INTRODUCTION TO PRECLINICAL DEVELOPMENT OF COMBINATION THERAPIES

NorCal SOT & PBSS Spring Symposium 2017

Joe Francisco

EVERY STEP OF THE WAY

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DISCLOSURE

- I am not an expert in combination drug development
- What I know about combination drug development I've learned from the guidance documents, attending seminars, and working on designing programs
  - "Approaches to Safety Assessment of Combination Therapeutic Agents", 2016 ACT annual meeting
    - Lorrene Buckley, Eli Lilly
    - Philip Gatti, FDA
    - Kristina Chadwick, BMS
    - Anne Chester, Gilead
    - Jessica Hawes, FDA
  - "Combination Therapy: Fundamentals, Advances & Case Studies", NorCal SOT & PBSS Spring Symposium 2017

AVAILABLE GUIDANCE

- ICH M3(R2), section 17: Combination drug toxicity testing (2009)
- FDA Guidance for Industry: Nonclinical Safety Evaluation of Drug or Biologic Combinations (2006)
- EMA: Guideline on the Non-Clinical Development of Fixed Combinations of Medicinal Products (2008)

- Similarities and some differences between these guidance documents
- Envision various forms of combinations:
    - Fixed dose combinations (single dosage form)
    - Co-packaged products
    - Adjunctive therapy (products for co-use other than FDC)

FACTORS INFLUENCING THE NEED FOR PRECLINICAL SAFETY STUDIES

- Status of the drugs/biologics intended for combination
  - Late stage entity or NME/NBE
  - 3 scenarios: LSE + LSE, LSE + NME, NME + NME
- What's known about individual drugs
  - Clinical and preclinical data for individual drugs
  - Prior human experience with combination: publications?
  - Similar or distinct target organ toxicities, preclinical and clinical?
  - Potential for PK / metabolic interactions?
  - Narrow or wide safety margins?
  - Clinical/preclinical experience with drug class?
  - Duration of use: acute versus chronic

SCENARIO 1: LSE + LSE

- Combination safety studies may not be needed, especially if:
  - Non-overlapping toxicities or MOA
  - Low risk of DDI
  - Wide safety margins
- What if combination safety studies are needed?
  - “Usually, assessment of the drug combination may be conducted in only one species…may be cases (for) conducting studies in two species.” FDA guidance
  - Which species? Factors include:
    - Relevant pharmacology/cross-reactivity for biologics
    - Target organs in animals and humans
  - What duration of studies
    - Typically “3 months’ duration could be considered for chronic indications.”

SCENARIO 1: LSE + LSE

- If combination safety studies are needed, what design?
  - Dose levels?
    - "The FDA suggests…several dose levels of the combination and a high dose of each drug alone."

		Drug A		
		Control	Low	High
Drug B	Control	X		X
	Low		X	
	High	X		X

SCENARIO 2: LSE + NME

- Standard battery of preclinical studies generally required for NME
- Combination toxicology studies up to 90 days required
    - Generally in one species but…see previous slide

SCENARIO 3: NME + NME

- Standard battery of preclinical studies generally required for NMEs
- Combination toxicology studies up to 90 days required
    - Generally in one species but…see previous slide
- HOWEVER
    - Toxicology studies with just the combination may be appropriate if the NMEs are to be marketed ONLY as combination

COMBINATION STUDIES WITH IMMUNO-ONCOLOGY AGENTS

- ICH S9: Nonclinical Evaluation for Anticancer Pharmaceutical
  - Individual agents should be well studied in toxicology studies.
  - In general, combination toxicology studies are not warranted.
  - BUT…“based on available information, a determination should be made (regarding combo tox).”

IMMUNO-ONCOLOGY COMBO: EXAMPLE 1

- Nivolumab + Ipilimumab (Selby et al PLOSone 2016)
  - Nivolumab: anti-PD1 antibody, FDA approval in 2014 for metastatic melanoma
  - Ipilimumab: anti-CTLA-4 antibody, FDA approval in 2011 for melanoma
- Combination toxicology
  - Cynomolgus monkeys, weekly x 4
    - 1) control, 2) Nivo 10 mg/kg + Ipi 3 mg/kg, 3) Nivo 50 mg/kg + Ipi 10 mg/kg
  - Results
    - Inflammatory events (GI) not seen in cynos with either agent alone
- Clinically Nivo + Ipi used for metastatic melanoma and NSCLC
- Was combination toxicology <u>required</u> by FDA or solely sponsor's initiative?

IMMUNO-ONCOLOGY COMBO: EXAMPLE 2

- Anti-PD1 antibody + kinase inhibitor (example borrowed from J Leighton, 2017 SOT)
  - Significant clinical experience with both agents
  - Presumably non-overlapping toxicities
    - Toxicology studies with kinase inhibitor indicated severe cardiac inflammation
- Path to combination clinical trial
  - No pharmacology or toxicology studies were required by FDA to support combination clinical trial
    - Starting dose with kinase inhibitor lowered

IMMUNO-ONCOLOGY COMBO: EXAMPLE 3

- 2 novel immuno-oncology agents (example borrowed from J Leighton, 2017 SOT)
  - No clinical information on either agent
  - Sponsor proposed initial trial as combination
    - No information presented on whether toxicology studies were single agent, combination, or both
- Path to combination clinical trial
  - Partial clinical hold
    - FDA required clinical dosing, at least one cohort, for each monotherapy before testing combination

CONCLUSIONS

- Guidance documents provide general concepts
- Each proposed combination program is unique and depends on numerous factors
    - Regulatory status of each drug, nonclinical/clinical data toxicities and target organs, clinical indication/duration, etc.
- IO agents present unique opportunities/challenges for combination studies
- In general, when combination toxicology studies are needed, 90 days max in 1 (or 2) species
- Consult with regulators before going too far

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