A pre-clinical PKPD framework for biomarker led decision making for prioritising dose and schedules for anti-cancer agents to test in the clinic

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Drivers for implementing model-based approaches

Need to maximise the effectiveness and durability of therapeutic strategies (single agent & combinations)

**Challenge**

- Multiple mechanisms with multiple potential therapeutic options for a disease segment
- Continuous dosing to MTD is not necessarily the best approach to maximise TI and manage resistance
- Personalised therapeutic strategies a reality
- How to effectively prioritise from the large number of possible novel-novel combinations

**Implication**

- Which is best for the patient: Need to differentiate compounds based on MoA, and combination options
- Need to explore intermittent dosing schedules
- Different doses required for different settings / patient populations
- Impossible to test all options in patients

Can pre-clinical / quantitative approaches influence decision making on dose and schedule?
Investigating a quantitative PK/PD/E framework to understand the relationship between drug exposure and therapeutic index (TI)

- Determine how the shape of the exposure and frequency of dose affect target(s) suppression
- Understand how extent and duration of target suppression modulates the pathway
- Linking pathway modulation to observed biological effects driving tumour efficacy and normal tissue effects

Does this molecule have the right profile for application A vs. Z?
Investigating a quantitative PK/PD/E framework to understand the relationship between drug exposure and TI

For both single & combination agents we understand:

- What is the extent and duration of target suppression required to deliver a biological effect(s)?
- How do effects on the pathway correlate with efficacy and effects on normal tissues?
- How does the PK-PD-E relationship change with time?
- What is the magnitude and time dependency for possible drug-drug interactions?
- How does therapeutic margin change with alternative target suppression profiles (scheduling)?
- What PK properties are required to deliver an acceptable target suppression profile?
Case Studies showing impact of implementing pre-clinical PKPD framework

Understanding how target inhibition drives pathway suppression & efficacy leading to the opportunity to use an intermittent schedule in the clinic to maximise TI for the AKT inhibitor AZD5363

Predicting the optimal human dose schedule that balances efficacy with hyperglycaemia for the Pi3Kα/δ inhibitor AZD8835 combined with the AKT inhibitor AZD5363

Combining mathematical models for both efficacy and toxicity (neutropenia) to identify optimal schedules to take into the clinic for the ATR inhibitor AZD6738 (see poster)

Building a quantitative understanding of target inhibition profile requirements to set a Phase II dose in PRCC patients for the MET inhibitor AZD6094 (see poster)
Using pre-clinical modelling to select dose and combinations for the PI3K pathway

PI3K pathway is one of the most mutated pathways in cancer:
• PI3KCA activation mutation
• PTEN loss or mutation
• AKT mutation

Monotherapy trials of 1st generation molecule were disappointing

Toxicity is a challenge

How do we optimise the use of these drugs
Understanding how target inhibition drives pathway suppression & efficacy leading to the opportunity to use an intermittent schedule in the clinic to maximise TI for the AKT inhibitor AZD5363

- AZD5363 is a selective AKT inhibitor in Phase II testing
- General kinase inhibitor toxicity (rash, diarrhoea..) plus hyperglycaemia anticipated prior to clinical testing
- Ph1 study involved a conventional approach of dosing a continuous schedule and to MTD

AZD5363: Discovered by AstraZeneca subsequent to a collaboration with Astex Therapeutics (and its collaboration with the Institute of Cancer Research and Cancer Research Technology Limited)
Continuous dosing of AZD5363 in patients shows dose limiting toxicities
Could TI be improved with an intermittent schedule?

- Continuous dosing shows increasing incidence and severity with dose
Intermittent dosing can deliver efficacy in mouse xenograft models

Evidence that high AZD5363 concentrations drive cell apoptosis

- Intermittent dosing can drive apoptosis in the BT474c xenograft model.
- Both regimens deliver same weekly AUC
- Anti proliferative effect (Ki67) observed on both schedules
- Additional apoptotic effect (CC3) observed at higher doses with intermittent schedule
Pathway PKPD model constructed to link AKT with important substrates

AKT and substrates simultaneously modelled

- AZD5363 blocks enzymatic activity of AKT – reduced phosphorylation of substrates
- Mechanistic model captures reduction of phosphorylation of substrates and mechanism related increase in pAKT
- pS6 used as a surrogate for anti-proliferative effects
- pGSK3b used as a surrogate for apoptotic effects
Using pathway model to predict mouse efficacy and prioritise schedules in clinic

Using the model to prioritise schedules in clinic

- The model predicts that alternative intermittent schedules are possible
  - 4 on 3 off schedule: requires +30% of unit dose
  - 2 on 5 off schedule: requires +70% of unit dose
- The total weekly drug burden is lower too

Simulating mouse efficacy

- pS6 and pGSK3β used as a function of tumour growth inhibition to simulate tumour efficacy
- Model adequately captures differences in efficacy observed across dose schedules

<table>
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<th>Continuous (mg bd)</th>
<th>4d on/3d off (mg bd) Relative to cont (x1.3)</th>
<th>2d on/5d off (mg bd) Relative to cont (x1.7)</th>
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<td>(370)</td>
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Conclusions:
Intermittent schedules deliver improved tolerability

- 480mg MTD for 4 days on /3 days off dosing > 400mg predicted to have same activity as 320mg cts MTD
- Implies 4/3 dosing expands therapeutic index (potential for better efficacy with same tolerability)

Based upon tolerability vs Modelled doses, Project takes 4/3 dosing forward
Predicting the optimal human dose schedule that balances efficacy with hyperglycemia for the Pi3Kα/δ inhibitor AZD8835 combined with the AKT inhibitor AZD5363

- AZD8835 is a selective (PI3Kα/δ inhibitor) that shows efficacy in Breast Xenograft Studies
- **Intra-pathway combination with the AKT inhibitor AZD5363 requires the exploration of schedules to optimise efficacy and tolerability**
- This includes the possibility that the combination of these agents will cause hyperglycaemia (Tox) due to primary Pharmacology
PK/PD/E/Tolerability model for AZD8835
Modelling both efficacy and effects on glucose/insulin

- Mechanistic PKPDE model established for AZD8835 using pAKT and CC3 as surrogates for MoA
- Effects on glucose / insulin also modelled to explore schedule options for TI
Intra-pathway Combination Dosing

Study Design: PK & toxicity of combining 2 compounds by different schedules and sequence

Similar study designs delivered for exploration of PD and efficacy
Glucose-insulin modelling
Single agent and combination effects captured by model

- 4 days dosing AZD8835 effects on Glucose and Insulin

- 2 days dosing AZD5363 followed by 2 days dosing AZD8835 effects on Glucose and Insulin
Conclusions
Model used as part of decision making

- Glucose / insulin modelling can explain differences across doses and schedules
- PD/Efficacy modelling has been used to explain why intermittent doses of AZD8835 are efficacious
- Simulations of TI suggested that hyperglycaemia will be manageable for the proposed intermittent doses predicted to be efficacious in patients
- Glucose has been selected as a biomarker of target engagement for the PhI study, offering a more rapid, higher-throughput, less costly biomarker compared to pAKT
- This model is being used as part of the decision making on dose escalation and cohort expansion
Summary and considerations to implement in drug discovery

Pre-clinical data and a PK/PD/E framework can provide a rational approach to explore dose & schedule options that maximise TI and prioritise options to test in patients

Data generation
- Generating and measuring a broader range of pathway biomarkers
- Test extremes of dose and schedules; use compounds with multiple profiles (PK / selectivity)
- Test in multiple in vivo models (reflect diversity of pathway response and population)
- Identify toxicities liabilities early in context of clinical application and build into program

Team working
- Close collaboration between pharmacologists and modellers
- Effective data management tools to share and exploit study data

Decision making
- Approach needs to be a core component of the project team
- Examined at key milestones
Why is this important?
Improving success by understanding failure!

**Outlook**

Lessons learned from the fate of AstraZeneca’s drug pipeline: a five-dimensional framework

David Cook, Deag Brown, Robert Alexander, Ruth March, Paul Morgan, Gemma Satterthwaite and Menelas N. Pangalos

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**Right target**
- Strong link between target and disease
- Differentiated efficacy
- Available and predictive biomarkers

**Right tissue**
- Adequate bioavailability and tissue exposure
- Definition of PD biomarkers
- Clear understanding of preclinical and clinical PK/PD
- Understanding of drug–drug interactions

**Right safety**
- Differentiated and clear safety margins
- Understanding of secondary pharmacology risk
- Understanding of reactive metabolites, genotoxicity, drug–drug interactions
- Understanding of target liability

**Right patients**
- Identification of the most responsive patient population
- Definition of risk–benefit for given population

**Right commercial potential**
- Differentiated value proposition versus future standard of care
- Focus on market access, payer and provider
- Personalized health-care strategy, including diagnostic and biomarkers

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**Drivers of failure**

- **Preclinical (33)**
  - Safety: 82%
  - PK/PD: 15%
  - Efficacy: 6%
  - Strategy: 8%

- **Phase I (27)**
  - Safety: 62%
  - PK/PD: 15%
  - Efficacy: 8%
  - Strategy: 8%

- **Phase IIa (26)**
  - Safety: 35%
  - PK/PD: 57%
  - Efficacy: 8%

- **Phase IIb (8)**
  - Safety: 12%
  - PK/PD: 88%
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