Using a model based approach to inform dose escalation in a Ph I Study by combining emerging clinical and preclinical information:

An example in oncology

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Innovative medicines , AstraZeneca R&D, UK

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AstraZeneca

Phase I in Oncology

Single and Multiple Ascending Dose

- **Primary:**
  - Safety
  - Tolerability
- **Secondary:**
  - Pharmacokinetics (PK)
  - Anti-tumour activity (Early Efficacy Signal)
- **Exploratory**
  - Pharmacodynamics (PD) and PoM Biomarkers

- **Oncology: Compounds generally unsuitable for healthy volunteers and studies often enrol patients for whom all other standard therapies have failed**
- **Sets recommended dose and schedule for rest of program e.g. Phase II/III**
- **Understand PK-PD-Safety-Efficacy relationship for future trials**
- **A range of administration schedules may also be studied e.g. intermittent vs. continuous**
- **Study design aim: To escalate the dose in steps to identify Maximum Tolerated Dose (MTD) and a Recommended Dose (RD) for future studies which balances safety and efficacy (PD effect) -and vs. maximising the number of patients that receive a therapeutic dose.**
- **Multiple dose escalation methods available**

Dose escalation methods (1)
Rule based/algorithmic approaches

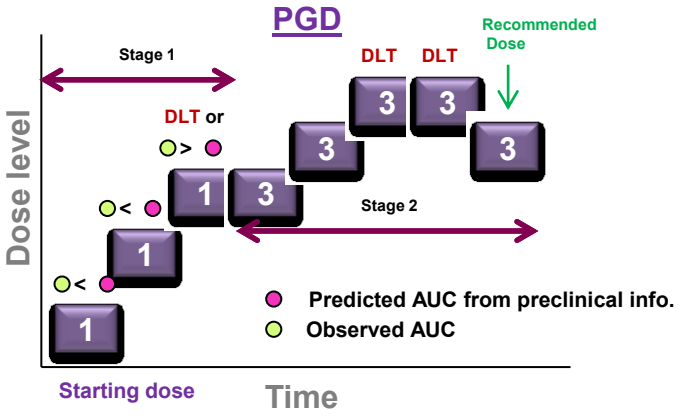
Common approaches in oncology.

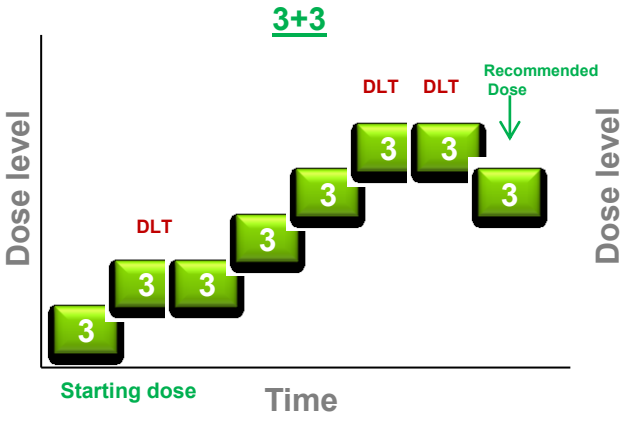
Main concept: a small group of patients is treated at a given dose and dependant on the observed number of dose-limiting toxicities (DLT), a decision based on pre-defined rules will be made:

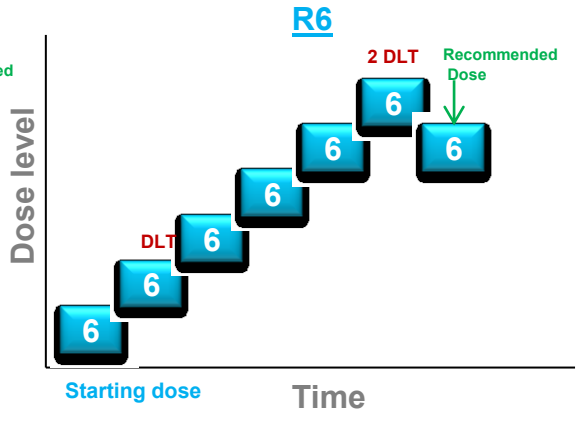
- Study a further group of patients at the next dose
- Study more patients at the same dose
- Declare MTD

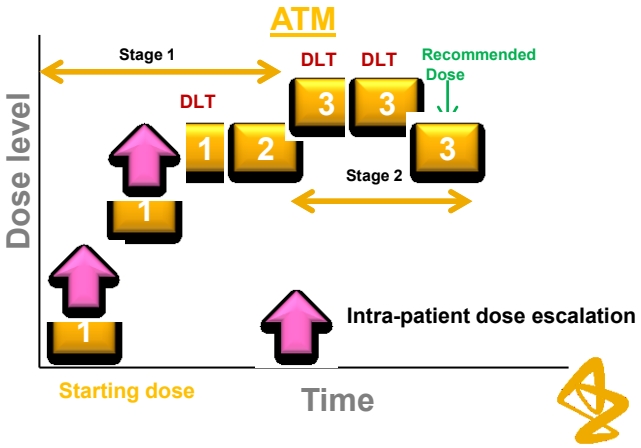
Examples:

- **3+3 other variants such as (2+4, 3+3+3) etc**
- **Rolling 6 (R6)**
- **Accelerated titration methods (ATM) – can be model based.**
- **Pharmacologically guided dose (PGD)**









Figuares adapted from Tourneau et al J Natl Cancer Inst 2009;101: 708 – 720
O'Quigley Biometrics 1990.

Dose escalation methods (2)

Model based approaches

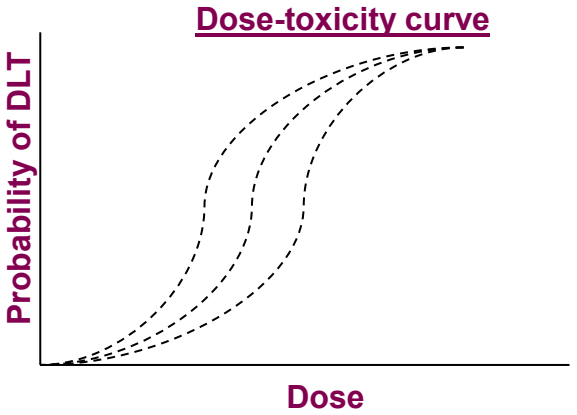
Less common approach but increasing in use.

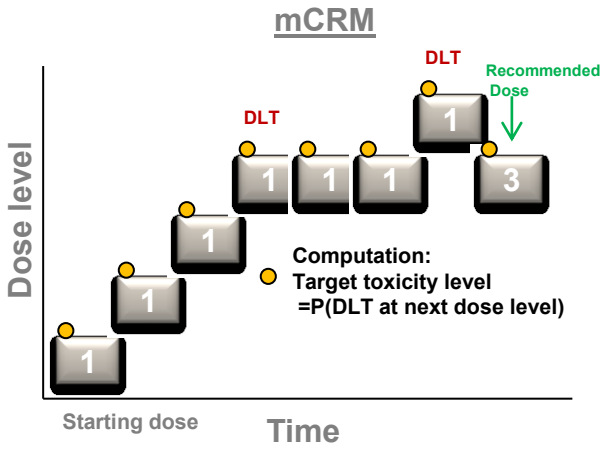
- **Probability of DLT**

Combines prior information of drug with observed current trial data to inform escalation decision.
Use minimally informative dose-response model

Bayesian adaptive design

- Modified Continual Reassessment Method (mCRM)
- Time to event continual reassessment method (TITECRM)
- Escalation with overdose control (EWOC)





e.g. CRM:
Single parameter working model
For fixed dose level *d* and parameter p=(a)

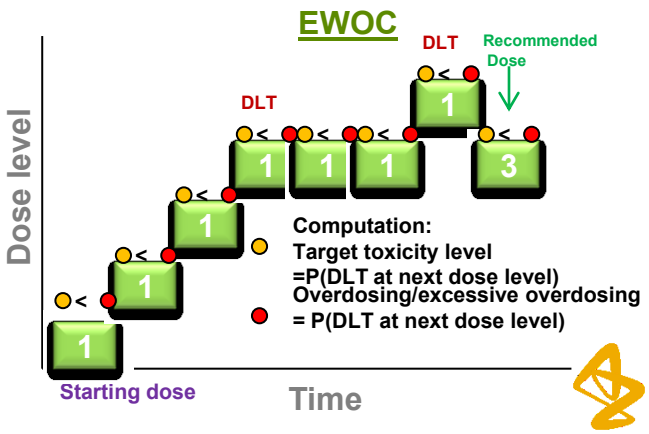
$$P(d_i, a) = \alpha_i^{\exp(a)}$$

$$0 < \alpha_1 < \ldots \alpha_k < 1$$

$$P(d_i, a) = \frac{\exp(-3 + a \cdot d_i)}{1 + \exp(-3 + a \cdot d_i)}$$

$$P(d_i, a) = \left(\frac{\exp(d_i)}{\exp(d_i) + \exp(-d_i)} \right)^a$$

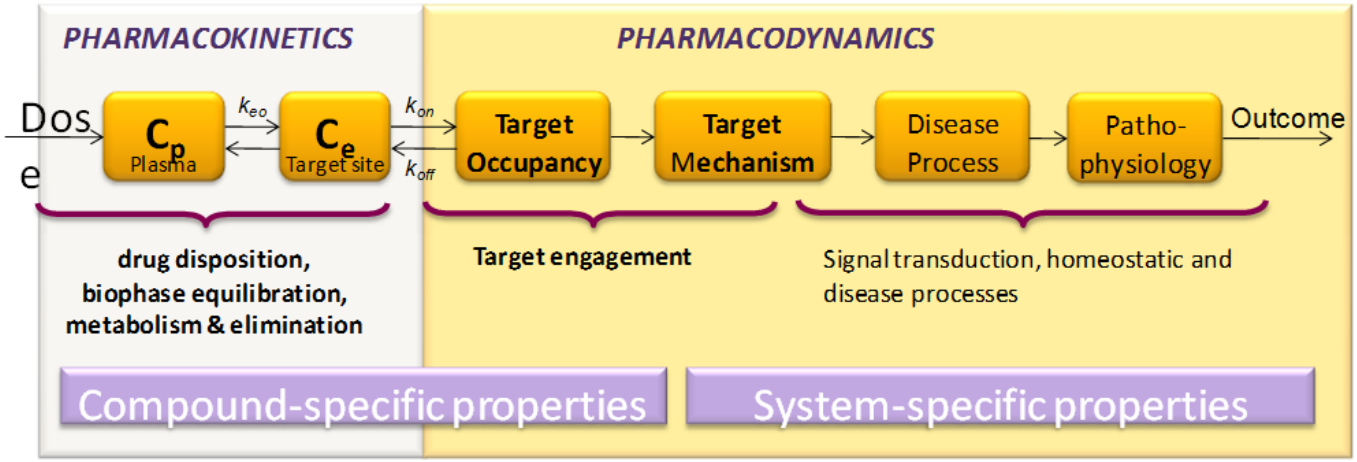
$$i = 1, \ldots k$$



Could a population model based approach be more suitable?

Data integration and variability assessment

- The rule based approach lacks of understanding of all the data available.
- The common model based approach lacks exposure-response at a population level.
- Integration:



Sandra Visser

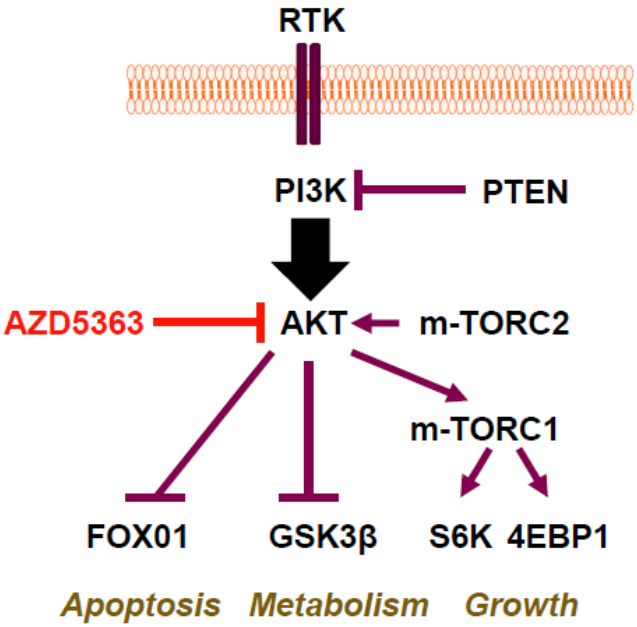
Emerging paradigm for efficacy – why not safety?

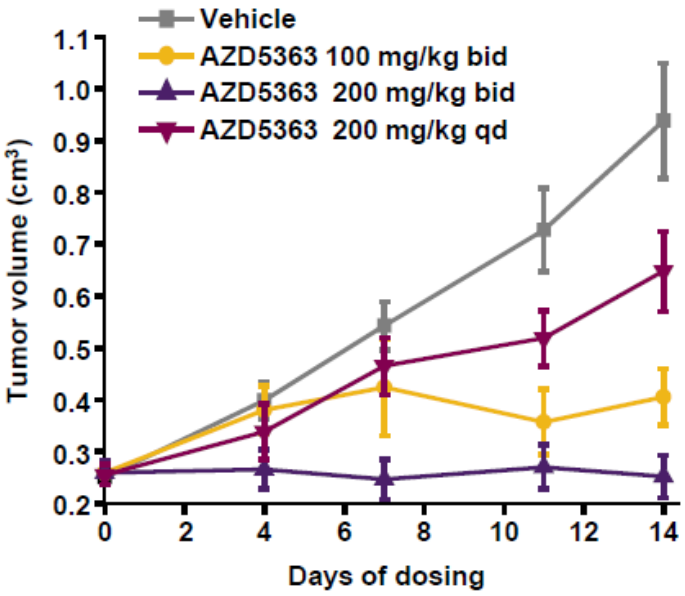
Hence the incorporation of:

- Preclinical modelling result/ information– enables model continuum
- Emerging trial data
- Population model based approach – allow understanding of underlying mechanism and relationship between exposure, target engagement and safety during escalation

AZD5363: pan – AKT inhibitor

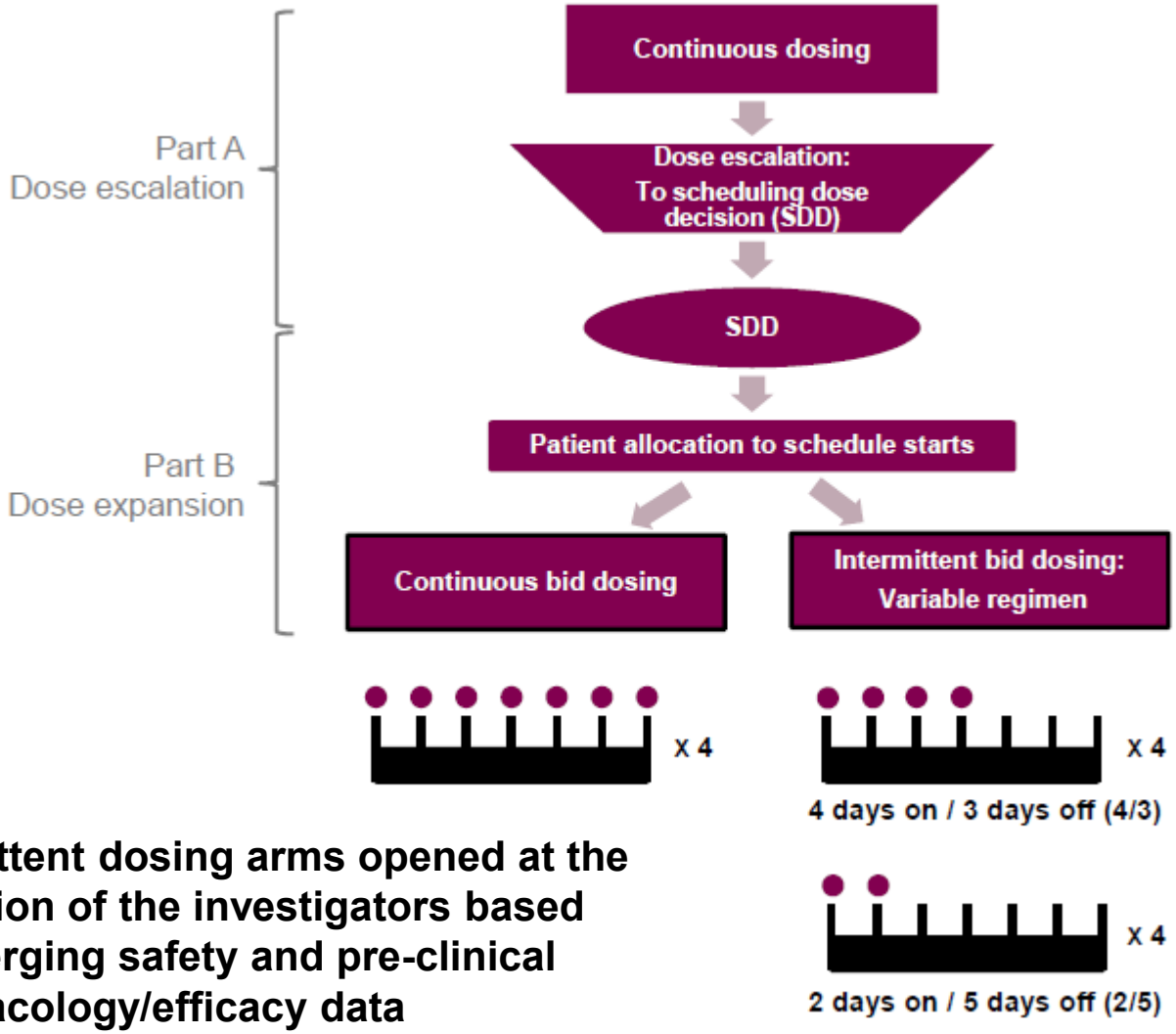
- Orally bioavailable selective pan AKT inhibitor of Akt 1, 2 and 3
- Dose and time dependent modulation of biomarkers observed
- Pre-clinically: PKPD and efficacy linkage understood





Davies BR et al. *Mol Cancer Ther 2012: 11: 873–887*

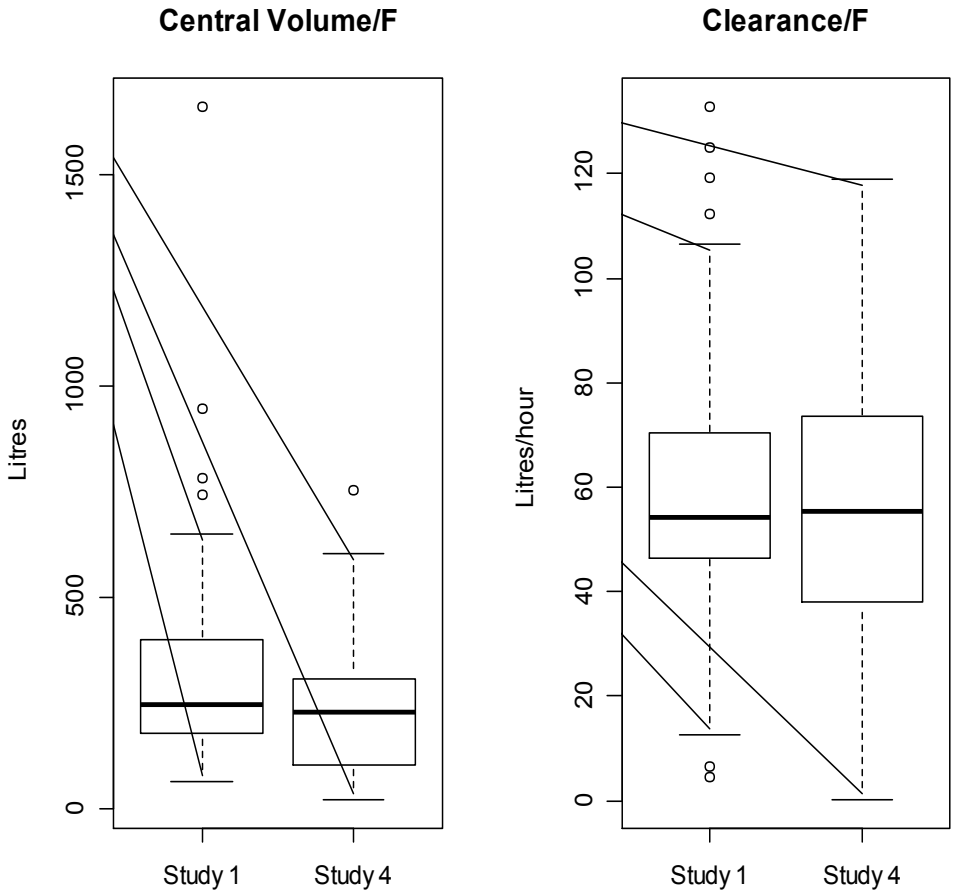
Western study is a Single/ Multiple Ascending Dose Study

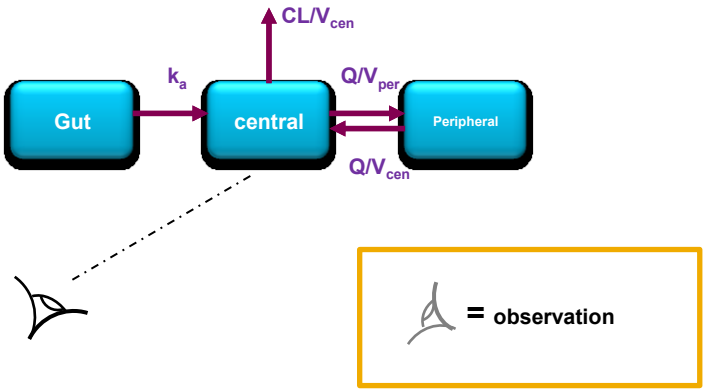


Intermittent dosing arms opened at the discretion of the investigators based on emerging safety and pre-clinical pharmacology/efficacy data

*** A study with similar design conducted in Japanese patients is also part of the programme**

Population PK analysis demonstrates similar pharmacokinetics in Western and Japanese patients





Confidence in similar dose escalation and scheduling approach

Study 1 = Western
Study 4 = Japanese

Simulating missed dose management strategy

Early Population PK is used to guide trial design

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	1	2	3	4	5	6	7
Example	√	X	X	√	√	!	!	√	√	√	√	!	!	!	√	√	√	√	!	!	!	√	√	√	√	!	!	!

Questions:

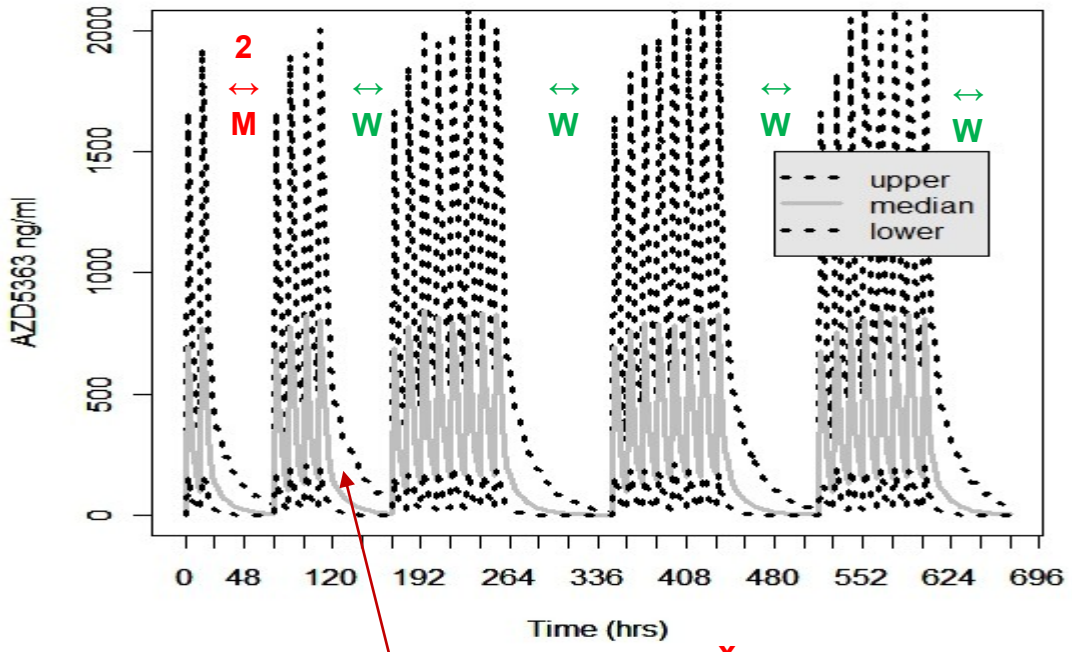
- **Can you resume and complete 4 days of dosing after an interruption due to toxicity?**
- **Should you stop and start at the next cycle?**

Based upon on the simulated upper exposure range:

- If only 1 day of dosing is missed, then it is acceptable to complete the 8 doses with a reduced washout period.
- If two days are missed then one can administer 6 doses on that cycle.

If more days are missed, then restart at the next cycle.

Intermitted BID simulation scenario



Completing 6 doses after interrupting 1st cycle, still provides adequate washout before 2nd cycle

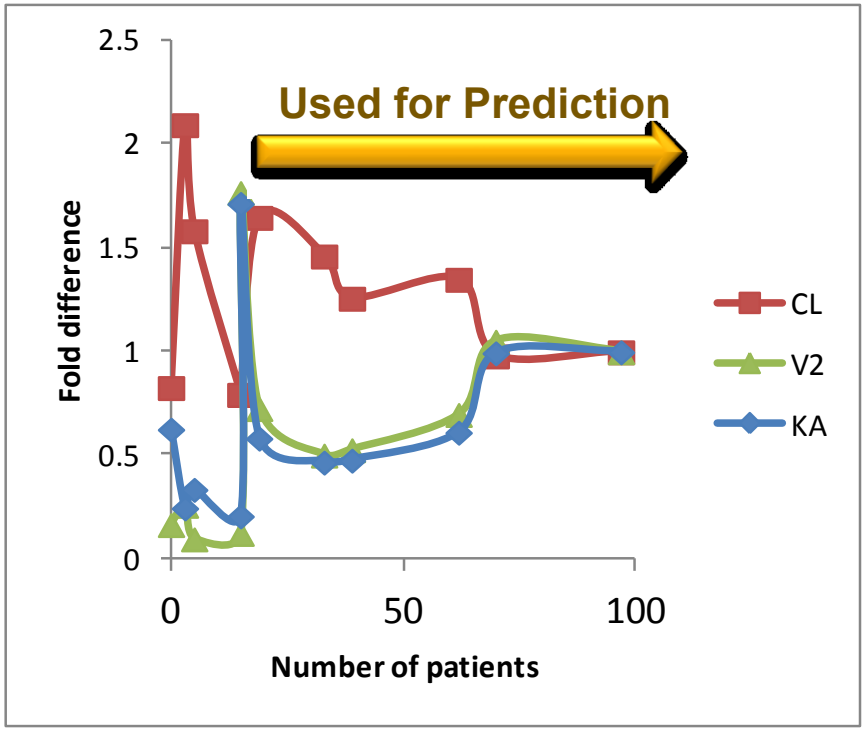
x
↔ M = x day missing doses

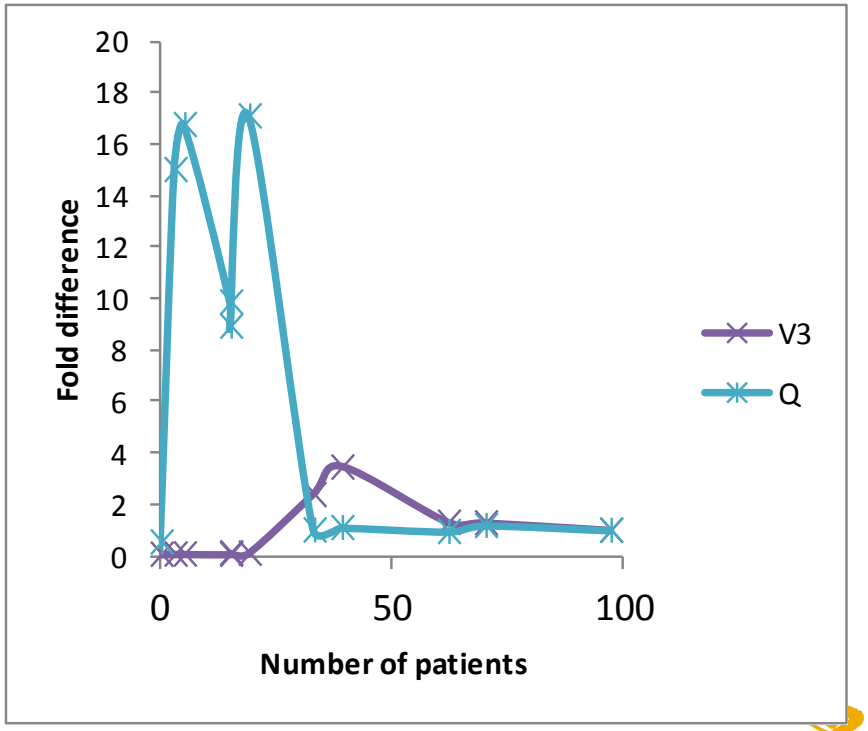
↔ W = washout period

Parameter estimates show continual learning about PK with early estimates representative of current estimates

Pre-clinical prior stabilised estimates in early phase

- Robustness of model is a function of data cleanliness not just quantity
- Data not as informative in early stages about peripheral compartment parameters
- NONMEM ADVAN4 TRANS4 parameterisation

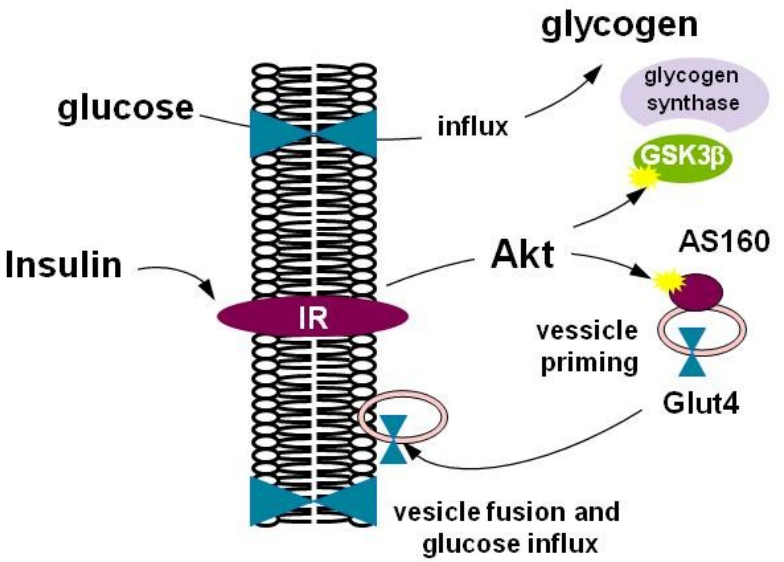


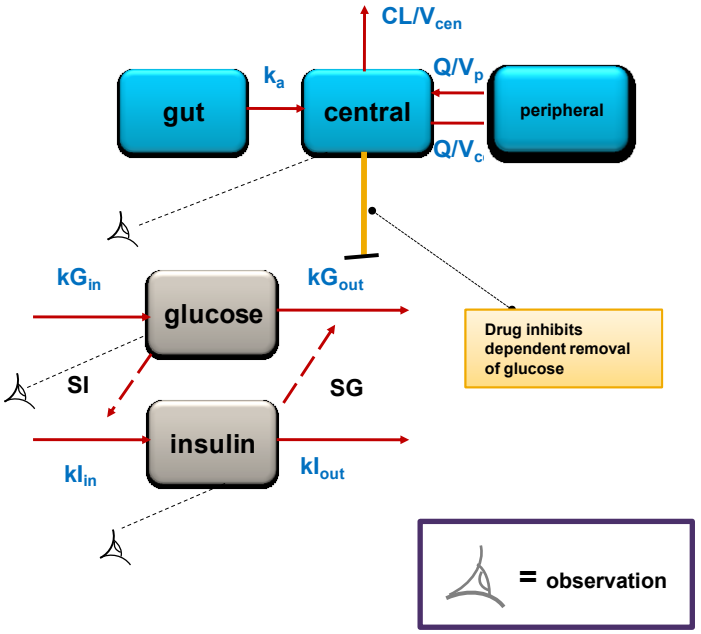


AKT component of insulin dependent glucose uptake

Model developed using pre-clinical data

Akt required for translocation of glucose transporters from cytoplasmic to fuctional plasma membrane location, in response to insulin receptor activation. Akt phosphorylation of GSK3β relieves inhibition of glycogen synthase and co-ordinates glucose influx and glycogen storage.



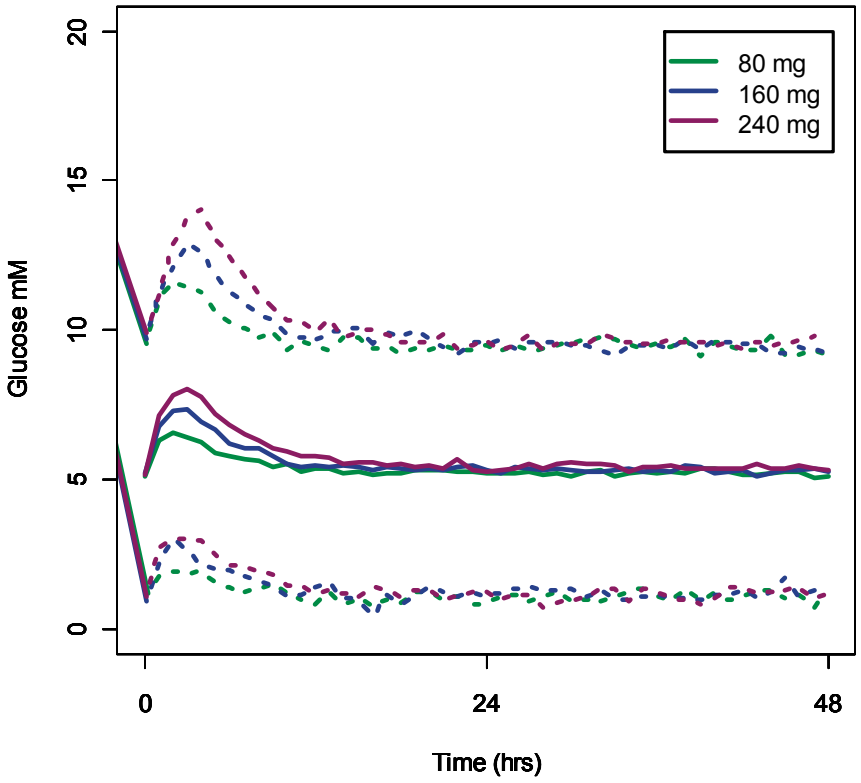


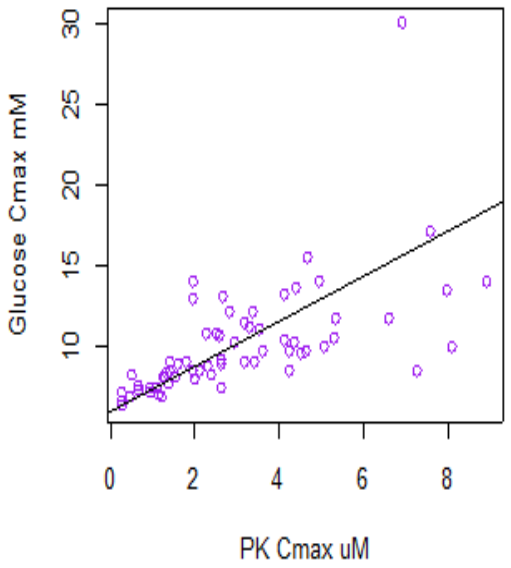
Akt inhibition by AZD5363 results in increased plasma glucose (inhibition of Glut4 function) and increased plasma insulin (dynamic response to elevated plasma glucose).

Population modelling guides dose escalation

PK- glucose relationship extrapolated to higher doses

Simulation of medium effects (97.5% upper quantile shown below)

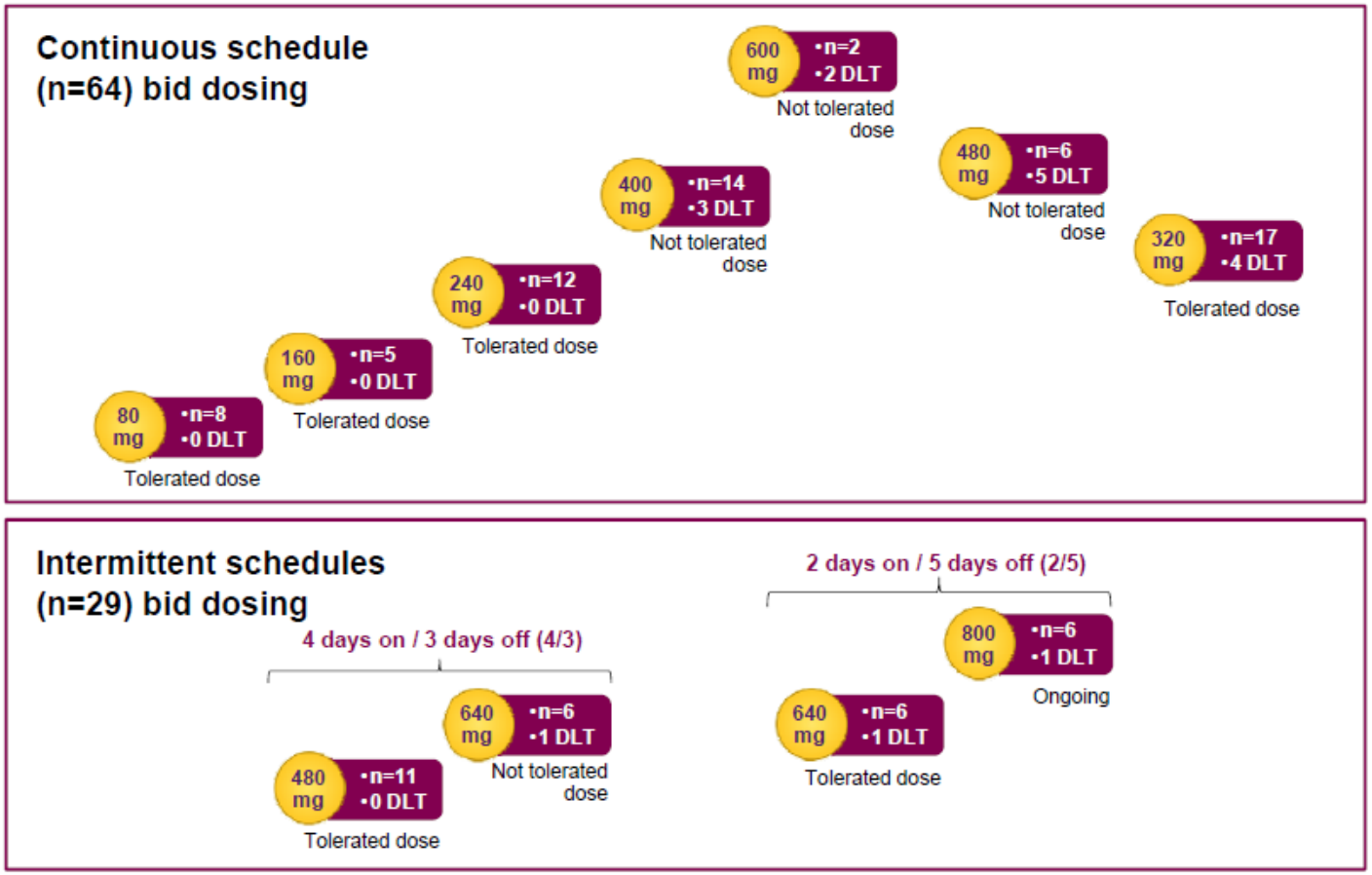




Blood sugar back to baseline during 'off drug' days

Study flow – Western and Japanese patients

Efficient escalation and exploration of schedules



7 DLT: Dose-limiting toxicity

Data cut off: Feb 18 2013
Unvalidated data

Ref: Results of two Phase I multicenter trials of AZD5363, an inhibitor of AKT1, 2 and 3: biomarker and early clinical evaluation in Western and Japanese patients with advanced solid tumors. Udai Banerji, Malcolm Ranson, Jan HM Schellens, Taito Esaki, Emma Dean, Marcelo Marotti et al. AACR13 Clinical Trials Symposium: The PI3 Kinase Pathway: Biomarkers and Clinical Targeting 2013

Population PKPD approach to dose escalation is advantageous

Greater flexibility of models

Allow:

- Comparison of populations
- Extrapolation to alternative schedules
- Model based translation of pre-clinical learning
- Guide cohort dose level and schedule decisions

Further work:

- Formal analysis of quantity of data required at each dose escalation
- There will be continued learning about PK, PD, safety profiles

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- Sponsored by AstraZeneca

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