Approaches to TB Drug Development (Past, Present, and Future)

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Disclosures

• Dr. Spigelman is a full time employee of the Global Alliance for TB Drug Development
Approaches to TB Drug Development
Past, Present, and Future

• Ensure explicit clarity on problem being attacked
• Provide practical, cost effective, implementable solution for the identified problem
  – getting a drug approved is necessary, but not sufficient
  – solution does not have to be optimized, but it does have to provide a net compelling benefit to the patient, payer, and health care system
    • would substituting a drug in first line therapy, but not shortening duration, increasing cure, or decreasing side effects provide a net benefit?
    • does adding an additional drug to poor second line regimens to obtain higher sputum conversion rates provide a net benefit?
TB Alliance – Approaches to TB Drug Development

Present

• Unified Pathway – moving forward
• Unified Pathway – moving backwards
Unified Drug Sensitive/Drug Resistant Regimen Development Path

**Stage**

**Testing Model**
- Mouse Model
- Healthy Subjects
- Monotherapy 2-Week EBA
- Combination/Regimen EBA
- Regimen 2-Month Study
- Registration

**Pre clinical**
- Single drug
- Combination regimen
- Relapse free sterilizing activity

**Phase 1**
- Single and repeat dose
- Safety, tolerability
- PK
- Drug Interactions

**Phase 2**
- Single drug
- Dose ranging
- DS patients (feasibility)

**Phase 3**
- Optimized dose in regimen
- Test final regimen
- DS patients
- DS and DR sensitive to regimen
- DS vs standard (HRZE)
- Are DR necessary?

**Go/No-Go Criteria:**
- PK to support daily dosing
- Clear effect to reduce CFU count
- As good as HRZE standard
- Better Than HRZE

**Unified Drug Sensitive/Drug Resistant Regimen Development Path**

**Phase**

**Testing of Model**
- Mouse Model
- Healthy Subjects
- Monotherapy 2-Week EBA
- Combination/Regimen EBA
- Regimen 2-Month Study
- Registration

**Study Attributes**
- PK to support daily dosing
- Clear effect to reduce CFU count
- As good as HRZE standard
- Better Than HRZE
Nix-TB Phase 3 Trial in XDR-TB

Patients with XDR-TB or who have failed or are intolerant to MDR-TB Treatment

- Pretomanid 200 mg qd
- Bedaquiline 200 mg tiw after 2 week load*
- Linezolid 1200 mg qd**

6 months of treatment
Additional 3 months if sputum culture positive at 4 months

Follow up for relapse-free cure over 24 months

**Amended from 600 mg bid strategy
Lack of “instantaneous” readout of response (degree of TB organisms killed) — Severely limits implementation of adaptive designs

Lack of a predictive quantitative relationship between “Phase 2 readout” (organisms killed) and “Phase 3 readout” (cure) — Unclear how to translate culture conversion into duration of therapy for effecting cure — Preclinical models, however, are predictive for rank order
Scheme for Mouse Relapse Experiments

(15) mice held for (3) months without treatment and then sacrificed to determine permanent cure without relapse
Mouse Relapse Data

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<th>M1.5 (+3)</th>
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<th>M3 (+3)</th>
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</tbody>
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Rank order: BPaMZ > BPaZ > BPaM > PaMZ > RHZ
Future Approaches to TB Drug Development

Without new technological advances

• Large simplified clinical trials
• Multiple arm Phase 3 studies with “large” non-inferiority margins
  – Examine multiple durations of therapy within single trial
Thank You!