An Integrated Approach to PK/PD/IG/Safety for Biologics

Moderator: Sanela Bilic, PharmD, MBA Novartis Oncology, Clinical Pharmacology
Speakers: Sebastian Spindledreher, PhD, DMPK-Bx, Novartis AG
Jennifer Sims, PhD, Integrated Biologix GmbH
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Notes

- Please turn your cell phones to silent or off
- We would like this to be a very interactive session, hence questions are welcome after each presentation as well as during the panel discussion
- Please do not take pictures of the slides
An Integrated Approach to PK/PD/IG/Safety for Biologics

Sanela Bilic, PharmD, MBA Novartis Oncology, Clinical Pharmacology
Alle Ding' sind Gift und nichts ohn' Gift; allein die Dosis macht, das ein Ding kein Gift ist.

"All things are poison and nothing is without poison, only the dose makes a thing be poison."
Optimal characterization of pharmacological and toxicological exposure-effect-time relationships and extrapolation to humans

- Scale data (*in vitro, in vivo*) and knowledge to human situation → Define safe starting dose(s) & dose escalation strategies
- Identify target organs of toxicity and endpoints for clinical monitoring
- Safety issues observed with biologics are generally related to
  - MoA (exaggerated or unintended pharmacology)
  - Antibody-drug-antibody (ADA)-related effects
  - Off-target effects exist but rare

Roadmap to trials in human requires:

- Use of pharmacologically relevant animal species for safety assessment
- Appropriate pharmacodynamic and safety biomarkers
- Appropriate study designs (dose, regimen and route), sampling time points for optimal description of PK-PD relationships
- Immunogenicity data to aid study interpretation and impact on PK-PD-toxicity relationships

A combined and integrated Safety + PKPD (in vitro and in vivo) + Bioanalytical approach

Slide adapted from Pascal Espie, PhD, Novartis Biologics (DMPK-Bx)
Comparison of target sequence homology between species
  - Polymorphisms in target sequence in humans and animal species and strains?

Relative target binding affinity and receptor occupancy or ligand capture

Kinetics and functional equivalence

Understand the limitations of animal species for the evaluation of risk to humans

Comparative target biology
  - Target expression, distribution and turnover
  - Signaling pathways, endogenous protein interactions and functions

Cross species data is there to allow better translation of preclinical data to humans
What else is needed for appropriate species selection? **In vitro functional assays matter!**

- Evidence is needed in appropriate systems that **target binding is functionally neutralizing or blocking** if this is the desired MoA.
- If desired MoA is target cell killing (ADCC, CDC, apoptosis...), need to **generate the relative in vitro functionality** in appropriate systems.

We need robust in vitro/in vivo PD data in pharmacologically relevant animal species and in vitro in humans (functional assays) for optimal translation of preclinical data to humans.
What else is needed for appropriate species selection?

In vivo PD biomarkers

Provide evidence for target engagement

- This is where an integrated PK-PD / BA strategy is extremely useful
- **Target occupancy** measured using independent occupancy assays, ... however, binding can be determined through ...
  - Nonlinearities in PK arising from binding cellular targets (Target Mediated Disposition)
    - Inflection point as a surrogate marker
  - Measuring the capture of soluble targets (e.g. cytokines)
  - Soluble ligand capture - **Total PD assay** (accumulation of the complex) vs. free assay
  - Increase in endogenous receptor ligand (e.g. IL2, anti-IL2R-basiliximab)
  - Increase in shed receptor

- **Other approaches include**
  - Modulation of a known biological response
  - Receptor down modulation/phosphorylation
  - Downstream signaling, pharmacological outcome

Slide adapted from Pascal Espie, PhD, Novartis Biologics (DMPK-Bx)
Benefits of an Integrated PK/PD-Safety Approach

- **Expression** (how much, where) and turnover
- **Variability**: normal vs. disease, species differences
- Identify ‘sinks’ (shed, decoy receptors), ‘off target’ binding, endogenous binding proteins
- An integrated PKPD(IG) approach can quickly identify appropriate dose and dosage regimen to achieve adequate target suppression/occupancy for desired duration

Target biology can affect PK behavior of NBEs and duration of action
Conclusions
The translational integrated PK/PD/IG and Safety 101

- **Preclinical** evaluation – Design *optimal program* of *in vitro* and *in vivo* studies in relevant animal species to support transition to the clinic

- It is imperative that we understand *target biology* and mechanism, *pharmacology* and *limitations* of preclinical data

- When evaluating a compound, one needs to understand and implement *functional assays*, and *in vivo* PD biomarkers (target engagement) as well as consider interspecies differences in *affinity* and *potency*.

- Combine PKPD, IG, Safety, Pharmacology endpoints in one study (e.g. DRF) to be able to plan and influence better preclinical and clinical studies

- Application of **PKPD modelling** approaches to the selection of appropriate starting doses

- An integrated approach for FIH dose selection need to include *pharmacology* and not just safety margin

- Robust measures of pharmacology/biomarkers
  - **Target engagement** *(e.g. receptor occupancy / ligand binding)*
  - **Mechanism** *(e.g. downstream signalling)*
  - **Effect** *(e.g. pharmacological / clinical response)*
Acknowledgements to many

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- And many, many more