD/efficacy of irreversible TKIs in EGFR Exon20Ins to support discovery of new drugs and gain insights into clinical observations for inhibitors being developed in this space.

Methods

- We have developed a mathematical model to describe the pharmacodynamics of irreversible inhibitors by integrating compound-target binding kinetics with a mechanistic description of EGFR phosphorylation and turnover.
- All model parameters depend on the biology of the system, except compound-specific kinetic parameters K_i and k_{inact} .
- The model was informed by SILAC MS experiments exploring mutated EGFR turnover rate, ELISA experiments on time-course of compound-mediated phosEGFR inhibition and compound-target binding kinetic experiments for the investigated small molecule (SMOL) inhibitors.

Interpretation of *in vitro* data and investigation of *in vitro/in vivo* correlation

By integrating data on target turnover, compound-target binding kinetics, and media degradation, the model can describe the time course of phosEGFR inhibition *in vitro*.

Compound A	
K_i	1.2 [uM]
k_{inact}	0.0116 [s ⁻¹]

The model, informed from *in vitro* data, was predictive of *in vivo* phosEGFR data from PKPD studies in xenografts, demonstrating good *in vitro/in vivo* consistency.

Dose → Mouse PK model → Concentration → PD model → phosEGFR → PD simulations vs observations from mouse PKPD studies

Establishing a PK/PD/efficacy link to inform efficacious dose prediction

A good correlation was observed between anti-tumour activity from mouse xenograft studies and simulated phosEGFR inhibition, suggesting that high and sustained phosEGFR inhibition over dosing interval (≥85-90%) is required to achieve robust tumour regression (TGI > 150%).

- Findings are in line with similarly challenging target engagement requirements observed for other TKIs (e.g., other EGFRmut, cMET [4-5])
- This analysis can be combined with human PK simulations to inform clinical efficacious dose predictions.

Clinical PD simulations to build confidence in preclinical to clinical translation

Osimertinib (3rd gen EGFR TKI)

Osimertinib clinical PD simulations suggest limited target engagement may contribute to low ORR% in Exon20Ins [6].

Dose	ORR (N)
80 mg QD	0% (N = 14) – 5% (N = 21)
160 mg QD	28% (N = 25)

Zapaterinib (EGFR Exon20Ins TKI)

Zapaterinib clinical PD simulations suggest doses 30-150 mg BID achieve >90% pEGFR_avg inhibition. Consistently, reported ORR% suggest a flat dose-response relationship [7].

Dose	cPRs (N)
≤ 65 mg BID	35% (N = 23)
100 mg BID	41% (N = 13)
150 mg BID	36.4% (N = 11)

Conclusions

- We combined *in vitro* data on protein turnover, potency time-course, and binding kinetics into a mechanistic PD model for description of phosEGFR inhibition induced by irreversible inhibitors in EGFR Exon20Ins mutated tumours. The model provided a good prediction of *in vivo* phosEGFR inhibition for a few irreversible small molecule inhibitors.
- Combination of tumour volume data and PD simulations showed that high and durable levels of target engagement should be achieved to ensure robust tumour regression.
- Combination of the developed PD model with clinical PK simulations of EGFR TKIs provides confidence in the preclinical to clinical translation of our findings.

References

- Yasuda, H., et al. (2012). Lancet Oncol 13(1): e23-31.
- Yang, G., et al. (2022). Front Pharmacol 13: 984503.
- Chon, K., et al. (2023). Clinical Cancer Research, 29(17), 3262-3266.
- Yates, J. W. T., et al. (2016). Molecular Cancer Therapeutics 15(10): 2378-2387.
- Jones, R. D. O., et al. (2021). British Journal of Pharmacology 178(3): 600-613.
- Yasuda, H., et al. (2021). Lung Cancer, 162, 140-146.
- Piotrowska, Z., et al. (2023). Journal of Clinical Oncology, 41(26), 4218-4225.

Acknowledgments

This study was sponsored by AstraZeneca.