Overview of CDER Nonclinical Resources and Guidance for Approaching First-in-Human (FIH) Studies in Oncology

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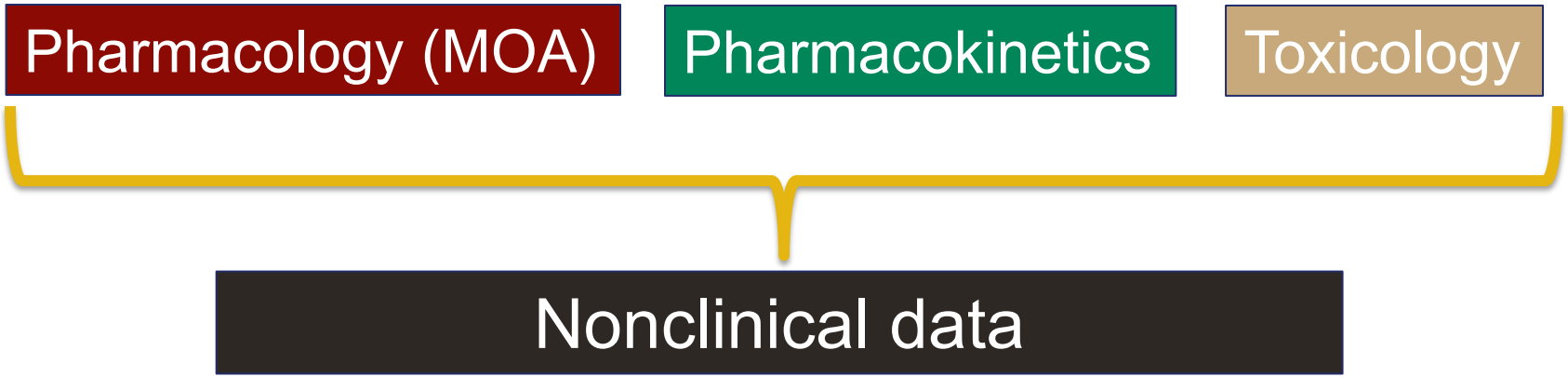
Overview

- Where to start
- What we are looking for
- Potential Pitfalls
- For your consideration

Nonclinical Review



→ Role of nonclinical is front-loaded

MOA = Mechanism of Action

You've your great idea, now what

- You've identified a target
- You've shown that your drug affects that target
- You've shown activity in an in vivo tumor model
- Is that enough? What's next?

Start with the Guidances

- **ICH S9: Nonclinical Evaluation for Anticancer Pharmaceuticals
- **ICH S9 Nonclinical Evaluation for Anticancer Pharmaceuticals Questions and Answers
- ICH S6: Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (and its Addendum)

Typical Recommendations for Anticancer Drugs

- ICH S9 explains basic recommendations for anti-cancer drugs
  - 28-day GLP-compliant toxicology studies in 2 species
  - For biologics (see ICH S6 and its addendum), if scientifically justified, a single GLP study in a pharmacologically relevant species is often acceptable
    - ❖ Primary data used to determine starting dose for FIH trials

Tip: Can initially submit *draft* tox reports with signed histopathology reports

ICH = International Council on Harmonization
GLP = Good Laboratory Practice

Special Consideration of Immune-Activating Drugs

- ICH S9 includes exception on standard toxicology-based methods for starting dose of immune agonists:
  - "For biopharmaceuticals with immune agonistic properties, selection of the start dose using a minimally anticipated biologic effect level (MABEL) should be considered."
- MABEL approach relies heavily on pharmacology studies
- Use the **totality of data** to justify the proposed FIH dose

Saber H et al., 2016, Regul Toxicol Pharmacol, 81:448-456
Saber H et al., 2017, Regul Toxicol Pharmacol, 90:144-152

DHOT Publications on FIH Dose Selection

- An FDA oncology analysis of immune activating products and first-in-human dose selection. PMID: 27743776.
- An FDA oncology analysis of CD3 bispecific constructs and first-in-human dose selection. PMID: 28887049.
- An FDA oncology analysis of antibody-drug conjugates. PMID: 25661711.
- An FDA oncology analysis of toxicities associated with PBD-containing antibody-drug conjugates. PMID: 31325532.
- Pharmacokinetic models for first-in-human dose selection of immune-activating products in oncology. PMID: 38561147.

DHOT = Division of Hematology Oncology Toxicology

What are my endpoints?

- The CFSAN Redbook
  - Detailed descriptions of toxicological endpoints to include
  - Large array of study types (gene- to chronic tox)

CFSAN = Center for Food Safety and Applied Nutrition (FDA)

Key Endpoints in GLP Tox Studies

- Mortality
- Clinical Observations
- Body Weight
- Food Consumption
- ECG (non-rodent)
- Ophthalmology
- Hematology
- Clinical Chemistry
- Gross Pathology
- Organ Weights
- Histopathology
- Toxicokinetics

-Additional endpoints as needed (e.g., cytokines)

Good Laboratory Practice

- GLP ≠ study with good controls, endpoints
- GLP = these things, but also details about archiving, study conduct, responsibility
- GLP is described in the Code of Federal Regulations (21 CFR part 58)

GLP cont.

- Consider the CRO or conducting lab
- Make sure they can format the data in SEND (*Standard for Exchange of Nonclinical Data*)
  - Single dose toxicity, repeat-dose toxicity, and carcinogenicity studies for commercial INDs initiated after December 17, 2017; Technical Rejection Criteria now active
  - Study Data Standards Resources
- MUST plan ahead! (schedule far in advance)
- These studies can be expensive but foundational

GLP cont.

- If you have questions/uncertainty about GLP study design:
  - Consult an expert first
  - Request a pre-IND meeting with FDA before initiating the study
    - We can provide general feedback on major red flags and missing endpoints

What else is recommended for FIH study?

- Depends on your product
- Proof-of-concept/MOA data
  - Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products
- Screening data
- Concentration response data

- Immunomodulators: In vitro Cytokine Release Assays
- Safety Pharmacology (hERG; in vivo endpoints)

Stumbling Blocks/Pitfalls

- Common *nonclinical* reasons for going on hold in oncology:
  - Concerns with FIH starting dose and/or dose escalation
  - Missing studies/supporting information
  - Severe toxicity
    - An FDA analysis of clinical hold deficiencies affecting investigational new drug applications for oncology products. PMID 31678263.

- Starting dose: Scale by BSA (mg/m^2) for small molecules/ADCs; body weight (mg/kg) for large biologics (BSA conversions; Table 3)
- GLP-related: *Need signed pathology report*
- Provide data supporting selection of pharmacologically relevant species for biologics/oligonucleotides

Special Considerations and Additional Resources

Radiopharmaceuticals	• Oncology Therapeutic Radiopharmaceuticals: Nonclinical Studies and Labeling Recommendations Guidance for Industry
ADCs	• ICH S9 Q&A; Saber H, Leighton JK. 2015; Saber H et al., 2019
Novel excipients	• FDA Guidance for Industry: Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients
Botanicals	• Consider how your product differs from what has been given to humans previously • Botanical Drug Development Guidance for Industry

ADCs = Antibody-drug conjugates

Request a Pre-IND Meeting!

- INTERACT meeting
  - FDA input on unique challenges; use of novel alternative methods (NAMs)
- Type B pre-IND meeting
  - Follow-up opportunities available
- Provide enough data that we can answer your question(s)- don't submit full study reports
- We won't agree to specific starting dose at pre-IND

INTERACT = INitial Targeted Engagement for Regulatory Advice on CBER/CDER ProducTs

Summary

- There is a lot of nonclinical data needed to open an IND
- Let ICH S9 be your starting point
- Invest in good GLP tox studies
- Seek out a regulatory consultant if needed
- Request a pre-IND meeting!

Closing Thought

*Use these tips to improve your nonclinical package for your next FIH IND submission for oncology indications

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