Berkeley School of Public Health

FORUM for Collaborative RESEARCH

Combination Working Group

Presenter
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HBV Forum 3
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Introduction

- Aim: Facilitate the advancement of regulatory science for HBV combination therapy development. Goal to facilitate open, adaptive, iterative design for testing combinations
- Objectives:
  - Develop a conceptual framework that provides adequate safeguards for trial participants while allowing rapid testing and innovation regarding clinical trials of new combinations
  - Focus on how to work creatively in Phase 2 to find combinations worthy of more exhaustive testing

Work Crystallized to 2 Deliverables After EASL

- White paper, suitable for publication, describing Working Group recommendations
  - Status: Author draft ready for review by full Working Group with submission to follow shortly
  - Authors from academia, FDA, EMA, industry
- Need identified to establish subgroup to provide guidelines and approach to deal with conundrum of separating disease flares from DILI
  - Status: Initial co-chairs unable to participate - subgroup in process of being re-constructed

General Principles Proposed in White Paper

1. There should be a *solid scientific rationale* for pursuing the combination being proposed
   - Generally should be backed up by appropriate pre-clinical work
2. There should be a *careful comparison of preclinical toxicology findings* with the candidate drugs to be used in combination:
   - to determine if target organs of toxicity overlap
   - consideration of conducting pilot combination toxicologic experiments

General Principles Proposed (cont'd)

3. There should be a *review of clinical adverse events and/or pharmacologic effects* information to again seek areas of overlapping toxicity.
   - May influence safety evaluations to be required within the clinical trial
   - May influence such elements as starting doses, titration rules, and stopping rules
   - May also point to the need for conducting combination toxicology
4. There should be a *review of the routes of metabolism and clearance* for candidate combination drugs to assess potential for interactions
   - Likewise, effect of each drug on metabolic pathways and transporters, again with an eye toward identifying possible interactions.
   - Might identify the need for pre-clinical or clinical assessments of pharmacokinetic interactions

General Principles Proposed (cont'd)

5. Determine handling of liver "flares" in all protocols
   - It is anticipated that effective combinations may produce more frequent, and possibly more exaggerated, flares than currently available drugs
   - Especially complicated when one or more drug in the combination has a toxicity signal in the liver in preclinical toxicology studies
   - Mechanisms should be included in trial procedures to be certain that flares are identified early, and any emergent changes in liver synthetic function
   - Any protocol directed procedures, including stopping rules, are observed
6. CHB patients with compensated *cirrhosis should not be studied until combinations have demonstrated* strong efficacy, acceptable safety, and progressed into phase III trials
   - Patients with advanced cirrhosis should be excluded and Childs A/B decompensated cirrhosis should not be a clinical target for HBV cure until safety in compensated cirrhosis established.

Additional Piece of Advice

Seek the advice of regulatory agencies

Timelines

- Submission of position paper: Goal would be before year end

- Establishment of DILI/Flare subgroup co-chaired by:
  - Robert Fontana (academic)
  - Maria Beumont-Mauviel (industry)

Where Do We Go From Here

- Flare Subgroup
  - Get organized and operational
  - Deliverable should minimally include operational recommendations for dealing with transaminase increases and other changes in liver function in the context of HBV clinical trials
- What's Next For Full Working Group?
  - With more drugs progressing into Phase II trials, there is the opportunity to monitor experiences
  - Share/disseminate relevant learnings and seek opportunities to facilitate safe combination use as experience gained

Working Group Members

- Ibironke Addy
- Nezam Afdhal
- Ryan Anderson
- Tanvir Bell
- Maria Beumont-Mauviel
- Carol Brosgart
- Nathaniel (Nat) Brown
- Jordan Feld
- Anuj Gaggar
- Edward Gane
- Bruce Given
- Redharkrishnan (Kris) Iyer
- Christine Kukka
- Pietro Lampertico
- Seng Gee Lim
- Stephen Locarnini
- Uri Lopatin
- Mala Maini
- Patricia Mendez
- Veronica Miller
- Jules O'Rear
- Sandra Palleja
- Daniela Paulsen
- Jean-Michel Pawlotsky
- Kimberly Struble
- David Suhy
- John Sullivan-Bolyai
- Andrew Vaillant
- Cynthia Wat
- Kelly Wong
- Teresa Wright
- Pedro Goicochea

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Thank You!