INTRODUCTION TO PRECLINICAL DEVELOPMENT OF COMBINATION THERAPIES

NorCal SOT & PBSS Spring Symposium 2017

Joe Francisco
• 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)
• 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.”

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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 required 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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