# Setting up success in the clinic through semi-mechanistic translational modelling

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**aaps PharmSci 360**

## PURPOSE

- FDA's Oncology Centre of Excellence launched Project Optimus [1], a new guidance on dose optimisation for Oncology therapeutics – which signals a cultural shift [2] from finding a tolerable limit to optimizing a dose which is efficacious and safe

- We demonstrate a novel data-driven approach combining early preclinical and available clinical data to predict clinical Objective Response Rate (ORR) which can be used to support dosing decisions and make early evaluations of candidate drugs

## OBJECTIVE(S)

To provide both rational dose selection and front-load efficacy evaluation of Oncology therapeutics via modelling and simulation.

## METHOD(S)

- The following step-wise translational approach was first assessed using data from the KRAS G12C inhibitor Sotorasib before being tested on Adagrasib:

  - The key equation for both approaches which links PK to PD to tumour growth is:

  $$\frac{dR}{dt} = g - d\,\frac{C(t)}{IC50 + C(t)}$$

  Where R(t) is the tumour radius at time, t, g the growth rate units mm/hour, d the drug induced decay rate units mm/hour, IC50 the free potency and C(t) the free drug concentration at time, t.

- Step-wise approach:

  1. Build a PK-PD-TGI model for Sotorasib using a single xenograft, MIA-PaCa-2, data from literature data [3, 4]

  2. Replace Sotorasib mouse PK with human [5]

  3. Replace the g and d values with clinically derived values [6]

  4. Replace the in-vivo MIA-PaCa-2 IC50 value with Horizon in-vitro cell-line IC50 distribution. Use Sotorasib in-vitro cell-line IC50 distribution

- For Step 2 to 5 we compared the model prediction of ORR with the observed

- Tested the best approach using data on Adagrasib

  - Swap out Sotorasib PK [7] and IC50 values for Adagrasib

## RESULT(S)

### Establishing a preclinical PK-PD-TGI model

- A preclinical PK-PD-TGI model was successfully established on the literature data.

- A 2-compartment PK model with non-dose proportional exposure captured the mean mouse PK profiles, see Figure 1a

- A PK-PD model successfully captured pERK modulation in MIA-PaCa-2, G12C mutated sensitive cell-line, xenografted mice, see Figure 1b

- Tumour growth inhibition in MIA-PaCa-2 was well captured by the final model where pERK modulation drove tumour growth inhibition, see Figure 1c

### Clinical translation

- Step-wise results were as follows for Sotorasib shown in top-panel of Figure 2:

  2. Predicted ORR from a single mouse was 99.9% (99%, 100%) which was significantly higher than the ORR, 37% (95%CI: 29-46) in the Phase II trial of non-small cell lung cancer (NSCLC) patients [6], Pred. (MIA-PaCa-2) in Figure 2

     - The inaccuracy was expected as the exposure-response was estimated on a single responsive cell-line - does not capture heterogeneity and used preclinical growth and decay rates

  3. Using clinically derived g and d values greatly improved the correlation to clinical ORR – new prediction of ORR 50% (95%CI: 42-58), Pred. (MIA-PaCa-2/NSCLC) in Figure 2

  4. These results were further improved by then swapping out the in-vivo IC50 point estimate for the in-vitro distribution, Pred. (CTG assay/NSCLC) in Figure 2

- In testing the model, by swapping out Sotorasib PK and in-vitro IC50 distribution for Adagrasib, we found good agreement with model predicted ORR and observed ORR [7] for Adagrasib, as shown in bottom panel of Figure 2.
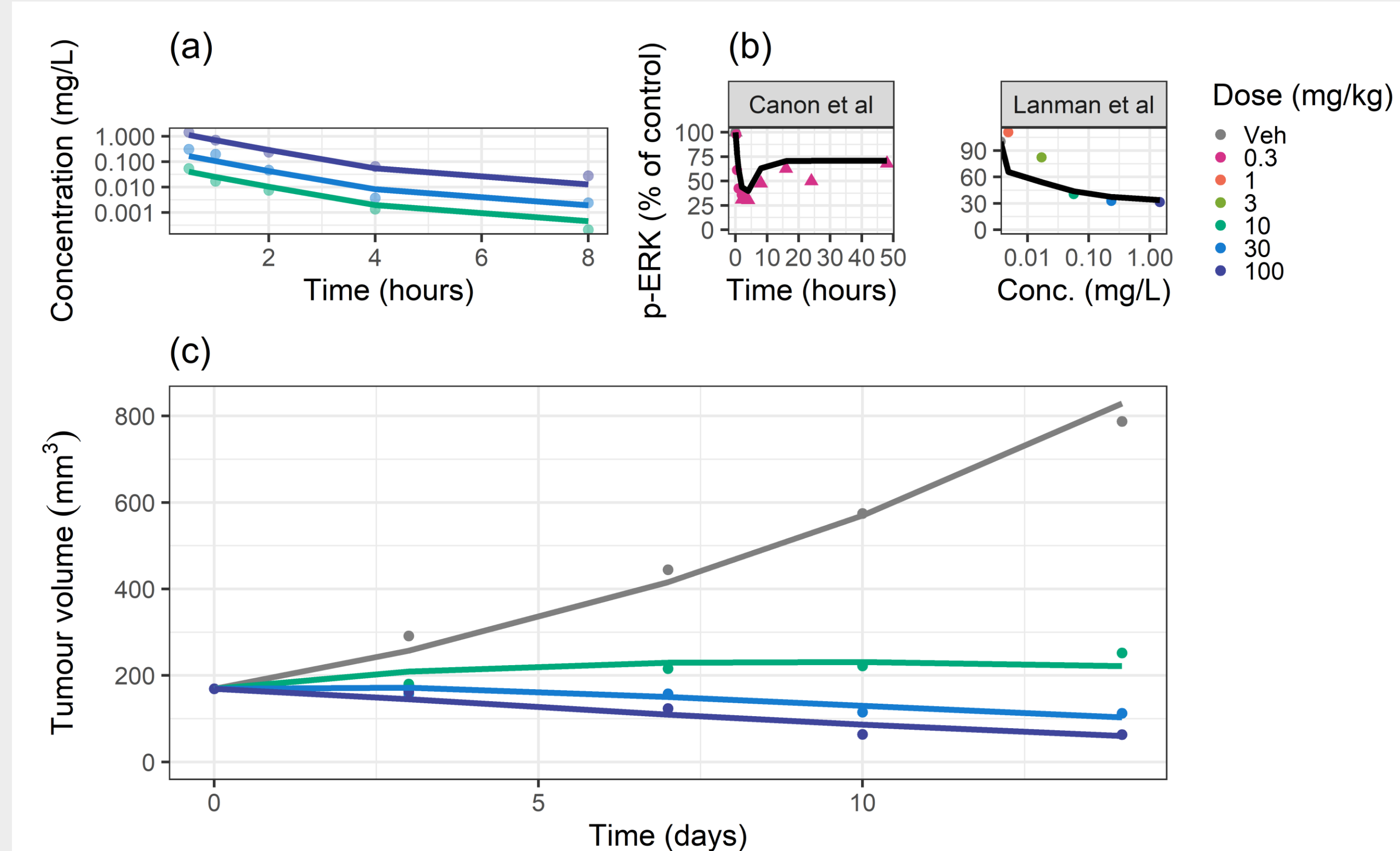


*Figure 1 Established preclinical PK-PD-TGI model established. (a) reported and fitted mouse PK data (b) reported and fitted pERK modulation data in MIA-PaCa-2 xenograft mice (c) reported and fitted tumour growth data in MIA-PaCa-2 xenograft mice*
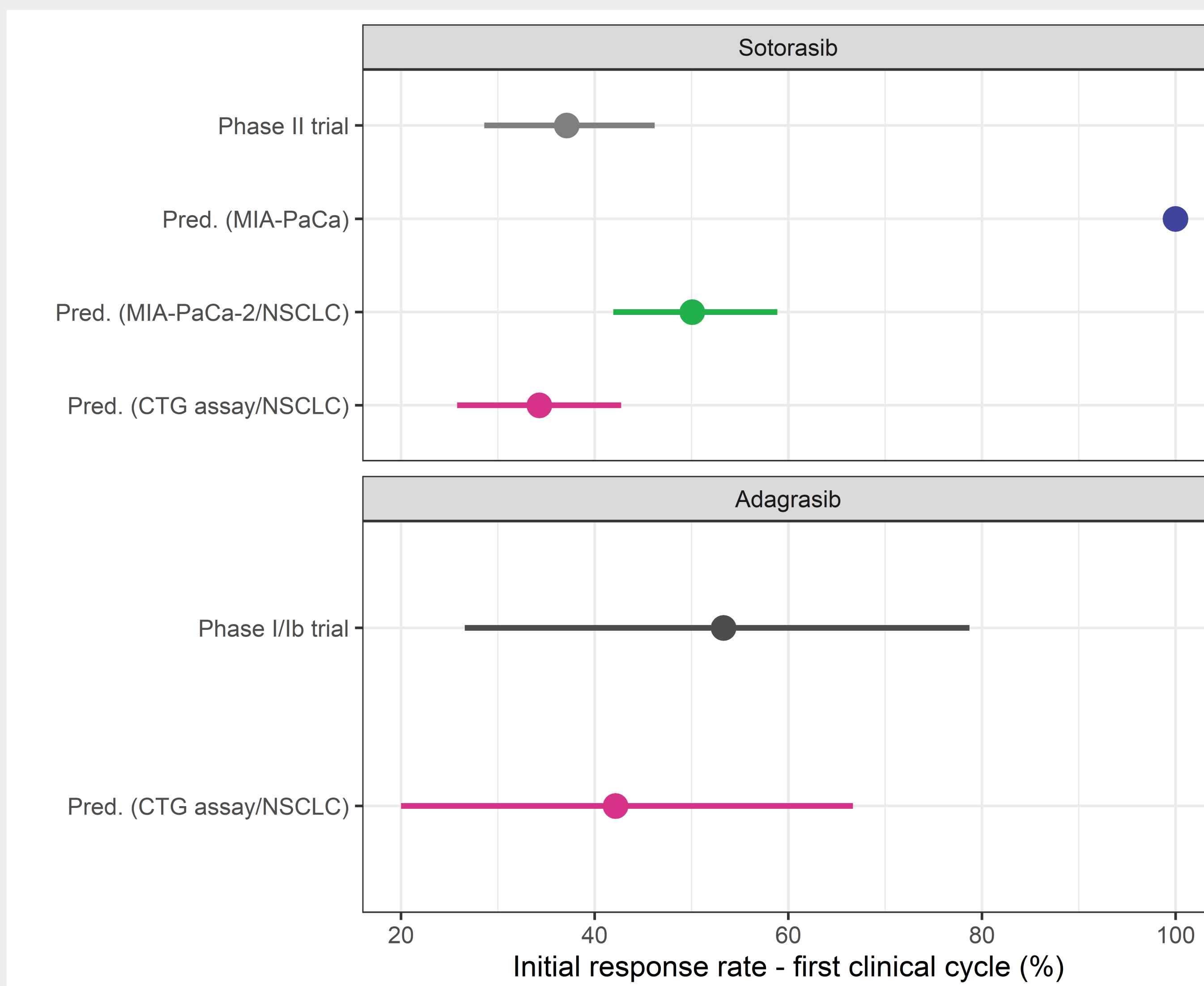


*Figure 2 Predicted and reported response rates for Sotorasib and Adagrasib with 95% confidence intervals*

## CONCLUSIONS

- We have proposed a modelling framework to predict ORR using preclinical data via the use of a PK-PD-TGI model

- Target modulation/drug potency drives tumour growth inhibition, that can be used to predict the response rate within a genetically defined population of a given dose

- We took a step-wise translational modelling approach and tested the suitability of each step

- The final proposed modelling framework incorporates preclinical in-vitro data from a panel of cell-lines and available clinical data, decay and growth rates, to predict ORR

- We successfully applied the framework to Sotorasib data and qualified the model on, another KRAS 12C inhibitor, Adagrasib.

- This translational approach will allow for an improved of selection of lead compounds and the optimal clinical exposure/dose to be selected and justified

## ACKNOWLEDGEMENTS

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