# Translational PK/PD Modelling of MEK inhibitors: Trametinib, Cobimetinib and Binimetinib \

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## Purpose

Propose a translational PK/PD framework that enables human dose estimation (HDE), compound ranking and to assess the clinical applicability of cancer cell-line-panels.

## Method

- **Objective**: Estimate efficacious doses in humans using translational PK/PD simulations.
- **Calibration and Benchmarking**: Modelling approach calibrated using Trametinib; Cobimetinib and Binimetinib were benchmarked against Trametinib for HDE.
- **PK Models and Drug Effect**: Population PK (popPK) models [1][2][3] used to simulate clinical PK; drug effect described by an $E_{max}$ model [4]. The average effect over time, $E_{avg}$, was calculated from the model simulation.
- ***in vitro* Efficacy Data**: Trametinib, Cobimetinib, and Binimetinib data extracted from PRISM screen within DepMap Public Access Portal [5].
- **$EC_{50}$ Distributions**: Derived from PRISM screening, focusing on cell lines which had same biological profile as target population, V600E mutated BRAF.

## Results

- PopPK/PD model integrates *in vitro* pharmacology from cancer cell panels and published PopPK models for MEK-inhibitors: Trametinib, Cobimetinib, Binimetinib
- Log-normal $EC_{50}$ distributions (Table 1) derived from V600E mutated BRAF cell-lines (Figure 1)

| Compound | EC50 distribution |
|---|---|
| Trametinib | $EC_{50}$ ~ Log-N(3.77, $1.71^2$) |
| Cobimetinib | $EC_{50}$ ~ Log-N(4.19, $1.36^2$) |
| Binimetinib | $EC_{50}$ ~ Log-N(4.76, $1.53^2$) |

*Table 1: Derived $EC_{50}$ distributions for each compound.*

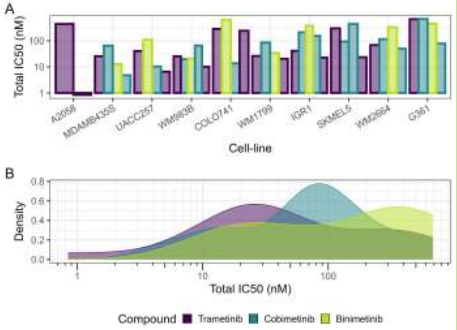


*Figure 1A-B: $EC_{50}$ values for V600E mutated BRAF cell-lines. A: represents reported EC50 against cell-line, per compound. B: represents distribution of $EC_{50}$s per compound.*

## Results

### Trametinib simulation

- Trametinib used as the benchmark compound.
- PK/PD profile simulated at the approved therapeutic dose of 2 mg QD
- Simulated PK profile shown in Figure 2
- $E_{avg}$ calculated (Figure 3A) and summarised: median $E_{avg}$ was 31%, with 25th and 75th percentiles at 13% and 57%, respectively (Figure 3B).

### Dose-response curves

- Dose-response curves simulated for Cobimetinib (Figure 3C) and Binimetinib (Figure 3D)

### Predicted HDE

- HDE defined as dose that results in an $E_{avg}$ comparable to Trametinib
- Cobimetinib: 10 mg QD 21/7 [50% Prediction Interval (PI): 6 – 15 mg QD 21/7]
- Binimetinib: 40 mg BID [50% PI: 15 – 95 mg BID]

### Model qualification

- Predicted HDE compared with reported maximum tolerable dose (MTD)
- Cobimetinib: Predicted HDE slightly lower than MTD (60 mg QD 21/7) [6], shown in Figure 3A.
- Binimetinib: Predicted HDE similar to MTD (45 mg BID) [7], shown in Figure 3B.

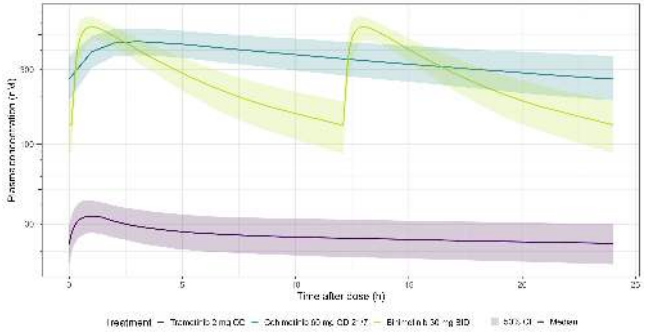


*Figure 2: Example Simulated clinical PK profiles at steady-state for Trametinib, Cobimetinib and Binimetinib.*

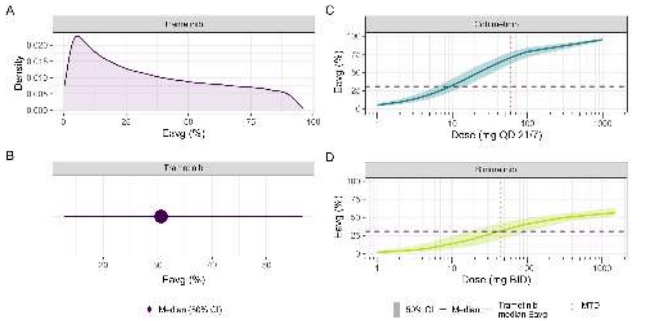


*Figure 3A-D: Simulated response for each compound. A: simulated $E_{avg}$ distribution at the Trametinib approved dose. B: summarised Trametinib Eavg distribution. C: Simulated Cobimetinib dose-response. D: Simulated Binimetinib dose-response.*

## Conclusions

- The translational PK/PD framework suggests routine cancer cell-line-panels, like the PRISM assay, may be suitable for HDE.
- Predictions could be improved with multiple *in vitro* systems and complex assays.
- The framework enables compound ranking, selection and aids in quantifying a clinical therapeutic window.

## Acknowledgments

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## References

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