Dose selection using pre-clinical PKPD
An oncology systems pharmacology approach to dose selection

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Problem statement

Early clinical trial data – what dose to take forward?

AZD9291: EGFR inhibitor

At the time this modelling was carried out:
1. Doses 20-160mg QD investigated
2. Responses observed at all doses
3. MTD not identified
4. Did not want to take MTD forward – take biologically effective dose forward with good safety profile
5. What is this dose?

(Part) of the solution: A mathematical model relating PK, PD and efficacy had been developed during the discovery program. Use this to put differences between mouse and human PK into context and simulate clinical dose response

Will discuss pre-clinical model development and application to make clinical dose decision
Mouse PK
Simultaneous modelling of active parent and metabolite

![Diagram showing the flow of PARENT and METABOLITE through Gut, Cen, and Per.]

**Parent** – Green
**Metabolite** – Maroon

![Graph showing plasma concentration over time, with Parent and Metabolite concentrations marked.]

**SCIDS**

Parent – Green
Metabolite - Maroon
Linking PK to pEGFR PD

Turnover model with irreversible binding combining parent and metabolite drug effect

Ratio of parent to metabolite potency fixed to in vitro value
pEGFR knock down – PKPD hysteresis plot
PK does not determine duration of effect
PD Model to explain efficacy

Determining the relationship between pEGFR reduction and efficacy

pEGFR reduction linked to cell death within mathematical model of tumour growth

Result is linkage between target engagement and efficacy
Human Half-life is much longer than mouse. How does this impact PKPD?

Simulate dose fractionation in mouse

**AZD9291 Dose fractionated PK in Nude mouse**

More frequent dosing gives lower $C_{\text{max}}$ – 4 fold difference between QD and 10D

**AZ5104 Dose fractionated PK in Nude mouse**

More frequent dosing gives higher $C_{\text{min}}$
Simulated dose fractionation suggested that frequency of delivery was not critical. If anything the flatter profile resulting from frequent dosing was most effective according to the model. This is encouraging given long half-life in human.
Capturing clinical PK variability
Varying CL captures a large amount of variability.

Not a formal pop PK analysis – used model of predicted human PK and updated based upon observed data
Lower end of exposure captured – important for biologically effective dose questions
AZD9291 clinical dose response simulation
Human PK combined with mouse PD-efficacy

95% Confidence intervals of efficacy
Even with variability effect saturates at low doses

Modelling suggests dose response against mutant EGFR saturates by 80mg
Observed Safety profile good at this dose
Conclusions

Use of pre-clinical modelling to guide clinical dosing

1. Integration of clinical PK with pre-clinical PD-efficacy relationship has provided a way to augment early clinical data with richer pre-clinical data set.

2. Allows the biologically effective dose (based upon animal models and clinical exposure) to be identified.

3. Potential to remove necessity to dose to MTD to maximise probability of clinical activity.

4. Ongoing question of quantitative translation of animal models of cancers to the clinic
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