Nonclinical Data to Support FIH Clinical Trials for Cancer Immunotherapies

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Disclaimer

- The views disseminated in this talk are my own and do not necessarily represent the views of the FDA
Regulation of Cancer Immunotherapy Products by FDA

CDER
- Monoclonal Abs
  - Rituximab
  - Ipilimumab
  - Pembrolizumab (2014)
  - Nivolumab (2014)
- Fusion proteins
  - Blinatumomab (2014)
- Cytokines
  - IL-2
  - INF-\(\gamma\)

CBER
- Genetically modified T cells
- Cancer Vaccines
  - Sipuleucel-T
- Oncolytic Vectors
  - Imlygic (2015)
Regulatory Guidances of Interest

International Conference on Harmonization
• S9 Nonclinical Evaluation for Anticancer Pharmaceuticals (2010)*
• S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals plus Addendum (2012)

FDA Guidance for Industry
• Preclinical Assessment of Investigational Cellular and Gene Therapy Products (2013)

*ICH S9 Concept Paper on Q&A’s published in October
Typical Requirements for Anticancer Drugs

• The ICH Guidance for Industry S9 explains the basic requirements for the development of anti-cancer drugs
  ❖ To initiate clinical trials for anti-cancer therapeutics you typically need 28-day toxicology studies in 2 species
  ❖ For biologics, as discussed in ICH S6 and its addendum a single pharmacologically relevant species is often acceptable
  ❖ These studies are the primary data used to determine the acceptability of the proposed starting dose for first-in-human trials
Goals of a Nonclinical Program

• Identify the pharmacologic properties of a pharmaceutical
• Estimate a safe initial dose level for the first human exposure
• Understand the toxicological profile of a pharmaceutical to help identify safety parameters for clinical monitoring
  – e.g., identification of target organs, exposure-response relationships and reversibility
Challenges with Cancer Immunotherapeutics

• Even more frequently than with therapeutic antibodies targeting non-immune associated targets (e.g. VEGFR/EGFR), species relevance has been an issue
Non-Immune Target: EGFR

Findings in monkey

- Skin toxicity-erythema, irritation, crust (often with secondary skin infections), flaky skin, loss of fur, abrasion and/or eyelid swelling and
- Eye redness (with associated secondary conjunctivitis)
- Infusion Reactions
- Mucosal toxicity

Erbitux Label

- Dermatologic and Soft Tissue Toxicity: Monitor for dermatologic and soft tissue toxicities and withhold or discontinue Vectibix for severe or life-threatening complications. Limit sun exposure. (5.1, 5.7)
- Increased tumor progression, increased mortality, or lack of benefit in patients with KRAS-mutant mCRC: Determine KRAS-mutant tumor status in an experienced laboratory using an FDA-approved test. (5.2)
- Electrolyte Depletion/Monitoring: Monitor electrolytes and institute appropriate treatment. (5.3)
- Infusion Reactions: Terminate the infusion for severe infusion reactions. (5.4)
- Pulmonary Fibrosis/Interstitial Lung Disease (ILD): Permanently discontinue Vectibix in patients developing ILD. (5.6)
- Ocular Toxicities: Monitor for keratitis or ulcerative keratitis. Interrupt or discontinue Vectibix for acute or worsening keratitis. (5.8)
Immune Targeted Biologic: Anti-PD-1

- Affinity of binding to human and cynomolgus monkey PD-1 has been similar for most products
- EC$_{50}$ for blocking interactions between the PD-1 receptor and its ligands is similar between species
- At exposures well above those seen clinically, there was no clear autoimmunity
Special Recognition of Immune-Targeting Drugs

• ICH S9 specifically mentions concerns about using standard methods based on toxicology studies alone to set the 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.”

• Determining a MABEL relies heavily on a variety of pharmacology studies
Calculating a MABEL

• There is no universal approach for determining a FIH dose based on a MABEL, regardless of indication

• Useful data inputs:
  – *In vitro* pharmacology data from target cells from human and toxicology species
  – Concentration-effect data from *in vitro* and *in vivo* studies
  – If using animal data, then provide a comparison of
    • Animal-human differences in exposure/drug distribution
    • Animal-human differences in expression level and distribution of target
    • Animal-human differences in affinity of target binding and intrinsic efficacy
    • Duration and reversibility of biologic effect
    • Dose-exposure relationship (PK/PD)
Things We are Looking For When We Receive an Immunotherapeutic

• Pharmacology of the targeted pathway
  – Is the target an agonist or antagonist of immune activity

• Assessment of Cytokine Release Potential

• Studies using human cells that take into account multiple mechanisms of action

• Receptor Occupancy
Case Example: Anti-X

- Target X is expressed on both activated immune cells and on normal epithelial cells.
- Interactions between the target on immune cells and on tumor cells inhibit immune activation resulting in tumor escape.
Points to Consider

• The antibody binds activated human PBMCs, but no binding was detected on monkey PBMCs despite binding to monkey protein via surface plasmon resonance

• This particular target was not as well described in the literature as PD-1 in regards to its immune related activity and its expression was not restricted to immune cells
Start Dose Considerations

• Because of the uncertainty about the relevance of the rhesus monkey and the indirect immune activating potential of the therapy, a MABEL approach was proposed

• PK data from the monkey toxicology study was considered in estimating a predicted human exposure at the starting dose
Combinations

- In general, combination toxicology studies are not required
- If a first-in-human study where there was no clinical experience with either product was proposed, then a combination study might be warranted
- In cases where there is limited clinical experience with one or both products, then combination pharmacology studies are often recommended
Case 2: 2 Products with Clinical Experience

• The Sponsor proposed the combination of a kinase inhibitor with an anti-PD1 antibody; there was significant clinical experience with both products

• No pharmacology or toxicology studies were submitted to support the combination
Issue

• There were findings of severe cardiac inflammation in the toxicology studies for the kinase inhibitor

• Clinically, no clear cardiac findings had been noted to date
Outcome

• Despite the lack of clinical findings to date, there was a concern about the potential of the combination to exacerbate this finding and make it clinically significant

• No additional nonclinical studies requested

• The Sponsor was asked to lower the starting dose of the kinase inhibitor to a dose with a predicted exposure ~20% of that causing cardiac inflammation in nonclinical studies
Combination Issues: Drugs with no Clinical Experience

• The Sponsor submitted an IND for a first-in-human study using 2 products with no clinical information.

• The IND was placed on partial clinical hold for initiation of the combination portion of the trial until
  - Clinical dosing had been completed for each of the monotherapies for at least 1 cohort
  - In vitro pharmacology studies were completed to help justify the combination dose.
Complete Response

• The Sponsor completed dosing of the first cohort for each product with no DLTs
• Proposal to use the 1st cohort doses for each product in the combination arm was still not supported with such limited experience and the potential for synergy

• Limited pharmacology data was submitted; used to determine a reasonable dose in combination with available clinical data
Final Thoughts

• There have been some limitations that have prevented a reliance on traditional toxicology studies for safety predictions of some immunotherapeutics

• A thorough examination of the mechanism of immune activity is critical throughout development to inform not only on the safety of first-in-human trials, but also throughout development and into postmarketing
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