Combination Drug Guidance and TB Therapeutics

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Challenges in TB Drug Development

• Epidemic affects impoverished countries with poor health infrastructure
  – Less incentive to invest
  – Difficulties in diagnosis, managing therapy, conducting trials
  – Need for multiple drug regimens and good adherence adds challenge

• Organism challenging treatment target
  – Slow replication, dormant state
  – Cell wall barrier to entry
  – Ability to develop resistance
Investigational Drug Co-Development Draft Guidance

• Issued in response to concerns by ID and cancer communities on need for combination therapies

• Both groups participated in submission of a draft guidance facilitated by Friends of Cancer Research

• FDA issued draft in 12/10; many comments received, mostly for additional clarification

• Should issue final soon
Concepts in Guidance

- Drug combo intended to treat a serious disease or condition
- Compelling biological rationale for combination use
- Data exist that strongly suggest the combination would be better than either alone—e.g., greater activity, more durable response or better toxicity profile
- Compelling reason not to develop as single agents
Toxicologic Workup

• Depends on clinical plan
• For drugs where Phase 1 data as single agents will be available, refer to ICH M3(R2) guidance on this specific subject
• For drugs very limited clinical data as single agents will be generated, more animal data on the combination needed
• Cancer drugs have specific ICH guidance (ICH S9)
Early Human Studies

• May or may not be feasible as single agents
• Desirable to have single agent dose-related toxicity and PK (often done in volunteers without the disease)
• Flexibility according to the ethics of the situation
Proof of Concept

• Various scenarios provided in guidance
• Goals include (to the extent not already established):
  – Demonstrate contribution of each component to the effect
  – Provide evidence of effectiveness of combo
  – Optimize dosing
Phase 3 Trials

• May be conducted with combo
• May wish to vary doses on different arms of study
• Should consult with Agency prior to finalizing protocol(s), and more generally, about entire drug development program
TB Drug Development Programs

- Resistance to TB therapies both MDR and XDR strains are eroding our ability to treat people with TB
- However, this is an exciting time in TB drug development with several new drugs in the process
- Important to have additional therapies for TB and MDR and XDR TB
Approach to TB Drug Development: Traditional

- New drug developed through Phase 1 in ordinary manner
- Studied in TB patients in combination with already approved drugs as add on vs standard therapy alone
- Used in patients where standard therapy is appropriate and clinically sound
Breakthrough Approach to Development of TB Drugs

- May be possible to combine several new agents to get a breakthrough in TB therapy
- Possible breakthroughs: shorter time to cure, effectively treat MDR TB
- Is it possible to drug patients with drug sensitive TB in 2-4 months?
- Can we get better tolerated regimens?
Breakthrough TB Therapy

• In setting of a breakthrough, would not expect clinical studies that establish the contribution of each of the component drugs
Pairing Traditional Approach with Breakthrough

• Manage inherent risk of breakthrough approach
• Develop single drugs in parallel with combination regimen development
• Helpful to understand contributions: could we get to a state more like other infections where choice of regimen is driven by individual susceptibility testing?
We Still Need Better Tools

• Outcome assessments
• Can we use drug development trials as a test bed to evaluate better outcome measures?
• Also need to improve diagnostics and susceptibility testing
• All measures need to be usable in settings where TB is epidemic
Working Together, We can Take the Steps Needed to Control this Disease Worldwide