Preclinical Development [CDER]: **Biological Therapeutics for Cancer Treatment**

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Disclaimer

- **The opinions expressed by Dr. McDougal are his, and do not reflect official policy of the US or FDA.**
- **Information presented was obtained from publicly available sources.**
- **No official support or endorsement by FDA is intended or should be inferred.**

Objectives for this Presentation

- **Present a FDA/CDER nonclinical reviewer's perspective**
- **Provide insight into our approaches for reviewing your IND-enabling, nonclinical safety data**
- **Introduce/remind you about current guidance for toxicology testing.**

CDER/Office of Oncology Drug Products (OODP) Regulates Biologic Cancer Therapies

OODP has 3 divisions:
•Division of Biologic Oncology Products (DBOP)

- **DBOP regulates:**
  - **Monoclonal antibodies**
  - **Recombinant proteins**
  - **Cytokines**
  - **Growth factors**
  - **Enzymes**
  - **Biological immunomodulators**
  - **Other (non-vaccine) therapeutic immunotherapies**
  - **Radiolabeled biologics for therapeutic use**

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OODP/DBOP

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- **OODP/DDOP** **(Division of Drug Oncology Products)**
  - **‘Traditional’ cytotoxic compounds and ‘small molecules’**
  - **Hormones and metabolic factors**
  - **Synthetic peptides**
  - **Oligonucleotides and siRNA**
  - **Small molecules conjugated to antibodies**

Examples of DBOP Regulated Products:

http://www.fda.gov/cder/Offices/OODP/DBOP_products.htm

Drug Name®	US Adopted name	Drug Name®	US Adopted name
Avastin	Bevacizumab	Aranesp	Darbepoetin alfa*
Bexxar	Tositumomab / I^{131} tositumomab	Epogen, Procrit	Epoetin alpha*
Campath	Alemtuzumab	Kepivance	Palifermin
Erbitux	Certuximab	Leukine	Sargramostim
Herceptin	Trastuzumab	Neuopgen	Filgrastim
Rituxan	Rituximab	Neulasta	Pegfilgrastim
Soliris	Eculizumab	Intron A	Interferon alfa-2b*
Vectibix	Panitumumab	Neumega	Oprelvekin
Zevalin	Irbrutumomab	Ontak	Denileukin diflitox
Elitek	Rasburicase	Proleukin	Aldesleukin
Elspar	Asparaginase	Roferon	Interferon alpha-2a*
Oncaspar	Pegaspargase		

*For cancer indications only

What Do We Need to See in an IND for a New Anti-Cancer Biologic?

- **Chemistry & Manufacturing Controls (Quality)**
- **Nonclinical (Pharmacology/Toxicology)**
- **Clinical**

Nonclinical:

1. **Pharmacodynamics (PD)**
   - **the biology, activity, mechanism of action, potency**
2. **Pharmacokinetics (PK)**
   - **Distribution, elimination – AUC, C_{max}, V_d, $T_{1/2}$**
   - **anti-product antibody – formation, clearance**
3. **Toxicology**
   - **Testing in relevant animal species**

Supporting the First-in-Human (FIH) Study– Nonclinical Reviewer Perspective (1)

- It is helpful if your IND clearly informs and explains HOW you have demonstrated safety.
- The FDA (nonclinical) Toxicologist may have a different perspective from the Industry Toxicologist if:
  - I've already reviewed an IND for this
  - I have access to FDA institutional knowledge
  - I evaluate your contract lab reports differently
- Alternative approaches may be acceptable. Please:
  - Consider requesting a pre-IND meeting to discuss.
  - Justify them in the IND.

Supporting the FIH Study– Nonclinical Reviewer Perspective (2)

- **Toxicologist's job: to verify that the nonclinical data support the safety of the proposed clinical trial.**

- **Toxicity:**
  - **Can we predict what the toxicities will be in patients?**
  - **Are they acceptable for this indication?**
  - **What is their progression / recovery?**
  - **Can we monitor clinically for the toxicity?**

Supporting the FIH Study– Nonclinical Reviewer Perspective (3)

- **Toxicologist's job: to verify that the nonclinical data support the safety of the proposed clinical trial.**

- **Appropriateness of:**
  - **Start dose,**
  - **Dose escalation scheme,**
  - **Maximum dose.**
  - **Schedule of dosing,**
  - **Maximum duration of dosing.**
  - **Exclusion / inclusion criteria,**
  - **Clinical monitoring,**
  - **Communication of concerns and risks.**

Supporting the FIH Study– Nonclinical Reviewer Perspective (4)

- **Demonstration of pharmacologic / biologic activity is the first step in the development of ANY new drug or biologic.**
- **Nonclinical does not review for clinical efficacy.**
- **'Proof of concept' studies are reviewed to understand the potential risks in context (risk:benefit).**
  - **For biologics, most toxicity is exaggerated pharmacology.**
  - **'Are the animal data predictive?'**
  - **'What does the animal response mean for patient safety?'**
  - **'Is this observation incidental or treatment-related?'**

Examples

- **Tumor vs normal cell growth inhibition ➲ show that healthy tissues are not targeted?**
- **I*n vivo* studies of anti-tumor activity in tumor xenograft models ➲ identify the lowest biologically active dose?**

Nonclinical Review: Step 1

Preliminary questions:

- **WHO ?**

  (the index [patient] population)

- **WHAT ?**

  (What is the intended pharmacological action?)

- **HOW ?**

  (the protocol)

- **All the nonclincial data get filtered through these lenses** (risk:benefit)**.**

Nonclinical Review: Step 2

1st question: What data directly predict effects of treatment in patients? *PD data*:

- **The target**
  - **Distribution / expression**
  - **Mechanism of Action (MOA)**
  - **Differences in healthy versus cancer**

- **How the product interacts with the target**
  - **Binding, affinity, specificity**
  - **Potency**
  - **Downstream effects**
  - **Effect of disease on the product**
  - **Other targets? Low affinity or off-target binding**

Nonclinical Review: Step 3

2nd question: Are the animal test species pharmacologically and toxicology relevant? *PD data*:

- **<u>Relevant species</u>:**
- **Does the animal respond to treatment the same way that humans will?**
  - Expression / distribution of the target
  - Homology / orthology
  - MOA, downstream effects
  - Binding, affinity, specificity, potency
  - PK

- **<u>Non-relevant species</u>:**
- **May miss some or all of the pharmacologic and toxicologic activities that will occur in humans.**
- **Underpredict toxicity ➲ Not useful for dose-setting.**

Why are the Pharmacokinetic (PK) Studies Important?

- PK of a new biologic allows estimation of:
  - Exposure to agent after any given dose
    - Correlation with pharmacologic/therapeutic effect
  - Duration of exposure (half-life)
    - Dosing interval for the clinical study
    - Time to reversal of any biologic or toxic effects
  - Development of anti-product antibodies
    - Both total and neutralizing activity
    - Do they affect clearance of the product?

Each pivotal *in vivo* toxicology study should include PK.

Toxicology Studies for Anti-Cancer Biologics (1) – Study Design

- Usually standard assays in healthy animals.
- For biologics, main groups and recovery groups at all doses.

- Should include a dose that exceeds the therapeutic effect (➲ exaggerated pharmacology)
- Dosing regimen should mimic the clinical trial
  - # of doses, timing of dosing

- Monitor PK & antibody development.
- Incorporate safety pharmacology into tox. studies.

Toxicology Studies for Anti-Cancer Biologics (2) - Duration

- **Nonclinical duration should equal at least 1 clinical cycle** (plus recovery period)**.**
- **For some indications, cancer patients may receive multiple cycles (until progression or SAE).**
- **Dosing to steady-state is recommended.**
  - **Ex- For a mAb with $t_{1/2}$= 8 – 11 days, 5 weekly doses to support FIH may be appropriate.**

Toxicology Studies for Anti-Cancer Biologics: Reviewer Perspective (1)

- **Expecting to see exaggerated pharmacology.**
  - Looking for toxicities secondary to the main effect.
  - Also looking for off-target toxicities.

- **Is there a no adverse effect level (NOAEL)?**
  - Critical target tissues/organs/systems
  - Severity, reversibility
  - Clinically monitorable

- **Do the observed effects correlate with PK?**
  - Dose-response
  - Reversibility after clearance
  - Anti-product antibody effects on PK

Toxicology Studies for Anti-Cancer Biologics: Reviewer Perspective (2)

- **For Biologics, NH Primates may be the only relevant model.**
- **Non-rodent studies are not powered for statistical significance.**
  - **Look for individual animal responses.**

- **Working with limited data, regulatory decisions are made based on reasonable assumptions**
  - **The observed effect *may* be treatment-related.**
  - **The observed effect *may* indicate unacceptable toxicity.**

Toxicology study results and setting the FIH dose

- Pivotal toxicology studies' route & dosing regimen should mimic proposed clinical use
  - Alternative routes/regimens acceptable in some cases

- Ideal: high-dose was toxic & mid- or low-dose was NOAEL

- **FIH dose extrapolated from animal results using adequate safety margins**
  - **Recognizing that biologics may have a smaller therapeutic index than 'small molecules'**
  - **For FIH trials with anti-cancer biologics, goal is to start at a biologically-active dose (MABEL)**

Specific Safety Concerns for Biologics?

1. **Many biologics are highly selective and specific. Not equally active across species.**
2. **PK differences between humans and animals, especially for humanized mAbs.**
3. **Anti-product antibodies may affect / limit *in vivo* testing.**
4. **Immunogenic responses (or lack of response) in animals may not predict human responses.**

Specific Safety Concerns for mAbs?

In addition to the concerns for all biologics:

- **Bind targets in healthy tissues (cross-reactivity).**
- **Exaggerated pharmacology.**
- **Slow elimination.**
- **Slow recovery from toxicity.**

Specific Safety Concerns for Cytokines & Growth Factors?

In addition to the concerns for all biologics,

- **Species-specificity**
- **Interactions with host endogenous cascade**
- **Tumor-promoting potential**
- **Immunogenicity/antibody production**
  - **effects on neutralization of endogenous counterpart to test agent**

CMC and Nonclinical – Reviewer Perspective

- Product development during preclinical testing phase is acceptable
- Use of non-GMP protein products allowed for nonclinical testing

- Need to know exactly what was tested, and how it differs from the clinical material
- Need demonstration of comparability of the pivotal nonclinical study's test material with the clinical grade material

Forthcoming Guidance

Coming soon…(?...)

- ***Guidance for Industry and Reviewers: Nonclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals***
- **Please send comments (when the drafts are published)**

ICH S9: Preclinical Guideline on Oncology Therapeutic Development

- **Concept paper endorsed 5/2007**
- http://www.ich.org/cache/html/3559-272-1.html

Some Further Resources

- **ICH Guidances** (www.ich.org/cache/compo/276-254-1.html)
  - **ICH S6: Safety Studies for Biotechnological Products**
  - **ICH M3: Timing of Pre-clinical Studies in Relation to Clinical Trials**
  - **ICH S5a: Detection of Toxicity to Reproduction for Medicinal Products**

- **Points to Consider**
  - **Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use - 1997**
    - www.fda.gov/cber/gdlns/ptc_mab.pdf
  - **Points to Consider in the Manufacture and Testing of Therapeutic Products for Human Use Derived from Transgenic Animals – 1995**
    - www.fda.gov/cber/gdlns/ptc_tga.txt

Thanks!

Goals of nonclinical testing are to protect patients, speed development, reduce waste, and inform consent.

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- **Thank you for listening.**
- **Comments and questions solicited.**

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