Treatment of Multidrug-resistant Tuberculosis (MDR-TB)


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National Jewish Health
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Disclosures

• Research grant
  – Insmed: Phase II multicenter randomized placebo controlled clinical trial of inhaled liposomal amikacin in pulmonary NTM infections

• Advisory Board:
  – Insmed
  – Johnson and Johnson
  – Spero Pharmaceuticals
  – Horizon Pharmaceuticals
  – Paratek

• Data Monitoring Committee
  – Otsuka
Treatment of Multidrug-resistant Tuberculosis (MDR-TB)

- What is MDR-TB?
- Brief epidemiology of MDR-TB
- Rapid diagnosis of MDR-TB
- Approach to Treatment
- New Drugs for Treatment of MDR-TB
Definitions for Multidrug and Extensively Drug Resistant TB

**Drug Susceptible**

**Any Drug Resistance**

**MDR-TB**: Resistance to at least isoniazid and rifampin

**XDR-TB**: MDR plus resistance to fluoroquinolones and one of the second-line injectable drugs (amikacin, kanamycin, or capreomycin)

10 million TB cases
Treatment of Multidrug-resistant Tuberculosis (MDR-TB)

- What is MDR-TB?
- Brief epidemiology of MDR-TB
- Rapid diagnosis of MDR-TB
- Approach to Treatment
- New Drugs for Treatment of MDR-TB
Global Prevalence of MDR-TB

558,000 MDR/RR-TB cases in 2017

- 3.5% of new MDR-TB cases
- 18% of previously treat MDR-TB cases

WHO Global Report, 2018
MDR-TB Globally

558,000 patients with MDR/RR-TB

160,684 cases of MDR-TB were detected and notified in 2017

139,114 (87%) were enrolled on treatment

55% treatment success
Primary MDR TB Among U.S.-Born versus Non-U.S.–Born Persons, United States, 1993–2017
Pathogenesis and Transmission of Drug-resistant TB

- M. tuberculosis
- Mutation → Nature
- Resistant Mutants
- Selection → Inadequate treatment
- Acquired Resistance
- Transmission → HIV
- Primary Resistance
- Inadequate infection control
- Diagnostic delay
Treatment of Multidrug-resistant Tuberculosis (MDR-TB)

• What is MDR-TB?
• Brief epidemiology of MDR-TB
• **Rapid diagnosis of MDR-TB**
• Approach to Treatment
• New Drugs for Treatment of MDR-TB
# Time to DST Results by Method

<table>
<thead>
<tr>
<th>Method</th>
<th>Solid Culture</th>
<th>1&lt;sup&gt;st&lt;/sup&gt;-line DST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microscopy</td>
<td>6-8 wks</td>
<td>3-4 wks</td>
</tr>
</tbody>
</table>

**Microscopy (24 hrs)**
- Solid Culture (6-8 wks)
- 1<sup>st</sup>-line DST (3-4 wks)

**MDR-TB diagnosis**
- after 9 to 12 weeks

**Liquid Culture (2-3 wks)**
- 1<sup>st</sup>-line DST (1-3 wks)

**MDR-TB diagnosis**
- after 3 to 5 weeks

**LPA (24 hrs)**
- 1<sup>st</sup>-line DST (24 hrs)

**RR-TB diagnosis**
- In 2 hrs

**MDR-TB diagnosis**
- after 9 to 12 weeks

**RR-TB diagnosis**
- In 2 hrs
# Molecular Markers for Resistance to *M. tuberculosis*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Gene</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampin</td>
<td><em>rpoB</em></td>
<td>97%</td>
<td>97%</td>
</tr>
<tr>
<td>Isoniazid</td>
<td><em>katG, inhA</em></td>
<td>86%</td>
<td>99%</td>
</tr>
<tr>
<td>Ethambutol</td>
<td><em>embB</em></td>
<td>79%</td>
<td>94%</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td><em>pncA</em></td>
<td>86%</td>
<td>96%</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td><em>gyrA, gyrB</em></td>
<td>79%</td>
<td>99%</td>
</tr>
</tbody>
</table>

Molecular Diagnostic Flow

Decentralized

MDR-TB suspect?

Xpert MTB/RIF

Centralized

RIF Resistant

GenoType MTBDRs/ VER 2.0

Treatment of Multidrug-resistant Tuberculosis (MDR-TB)

• What is MDR-TB?
• Brief epidemiology of MDR-TB
• Rapid diagnosis of MDR-TB
• Approach to Treatment
• New Drugs for Treatment of MDR-TB
# Grouping of MDR-TB Drugs

<table>
<thead>
<tr>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>Group D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoroquinolone</td>
<td>Second-line injectable</td>
<td>Other Core Second-line</td>
<td>Add-on agents</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>Amikacin</td>
<td>Ethionamide/Prothionamide</td>
<td>D1: Pyrazinamide</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>Capreomycin</td>
<td>Cycloserine/Terizidone</td>
<td>Ethambutol</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>Kanamycin (Streptomycin)</td>
<td><strong>Clofazimine</strong></td>
<td>High-dose INH</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Linezolid</strong></td>
<td>D2: Bedaquiline</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Delamanid</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>D3: <strong>P-aminosalicylic acid</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Imipenem/meropenem</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Amoxacillin/Clavulanate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Thioacetazone)</td>
</tr>
</tbody>
</table>

**Other Core Second-line**
- D1: Pyrazinamide
- Ethambutol
- High-dose INH
- D2: Bedaquiline
- Delamanid
- D3: **P-aminosalicylic acid**
  - Imipenem/meropenem
  - Amoxacillin/Clavulanate
  - (Thioacetazone)
## Grouping of MDR-TB Drugs

<table>
<thead>
<tr>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Core Drugs</strong></td>
<td><strong>Clofazimine</strong>&lt;br&gt;<strong>Cycloserine OR</strong>&lt;br&gt;<strong>Terizidone</strong></td>
<td><strong>Ethambutol</strong>&lt;br&gt;<strong>Delamanid</strong>&lt;br&gt;<strong>Pyrazinamide</strong>&lt;br&gt;<strong>Imipenem-cilastin OR</strong>&lt;br&gt;<strong>meropenem</strong>&lt;br&gt;<strong>Amikacin OR</strong>&lt;br&gt;<strong>(Streptomycin)</strong>&lt;br&gt;<strong>Ethionamide OR</strong>&lt;br&gt;<strong>Prothionamide</strong>&lt;br&gt;<strong>P-aminosalicylic acid</strong></td>
</tr>
<tr>
<td>Levofloxacin OR&lt;br&gt;Moxifloxacin&lt;br&gt;Bedaquiline&lt;br&gt;Linezolid</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Red – moved up  Blue - moved down
# Building a Treatment Regimen with 2016 Update

## Step 1
**Group A (Include all 3)**
- Levofloxacin (Moxifloxacin)
- Bedaquiline
- Linezolid

**Goal:** \( \geq 4 \) likely effective drugs and \( \geq 3 \) after bdg is stopped

## Step 2
**Group B (Add one or both)**
- Clofazimine
- Cycloserine (terizidone)

## Step 3
**Group D1 (Add to complete the regimen)**
- Ethambutol
- Delamanid
- Pyrazinamide
- Imipemen/Meropenem*
- Amikacin (streptomycin)
- Ethionamide (prothionamide)
- PAS

* Plus amoxacillin/clavulanate
Relative Risk for Treatment Failure or Relapse and Death vs. Success

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Treatment failure or relapse versus treatment success</th>
<th>Death versus treatment success</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number treated</td>
<td>Adjusted odds ratio (95% confidence limits)</td>
</tr>
<tr>
<td>A Levofloxacin OR moxifloxacin</td>
<td>3,143</td>
<td>0.3 (0.1–0.5)</td>
</tr>
<tr>
<td>Bedaquiline</td>
<td>1,391</td>
<td>0.3 (0.2–0.4)</td>
</tr>
<tr>
<td>Linezolid</td>
<td>1,216</td>
<td>0.3 (0.2–0.5)</td>
</tr>
<tr>
<td>B Clofazimine</td>
<td>991</td>
<td>0.3 (0.2–0.5)</td>
</tr>
<tr>
<td>Cycloserine OR terizidone</td>
<td>5,483</td>
<td>0.6 (0.4–0.9)</td>
</tr>
</tbody>
</table>

WHO Consolidated Guidelines on Drug-resistant TB, 2019
Relative Risk for Treatment Failure or Relapse and Death vs. Success

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Treatment failure or relapse versus treatment success</th>
<th>Death versus treatment success</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number treated</td>
<td>Adjusted odds ratio (95% confidence limits)</td>
</tr>
<tr>
<td>C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethambutol</td>
<td>1 163</td>
<td>0.4 (0.1–1.0)</td>
</tr>
<tr>
<td>Delamanid</td>
<td>289</td>
<td>1.1 (0.4–2.8)*</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>1 248</td>
<td>2.7 (0.7–10.9)</td>
</tr>
<tr>
<td>Imipenem–cilastatin OR meropenem</td>
<td>206</td>
<td>0.4 (0.2–0.7)</td>
</tr>
<tr>
<td>Amikacin</td>
<td>635</td>
<td>0.3 (0.1–0.8)</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>226</td>
<td>0.5 (0.1–2.1)</td>
</tr>
<tr>
<td>Ethionamide OR prothionamide</td>
<td>2 582</td>
<td>1.6 (0.5–5.5)</td>
</tr>
<tr>
<td>p-aminosalicylic acid</td>
<td>1 564</td>
<td>3.1 (1.1–8.9)</td>
</tr>
<tr>
<td>Other medicines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kanamycin</td>
<td>2 946</td>
<td>1.9 (1.0–3.4)</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>777</td>
<td>2.0 (1.1–3.5)</td>
</tr>
<tr>
<td>Amoxicillin–clavulanic acid</td>
<td>492</td>
<td>1.7 (1.0–3.0)</td>
</tr>
</tbody>
</table>

WHO Consolidated Guidelines on Drug-resistant TB, 2019
### Serious Adverse Events in Patients on Longer MDR-TB Regimen

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Absolute risk of SAE</th>
<th>95% credible interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bedaquiline</td>
<td>2.4</td>
<td>[0.7, 7.6]</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>2.9</td>
<td>[1.4, 5.6]</td>
</tr>
<tr>
<td><em>Amoxicillin–clavulanic acid</em></td>
<td>3.0</td>
<td>[1.5, 5.8]</td>
</tr>
<tr>
<td>Clofazimine</td>
<td>3.6</td>
<td>[1.3, 8.6]</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>4.0</td>
<td>[2.4, 6.8]</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>4.1</td>
<td>[1.9, 8.8]</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>4.5</td>
<td>[2.3, 8.8]</td>
</tr>
<tr>
<td>Cycloserine/terizidone</td>
<td>7.8</td>
<td>[5.8, 10.9]</td>
</tr>
<tr>
<td><em>Capreomycins</em></td>
<td>8.4</td>
<td>[5.7, 12.2]</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>8.8</td>
<td>[5.6, 13.2]</td>
</tr>
<tr>
<td>Ethionamide/prothionamide</td>
<td>9.5</td>
<td>[6.5, 14.5]</td>
</tr>
<tr>
<td>Amikacin</td>
<td>10.3</td>
<td>[6.6, 17.0]</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>10.8</td>
<td>[7.2, 16.1]</td>
</tr>
<tr>
<td><em>p</em>-aminosalicylic acid</td>
<td>14.3</td>
<td>[10.1, 20.7]</td>
</tr>
<tr>
<td>Thioacetazone</td>
<td>14.6</td>
<td>[4.9, 37.6]</td>
</tr>
<tr>
<td>Linezolid</td>
<td>17.2</td>
<td>[10.1, 27.0]</td>
</tr>
</tbody>
</table>

WHO Consolidated Guidelines on Drug-resistant TB, 2019
Treatment Duration of Longer MDR-TB Regimens

Intensive: 6-7 months

Culture conversion: 15-17 months after conversion

Continuation: 18-20 months

WHO Consolidated Guidelines on Drug-resistant TB, 2019
WHO Policy Recommendation
Shorter Course MDR-TB Regimen

Recommendation:
In patients with RR or MDR-TB
• who have not been treated with second-line drugs and
• in whom resistance to FQNs and SLI agents has been excluded or is considered to be highly unlikely
a shorter MDR-TB regimen of 9-12 mos may be used instead of a conventional regimen
(conditional recommendation, very low certainty in the evidence)
**Shorter Course Regimen**

“Bangladesh Regimen”

- Observational study
- (1997-2007)
- Previously untreated with SLD
- Serial introduction of regimens aimed at improving treatment success

Short Course Standardized Regimen for MDR-TB

1+2: Oflo-based, Pth plus INH throughout
3: Oflo-based, Pth throughout, no INH
4: Oflo-based, Pth intensive phase, INH throughout
5: Oflo-based, Pth intensive phase, INH and Clo throughout
6: Gati-based, Pth and INH intensive phase, Clo throughout

4(+)KCGEHZP/5 GEZC

Completion – 5.3%  Death – 5.3%
Cure – 82.5%  Default – 5.8%
Success – 87.8%  Failure – 0.5%
Relapse – 0.5%

## Shorter Course Regimen in 9 African Countries: Treatment Outcomes

<table>
<thead>
<tr>
<th>Treatment Outcomes</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cured</td>
<td>728 (72.4%)</td>
</tr>
<tr>
<td>Completed</td>
<td>93 (9.2%)</td>
</tr>
<tr>
<td><strong>Success (Cure + Completed)</strong></td>
<td><strong>81.6%</strong></td>
</tr>
<tr>
<td>Failure</td>
<td>59 (5.9%)</td>
</tr>
<tr>
<td>Death</td>
<td>78 (7.8%)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>48 (4.8%)</td>
</tr>
</tbody>
</table>

STREAM Trial

Phase 3, randomised controlled trial with a non-inferiority design

Regimen A: WHO-approved MDR-TB Regimen. 20 mos
Regimen B: KM+INH+PTO+ MFX+CFZ+EMB+PZA 9-1 mos

Primary outcome – favorable status at 132 wks

STREAM Trial
Results

424 patients randomized, 383 included in modified intention to treat population

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Shorter regimen</th>
<th>Longer regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable status*</td>
<td>78.8%</td>
<td>79.8%</td>
</tr>
<tr>
<td>Death</td>
<td>8.5%</td>
<td>6.4%</td>
</tr>
<tr>
<td>Adverse Reactions (Grade 3 or 4)</td>
<td>48.2%</td>
<td>45.4%</td>
</tr>
<tr>
<td>QTc prolongation $\geq$ 500 ms</td>
<td>11.0%</td>
<td>6.4%</td>
</tr>
<tr>
<td>Acquired resistance</td>
<td>3.3%</td>
<td>2.2%</td>
</tr>
</tbody>
</table>

*Cultures negative for *M. tuberculosis* at 132 weeks and at a previous occasion with no intervening positive culture or previous unfavorable outcome

Choosing the MDR-TB Regimen

Is any of the following present?
- Preference by the clinician and patient for a longer MDR-TB regimen
- Confirmed resistance to or suspected ineffectiveness of a medicine in the shorter MDR-TB regimen (except isoniazid resistance)*
- Exposure to one or more second-line medicines in the shorter MDR-TB regimen for >1 month (unless susceptibility to these second-line medicines is confirmed)
- Intolerance to medicines in the shorter MDR-TB regimen or risk of toxicity (e.g. drug-drug interactions)
- Pregnancy
- Disseminated, meningeal or CNS TB
- Any extrapulmonary disease in PLHIV
- One or more medicines in the shorter MDR-TB regimen not available

**YES**

Failing shorter regimen or non-response, drug intolerance, emergence of any other exclusion criterion

- Individualized, longer MDR-TB regimens

**NO**

Standardized, shorter MDR-TB regimen may be offered (conditional recommendation)

* Strains from MDR/RR-TB patients should ideally be tested for resistance to fluoroquinolones and other regimen components regardless of the type of MDR-TB treatment regimen offered.
Eligibility For Short-course Regimen for MDR-TB in Europe

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Drug Resistance in MDR-TB (%)</th>
<th>Eligible for Short-Course Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>SLID</td>
</tr>
<tr>
<td>Austria</td>
<td>80</td>
<td>41</td>
</tr>
<tr>
<td>France</td>
<td>114</td>
<td>30</td>
</tr>
<tr>
<td>Germany</td>
<td>70</td>
<td>23</td>
</tr>
<tr>
<td>Portugal</td>
<td>200</td>
<td>51</td>
</tr>
<tr>
<td>TBnet*</td>
<td>148</td>
<td>28</td>
</tr>
<tr>
<td>Total</td>
<td>612</td>
<td>37</td>
</tr>
</tbody>
</table>

*16 countries in Europe

Lange C, et al. AJRCCM 2016;194:1029
Treatment of Multidrug-resistant Tuberculosis (MDR-TB)

- What is MDR-TB?
- Brief epidemiology of MDR-TB
- Rapid diagnosis of MDR-TB
- Approach to Treatment
- New Drugs for Treatment of MDR-TB
Bedaquiline (TMC207)

- **Drug Class** – oxazolidinone
- **Mode of action** – inhibits mycobacterial ATP synthase
- **Dosage** – 400 mg/day for 14 days then 200 mg/day three times weekly (very long half-life of about 5 months)
- **Activity** – sterilizing and bactericidal
- **Toxicity** – well tolerated, QTc prolongation
- **Drug interactions** – Substrate of cytochrome P450 3A4 (CYP3A4)

Bedaquiline (TMC207) for MDR-TB

- Phase 2, randomized, controlled trial
- 47 patients with MDR-TB randomized to TMC207 or placebo plus standard five-drug regimen
- Results
  - Reduced time to conversion
  - Increased proportion that converted (48% vs 9%)
  - Mild to moderate AEs with nausea more common with TMC207 (26% vs 4%)

Diacon AH, et al. NEJM 2009;360:2397
# Mortality in Bedaquiline Phase II Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>No. of deaths</th>
<th>Bedaquiline</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>No.</td>
<td>(%)</td>
</tr>
<tr>
<td>C202</td>
<td>Randomized, open-label, dose ranging EBA study</td>
<td>2/45</td>
<td>4.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>C208 (Stage 1)</td>
<td>2/23</td>
<td>8.7</td>
</tr>
<tr>
<td></td>
<td>Double-blind, randomized, placebo-controlled superiority trial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C208</td>
<td></td>
<td>C208 (Stage 2)</td>
<td>10/79</td>
<td>12.6</td>
</tr>
<tr>
<td></td>
<td>Double-blind, randomized, placebo-controlled superiority trial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C209</td>
<td>Noncomparative, single-arm open label trial</td>
<td>16/233</td>
<td>6.9</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>30/380</td>
<td>7.9</td>
<td></td>
</tr>
</tbody>
</table>

CDC MMWR 2013;62;1-12
Safety and Efficacy of Bedaquiline in Treatment of MDR/XDR-TB

- Phase 2, multicenter, open-label single-arm study
- 31 sites, 11 countries
- 233 patients with MDR-TB
  - 19% pre-XDR
  - 16% XDR
- Treated with background regimen plus 24 weeks of bedaquiline

Proportion of Patients Culture Positive

- 72% converted

QTcF Interval in Patients Treated with Bedaquiline for 24 Weeks

2 patients had QTcF > 500 msec (both on clofazimine and one with hypokalemia)

Effectiveness and Safety of Bedaquiline for Treatment of MDR/XDR-TB

- Retrospective study
- 25 sites in 15 countries
- 428 MDR-TB patients
  - 21% HIV +
  - 45.6% XDR-TB
- Treated with individualized regimen
- Median exposure to BDQ – 168 days
- Median overall treatment duration – 18 months

### Treatment Outcomes for Bedaquiline Containing Regimen

<table>
<thead>
<tr>
<th>Outcome</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Success</td>
<td>176 (71%)</td>
</tr>
<tr>
<td>Cure</td>
<td>154 (62%)</td>
</tr>
<tr>
<td>Completion</td>
<td>22 (9%)</td>
</tr>
<tr>
<td>Death</td>
<td>33 (13%)</td>
</tr>
<tr>
<td>Default</td>
<td>18 (7%)</td>
</tr>
<tr>
<td>Failure</td>
<td>19 (8%)</td>
</tr>
<tr>
<td>Transfer out</td>
<td>1 (0.4%)</td>
</tr>
</tbody>
</table>

Delamanid (OPC-67683)

• **Drug Class** – nitroimidazole
• **Mode of action** – inhibits cell wall synthesis
• **Dosage** – 100mg/day twice daily first 2 months then 200 mg daily for 4 months
• **Activity** – bactericidal
• **Toxicity** – well tolerated, QTc prolongation
• **Drug interactions** – not significant
Delamanid for MDR-TB
Trial 204

- Phase 2 randomized, placebo-controlled trial
- 481 MDR-TB patients were randomized to delamanid or placebo plus WHO regimen
- Results
  - Increased proportion that converted by 2 months
    - 100 mg 45.4%
    - 200 mg 41.9%
    - Placebo 29.6%
  - AEs evenly distributed
    - QT prolongation more common with delamanid

Gler MT, et al. NEJM 2012;366:2151
Delamanid
Trial 213

- **Design:** Randomized, placebo controlled Phase III trial
  - 511 randomized to: DLM+OBR vs PLC OBR

- **Primary end-point:** distribution of time to sputum culture conversion (SCC) over 6 months using MGIT

- **Results:**
  - DLM+OBR had 6 day shorter median time to SCC (P=0.0562)
  - With “bookending” analysis, DLM+OBR had a 13 day median time to SCC (P=0.0052)
  - Subjects with risk factors for negative outcomes were over-represented in DLM+OBR group – those with bilateral cavitation and fluoroquinolone resistance (5% vs 0%)

Source: Otsuka
Delamanid
Trial 213 Safety Results

- No new safety findings
- Discontinuation due to AEs occurred in about 2% in each arm
- QTcF prolongation occurred in 5% on DLM vs 3% on placebo
  - QTcF values were about 50% lower at peak affect compared with trial 204 (Phase II), even with >20% receiving moxifloxacin
  - Low albumin was not associated with QTcF prolongation
- No additional safety findings in HIV+ patients

Source: Otsuka
# Treatment Outcomes with Delamanid in Programmatic Settings

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Population</th>
<th>Culture Conversion</th>
<th>QTc Prolongation &gt; 500 ms</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hafkin, 2017</td>
<td>Europe, Asia, Africa</td>
<td>77 MDR, XDR*</td>
<td>80%</td>
<td>3.8%</td>
<td>8 (10%)</td>
</tr>
<tr>
<td>Kuksa, 2017</td>
<td>Latvia</td>
<td>10 MDR, preXDR, XDR</td>
<td>100%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Chang, 2018</td>
<td>Hong Kong</td>
<td>11 preXDR or XDR</td>
<td>94% at 24 wks</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mok, 2018</td>
<td>S. Korea</td>
<td>32 MDR, XDR</td>
<td>94% at 24 wks</td>
<td>9%</td>
<td>0</td>
</tr>
<tr>
<td>Mohr, 2018</td>
<td>S. Africa</td>
<td>103 MDR/XDR (77% HIV+)</td>
<td>81% within 6 mos</td>
<td>2%</td>
<td>5 (11%)</td>
</tr>
</tbody>
</table>

*compassionate use
Early Safety and Efficacy of Combination of Bedaquiline and Delamanid

- Retrospective study
- 28 patients with MDR-TB from Armenia, India, South Africa
  - 11 (39% HIV +)
  - 24 (86% FQ resistant)
  - 14 (50%) XDR-TB
- Treatment with median of 7 drugs including bedaquiline and delamanid
- Results
  - 75% converted cultures to negative by 6 months
  - 16 SAE in 7 patients
  - No QTc > 500 msec

2018 Global New TB Drug Pipeline

**Discovery**
- Diarylthiazoles
- DprE1 Inhibitors
- InhA Inhibitor
- Mtb energy metabolism
- Macrolides
- Mycobacterial Gyrase Inhibitors
- Arylsulfonamides
- Inhibitors of MmpL3, Translocase-1, Clp, PKS13
- Oxazolidinones
- Squaramides

**Preclinical Development**
- Early Stage Development
  - CPZEN-45*
  - Spectinamide - 1810*
  - SPR720*
  - TB-47*
  - Sanfetrinem
  - S-004992*
- GMP/GLP Tox.
  - TBAJ-587
  - TBAJ-876
  - GSK-286*
  - TBI-223
  - S-004992*

**Clinical Development**
- Phase 1
  - BTZ-043*
  - TBI-166
  - Macozinone* (PBTZ-169)
  - OPC-167832*
  - GSK-656* (070)
  - TBA-7371*
  - Contezolid (MRX-4/MRX-1)
  - Macozinone* (PBTZ-169)

- Phase 2
  - Telacebec (Q203*)
  - Delpazolid (LCB01-0371)
  - Sutezolid (PNU100480)
  - SQ-109*

- Phase 3
  - Bedaquiline* (TMC-207)
  - Delamanid* (OPC-67683)
  - Pretomanid* (PA-824)

*New chemical class. Known chemical classes for any indication are color coded: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide, beta-lactam.

1 New Molecular Entities not yet approved, being developed for TB or only conditionally approved for TB. Showing most advanced stage reported for each. Details for projects listed can be found at [http://www.newtbdrugs.org/pipeline/clinical](http://www.newtbdrugs.org/pipeline/clinical)

Ongoing projects without a lead compound series identified: [http://www.newtbdrugs.org/pipeline/discovery](http://www.newtbdrugs.org/pipeline/discovery)

Underline = new to Phase since March 2018

**Working Group on New TB Drugs**

www.newtbdrugs.org

Updated: October 2018
Pretomanid (PA-824)

- **Drug Class** - nitroimidazole
- **Mode of action** – Reactive nitrogen compound, inhibits cell wall synthesis
- **Dosage** – 100-200 mg/day
- **Activity** – sterilizing and bactericidal
- **Toxicity** – well tolerated
- **Drug interactions** – not significant
Nix-TB Trial in MDR/XDR-TB:

Pretomanid + bedaquiline + linezolid for 6 months

Patients with XDR-TB or Who Have Failed MDR -TB Treatment

- 109 subjects (62% XDR, 51% HIV+)
- Results of 1st 75 patients
  - Cure at six months – 89%
  - Relapse – 2 patients
  - Death – 8 patients (6 in early stages of treatment)

Follow up for relapse-free cure over 24 months

Additional 3 months if sputum culture positive at 4 months

Conradie F, et al. IUATLD 2018
Regimens in Clinical Trials
Injectable Free!

<table>
<thead>
<tr>
<th>Clinical trial</th>
<th>Regimen</th>
<th>Duration (wks)</th>
<th>Completed</th>
</tr>
</thead>
<tbody>
<tr>
<td>NiX-TB</td>
<td>Bdq, Pa, Lzd</td>
<td>24-36</td>
<td>Yes</td>
</tr>
<tr>
<td>MDR END</td>
<td>Dlm, Lzd, Lfx, Z</td>
<td>36-52</td>
<td>Ongoing</td>
</tr>
<tr>
<td>STREAM 2 # C</td>
<td>Bdq, Cfz, E, Z, Lfx, H, Pto followed by Bdq, Cfz, E, Z, Lfx</td>
<td>16, 24</td>
<td>Ongoing</td>
</tr>
<tr>
<td>PRACTECAL # 1</td>
<td>Bdq, Pa, Lzd</td>
<td>36</td>
<td>Ongoing</td>
</tr>
<tr>
<td>PRACTECAL # 2</td>
<td>Bdq, Pa, Lzd, Cfz</td>
<td>36</td>
<td>Ongoing</td>
</tr>
<tr>
<td>PRACTECAL # 3</td>
<td>Bdq, Pa, Lzd, Mfx</td>
<td>36</td>
<td>Ongoing</td>
</tr>
<tr>
<td>endTB # 1</td>
<td>Bdq, Lzd, Mfx, Z</td>
<td>36</td>
<td>Ongoing</td>
</tr>
<tr>
<td>endTB # 2</td>
<td>Bdq, Cfz, Lzd, Lfx, Z</td>
<td>36</td>
<td>Ongoing</td>
</tr>
<tr>
<td>endTB # 3</td>
<td>Bdq, Dlm, Lzd, Lfx, Z</td>
<td>36</td>
<td>Ongoing</td>
</tr>
<tr>
<td>endTB # 4</td>
<td>Dlm, Cfz, Lzd, Lfx, Z</td>
<td>36</td>
<td>Ongoing</td>
</tr>
<tr>
<td>endTB # 5</td>
<td>Dlm, Cfz, Mfx, Z</td>
<td>36</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>


Courtesy: KJ Seung
Summary

• Either a shorter course or longer standard course can be used
• Current treatment regimens should include ≥ 4 likely effective drugs when using a longer course regimen
• Bedaquiline and delamanid appear to be effective drugs that are well tolerated
• Pretomanid, in combination with other active drugs, is highly effective
• New drugs currently in Phase II trials will hopefully provide even more active and well tolerated options