TB Alliance R&D Update

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Stakeholders Association Meeting November, 2010

TB Alliance Portfolio

Discovery			Preclinical Development	Clinical Development		
TARGET OR CELL-BASED SCREENING	LEAD IDENTIFICATION	LEAD OPTIMIZATION		CLINICAL PHASE I	CLINICAL PHASE II	CLINICAL PHASE III
Natural Products IMCAS	**Whole-Cell Hit to Lead Program** GSK	**Mycobacterial Gyrase Inhibitors** GSK	**Nitroimidazoles** U. of Auckland/ U. Ill Chicago		**PA-824** Novartis	**Moxifloxacin (+ H, R, Z)** Bayer
Protease Inhibitors IDRI	**Malate Synthase Inhibitors** GSK/TAMU	**InhA Inhibitors** GSK	**Preclinical TB Regimen Development** JHU/U. Ill Chicago		**TMC207** Tibotec	**Moxifloxacin (+ R, Z, E)** Bayer
TB Drug Discovery Portfolio NITD		**Diarylquinolines** Tibotec/U. of Auckland			**PA-824/Pyrazinamide**	
Topoisomerase I Inhibitors AZ/NYMC	**Gyrase B Inhibitors** AZ	**Riminophenazines** IMM/BTTTRI			**TMC207/Pyrazinamide**	
	Folate Biosynthesis Inhibitors AZ	**Pyrazinamide Analogs** Yonsei			**PA-824/ Moxifloxacin/ Pyrazinamide**	
	Whole-Cell Hit to Lead Program AZ					
	RNA Polymerase Inhibitors AZ/Rutgers					
	Energy Metabolism Inhibitors AZ/U. Penn					
	Phenotypic Hit to Lead Program U. Ill Chicago					
	Menaquinone Biosynthesis Inhibitors CSU					

Novel TB regimen development

Current first-line TB treatment consists of : isoniazid (H) + rifampicin (R) + pyrazinamide (Z) + ethambutol (E)

Current TB Therapy and Unmet Needs

Patient Population	Current Therapy	Unmet Needs
Drug-Susceptible DS-TB	4 drugs; ≥6 month therapy (2RHZE* + 4RH)	Shorter, simpler therapy
Drug-Resistant M(X)DR-TB	Few good drugs (including injectables); ≥18 months; toxicities; cost	Totally oral, shorter, more efficacious, safer, affordable therapy
TB/HIV Co-Infection	Drug-drug interactions (DDI) with ARVs	No or low DDI, co-administration with ARVs
Latent TB Infection	6-9 months H	Shorter, safer therapy

* Rifampin (R), Isoniazid (H), Pyrazinamide (Z), Ethambutol (E)

- Need shorter, simpler therapies against both DS and DR-TB
- To accomplish, will need to replace all or most current drugs

Accomplishments—Preclinical

- Further refinement of discovery portfolio, with focus on pharma mini-portfolio and next generation programs
- Initiated AZ collaboration and successfully consolidated 3 early-stage projects into AZ mini-portfolio
- Initiation of pyrazinamide next generation program, a critical agent for future regimens
- Advancement of DNDi collaboration; preclinical candidate for VL identified
- Further advancement of preclinical novel drug combination program; promising regimens identified

AstraZeneca Collaboration (Mini-Portfolio)

- Projects from AZ:
  - GyrB inhibitor
  - FolB inhibitor
  - Whole-cell hit
- Projects from TB Alliance:
  - RNAP inhibitors (Rutgers)
  - Energy metabolism inhibitors (Penn)
  - Topo I inhibitors (NYMC)

Projects Terminated

Milestones not met for:

- Bifunctional molecules
- Tryptanthrins
- Benzoxaboroles (LeuRS)

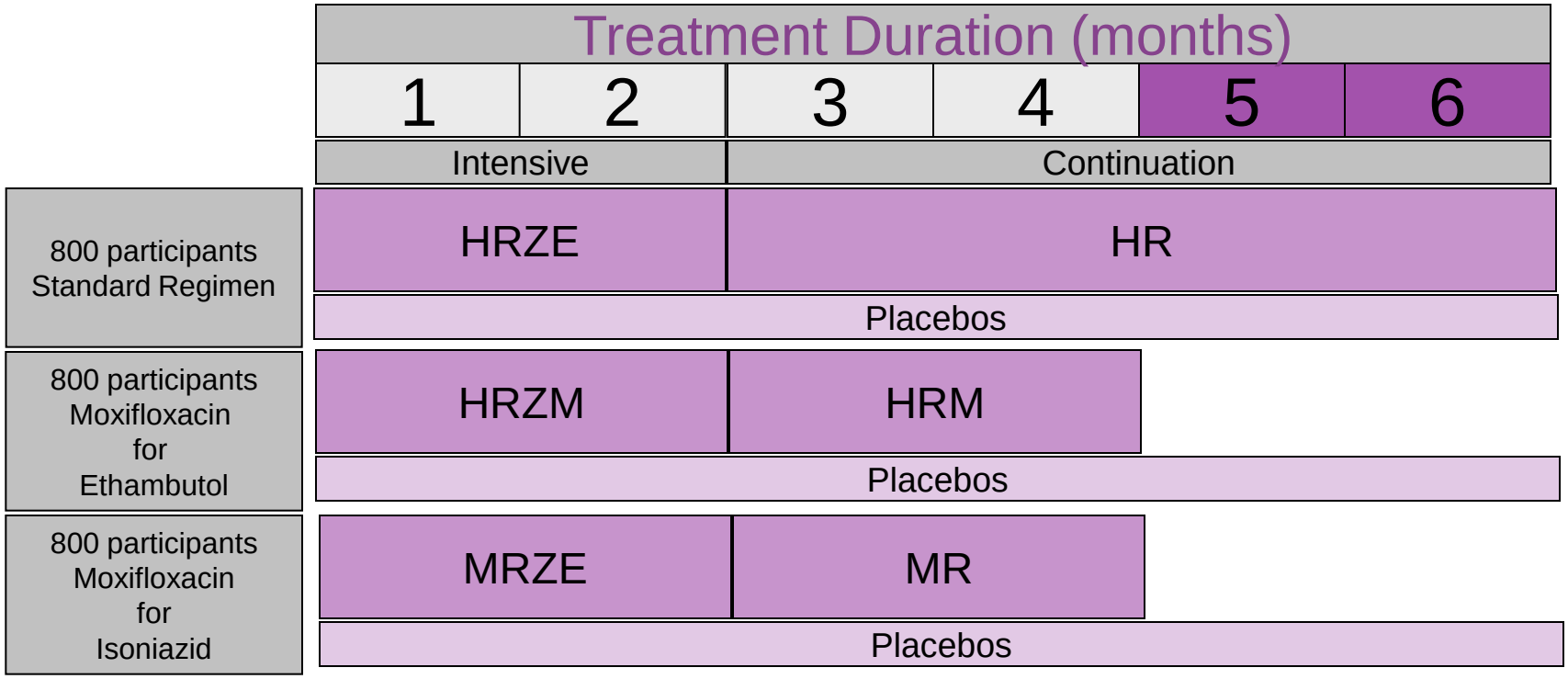
Accomplishments--Clinical

- REMox Ph 3 enrollment progressing well
- PA-824 dose ranging EBA study completed and clinical dose selected
- TMC207 dose ranging EBA study completed
- Further advancement of clinical novel drug combination program (regimen development)
  - Novel 3-drug regimen advanced into Ph 2 EBA study
  - TMC207-PZA synergy being tested in Ph 2 EBA study

REMox TB Trial Update

Phase 3 REMoxTB Trial Design

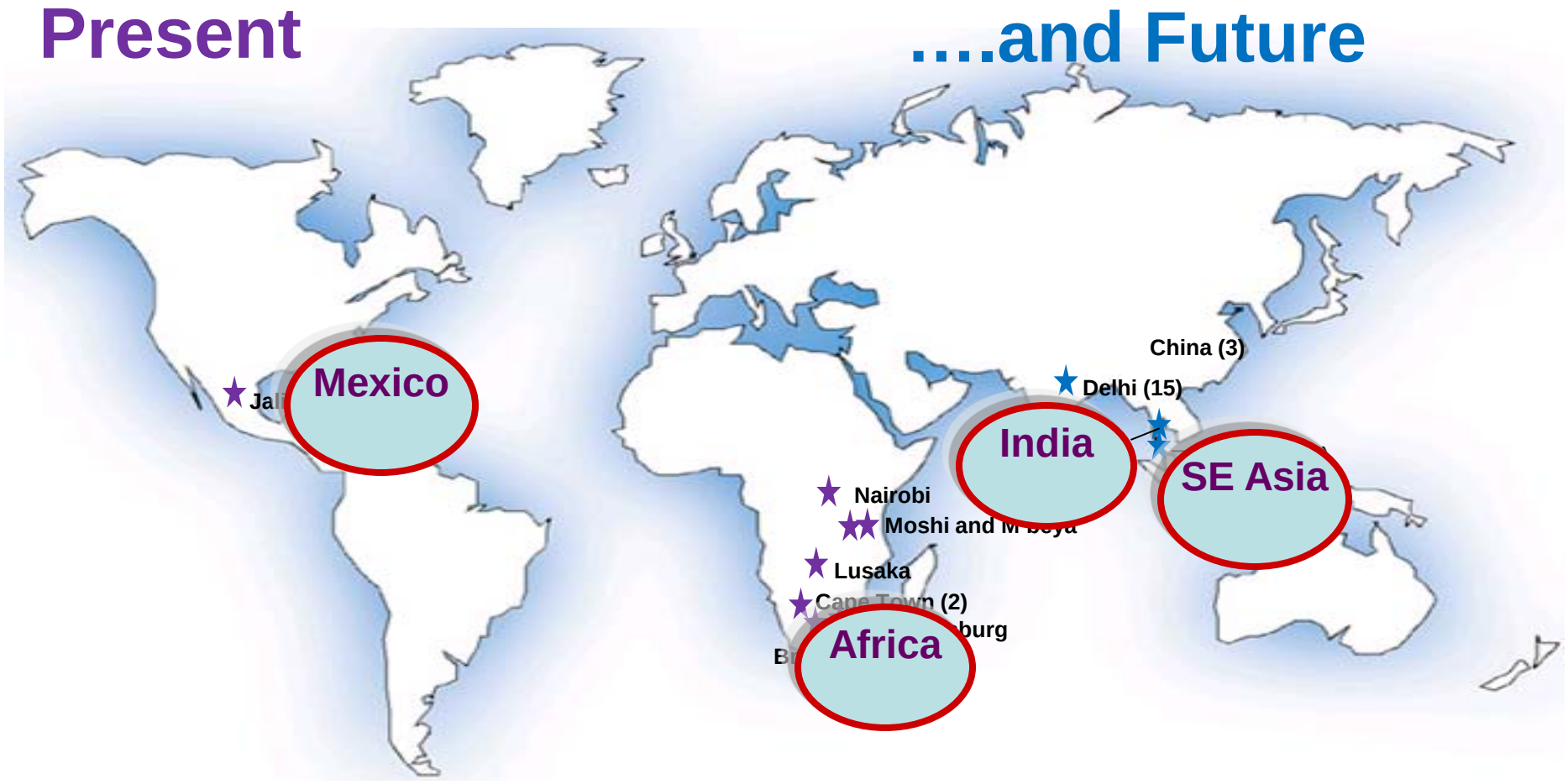
Randomized, Double-blind; Non-inferiority



All participants followed for 12 months post-treatment

H = isoniazid; M = moxifloxacin; R = rifampin; Z = pyrazinamide; E = ethambutol

Participating Sites



REMoxTB Timelines

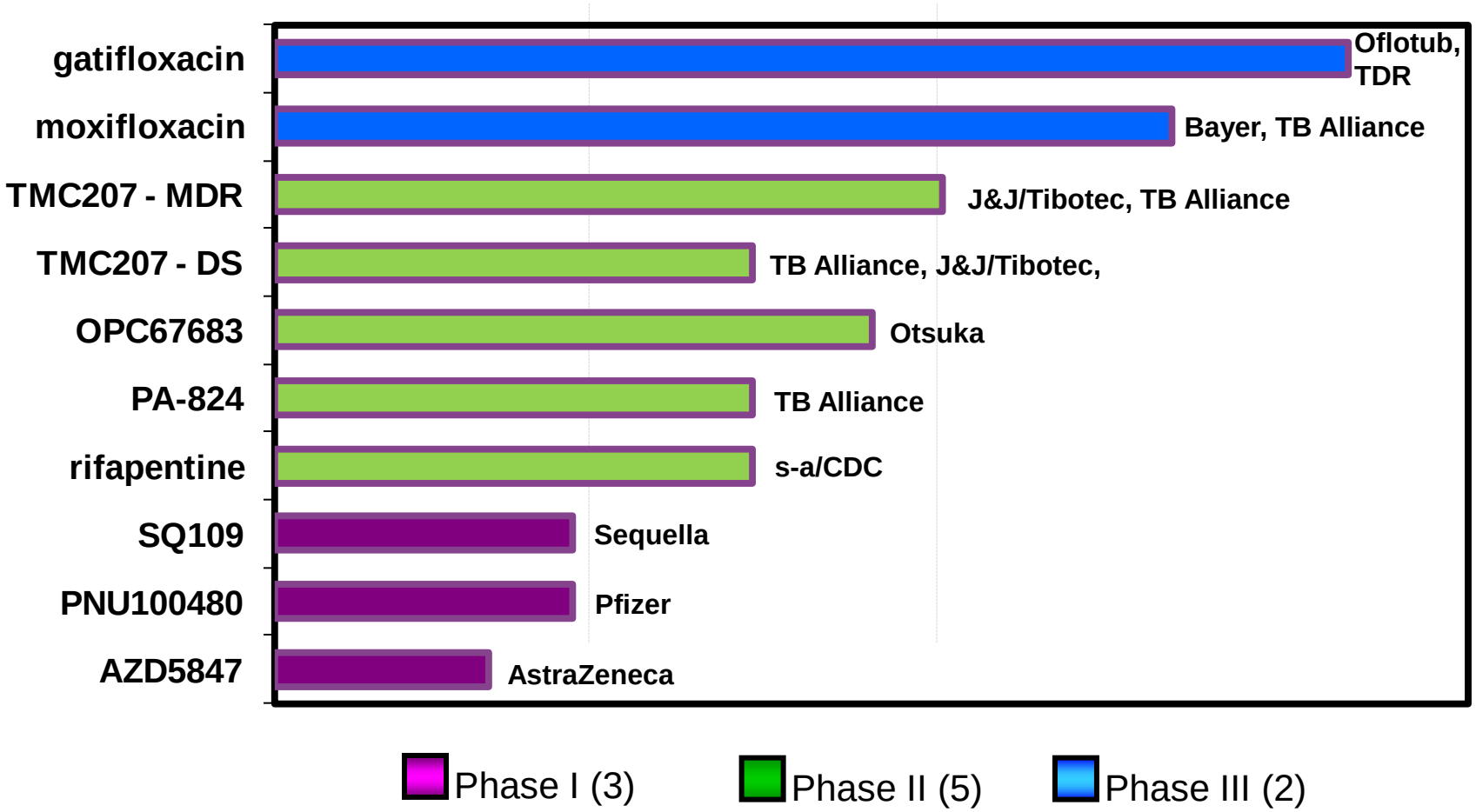
- Last Patient In 4Q 2011
- Last Patient Out 2Q 2013
- Database Lock 3Q 2013
- Submission 1Q 2014

Consortium for TB Biomarkers Substudy

- Objective:
  - *Long-term repository of biospecimens in order to discover and validate drug-effect biomarkers and surrogate endpoints, and ultimately streamline the clinical trial process for TB drug development*
  - *Panel of external experts will review and approve proposals solicited from the TB R&D community*
- Collaborative effort with ACTG, TBTC
- Parameters:
  - Blood, Urine, Sputum collected and stored
  - No human genetic testing
- Status: FDA grant awarded September 17, 2010
  - One year grant with possible extension out to three years
  - Number of patients: 250-350 to be contributed by each organization
  - Next steps: Meeting with FDA, ACTG and TBTC

TB Regimen Testing: Approach and Status

TB Drugs in Clinical Development
Global Portfolio



Sources: WGND & clintrials.gov

Opportunity

For the first time in history, the opportunity exists to develop a truly novel regimen, containing multiple new chemical entities with novel mechanisms of action

→ **TB treatment of ≤ 4 months for DS- and DR-TB**

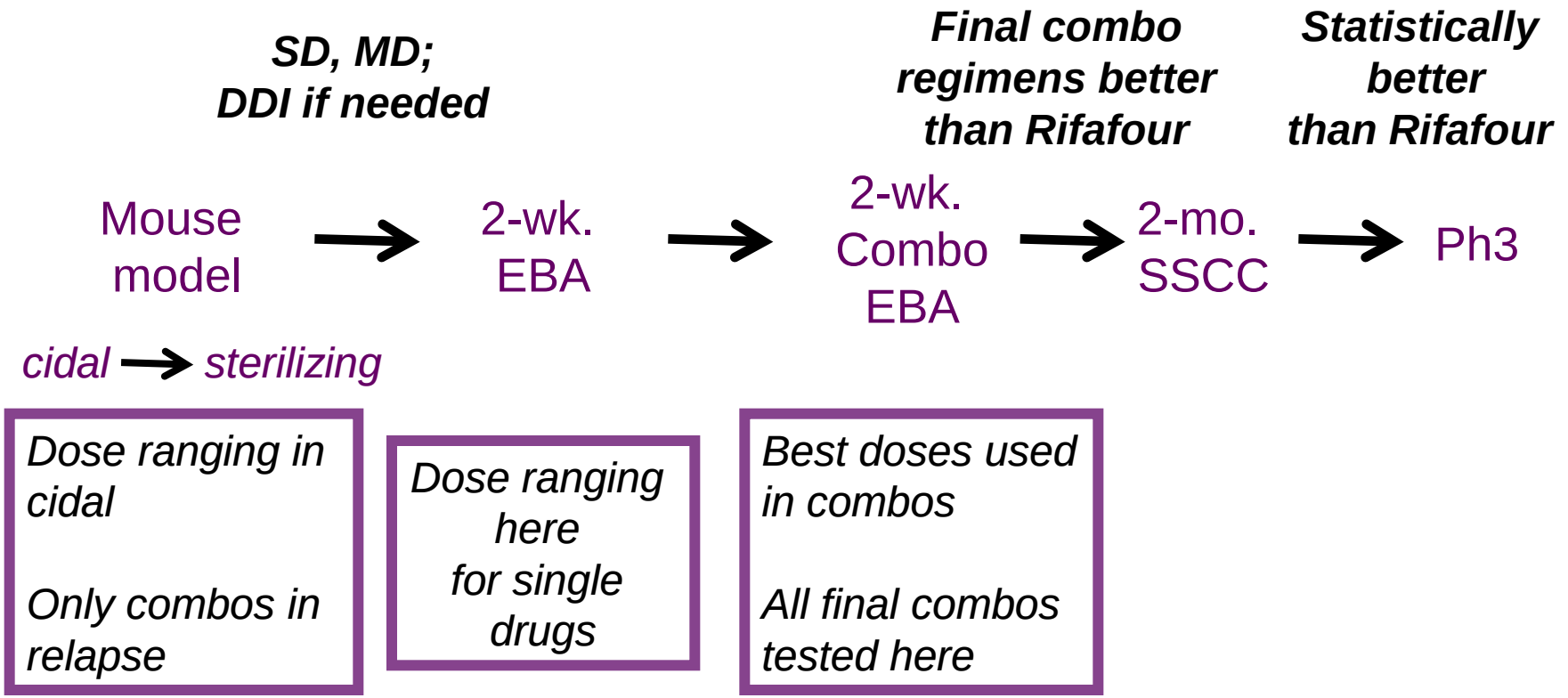
New Regimen: Optimal Target Profile

- Shorten and simplify treatment
  - Active against drug-persistent *Mtb* populations
- Equally effective against M(X)DR-TB
  - Novel mechanisms of action
- Easy, safe, co-administration with ARVs
  - No P450 mediated drug-drug interactions
- Excellent safety/tolerability
- Oral, once daily dosing
- Low cost of goods

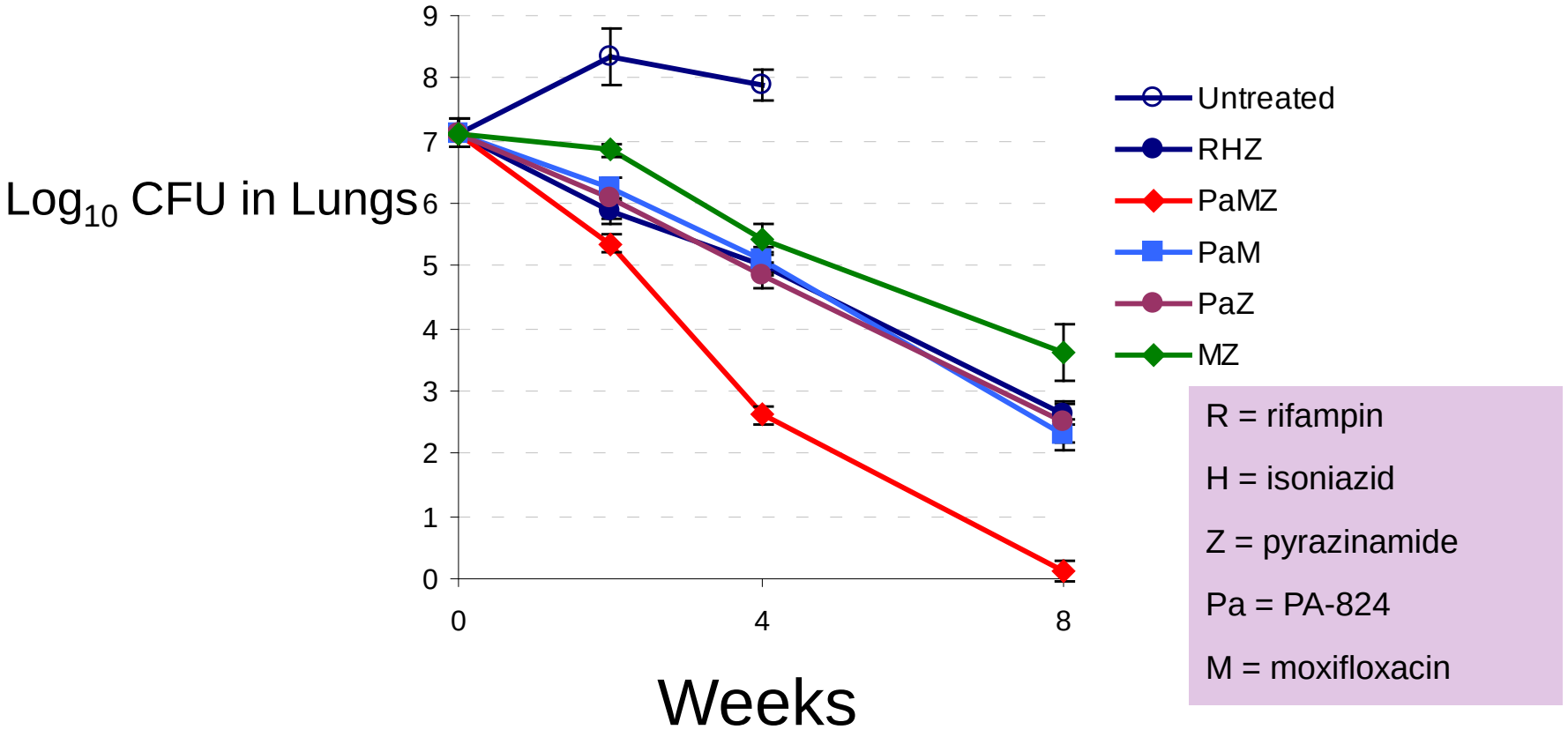
Approach to Novel Regimen Development

- Use animal model(s) to identify most promising combinations
- Conduct full preclinical, Phase I and Phase II EBA evaluations of each drug singly
- Explore drug-drug interactions and, as appropriate, preclinical tox of the combination
- Take *combination (regimen)* into clinical development (Phase II, III)

TB Regimen Development Path



Bactericidal Activity of Different Treatment Regimens in the Mouse



R = rifampin

H = isoniazid

Z = pyrazinamide

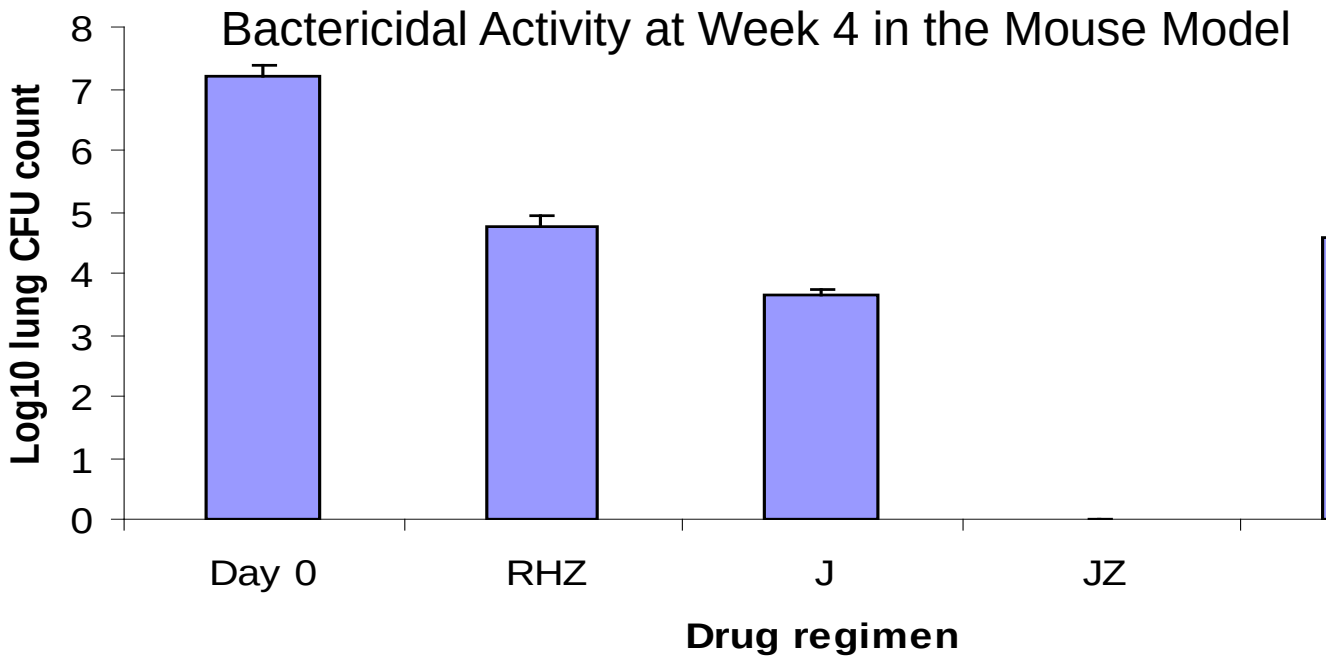
Pa = PA-824

M = moxifloxacin

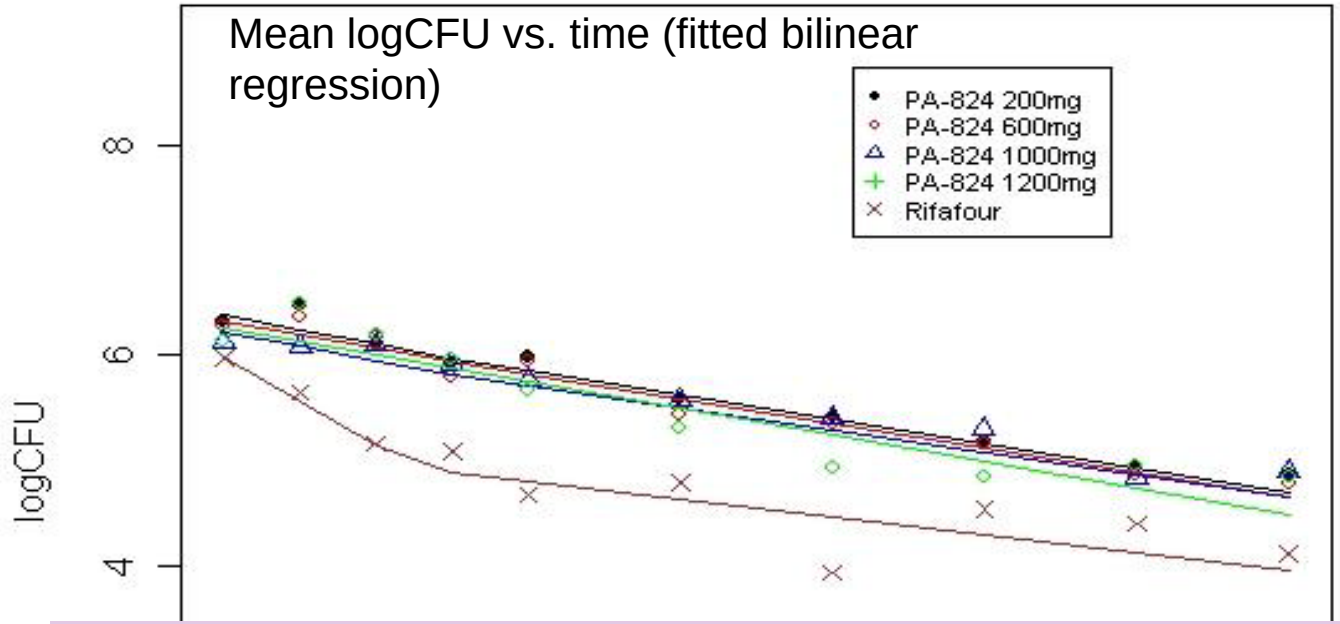
Use of EBA to Test Principles Learned from Preclinical Models

J-Z Synergy:

If confirmed in the clinic, will serve as a core for novel regimens



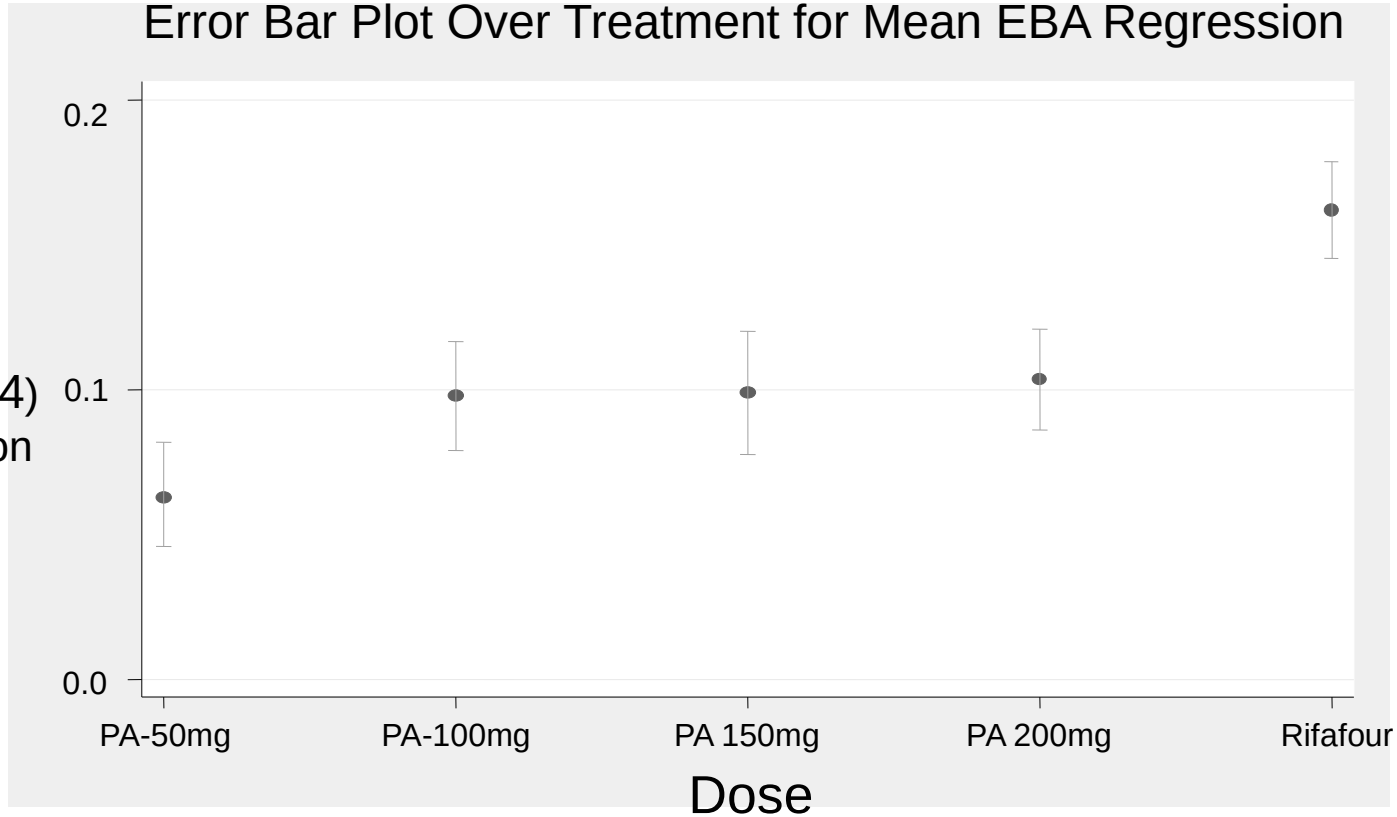
PA-824: First EBA Study



Conclusions:

- PA-824 is as effective at 200 mg as at 1200 mg
- Slope of curves over Days 0-2: Rifafour (isoniazid) appears to have more 'cidal activity than PA-824, alone
- Slope of curves over Days 2-14: PA-824, alone, even at 200mg, appears as sterilizing as all 4 first-line drugs together (Rifafour)

PA-824: Second EBA Study



First Novel Combo EBA: NC-001

14-day EBA to test two concepts (based on results from the mouse):

1) PA824-moxi-PZA will be a novel efficacious 3-drug regimen, potentially suitable for MDR-TB as well as DS-TB
   - Arms: Pa824+PZA; Pa824+moxi+PZA
   - Rifafour arm as control
2) TMC207 and PZA will be synergistic in humans
   - Arms: TMC207; TMC207+PZA (same Rifafour control as above)

➢ FPI week of Oct 11, 2010; results May, 2011

CPTR Organization

CPTR Initiative

BMGF—in association with the TB Alliance and C-Path—will work to accelerate the development of new TB drug regimens

1	2	3
CPTR Tools Consortium "Regulatory Science"	**CPTR Drug Coalition** "Drug Development"	**CPTR Infrastructure** "Key Success Factors"
Focus		
• Data standards/integration • Qualified biomarkers • Disease progression models	• New clinical trial designs • Drug combination testing and development	• Clinical trial capacity • Regulatory harmonization • Funding
Participants		
• Pharma companies • TB Alliance • TB experts • Regulators • Patient representatives • Others?	• Pharma companies • TB Alliance • TB experts • Others	• Pharma companies • TB Alliance • Regulators • Patient representatives • Reagan-Udall Foundation • NIH • CDC • BMGF • Other funders

Thank you