Application of Phase 2C – The CRUSH-TB Trial

(Combination Regimens for Shortening TB Treatment)

TBTC CRUSH TB Working Group

INTER-TB Meeting, London, UK

September 9, 2019
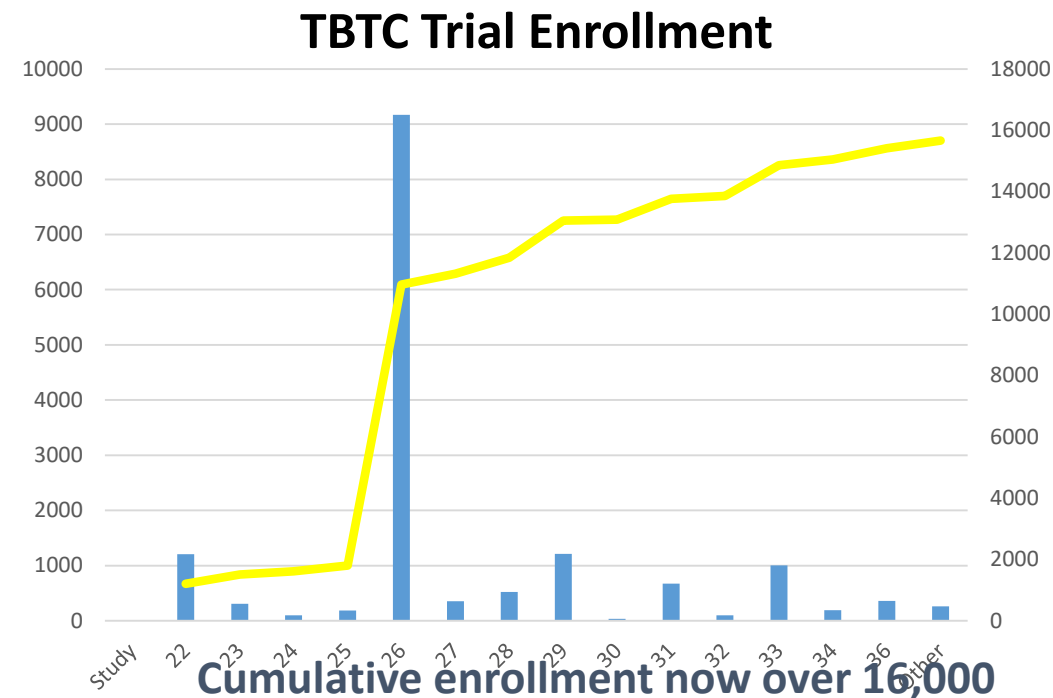
TBTC CRUSH TB Protocol Team Members

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Microbiology, pharmacology, pediatrics, community, clinicians, biomarkers, drugs, international/US, young/old

TBTC Trial Enrollment

Cumulative enrollment now over 16,000

TBTC mission (from By Laws):

"… to conduct programmatically relevant clinical, laboratory, and epidemiologic research concerning the diagnosis, clinical management, and prevention of tuberculosis infection and disease."

Slide from A. Vernon

CRUSH-TB Working Group Mandate

- **Middle Development**
  - Identify <u>regimens</u> likely to successfully shorten TB treatment
  - Working in the phase 2b/2c space
    - At least early evidence for efficacy (EBA/Phase 2a)
  - Efficiently select candidates for further study (phase 3)

- **Programmatically Relevant**
  - Regimens have potential for administration under routine program conditions

- **Unmet medical need**
  - Choice/options, for patients and clinicians
  - Shortened duration, for patients and programs

Some innovations, broadly useful to TB field

Phase 2C

- Treatment consists of promising new regimen(s) (focus on **shorter-course**), typically **given for intended duration, plus a standard control**

  - **Microbiologic endpoint** (8-wk culture conversion/time to conversion) is primary, but **follows all patients for failure/relapse** to capture this crucial endpoint

  - The **failure/relapse endpoint is critical**, can provide a probabilistic assessment of how likely the novel regimens will be successful if studied in a phase III trial that enrolls similar participant population

Adaptive design

  - Allows you to add regimens later in the trial, when more safety/efficacy information is available for promising drugs

Parallel animal model studies examining same regimens

Embedded biomarker (sputum LAM?)

ADVANTAGES: safety/microbiology for full duration (e.g. 4 mos); early information about relapse for decision-making; flexibility in light of emerging data in a rapidly evolving field; building translational and inter-phase modeling

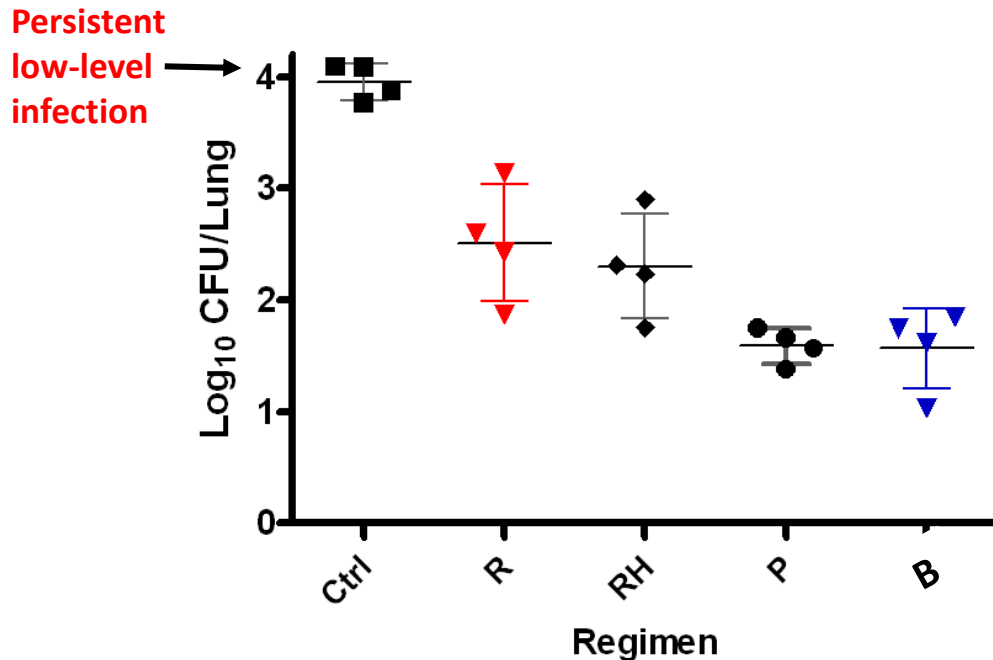See WHO http://www.who.int/tb/publications/2018/WHO-CDS-TB-2018.17-eng.PDF?ua=1
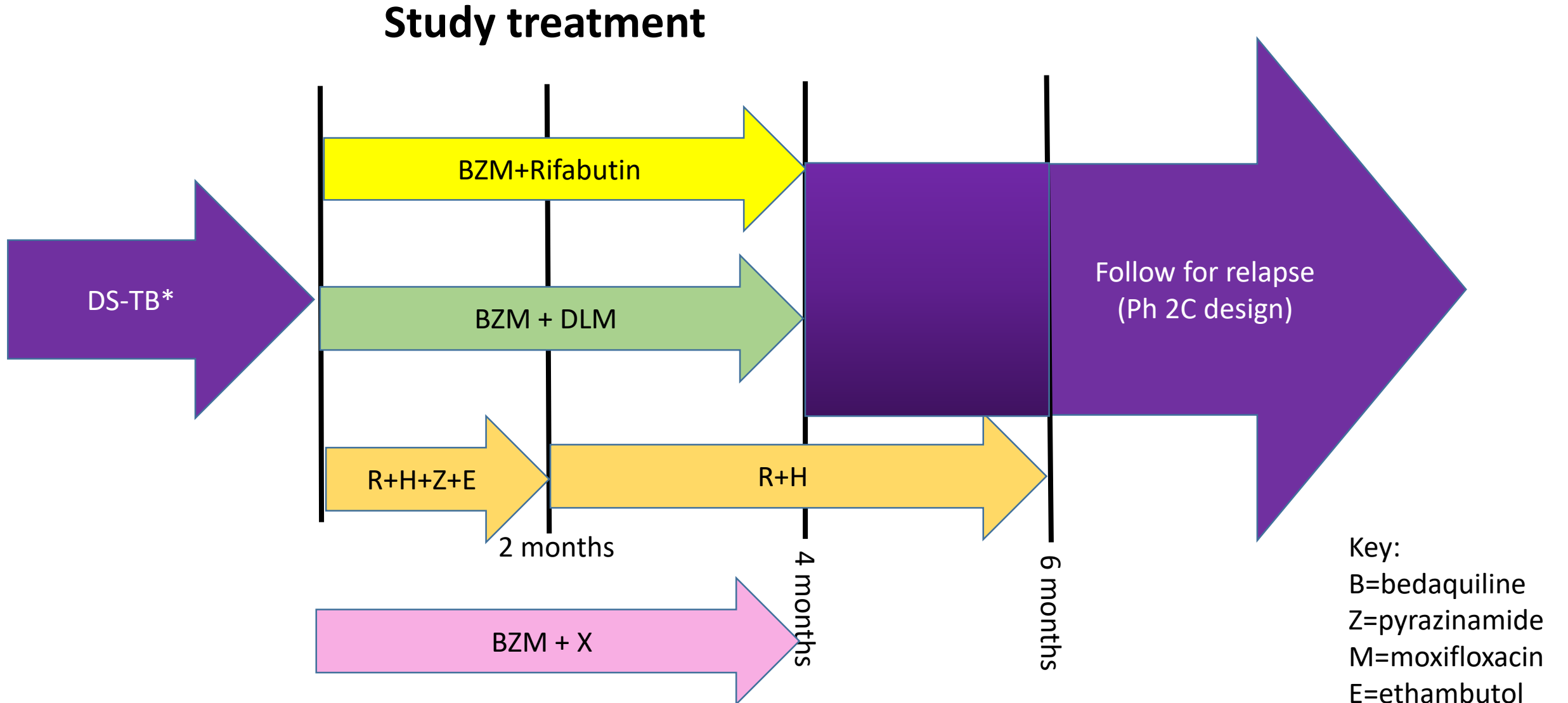
Study Schema

The Drugs

Regimen components– rationale
Drug #1: Bedaquiline (highest treatment shortening potential of new drugs to date)

Lung CFU counts after 1 month of treatment

Persistent low-level infection →

Relapse rates after treatment

Regimen	M1	M2	M3	M4
		Proportion (%) relapsing after stopping treatment at:		
R		15/15 (100%)	13/15 (87%)	6/13 (46%)
RH		14/15 (93%)	7/13 (54%)	
P	10/15 (67%)	0/15 (0%)		
B		13/15 (87%)	2/14 (14%)	4/14 (28%)

Bedaquiline (B) has sterilizing activity ≥ rifampin (R) in mice

Bedaquiline- emerging efficacy and safety data

Fig. 10. Forest-plot of adjusted Hazard Ratios on a number of co-variates for Cox regressions and Logistic regression analyses

2. Logistic regression

|		
a. Excluding BCAP patients		0.39 (0.31, 0.51)
b. No history of TB treatment		0.42 (0.28, 0.62)
c. History of TB treatment		0.38 (0.28, 0.53)
d. MDR-TB patients		0.51 (0.37, 0.68)
e. MDR-TB ($_{+FQ}$ or $_{+SLI}$) patients		0.49 (0.25, 0.97)
f. XDR-TB patients		0.34 (0.19, 0.58)
g. HIV negative patients		0.67 (0.43, 1.06)
h. HIV positive patients not on ART		0.11 (0.02, 0.48)
i. HIV positive patients on ART		0.35 (0.26, 0.47)

0   .1   1   1.5

Favors bedaquiline (reduced deaths)   Favors control (increased deaths)

GDG Bedaquiline 2017: http://www.who.int/tb/publications/2017/GDGreport_Bedaquiline/en/

Regimen components– rationale
Drug #2: Pyrazinamide
(Do we need this drug? What does it add?)

IV infxn of outbred Swiss mice

Aerosol infxn of inbred BALB/c mice

Group[b]	Bacterial count (log_{10} CFU) (mean ± SD)			% of mice culture negative at 2 mo
	Day 0	1 mo	2 mo	
Untreated	7.2 ± 0.5			
J		4.1 ± 1.8	2.3 ± 0.7	22
JZ		1.6 ± 1.6	0, 0	100
JR		4.7 ± 1.1	1.9 ± 1.0	30
JH		3.8 ± 1.9	1.9 ± 1.0	20
JM		4.6 ± 0.5	2.1 ± 1.1	22
RZ		5.4 ± 0.6	1.9 ± 0.9	20
RM		5.5 ± 0.9	3.1 ± 0.5	20
RH		5.1 ± 0.4	3.1 ± 1.1	0
HZ		5.5 ± 0.6	3.9 ± 0.7	0
JZM		1.4 ± 1.2	0.03 ± 0.1[c]	78
JZR		2.3 ± 1.5	0.07 ± 0.2[d]	70
JZH		1.7 ± 1.4	0.18 ± 0.5[e]	78
JRH		4.4 ± 1.1	1.2 ± 1.1	20
JRM		4.4 ± 0.3	1.4 ± 0.8	11
RMZ		4.6 ± 0.8	1.4 ± 0.4	20
RHZ		3.9 ± 0.7	2.2 ± 0.6	0

* p < 0.05 vs. JZ
** p < 0.01 vs. JZ
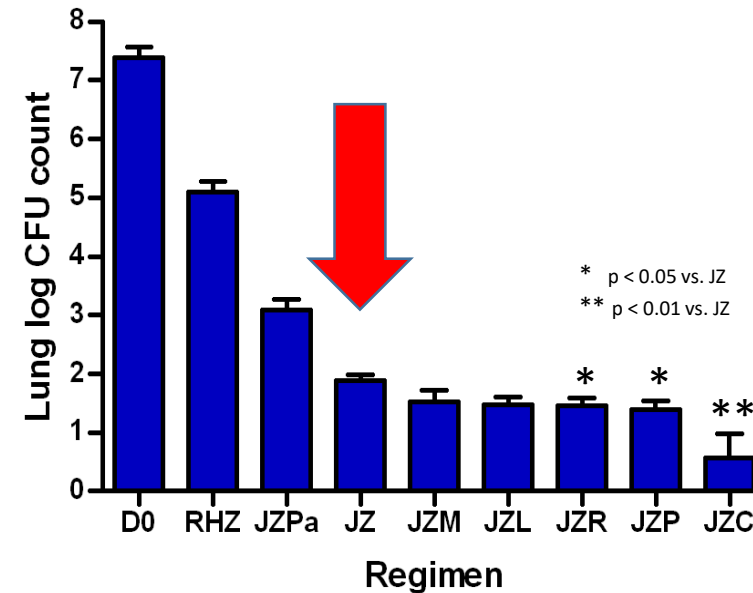
B + Z=Potent sterilizing combo

Slide from Eric

Ibrahim et al, AAC 2007

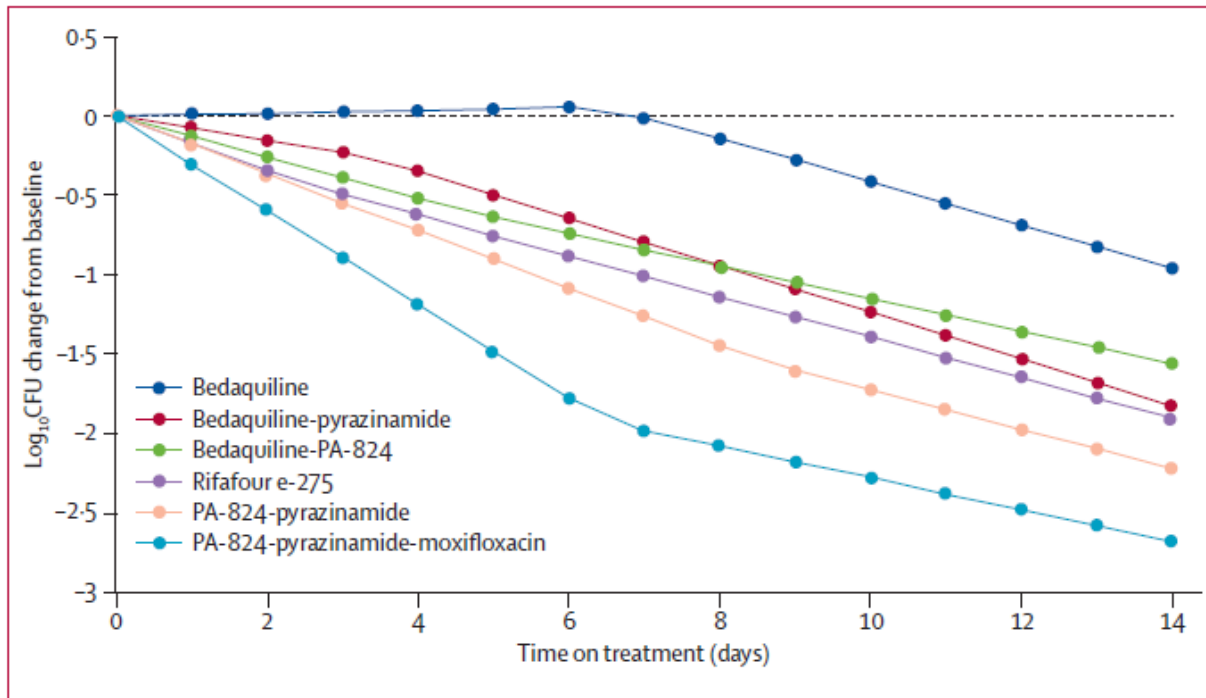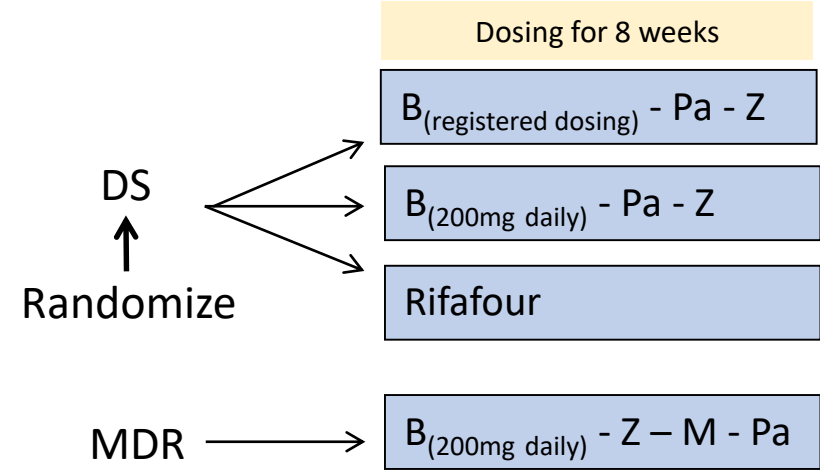Tasneen et al, AAC 2011

Clinical results: JZ in *extended* EBA

Figure 2: Bilinear regression showing the fall in mean log₁₀CFU from baseline
CFU=colony forming unit.

	Days 7–14
Bedaquiline	14 (0·123 [0·097])
Bedaquiline-pyrazinamide	15 (0·152 [0·120])
Bedaquiline-PA-824	14 (0·114 [0·069])
PA-824-pyrazinamide	14 (0·124 [0·080])
PA-824-moxifloxacin-pyrazinamide	13 (0·175 [0·146])
Isoniazid-rifampicin-pyrazinamide-ethambutol	10 (0·136 [0·102])

Diacon et al 2012 Lancet

Clinical results: BZM(Pa) in NC-005 (TB Alliance)

Design

Dosing for 8 weeks

DS →
- B(registered dosing) - Pa - Z
- B(200mg daily) - Pa - Z
- Rifafour

↑ Randomize

MDR → B(200mg daily) - Z – M - Pa

n.b. M added to shore up the B-Z-Pa regimen in patients with MDR-TB

Results

% culture negative at 2 months

Regimen	Population	Liquid cx Overnight	Solid cx Overnight
B(loading)ZPa	DS	66%	89%
B(200mg)ZPa	DS	75%*	84%
BZM-Pa	MDR Z-sensitive	96%*	100%*
BZM-Pa	MDR Z-resistant	78%*	95%*
HRZE control	DS	51%	86%

* statistically significant vs HRZE

Regimen components– rationale
Drug #3: Moxifloxacin– bactericidal (we need this) AND gets into lesions AND has anaerobic/sterilizing activity

BALB/c mice, Aerosol infection

Treatment	% (proportion) relapsing after treatment for:		
	1 month	2 months	4 months
2RHZ/3RH			100% (15/15)
PZM	100% (15/15)	100% (15/15)	
BZM	100% (15/15)	33% (5/15)	0% (0/14)

1. BZM shortens treatment by ≥3 months compared to RHZ
2. BZM is superior to PZM

Swiss mice, IV infection

Treatment	% (proportion) relapsing after treatment for:			
	3 month	4 months	5 months	6 months
2RHZ/3RH			50% (10/20)	27% (5/18)
PZM	100% (20/20)	32% (5/19)		
BZM			18% (3/16)	0% (0/20)

1. BZM is superior to RHZ
2. BZM is comparable to PMZ

BZM is treatment-shortening in mice
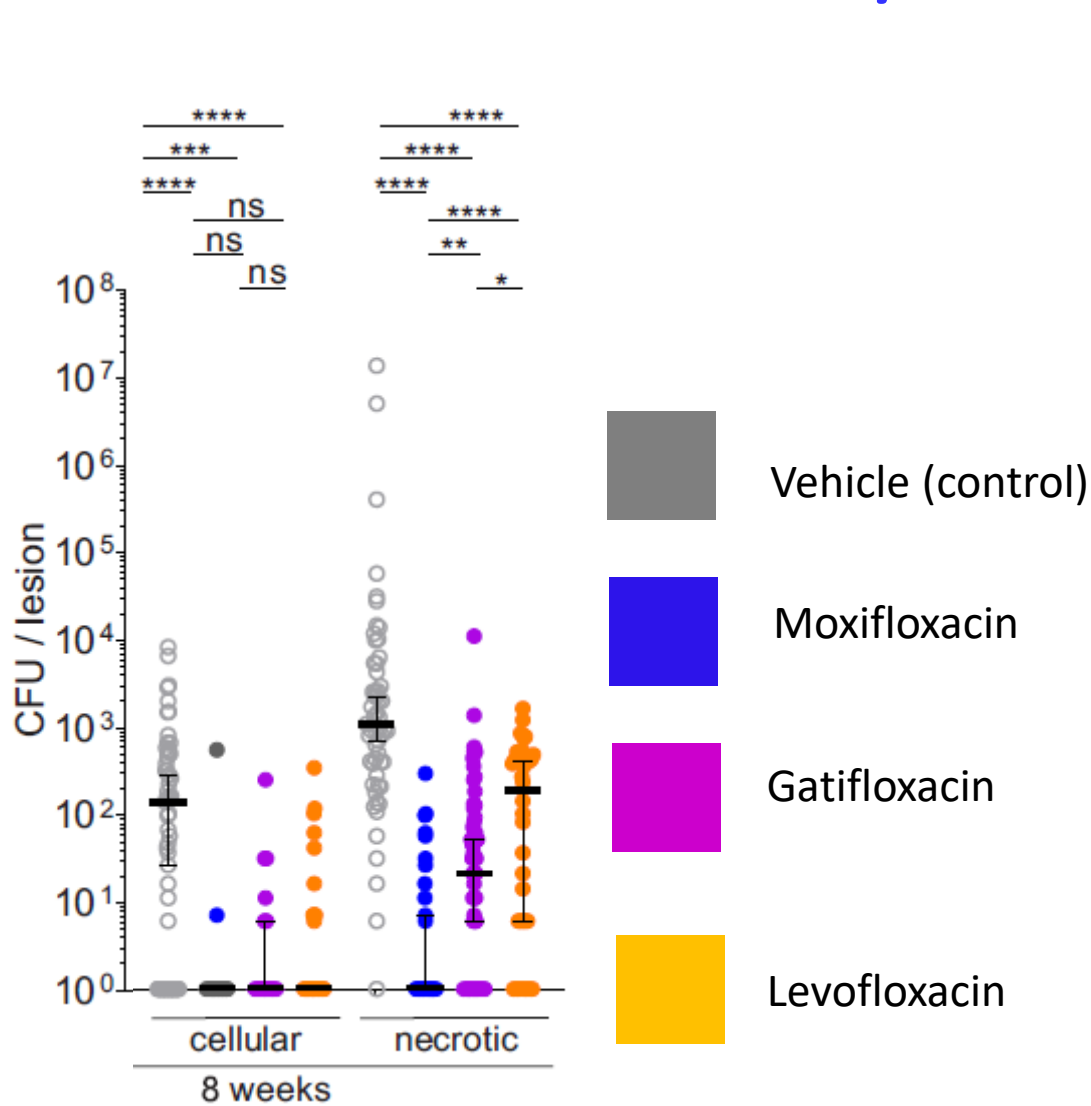
Tasneen et al, AAC (2011);55:5485

Andries et al, AAC (2010);54:4540
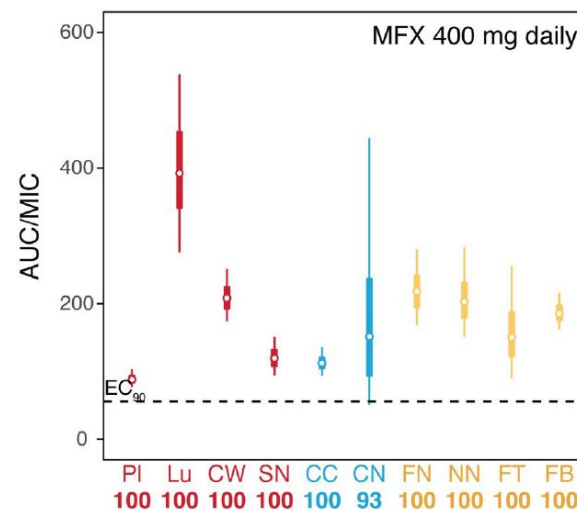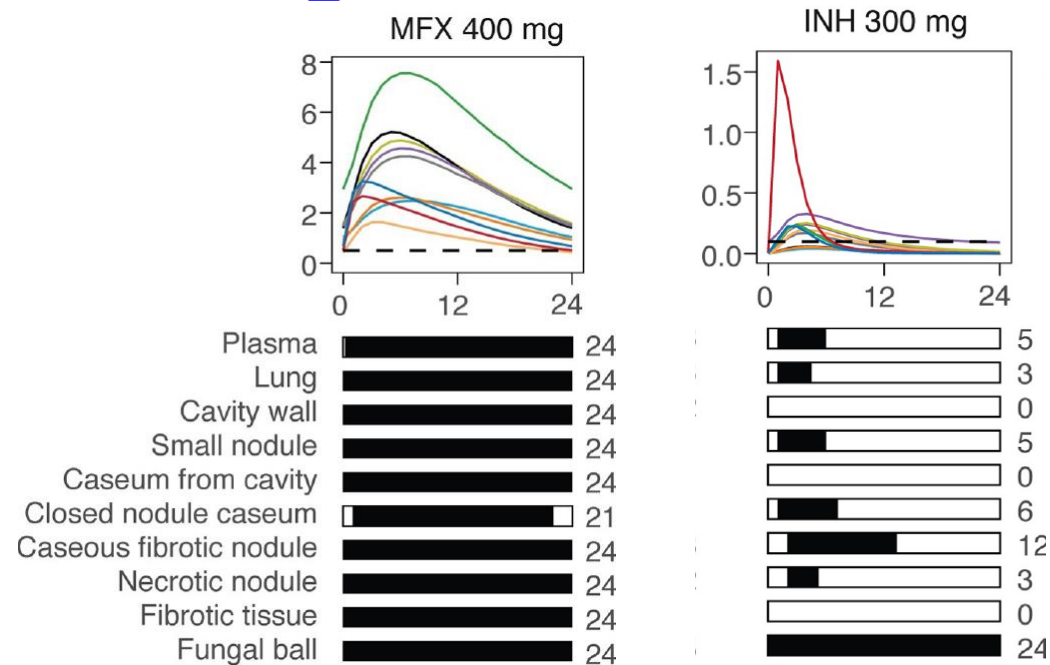
M contributes to efficacy of BMZPa regimen

Drug regimen	Proportion (%) of mice relapsing after treatment for:					
	M1	**M1.5**	**M2**	**M3**	**M4**	**M5**
RHZ					15/30 (50)	2/15 (13)
BPaZ		25/29 (86)	2/30 (7)	0/15 (0)		
BPaMZ	15/15 (100)	7/32 (22)	0/30 (0)	0/15 (0)		

Composite results of 2 experiments

Li et al, AAC (2017);61

Lesion PK and activity– new findings in rabbits and humans

Sarathy et al AAC 2019

Strydom 2019 PLoS Medicine

Back to NC-005...

Design

Dosing for 8 weeks

B(registered dosing) - Pa - Z

B(200mg daily) - Pa - Z

Rifafour

DS ← Randomize

MDR → B(200mg daily) - Z – M - Pa

n.b. M added to shore up the B-Z-Pa regimen in patients with MDR-TB

Results

% culture negative at 2 months

		Liquid cx	Solid cx
Regimen	**Population**	**Overnight**	**Overnight**
B(loading)ZPa	DS	66%	89%
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* statistically significant vs HRZE

QTc considerations

- Change in QTcF interval from baseline in NC-005 trial

|	Mean Change (msec)	95% Confidence Interval
B(loading)PaZ	21.9	18.2 – 25.7
B(200mg)PaZ	20.4	15.1 - 25.7
BPaZM (MDR)	21.9	18.7 – 25.0
HRZE control	10.2	7.0 – 13.4

- In US, when BDQ is used for 24 weeks–
  - ECG at baseline, 2, 12, and 24 weeks
  - Note that ECG changes with BDQ peak at 8 weeks and then stabilize
  - Note that M's QT effects go away immediately when drug stopped

- French cohort- Among patients getting BDQ for prolonged course, QT prolongation >500ms associated with high-dose MXF (800mg) or methadone, not moxifloxacin 400mg Guglielmetti Eur Resp J 2017

- **ACTG A5343, DLM Phase 3– Adding DLM to any regimen increases QT by just <u>8 ms</u>**

Regimen components– rationale
Drug #4: Do we need one? What are best options?

B A L B /c

N u d e
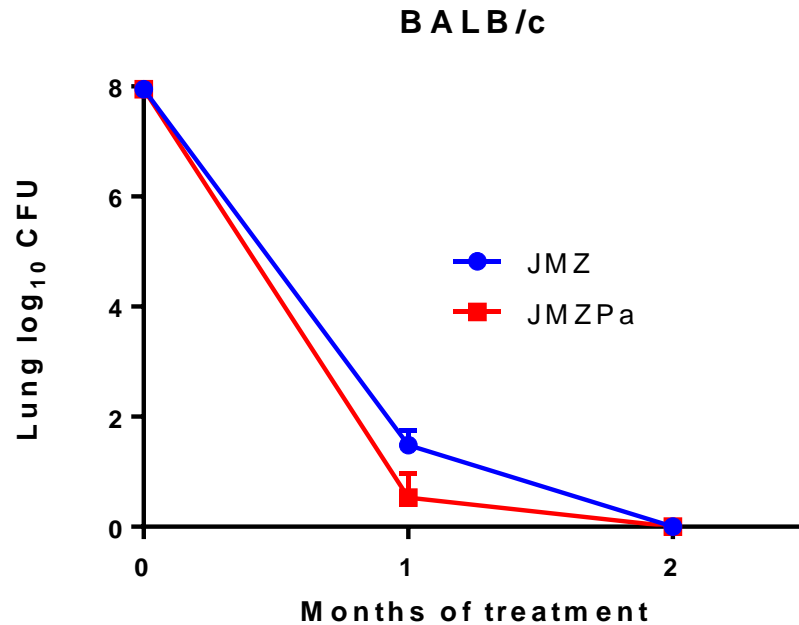
	Proportion relapsing after treatment for:		
Regimen	**1 month**	**1.5 months**	**2 months**
JMZ	13/13	2/15 (13%)	0/15
JMZPa	n.d.	3/15 (20%)	0/16
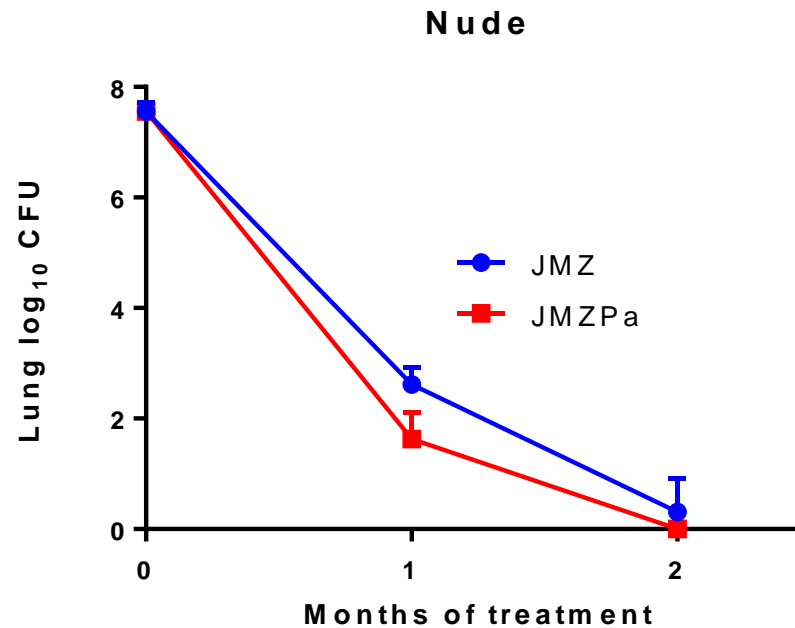
	Proportion relapsing after treatment for:
Regimen	**2.5 months**
JMZ	4/16 (25%)
JMZPa	1/18 (6%)

Pa contributed bactericidal activity to the JMZPa regimen but
no significant contribution to sterilizing activity was detected
**Yes, probably--4th drug may reduce relapse in hard-to-treat patients**

Regimen components– rationale
Drug #4: What are best options? Argument for <u>delamanid</u>

NOS2-deficient mice with hypoxic necrotizing lung lesions predict outcomes of tuberculosis chemotherapy in humans

Martin Gengenbacher[1,2], Maria A. Duque-Correa[1,7], Peggy Kaiser[1], Stefanie Schuerer[1], Doris Lazar[1], Ulrike Zedler[1], Stephen T. Reece[1,8], Amit Nayyar[3,9], Stewart T. Cole[4], Vadim Makarov[5], Clifton E. Barry III[3,6], Véronique Dartois[2] & Stefan H. E. Kaufmann[1]

Gengenbacher (Dartois, Barry, Cole, Kaufmann) 2017 Scientific Reports
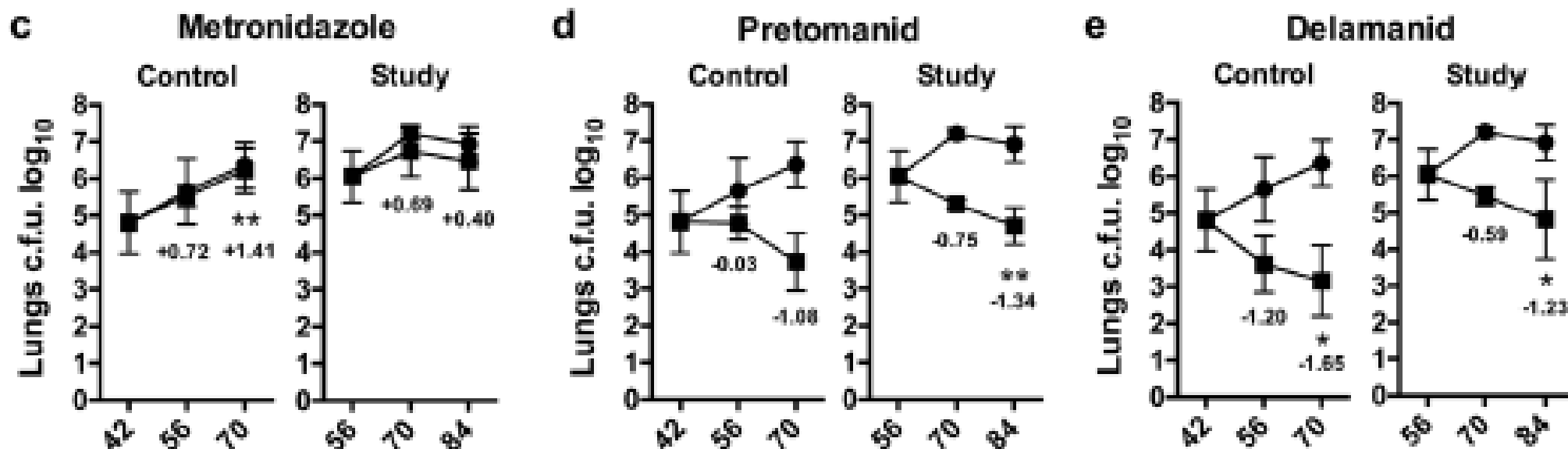
Nitroimidazoles kill those bacilli that are hard-to-kill in necrotic lesions

Regimen components– rationale
Drug #4: What are best options? Argument for <u>rifamycin</u>

Relapse data, chronic mouse model
Day -17: log CFU 4.41; Day 0: log CFU 8.32

	% (proportion) relapsing		
	W6 (+12)	**W8 (+12)**	**W10 (+12)**
PZM		47% (7/15)	13% (2/15)
BZ	93% (14/15)	67% (10/15)	53% (8/15)
BZ<u>P</u>	33%[1] (5/15)	0%[1] (0/15)	

[1]p≤ 0.005 vs. BZ

Adding a rifamycin to BZ gives impressive increase in activity

Williams et al, AAC (2012); 56:3114

Swiss mice, IV infection

BZR > RMZ > RHZ
BZH ≥ RMZ > RHZ

Treatment group	Proportion (%) with positive *M.tb* cultures 3 mo after completing treatment for:			
	2 months	**3 months**	**4 months**	**6 months**
2RHZ/4RH				17% (5/30)
2RMZ/2RM		84% (16/19)	42% (8/19)	
2BZR/2BR	56% (10/18)	28% (5/18)	13% (2/15)	
2BZH/2BH	68% (13/19)	72% (13/18)	29% (5/17)	

Combos of BZ plus R or H are treatment-shortening, R >H

Ibrahim et al, AJRCCM (2009);180:553

Regimen components– rationale
Drug #4: What are best options? Which rifamycin?

Typical concentration–time profiles
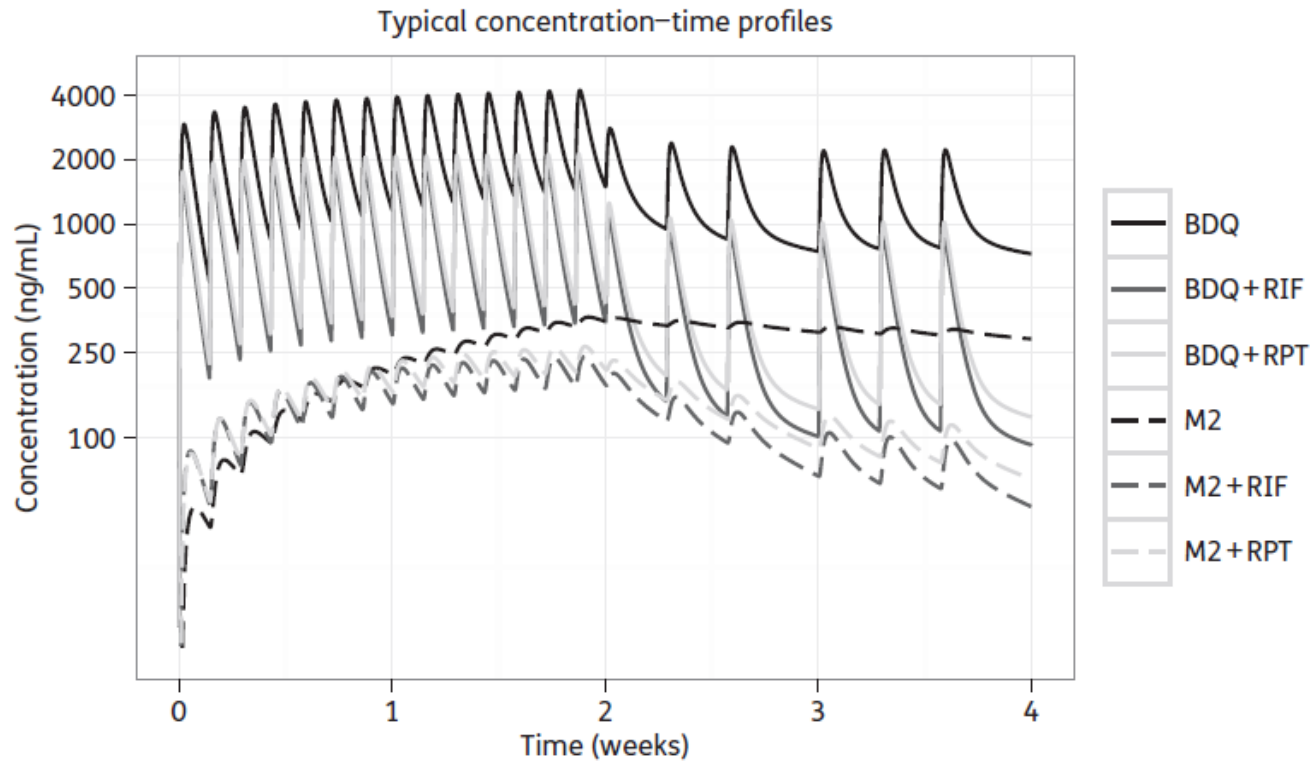

Legend:
- BDQ
- BDQ+RIF
- BDQ+RPT
- M2
- M2+RIF
- M2+RPT

TABLE 5 Effect of steady-state rifamycin on bedaquiline pharmacokinetic parameter estimates

Parameter	Rifabutin		Rifampin	
	GMR	CI	GMR	CI
C_{max}	0.910	0.776–1.068	0.803	0.705–0.915
$t_{1/2}$	1.012	1.037–1.172	1.056	1.002–1.112
AUC_{0-336}	0.901	0.789–1.028	0.554	0.519–0.599
$AUC_{0-\infty}$	0.918	0.808–1.044	0.565	0.523–0.610
CL/F	1.089	0.958–1.238	1.771	1.640–1.912
V/F	1.200	1.067–1.350	1.869	1.689–2.068

[a]GMR, geometric mean ratio; CI, confidence interval.

Rifabutin does not meaningfully reduce BDQ exposures

Rifapentine and rifampin reduce bedaquiline concentrations (would need 1000 QD for 2 weeks, then 1000 TIW)

Healan 2018 AAC

Svensson 2015 JAC

Linkages to other treatment-shortening studies in DS-TB

- PANACEA 2 STAGE STUDY (Phase 2B SUDOCU, then 4-mo 2C):
  - High-dose rifampin with or without high-dose PZA
  - **Bedaquiline/Delamanid/Moxifloxacin + Sutezolid (U)** (dose finding for U, then including that dose in 2C)
- TBA SimpliciTB (Phase 2/3): **Bedaquiline/moxi/pretomanid/PZA**
  - 4 BPaMZ
- BMRC TRUNCATE-TB (Phase 3): Multiple drugs
  - 2 HR_{35}ZELinezolid (extend to 3 mos for persistent + sx/smear)
  - 2 HR_{35}ZEClofaz
  - 2 HP_{1200}ZLinezolidLevoflox
  - **2 HBZELevoflox**

Adaptive design– to consider:
DprE1 inhibitors- completely new drug class

*DprE1 inhibitor - Inhibits decaprenyl-phosphoribose epimerase (DprE1) involved in cell wall arabinan biosynthesis			
OPC-167832	Otsuka Pharmaceutical Development & Commercialization, Inc.	Activity against replicating and dormant intracellular bacilli; Active in acute and chronic murine models; No antagonism with other TB drugs; Additive effect with Dlm exceeding RHZE	NCT03678688 (1-2, enrolling)
BTZ043	University of Munich, Hans-Knöll Institute, Jena, German Center for Infection Research (DZIF)	Superior to INH at 2 months in mice (6 month pending) No antagonism with existing drugs, apparent synergy in vivo with Bdq-Rif Low level CYP450 interaction	NCT03590600 (1, enrolling)
Macozinone, PBTZ169	iM4TB-Innovative Medicines for Tuberculosis, Bill & Melinda Gates Foundation, Nearmedic Plus LLC	Highly active against replicating bacteria; No antagonism with RHZE, synergy in vitro with Bdq, Cfz, Dlm, sutezolid Prior formulation with good tolerability, bactericidal activity against DS TB at 640mg	NCT03776500 (1, pending)
TBA-7371	TB Alliance	Efficacy in vitro and in mice Phase 1 trial complete on food effect, optimal dose, DDI, PK, PD as single dose or multiple doses	NCT03199339 (1, complete; 2, pending)

The Design

Study design: CRUSH-TB

Rationale: Optimization of new and existing drugs to make a <u>complete regimen</u>, considering properties needed to shorten treatment duration plus safety, for a public health purpose

Design: **Phase IIC**, randomized, open-label, $\geq$3-arm trial assessing the safety and efficacy of 4-month BZM-based regimens compared to 6-month standard of care among adult patients with drug-sensitive pulmonary TB

Arm	Weeks 0-8	Weeks 9-17	Weeks 18-26
1	BMZ+Rb	BMRb	--
2	BMZ+D	BMD	--
3 (standard Rx)	HRZE	HR	HR

Rb=rifabutin; M=moxifloxacin; B=bedaquiline; D=delamanid; H=isoniazid; E=ethambutol; Z=pyrazinamide; R=rifampicin

<u>**Duration**</u>: Until last participant reaches 12 months of follow-up

<u>**Sample size**</u>: 90/arm

Inclusion/Exclusion Criteria

Inclusion

- Pulmonary TB without concurrent CNS or bone involvement
- Age 12 and older
- AFB smear-positive (at least 1+) or GeneXpert positive (medium/high)
- If HIV+, CD4 at least 100 cells/mm^3

Exclusion

- >5 days of TB treatment in past 6 months
- Resistance to INH, RIF, or fluoroquinolones
- Pregnancy
- QT prolongation
- Unacceptable baseline labs
- History of aortic dissection/aneurysm

Endpoints

- **Primary**
  - Time to sustained sputum culture conversion in liquid media

- **Secondary**
  - Safety (proportion of grade 3-5 AEs by arm)
  - Tolerability (all-cause discontinuation by arm)
  - Alternative microbiologic endpoints (e.g. solid media, 8-week culture conversion)
  - Pharmacodynamic analyses
  - Long-term efficacy outcome (phase 2C outcome)

Procedural Highlights

- Randomization stratified by site (African/not African) and cavity (Y/N)
- 7/7 dosing with 5/7 DOT and SAT doses on weekends
- Intensive PK sampling in convenience sample, sparse PK sampling in all
- Serial microbiologic and safety monitoring, including ECG
- Follow-up until last participant is 12 months post treatment completion
  - Provides extra information on delayed relapse while keeping the trial short

Key Issues Debated and +/- Decided

- Dosing schedule for bedaquiline (200 QD x 8 weeks, then 100 QD)
- Dosing schedule for delamanid (200mg QD) (with food)
- Flat vs. weight-based dosing for pyrazinamide (1500 $\leq$50kg, 2000>50kg)
- Duration of pyrazinamide (2 months)
- Biomarkers: sputum LAM
- Media type/standardization (solid YES and not standardized; liquid YES)

To sort still:
- resistance testing for bedaquiline and delamanid
- Logistics of ECG evaluations
- CDA$\rightarrow$ CTA

Preclinical link

(Stay tuned– Nuermberger lab to test different combinations in different mouse models....)

CRUSH Summary

- Phase 2C trial, 3+ arms, 90/arm

- Estimated 18 months to enroll, additional 12 months of followup after last participant=total trial duration ~30 months

- Will complement efforts by other groups, elucidating some key questions (e.g. additional activity of rifamycin plus bedaquiline, activity of delamanid vs. pretomanid in regimen)

- BZM backbone
    - BZ is most potent two-drug regimen in mice; B with sterilizing activity better than rifamycins; BZM backbone performed extremely well in human trials (NC-005); drug with good bactericidal activity in the regimen (M); Oral, once daily, few side effects, all drugs taken by hundreds of patients with good safety profile; Compatible with first-line ART regimen (dolutegravir) without dose adjustment

- With 4th drug to shore things up, give best shot at exceptional activity (rifabutin, delamanid, maybe a DprE1 inhibitor added via adaptive design)

- PhC format will provide concrete guidance on likelihood of success in phase 3, facilitating planning of "next trial"; concurrent preclinical work for translational links

Thanks again-- CRUSH TB Protocol Team Members

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- Jessica Ricaldi, MD, PhD
- Nigel Scott, MS
- Katya Kurbatova, MD, PhD, MPH

Microbiology, pharmacology, pediatrics, community, clinicians, biomarkers, drugs, international/US, young/old

Extra slides

Most promising (currently-available) backbone for treatment shortening: rationale for BZM

- BZ is most potent two-drug regimen in mouse model; B with sterilizing activity better than rifamycins

- BZM backbone performed extremely well in human trials (NC-005)

- We need to have a drug with good bactericidal activity in the regimen (M)

- Oral, once daily, few side effects, taken by hundreds of patients with good safety profile, well-tolerated

- Compatible with first-line ART regimen (dolutegravir) used in US and increasingly globally, without dose adjustment

4th drug (to add activity, prevent resistance)- on-the-shelf possibilities to demonstrate JZM shortening safely

- **BZM+rifamycin**
  - Highest potency in animal models, this regimen has 4 drugs with sterilizing activity
  - Proof of concept with rifabutin (and if the rifamycin is *needed* to shorten therapy, then can consider Rifapentine (P) with B dose adjustment because of DDI)
  - Effective for INH-monoresistant TB (present in $\geq$10% of isolates globally)

- **BZM+delamanid**
  - JZM alone may or may not be adequate to shorten treatment
  - Nitroimidazoles add some activity to BZM regimen, very active in necrotic lesions
  - DLM has nice safety profile, is registered in several settings
  - Rifamycin- and isoniazid-sparing
  - Regimen could be used in INH-resistant TB (and MDR TB where PZA is active)
  - Comparison can be made to similar regimens in SimpliciTB (BZMPa) and PanACEA (BDSM) trials
        --Is Z needed? Is Pa = D, or is Pa better?

  S=sutezolid, M=moxifloxacin, B=bedaquiline, Pa=pretomanid, D=delamanid