TB Drug Pipeline and New Treatment Combinations for MDR-TB

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Outline

- Background
- Repurposable drugs for MDR-TB
- New drugs for MDR-TB
- Ongoing clinical trials of MDR-TB disease
- Designing the optimal MDR/XDR-TB regimen

MDR-TB - Background

- Estimated 450,000 new cases last year
- Less than 25% treated
- Recommended treatment takes 18-24 months, cures only ~65%, 15+% mortality
- No systematic study of currently recommended regimens
- Second-line drugs are associated with substantial toxicity
- Emergence of additional resistance in 9-15%

Goals of a New Regimen for MDR-TB

- Shorten duration of treatment from 20-24 months
- Improve on 60% cure proportion
- Improve tolerability
- Prevent the emergence of further resistance

REPURPOSING OLD DRUGS FOR MDR-TB

Tolerability of 3rd-Generation Fluoroquinolones

Class-specific:

- Peripheral neuropathy
- Tendon rupture
- Hepatotoxicity
- *C. difficile* superinfection

Moxifloxacin:

- QT-prolongation

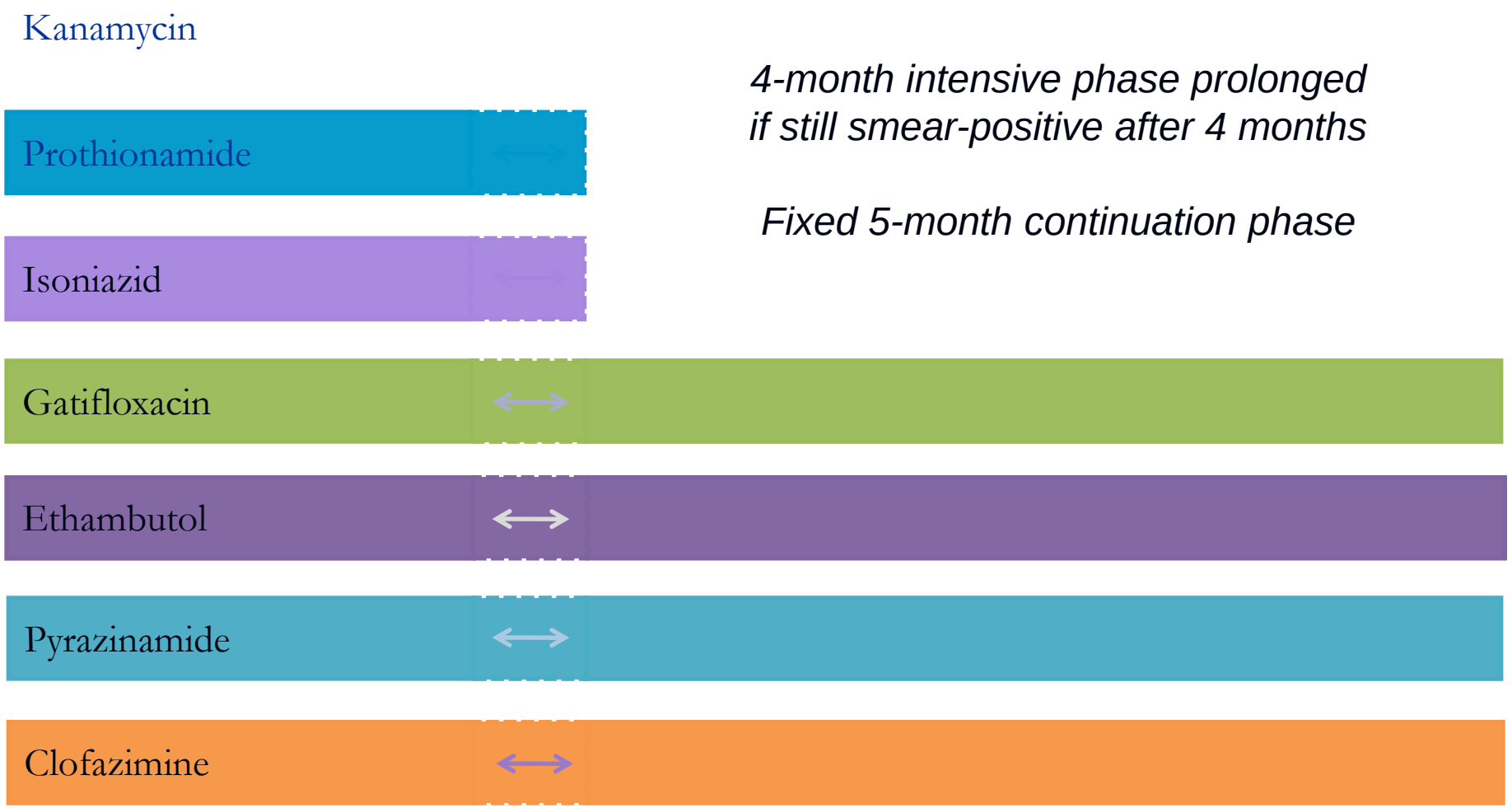
Potential “Repurposable” Drugs

- PZA (WHO Group 1)
- Moxifloxacin (WHO Group 3)
- Levofloxacin (WHO Group 3)
- Linezolid (WHO Group 4)
- Clofazimine (WHO Group 5)
- Amoxacillin/Clavulinate (WHO Group 5)
- Imipenem/Cilastin (WHO Group 5)
- Clarithromycin (WHO Group 5)

Tolerability of Clofazimine

- Skin discoloration (75-100%)
- Gastrointestinal intolerance (40-50%)
- Eosinophilic enteritis
- Interstitial nephritis
- Rash, dry skin, ichthyosis
- QT prolongation

A 9-month regimen for MDR-TB in Bangladesh



AJRCCM 2010:182:684-92

Bangladesh Regimen: Efficacy

206 patients

- 170 Cures (84.2%)
- 11 Completions (5.3%)
- 11 Deaths (5.3%)
- 12 Defaults (5.8%)
- 1 Failure (0.5%)
- 1 Relapse (0.5%)

AJRCCM 2010:182:684-92

Bangladesh Regimen: Tolerability

- 206 patients
  - 44 Vomiting (21.4%)
  - 13 Hearing Difficulties (6.3%)
  - 8 Dysglycemia (3.9%)
  - 8 Ataxia (3.9%)
  - 2 Arthralgia (1%)
  - 1 “Mental” (0.5%)

AJRCCM 2010:182:684-92

Tolerability of Linezolid in 72 Patients with MDR-TB*

- Peripheral neuropathy (40%)
- Anemia (25%)
- Optic Neuritis (10%)
- Thrombocytopenia (10%)
- GI disorders (8%)
- Neutropenia (2%)

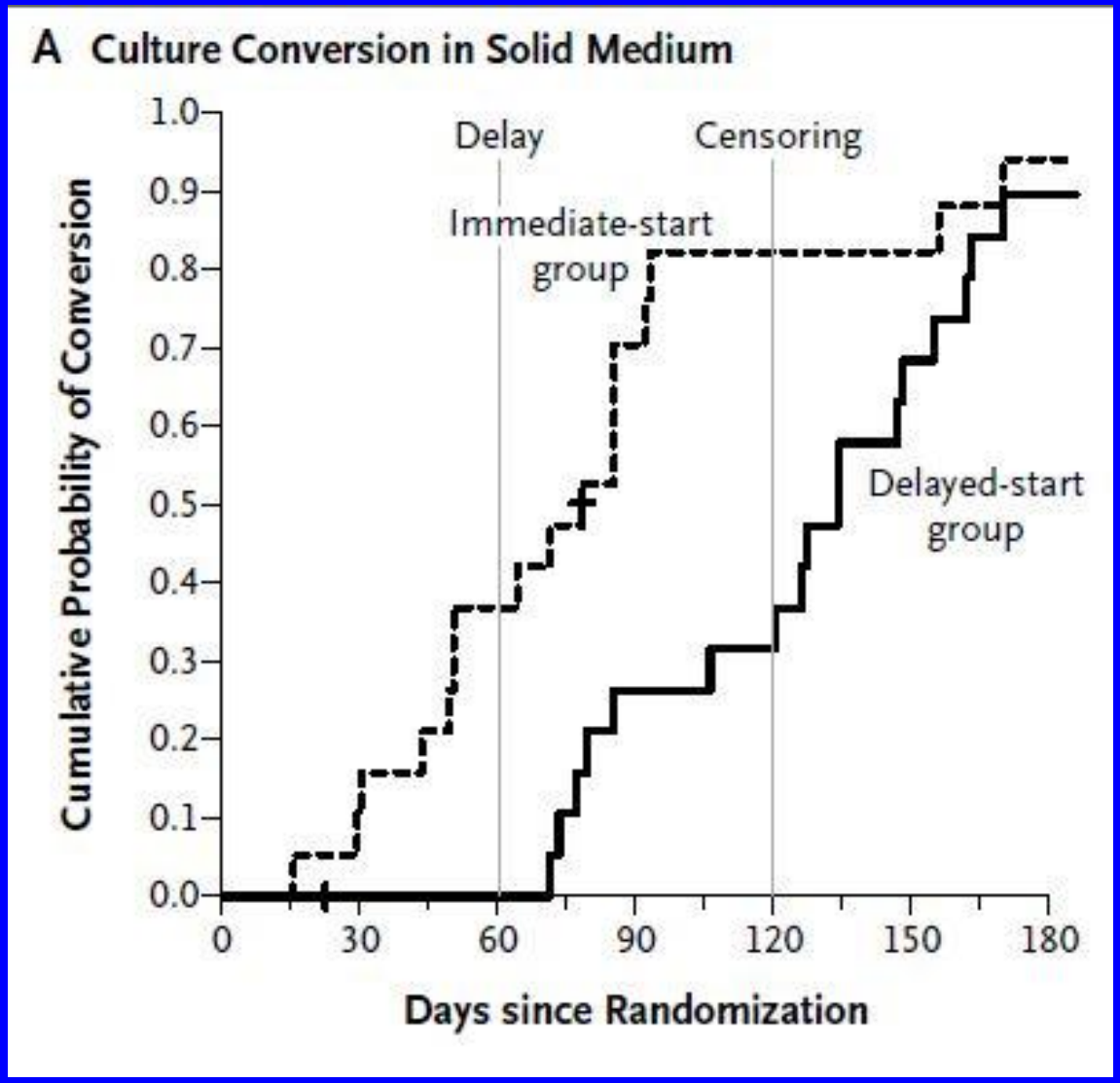
*Dose ≤ 600mg/day

Eur Resp J 2012;40:1437

Prospective Study of Linezolid in XDR-TB Treatment

- 40 patients with XDR-TB in Korea
- Randomized to 300mg qd or 600mg qd
- Further randomized to immediate versus 2 month delayed linezolid (both with OBR)
- 36/40 converted sputum cultures (mean 90 days)
- 4 failures were all resistant to linezolid

Linezolid in the Treatment of XDR-TB



NEJM 2012;367:1508-18

Tolerability of Linezolid in XDR-TB Treatment Trial

22 Patients treated with 600 mg/day

- Peripheral neuropathy (60%)
- Myelosuppression (20%)
- Optic Neuropathy (10%)

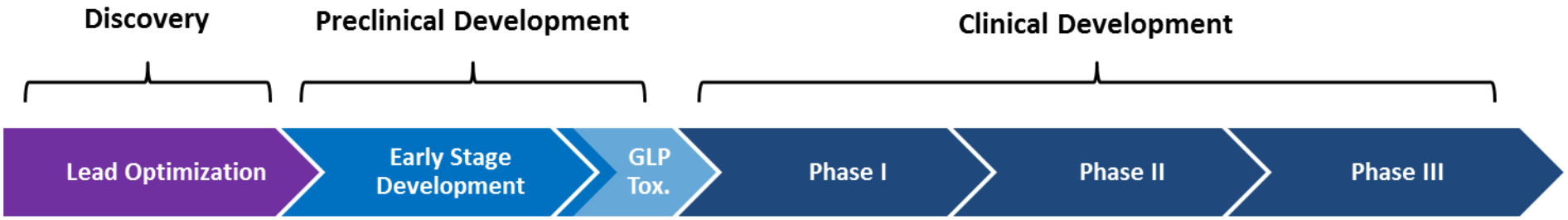
16 Patients on 600 mg then 300 mg after 2 months

- Peripheral neuropathy (50%)
- Myelosuppression (not seen)
- Optic Neuropathy (17%)

NEJM 2013;367 (on-line supplement)

NEW DRUGS FOR MDR-TB

Global TB Drug Pipeline [1]



Lead Optimization

- Cyclopeptides
- Diarylquinoline
- DprE Inhibitors
- InhA Inhibitor
- LeuRS Inhibitor
- Macrolides
- Mycobacterial Gyrase Inhibitors
- Pyrazinamide Analogs
- Ruthenium(II) Complexes
- Spectinamides
- Translocase-1 Inhibitor

Early Stage Development

- CPZEN-45
- DC-159a
- Q203
- SQ609
- SQ641
- TBI-166

GLP Tox.

- PBTZ169
- TBA-354

Phase I

- AZD5847
- Bedaquiline (TMC-207)
- Linezolid
- Novel Regimens[2]
- PA-824
- Rifapentine
- SQ-109
- Sutezolid (PNU-100480)

Phase III

- Delamanid (OPC-67683)
- Gatifloxacin
- Moxifloxacin
- Rifapentine

Chemical classes: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone

[1] Details for projects listed can be found at http://www.newtbdrugs.org/pipeline.php and ongoing projects without a lead compound series identified can be viewed at http://www.newtbdrugs.org/pipeline-discovery.php.

[2] Combination regimens: NC-001 -(J-M-Pa-Z), phase 2a, NCT01215851; NC-002-(M-Pa-Z), phase 2b, NCT01498419; NC-003-(C-J-Pa-Z), phase 2a, NCT01691534; PanACEA-MAMS-TB-01-(H-R-Z-E-Q-M), phase 2b, NCT01785186.

WORKING GROUP ON NEW TB DRUGS

www.newtbdrugs.org

Updated: June 2013

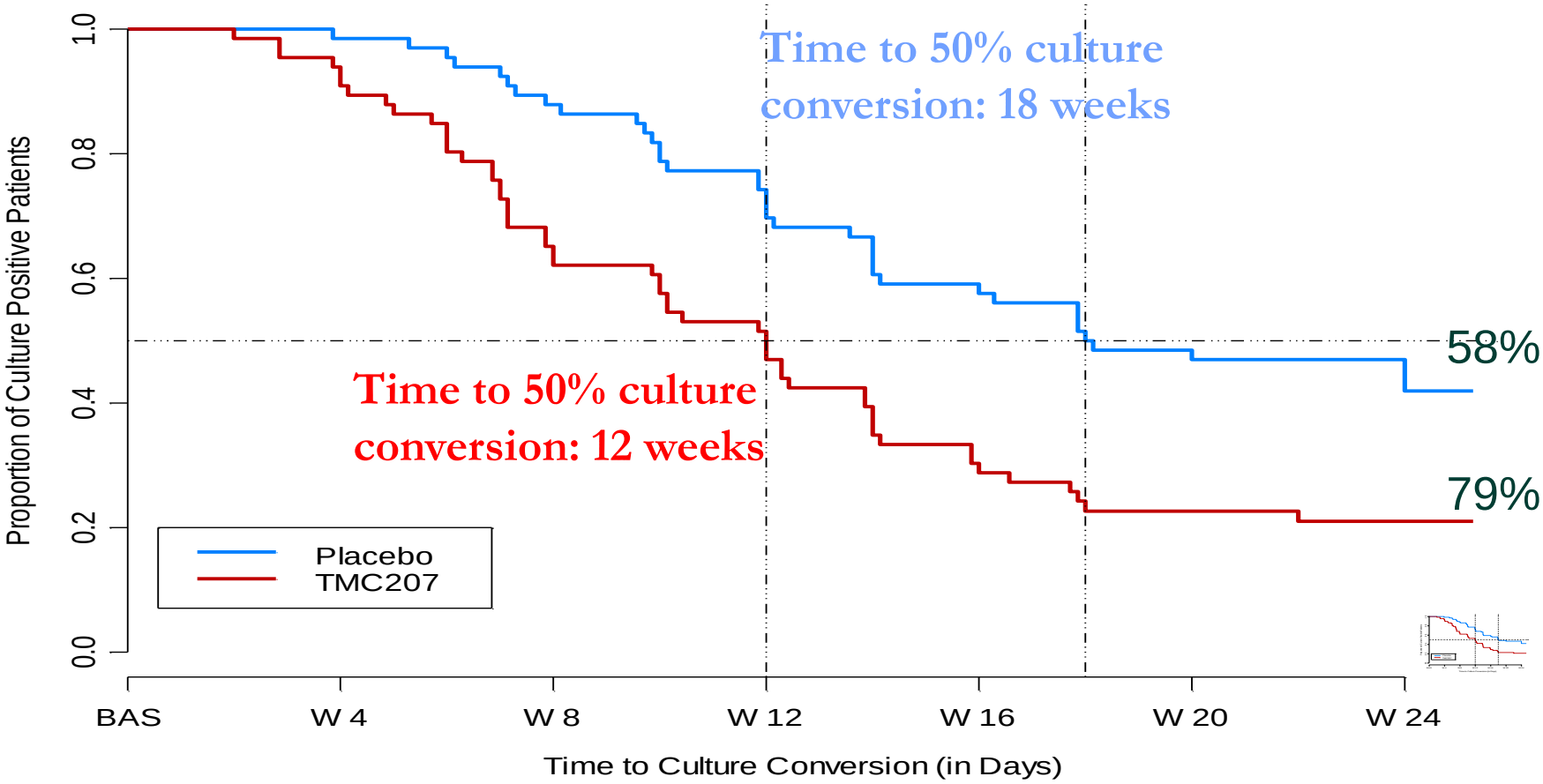
New MDR-TB Drugs in Clinical Development, 2014

Drug	Class	Company	Status
Bedaquiline	Diarylquinolone	Tibotec	Phase 2
Delamanid	Imidazooxazole	Otsuka	Phase 3
PA-824	Imidazooxazine	GATB	Phase 2
SQ-109	Ethylene Diamine	Sequella	Phase 2
Sutezolid	Oxazolidinone	Sequella	Phase 2
AZD-5847	Oxazolidinone	AstraZenica	Phase 2

Bedaquiline Study C208 (Phase 2)

- Description: Addition of Bedaquiline to OBT for 6 months, followed by OBT for 18 months
- Regimens: OBT+Bedaquiline
  OBT+Placebo
- Sponsor: Janssen
- Target population: newly-diagnosed, smear+ MDR-TB, adults, CD4>300 if HIV+
- Outcome: Time to sputum culture conversion
- Size: 200 patients

Bedaquiline Phase 2 MDR-TB Study
Time to sputum culture conversion (MITT analysis)



Diacon, IUATLD 2013.

Bedaquiline Study C208
Final results

	Bedaquiline+OBT	Placebo+OBT
Number	79 patients	81 patients
Median Conversion	12 weeks	18 Weeks*
Cure at week 120	58%	32%**
Adverse Events	23%	19%
Deaths	13%	2.5%**

*p=0.01
**p=0.01

Diacon, IUATLD Nov 2013

Tolerability of Bedaquiline

- Nausea (~22%)
- Increased hepatic enzymes (?)
- QT prolongation

NEJM 2009;360:2397-405

Delamanid Study 204 (Phase 2)

- Description: Addition of Delamanid (D) to OBT
- Regimens: OBT+D 100 mg bid

  OBT+D 200mg bid

  OBT+Placebo
- Target population: Adults with pulmonary MDR-TB, CD4>350 if HIV+
- Outcome: Sputum conversion at *8 weeks*
- Size: 430 patients

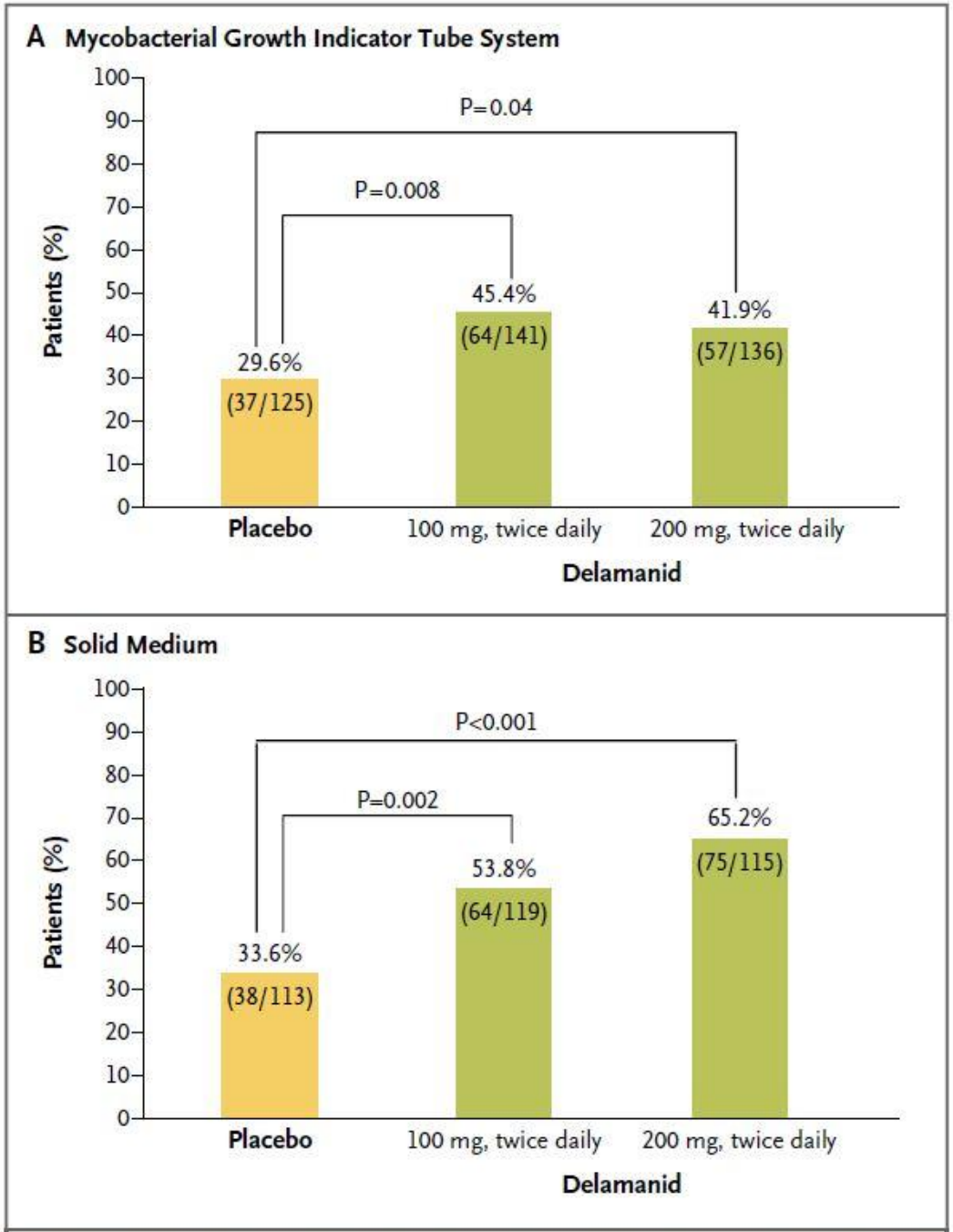


Figure 2. Proportion of Patients with Sputum-Culture Conversion by Day 57.

NEJM 2012;366:2158

Tolerability of Delamanid

- QT prolongation

NEJM 2012;366:2157

MDR-TB Clinical Trials in Progress

- AZD-5847 Phase 2
- NC-002 (PA-824)
- STREAM
- Delamanid Phase 3
- Opti-Q Phase 4

PA-824 (NC-002 Trial)

- Description: 8 week trial of PA-824 in combination with moxifloxacin and PZA
- Regimens: PA_{100}-M-Z for DS-TB
  PA_{200}-M-Z for DS-TB
  PA_{200}-M-Z for MDR-TB (FQ and Z susceptible)
  HRZE for DS-TB
- Sponsors: GATB
- Target population: smear+ MDR-TB, adults
- Outcome: quantitative sputum cultures
- Size: 230 patients – 100% enrolled
- Sites: Tanzania and South Africa
- Expected results: 2014

STREAM Study (Phase 3)

- Description: Modified Bangladesh regimen (with moxifloxacin in place of gatifloxacin) compared to "standard" MDR-TB regimen
- Regimens: 7-drug regimen (9 months)
  4-5 drugs (18-24 months)
- Sponsors: IUATLD, USAID
- Target population: smear+ MDR-TB, adults
- Outcome: Failure, relapse, default or death
- Size: 400 patients – 50% enrolled
- Sites: Ethiopia, Vietnam, South Africa
- Expected completion: 2016

Delamanid Confirmatory Trial (Phase 3)

- Description: Addition of D to OBT
- Regimens:OBT+D 100 mg (D 6 months/OBT 18 months)
  OBT+D 50 mg (D 6 months/OBT 18 months)
  OBT+Placebo (24 months)
- Sponsor: Otsuka Pharmaceutical Development
- Target population: Adults with pulmonary MDR-TB, CD4>350 if HIV+
- Outcome: Time to sputum conversion through 6 months
- Size: 430 patients
- Duration: 2015
- Status: 100% enrolled

Constructing a new MDR-TB Regimen: Principles

- At least 3 new drug classes
- Avoid overlapping toxicities
- Strive for all-oral regimen
- Estimate duration based on 2 month sputum culture conversion

MDR-TB Drug Menu

Class	
Diarylquinolone:	bedaquiline
Nitroimidazole:	delamanid, PA-824
Oxazolidinone:	linezolid, sutezolid, AZD-5847, others?
Fluoroquinolone:	levofloxacin, moxifloxacin, (gatifloxacin)
Riminophenazine:	clofazimine
Other:	PZA

MDR-TB Clinical Trials in Preparation

- Bedaquiline Phase 3
- MARVEL (ACTG A5319)
- Bedaquiline/Delamanid DDI
- PA-M-Z
- NiX-TB (for XDR-TB)

Conclusions - I

- New TB drug classes may increase treatment response rates, shorten treatment duration and decrease mortality
- Tolerability of a number of the new agents remains to be defined, especially when used in combination
- Combination studies are needed to assure that DDI with other TB drugs and ART will not preclude their concurrent use

Conclusions - II

- Trials currently in progress and under consideration will hopefully clarify DDI and overlapping toxicity issues
- A major challenge will be preventing the emergence of resistance to the new drugs
- Increased capacity for MDR-TB clinical trials will also be needed