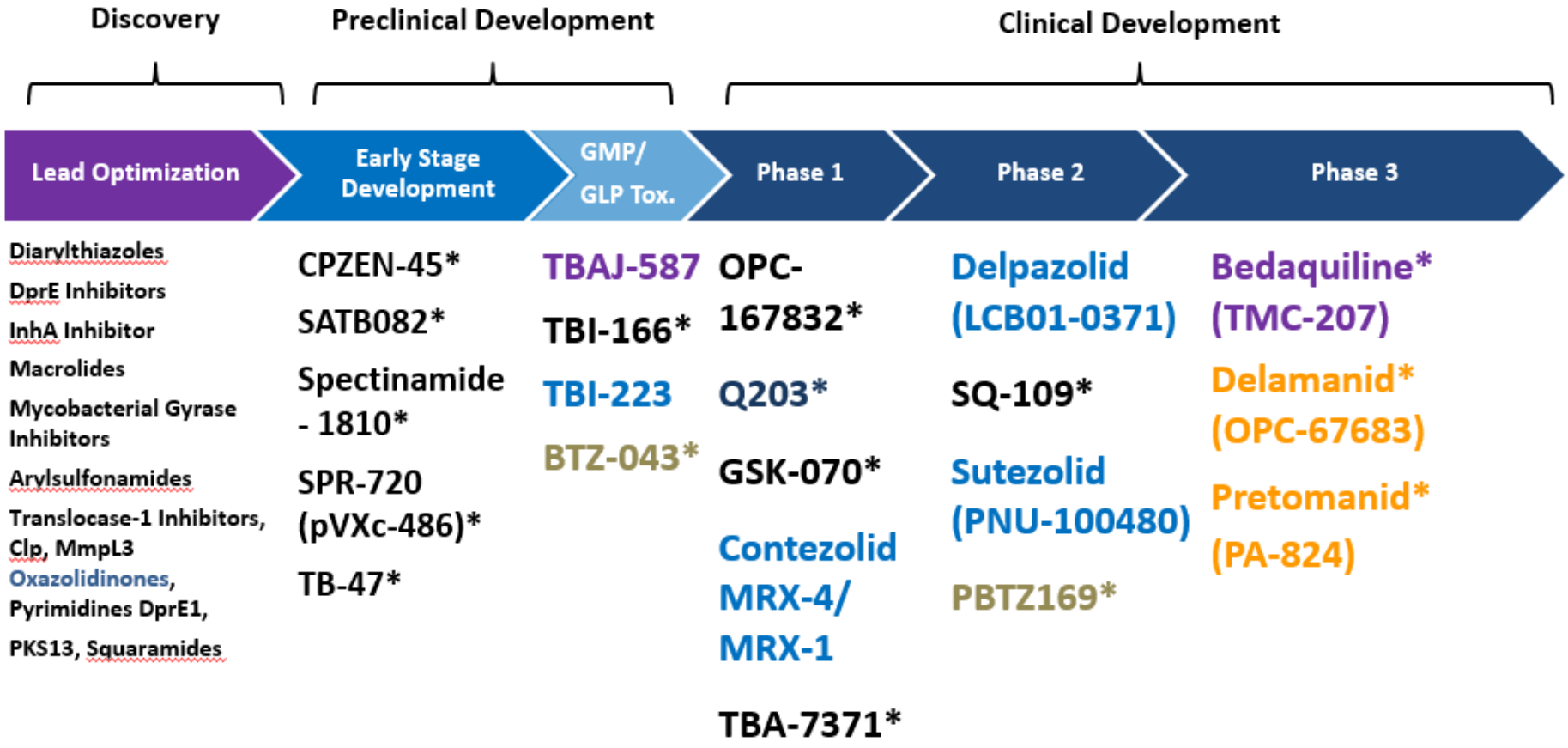
MDR-TB Clinical Trials Landscape: Current and Future Trials

C. Robert Horsburgh, Jr.
Boston University

Outline

- New drugs for MDR-TB treatment
- “Repurposed” drugs for MDR-TB treatment
- New regimens under study for treatment of Multidrug-Resistant TB (MDR-TB)
- Regimens for treatment of LTBI with MDR
- MDR-TB Trials of the future

Global New TB Drug Pipeline [1]



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

[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

Ongoing projects without a lead compound series identified can be viewed at http://www.newtbdrugs.org/pipeline/discovery

WORKING GROUP ON NEW TB DRUGS

www.newtbdrugs.org

Updated: September 2017

New Antituberculosis Drugs in Clinical Development, 2018

Drug	Class	Company	Status
Bedaquiline	Diarylquinolone	Janssen	Phase 3
Delamanid	Imidazooxazole	Otsuka	Phase 3
Pretomanid	Imidazooxazine	GATB	Phase 3
Sutezolid	Oxazolidinone	Sequella, GATB	Phase 2
Delpazolid	Oxazolidinone	LegoChem	Phase 2

“Repurposed” Drugs for TB Treatment

Repurposed Antituberculosis Drugs in Clinical Development, 2016

Drug	Class	Company	Status
Rifampicin	Rifamycin	Various	Phase 2
Levofloxacin	Fluoroquinolone	Various	Phase 2
Clofazimine	Iminophenazine	Novartis	Phase 3
Linezolid	Oxazolidinone	Pfizer	Phase 2
Rifapentine	Rifamycin	Sanofi-Aventis	Phase 3
Moxifloxacin	Fluoroquinolone	Bayer/GATB	Phase 3

Clofazimine in MDR-TB Treatment

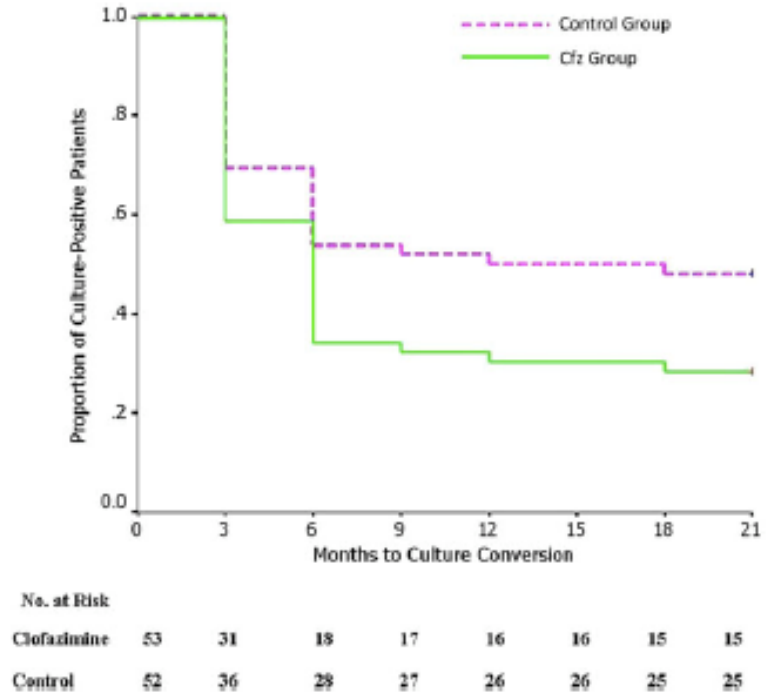


Figure 2. Kaplan–Meier plots of the proportion of patients with positive sputum cultures and time to conversion. Sputum culture conversion to negative was earlier in patients who received clofazimine (Cfz) vs controls ($P = .042$ by log-rank test).

Table 2. Treatment Outcomes

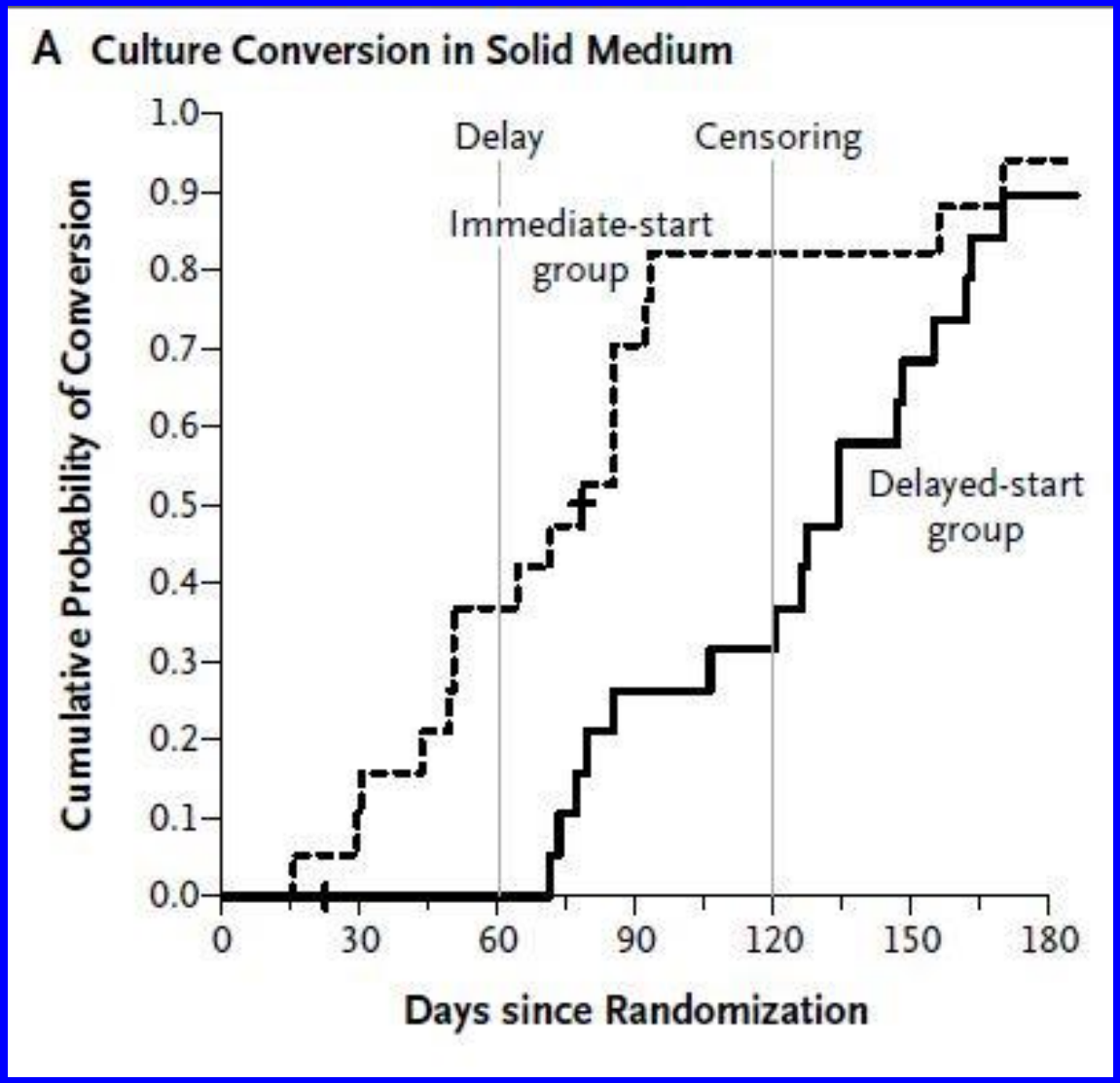
Treatment Outcomes	Cfz Group (n = 53), No. (%)	Control Group (n = 52), No. (%)	*P* Value
Treatment success	39 (73.6)	28 (53.8)	.04
Cure	27 (50.9)	20 (38.5)	.20
Treatment completion	12 (22.6)	8 (15.4)	.34
Poor treatment outcomes	14 (26.4)	24 (46.2)	.04
Death	4 (7.5)	4 (7.7)	1
Failure	6 (11.3)	15 (28.8)	.03
Default	4 (7.5)	5 (9.6)	.74

Abbreviation: Cfz, clofazimine.

105 patients randomized to OBT+CFZ vs. OBT+Placebo

Clin Infect Dis 2015;60:1361

Linezolid in the Treatment of XDR-TB



NEJM 2012;367:1508-18

Phase 2 Trials to optimize dosing and Minimize DDI and Adverse Effects

- ACTG 5312 (High dose INH for inhA mutations)
- Opti-Q (optimization of levofloxacin dosing)
- ACTG 5356 (optimization of linezolid dosing)
- ACTG 5343 (BDQ and DLM QT interactions)
- C211 Study (Pediatric PK of BDQ)
- IMPAACT P1108 Trial (Pediatric PK of BDQ)
- Otsuka Pediatric PK Trial (Pediatric PK of DLM)

Phase 3 Clinical Trials for MDR-TB

Goal: Shorten treatment and improve upon ~75% relapse-free cure

Trials to replace injectable

- MDR-END Trial– Phase 2/3 (2019)
- NEXT Trial – Phase 3 (2020)
- STREAM Stage 2 Trial– Phase 3 (2020)
- endTB Trial – Phase 3 (2021)

MDR-END Trial (Phase 2/3)

- Description: Injectable-free DLM-based regimen vs SOC
- Regimens:
  - SOC (WHO 20-24 months)
  - DLM+LZD+LFX+PZA for 9-12 months
- Sponsor: Korean government
- Target population: smear+ MDR-TB, adults 18+
- Outcome: Failure, relapse, default or death
- Size: 96 Patients
- Sites: Korea
- Expected completion: 2019

NeXT Trial – Phase 3

- Description: 6-9 month trial of bedaquiline in combination with other oral agents (duration dependent on culture conversion)
- Regimens: BDQ+LZD+LFX+ETA/INHH+PZA (6-9 Mo)
  MXF+ETH+TER+KM+PZA (21-24 Mo)
- Sponsors: MCC
- Target population: MDR-TB, adults
- Outcome: “favorable outcome” at 24 months
- Size: 300 patients
- Sites: South Africa
- Expected results: 2020

STREAM Trial, Stage 2

- Description: Addition of two new arms to STREAM
- Regimens:

  SOC (continues both WHO and Bangladesh)

  BDQ+CFZ+EMB+LFX+PZA+4(INH_H+PTO) – 9 mos
- Sponsor: USAID, others
- Target population: smear+ MDR-TB, adults
- Outcome: Failure, relapse, default or death
- Size: 1100 patients
- Sites: Ethiopia, Vietnam, South Africa, Mongolia
- Expected completion: 2020

endTB Trial (Phase 3)

- Description: Combination regimens, adaptive randomization
- Regimens:WHO SOC (20-24 months)
  - BDQ+LZD+MXF+PZA for 9 months
  - BDQ+CF+LZD+LFX+PZA for 9 months
  - BDQ+DEL+LZD+LFX+PZA for 9 months
  - DEL+CF+LZD+LFX+PZA for 9 months
  - DEL+CF+MFX+PZA for 9 months
- Sponsor: MSF/Unitaid
- Target population: smear+ MDR-TB, adults 15+
- Outcome: Failure, relapse, default or death
- Size: 750 Patients
- Sites: Georgia, Kazakhstan, Kyrgyzstan, Lesotho, Peru
- Expected completion: 2021

Trials to shorten duration

- NiX-TB Trial
- ZeNiX Trial
- TB-PRACTECAL Trial

Pretomanid (NiX-TB) – Phase 2/3

- Description: 6 month trial of Pretomanid in combination with Bedaquiline and Linezolid
- Regimen: BDQ+PTM+LZD (Single Arm)
- Sponsor: GATB
- Target population: XDR-TB, adults
- Outcome: relapse-free cure
- Size: 100 patients
- Sites: South Africa
- Expected results: 2018

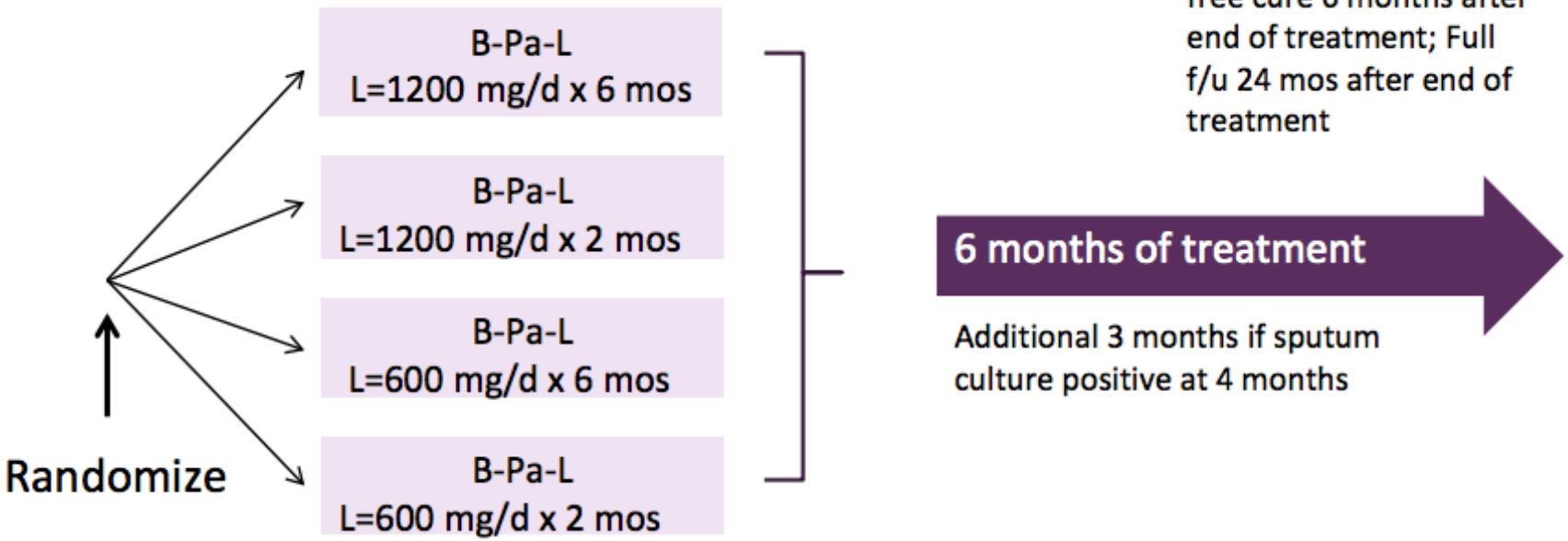
Status of Participants in Nix-TB

- 109 participants enrolled as of end enrollment November 15, 2017
  - 80 have completed treatment
  - 56 have reached their primary endpoint (6 months after end of treatment; NDA cutoff)
  - 10 patients have completed the study (Month 30)
- Overall relapse-free cure of TB disease among the first 30 followed to primary endpoint 6 months after end of therapy:
  - 26 / 30 = 87% (vs. historical up to 85% failure rate)
- Enrollment ended November 15, 2017
  - Transition to ZeNix

ZeNix: Linezolid Optimization Trial

ZeNix

Patients with XDR-TB, Pre-XDR-TB or who have failed or are intolerant to MDR-TB treatment



N=30 XDR-TB per group AND
up to 15 pre-XDR or intolerant/non-responsive MDR-TB per group

Pa dose = 200 mg daily; B Dose = 200 mg daily x 8 weeks, 100 mg x 18 weeks

TB-PRACTECAL Trial (Phase 2/3)

- Description: Staged trial of BDQ/PTM/LZD regimens:
  - SOC (WHO 20-24 month regimen)
  - BDQ+PTM+LZD+MFX for 6 months
  - BDQ+PTM+LZD+CF for 6 months
  - BDQ+PTM+LZD for 6 months
- Sponsor: MSF
- Target population: smear/Xpert+ MDR-TB, adults 18+
- Outcome: Failure, relapse, default or death
- Size: 630 Patients
- Sites: Uzbekistan, Swaziland, Belarus
- Expected completion: 2021

MDR-TB Trials of the future

- Bedaquiline plus Delamanid or Petomanid
- New Oxazolidinones (Sutezolid, Tedazolid, Delpazolid, Contazolid)
- Benzothiazinones (BTZ 043, PBTZ 169)
- Continued regimen efficacy optimization
- Continued regimen toxicity reduction
- Additional regimen shortening
- Prevention of emergence of drug resistance

Conclusions

- The pipeline for new TB drugs has been productive since 2000
- Six new drugs (4 classes) are now in Phase 2 & 3 clinical trials
- Five additional drugs have recently entered Phase 1 trials
- Emergence of resistance to the new agents is already being seen
- The optimal way to use the new and repurposed drugs is still unknown

To follow developments in MDR-TB diagnosis and treatment:

RESIST-TB Website

www.resisttb.org