The Tuberculosis Drug Development Pipeline

Harnessing Current (& Future) Knowledge to Address Highly Drug-Resistant TB

Kelly Dooley, MD, PhD

Symposium on Emerging Resistance to Novel Tuberculosis Drugs

Columbia University, New York, NY

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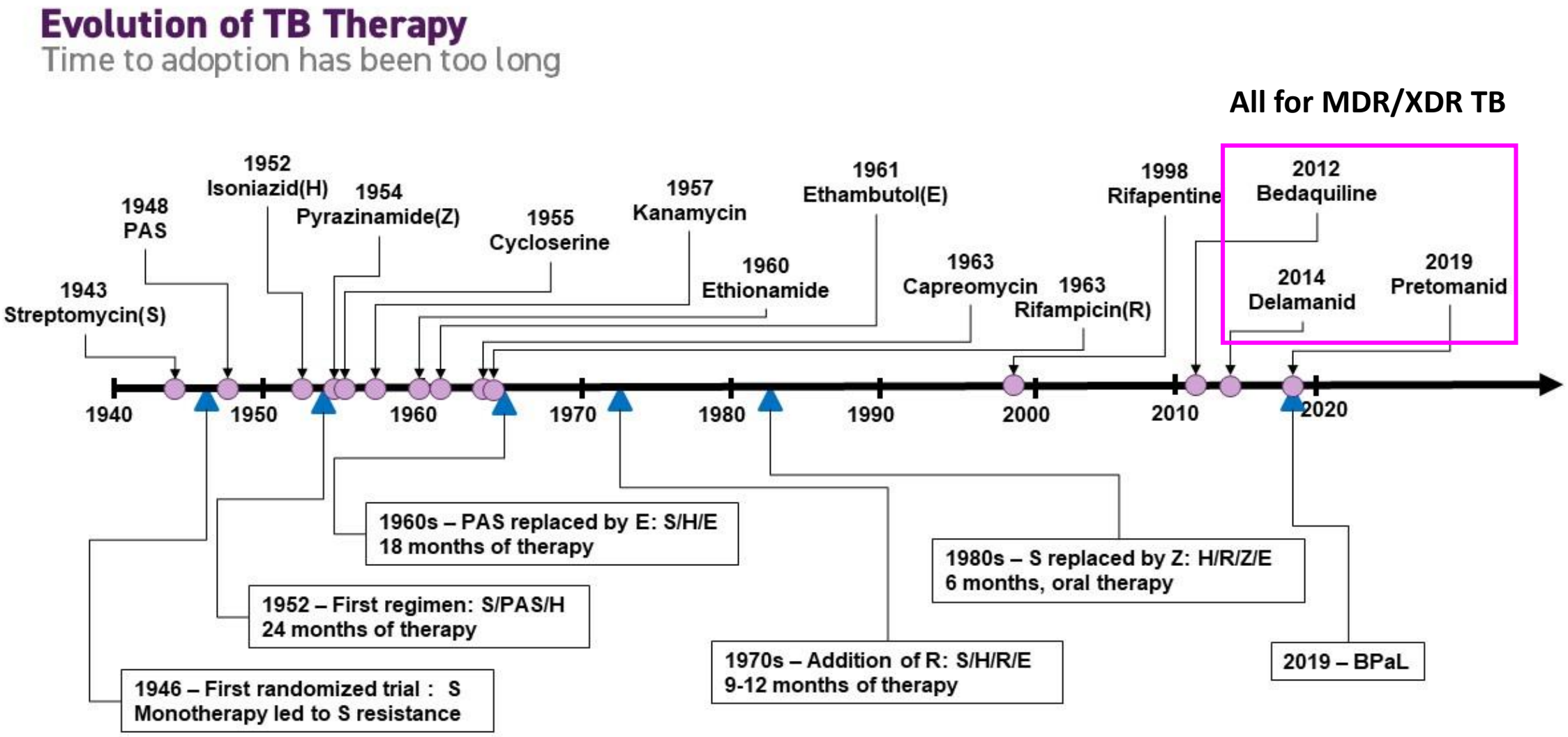
VANDERBILT UNIVERSITY
MEDICAL CENTER

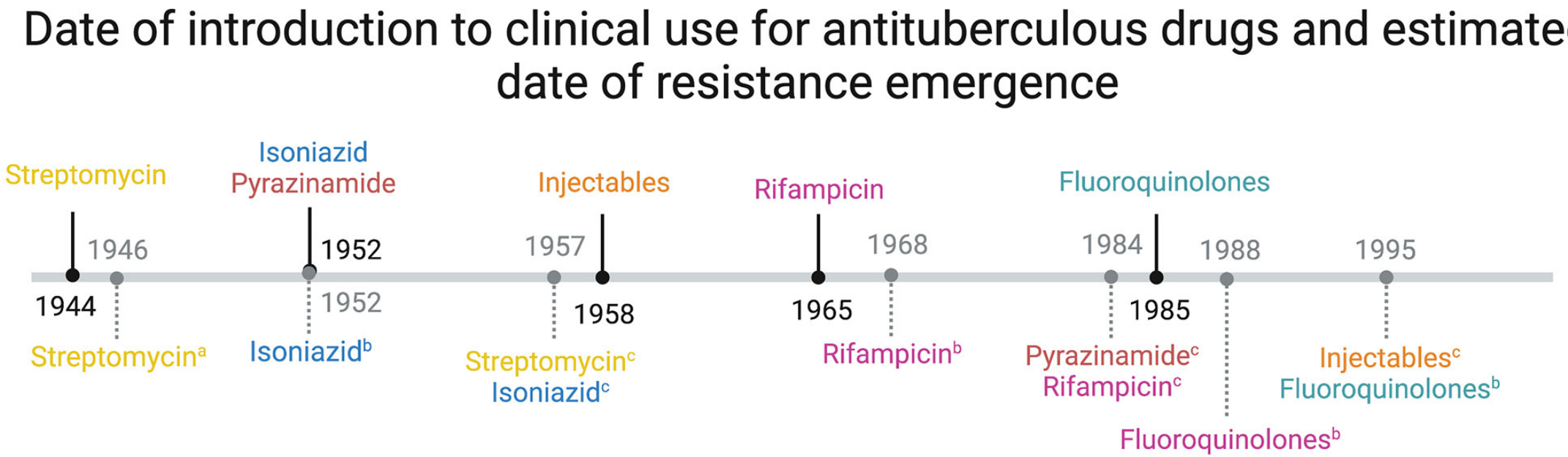

TB ANYWHERE IS EVERYWHERE
The image
The dandelion is a plant which propagates itself by airborne means. In the same way, social action can spread and take root, carried on the winds of our efforts and the global determination to overcome this disease.
ge also represents the vulnerability of
here the disease, located anywhere,
d everywhere.
reventable and curable.
BAL PLAN TO STOP TB.
WORLD TB DAY
REUTERS

TB drug development- three new drugs this century



https://www.tballiance.org/sites/default/files/assets/TB-Alliance_TB-Therapy-Evolution_Graphic.jpg

Emergence of resistance for anti-TB drugs: Rapid, predictable



a Clinical case series report (Youmans et al. 1946)
b Global lineage 4 (Brynildsrud et al. 2018)
c Tugela Ferry XDR (Cohen et al. 2015)

Fortunately, we have a robust pipeline & trials landscape

Or do we?

Current Antimicrobial Therapy Trials Landscape: Drug-Sensitive TB

1. HIGH-DOSE RIFAMYCINS

RIFASHORT
2 $HR_{1200}ZE$/2 HR_{1200}
2 $HR_{1800}ZE$/2 HR_{1800}

TBTC S31/ ACTG A5349
2 HPZE/2 HP
2 HPZM/2 HPM

ACTG Clo-Fast
4 HPZEClofaz

ACTG A5414
HPZM, stratified, duration-randomized

2. REPURPOSING OLD DRUGS
(CLOFAZIMINE, LINEZOLID, FLUOROQUINOLONES)

BMRC TRUNCATE-TB
2 HR_{35}ZELinezolid (up to 3 mos for persistent + sx/smear)
2 HR_{35}ZEClofaz
2 HP_{1200}ZLinezolidLevoflox
2 HBZELevoflox

PANACEA SUDOCU
Hd* R +/- Hd PZA
Bedaquiline/ Delamanid/ Moxifloxacin + Sutezolid (S)

DECODE
BDM+ delpazolid

*Hd= High Dose

TBA SimpliciTB
4 BPaMZ

TBTC S38/ CRUSH-TB
•2 BMZRb/2 BMRb
•2 BMZD/2 BMD

3. EXPLORING NEW & NEWER DRUGS
(E.G. BEDAQUILINE, PRETOMANID, NEW CHEMICAL ENTITIES (NCE))

UNITE4TB
Control arms: HRZE/HR, BDM/HR
GSK656 Arms: BD**G** + M, L, or Z
BTZ043 Arms: BDT + M, L, or Z
BDM, BDGT

ACTG RAD-TB
1: BPaL vs. BPa(TBI223) vs. BPaS vs. HRZE

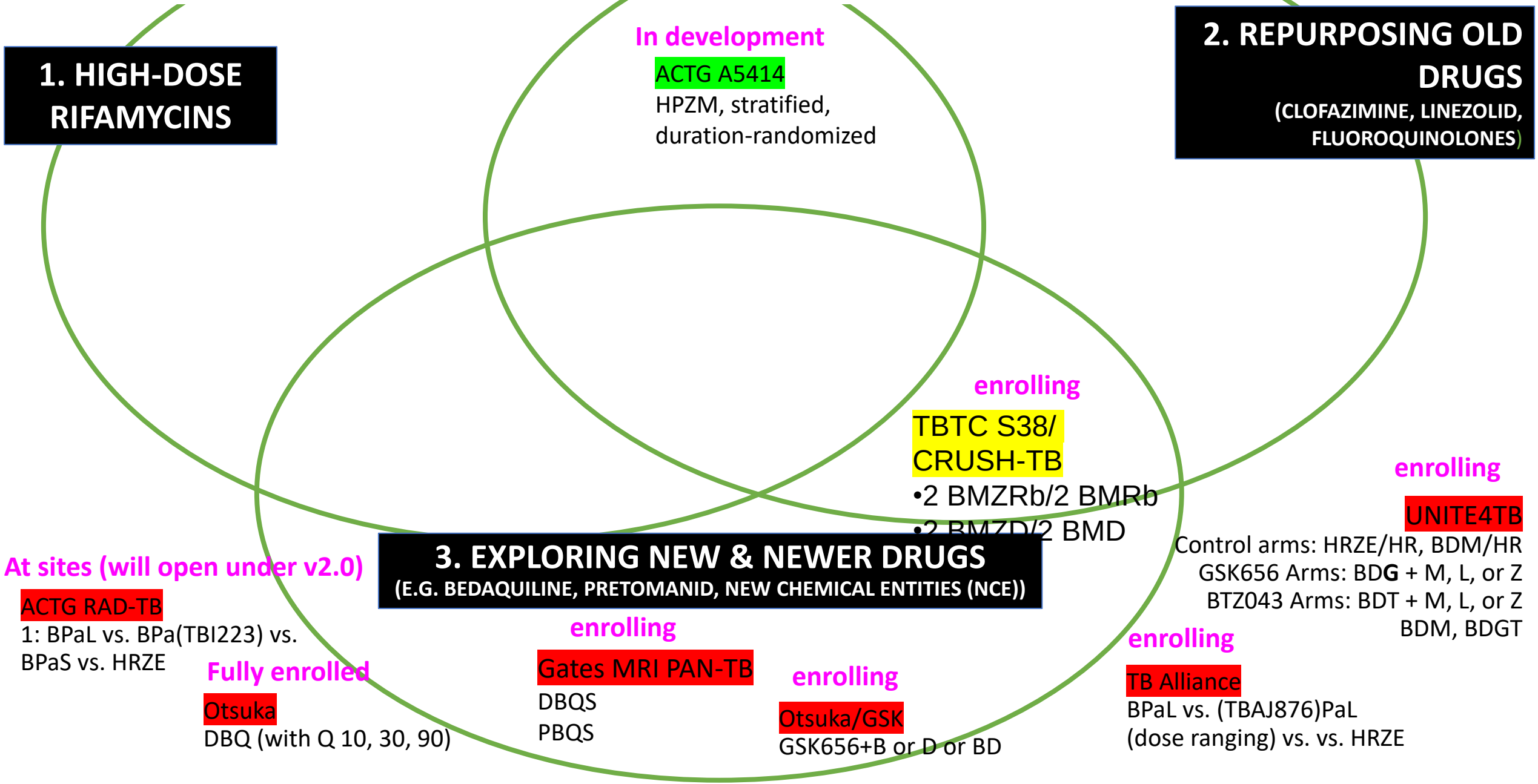
Gates MRI PAN-TB
DBQS
PBQS

Otsuka
DBQ (with Q 10, 30, 90)

Otsuka/GSK
GSK656+B or D or BD

TB Alliance
BPaL vs. (TBAJ876)PaL (dose ranging) vs. vs. HRZE

Current Antimicrobial Therapy Trials Landscape: Drug-Sensitive TB (removing completed/closed trials)



Drug-Resistant TB Trials Landscape

- **Nix-TB, ZeNix-TB, TB-PRACTECAL, endTB**
  - Completed, resulting in:
    - 6-month BPaL_z (+/- FQ) regimen
    - 9-month BL_zMZ, BCLL_zL_fZ, BDL_zL_fZ regimens; DCMZ as back-up

- **Still in progress**
  - EndTB-Q (BDCL_z 6-9m vs. SOC)
  - ACTG A5356 (BDCL_z x 6 m)

All contain B (or C)

Bedaquiline resistance- the time to worry is now

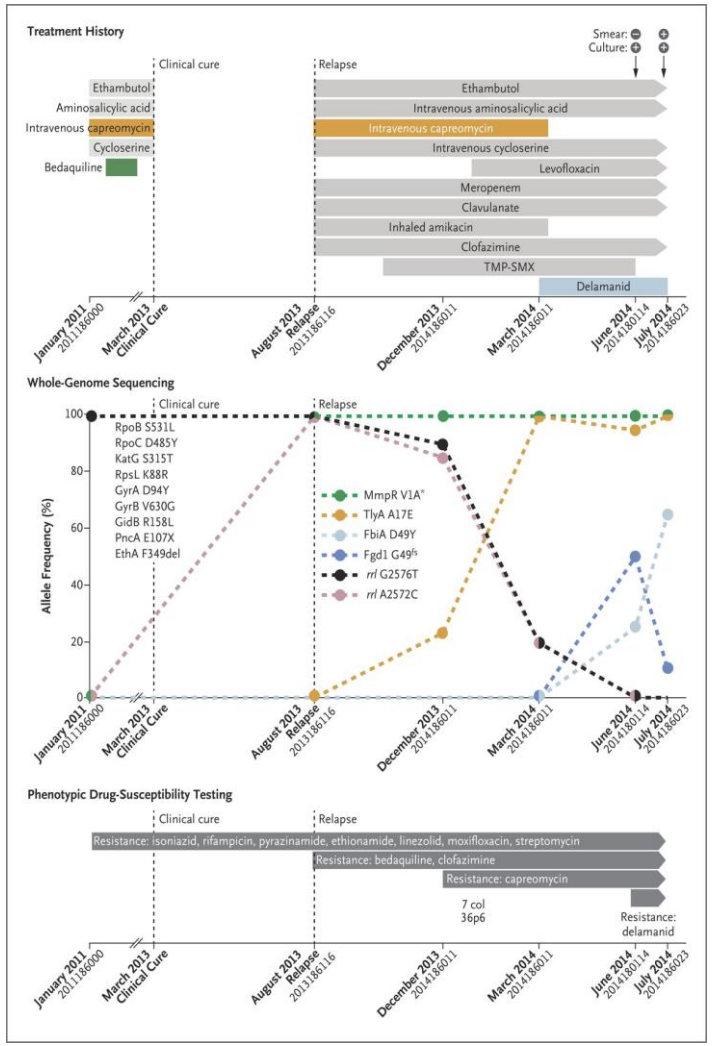


Fig 1. Clinical Features, Treatment History, Amplification of Drug Resistance, and Phenotypic Drug-Susceptibility Testing in the Patient. Bloemberg et al NEJM 2015 373: 1986.

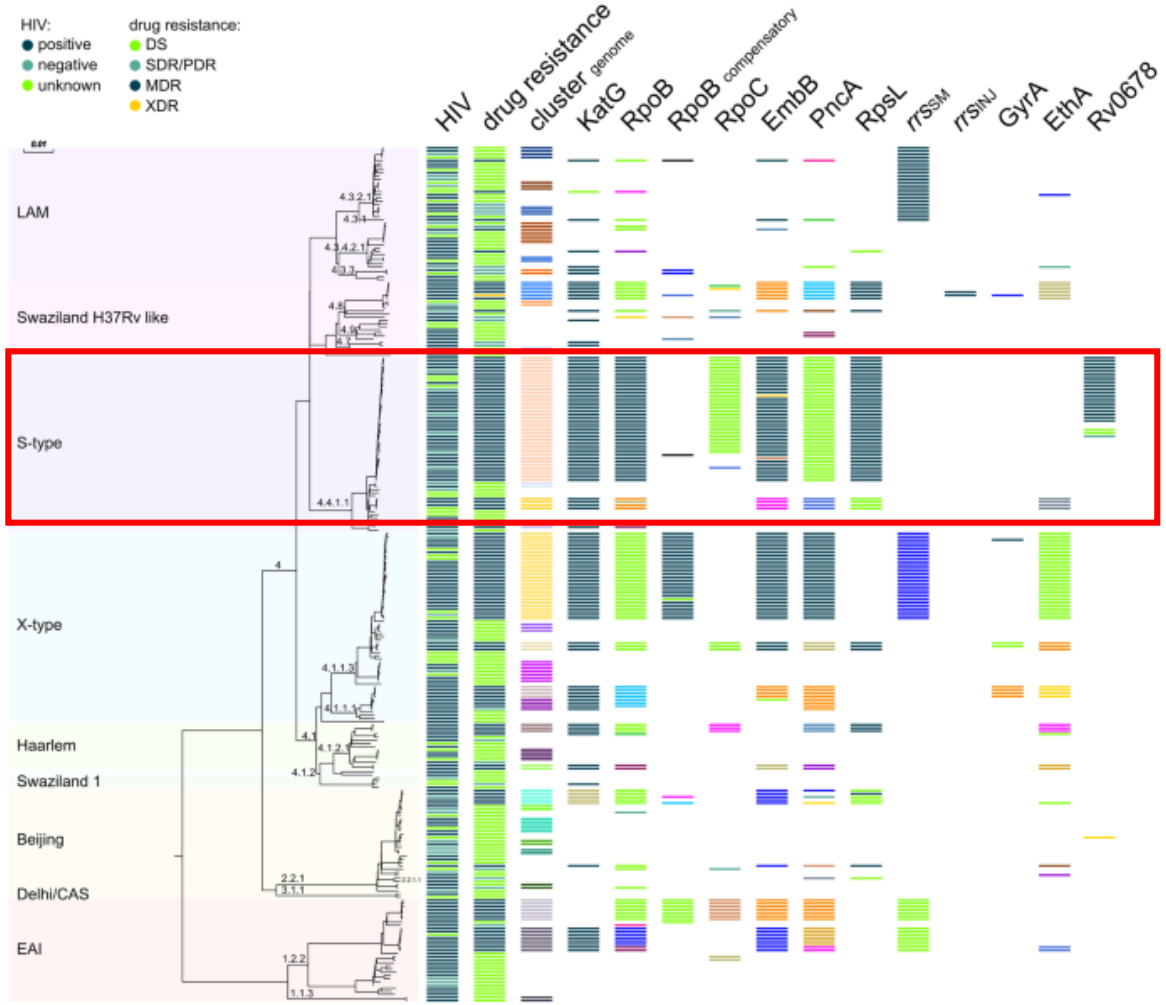


Fig 1. MDR *M. tuberculosis* outbreak strain in Eswatini missed by Xpert has elevated bedaquiline resistance dated to the pre-treatment era. Beckert et al Genome Medicine 2020

2024 Global New TB Drug Pipeline[1]

Discovery | Preclinical Development | Clinical Development

Lead Optimization

Indazole sulfonamides

Diarylthiazoles

DprE1 Inhibitors

Direct InhA Inhibitors

Mtb energy metabolism

Gyrase Inhibitors

Arylsulfonamides

Inhibitors of MmpL3, Translocase-1, ClpC1, ClpP1P2, PKS13, F-ATP synthase, RNAP

Oxazolidinones

DnaE1 / Nargenicin analogs

Early Stage Development

FIM-253

TBD10 (MK-3854)

CLB-073*

SPR720*

MPL-447*

JSF-3285*

CPZEN-45*

NTB-3119*

MBX-4888A (1810)*

FNDR-20364*

GMP / GLP Tox.

GSK-839*

OTB-658

Phase 1

TBD09 (MK-7762)

GSK-286*

TBAJ-587

TBI-223

Macozinone* (PBTZ-169)

Phase 2

Telacebec* (Q203)

Alpibectir (BVL-GSK098)*

TBAJ-876

Sanfetrinem

Delpazolid, Sutezolid, Tedizolid

BTZ-043*

TBA-7371*

Quabodepistat (OPC-167832*)

Ganfeborole (GSK-656*/070)

Pyrifazimine (TBI-166)

SQ-109*

Phase 3

Sudapyridine (WX-081)

Bedaquiline*

Delamanid*

Pretomanid*

Regulatory Market Approvals

*New chemical class. Known chemical classes for any indication are color coded: 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

Ongoing projects without a lead compound identified: http://www.newtbdrugs.org/pipeline/discovery

Underline = updates since November 2022

WORKING GROUP ON NEW TB DRUGS

www.newtbdrugs.org

Updated: March 2024

TB Drug Pipeline- drugs in clinical testing

***Drugs in red will bypass dedicated EBA studies**

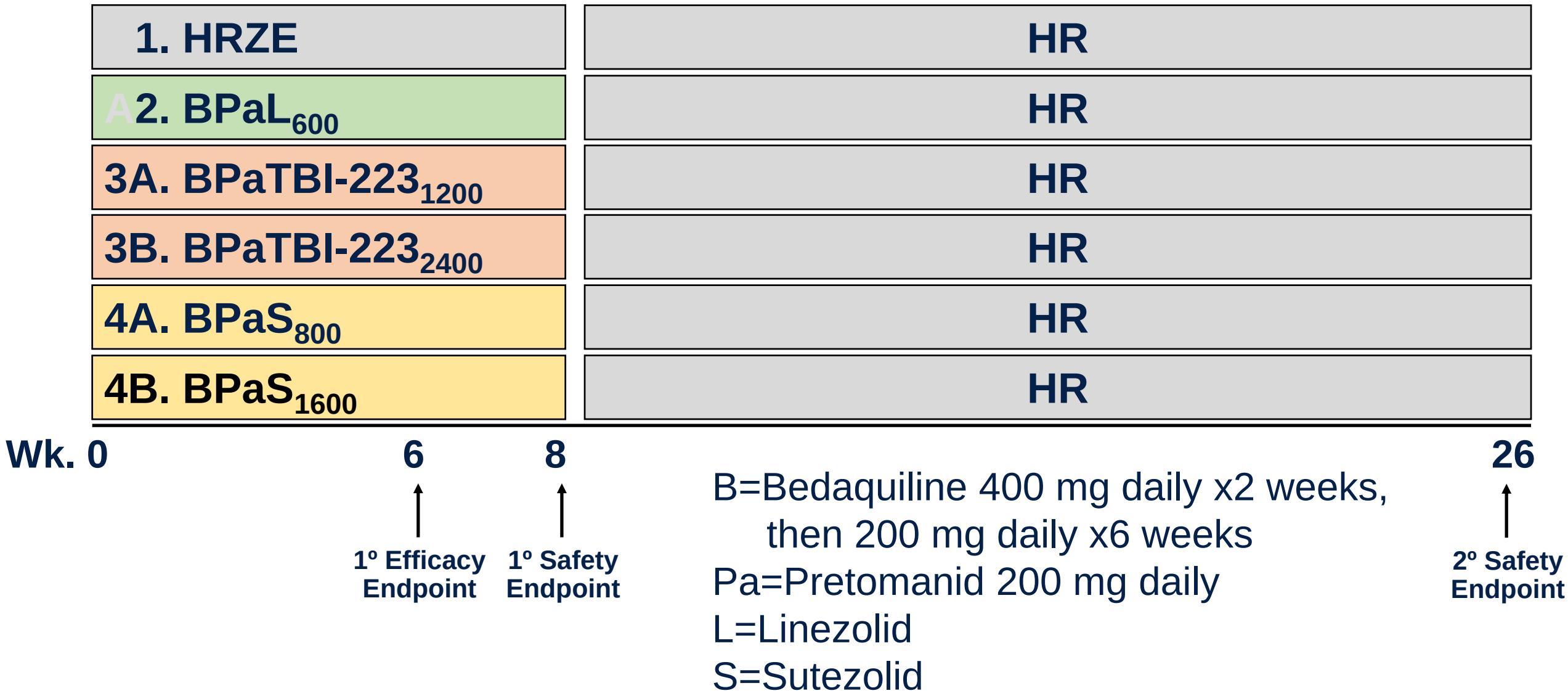
****Drugs in similarly-shaded boxes are from same drug class**

Phase 1	Phase 2	Owner	Data
GSK-286*	Telacebec (Q203)	TB Alliance	EBA +
TBAJ-876 →	Alpibectir (BVL-GSK098)/Eth	BioVersys/GSK	EBA +
TBAJ-587	Sanfetrinem	GSK	EBA underway
TBI-223 →	Delpazolid	LegoChem Biosciences	Ph2 4BDM+Dpz completed
MK-7762	Sutezolid	TB Alliance	Ph2 4BDM+Stz resulted
	BTZ-043	LMU	EBA +
	TBA-7371	TB Alliance	EBA +
	Quabodepistat (OPC-167832)	Otsuka	+ EBA; DBO completed
	Ganfeborole (GSK-656)	GSK	EBA +
	Sudapyridine (WX-181)	Shanghai Jiatan Pharmatech	In Ph3

Oxazolidinones (like linezolid) Diarylquinolines (like bedaquiline) DprE1 inhibitors

- **Some drugs from completely novel classes**
- **Others from familiar classes, but potential for better therapeutic window**

ACTG A5409: A Phase 2A+ Randomized, Adaptive, Dose-Ranging, Open-Label 6-Week Trial of Novel TB Treatment Regimens: WAVE 1



B=Bedaquiline 400 mg daily x2 weeks, then 200 mg daily x6 weeks

Pa=Pretomanid 200 mg daily

L=Linezolid

S=Sutezolid

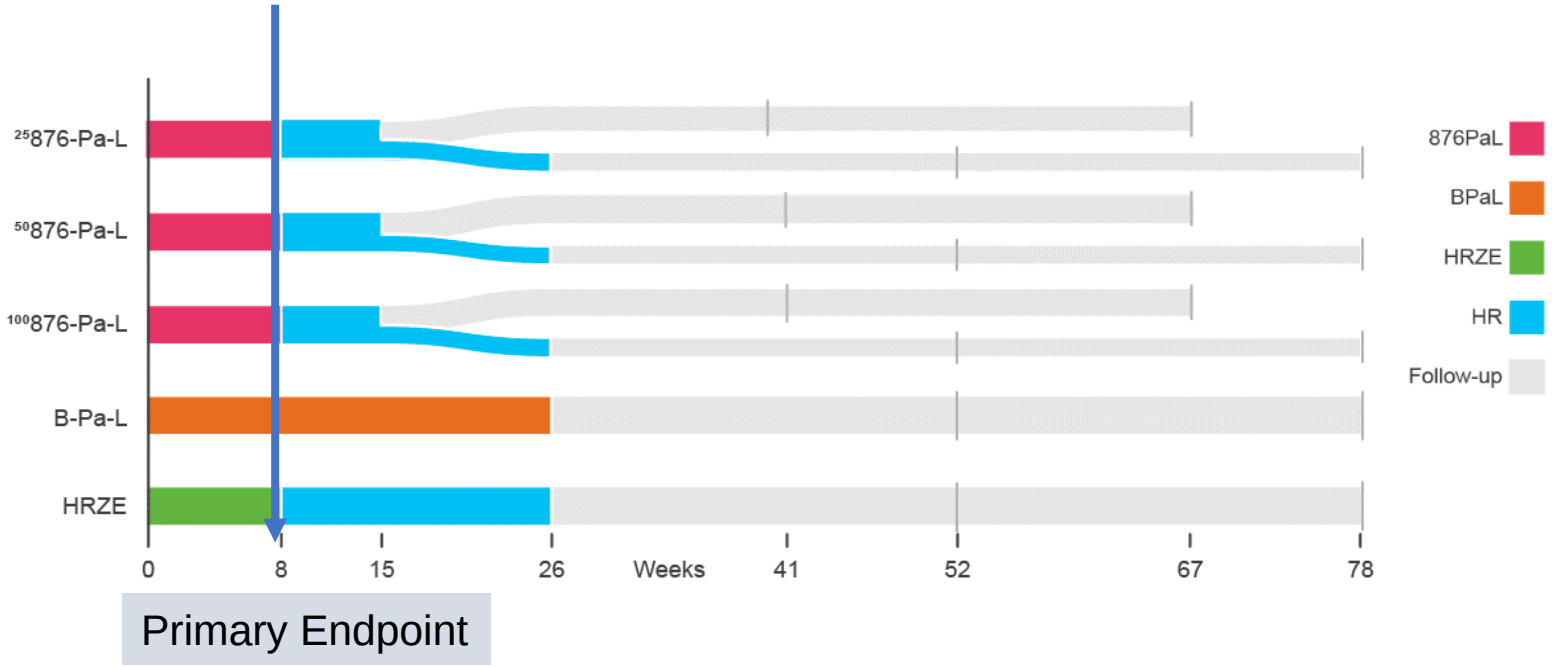
NC-009 Study Design

≥ 300 DS-TB participants randomized to 1:1 to 5 treatment arms (N=~60)

- Newly diagnosed DS-TB ± HIV; Stratified by Region and Severity of disease

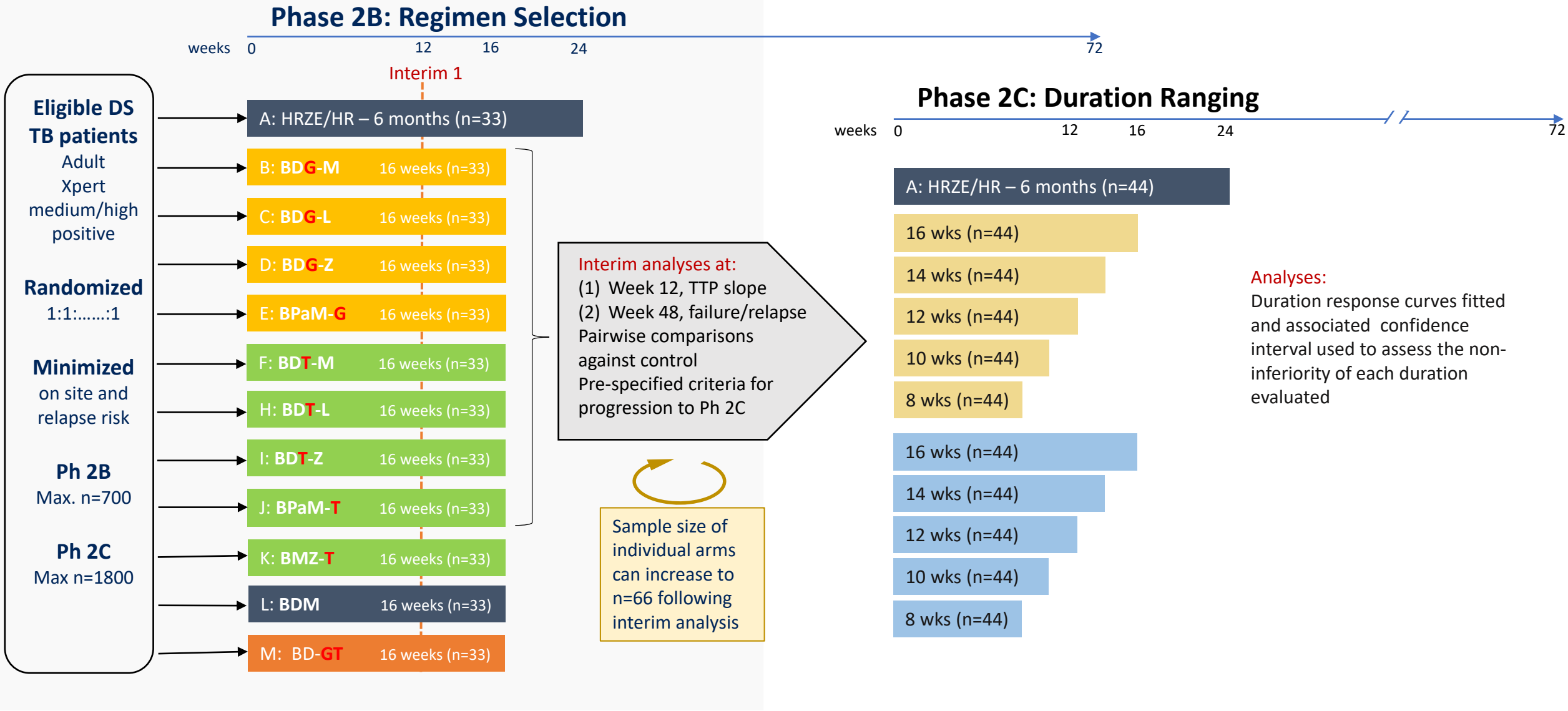
Key objectives:

1. TBAJ-876 Dose selection
2. Compare efficacy of TBAJ-876 vs BDQ
3. Evaluate BPaL in DS-TB
4. Explore shorter treatment
5. Compare safety of TBAJ-876 vs BDQ
6. Compare safety of BPaL vs HRZE



TBAJ-876 and B are blinded (first 8 weeks)
Pretomanid and linezolid (600 mg) are open label; Linezolid dose adjustments are possible and treated equally across arms.
Biomarker exploratory assessments are included

UNITE4TB-01 seamless Phase 2B/C study design: PARADIGM

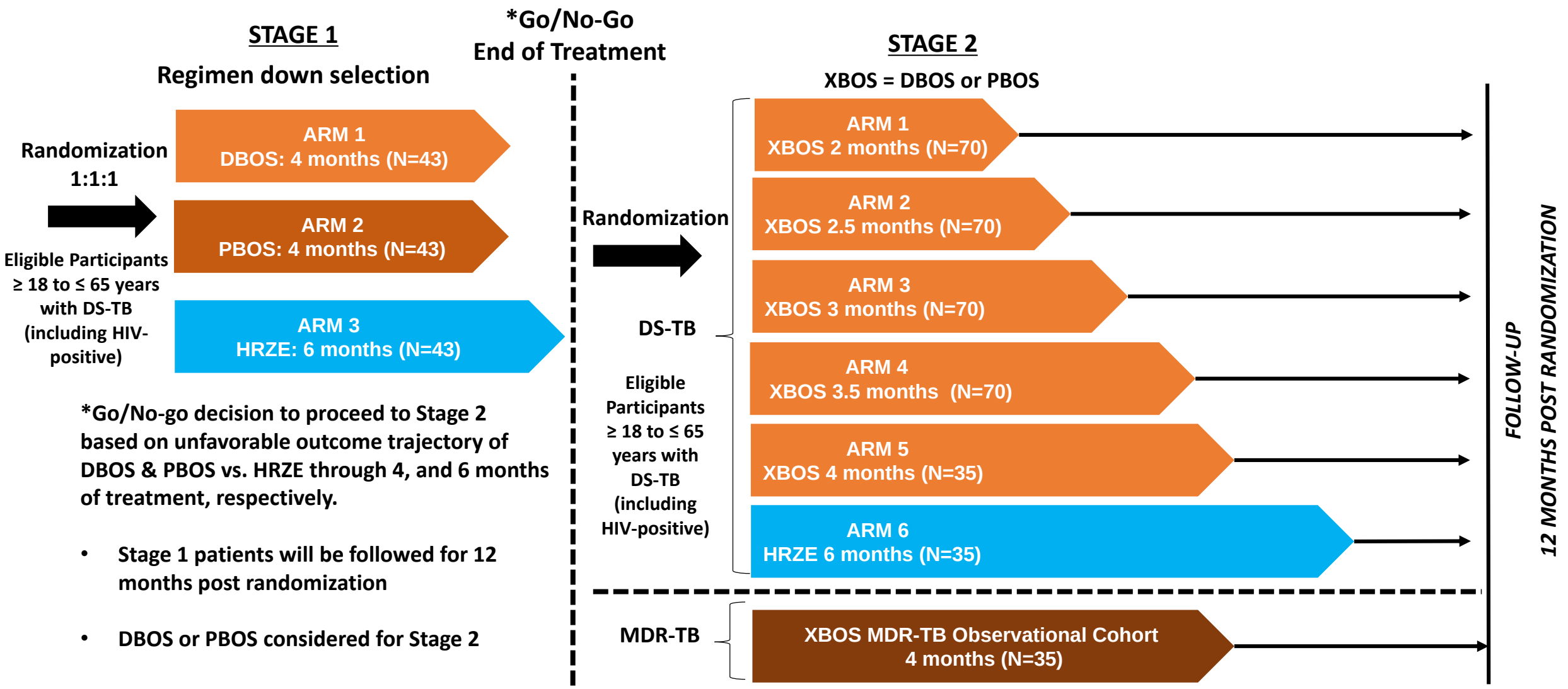


G = GSK 656 (ganfeborole)
T = BTZ-043

B = Bedaquiline
D = Delamanid
M = Moxifloxacin

L = Linezolid
Z = Pyrazinamide
Pa = Pretomanid

PAN-TB Ph2b/2c 2-Stage, De-risking Design



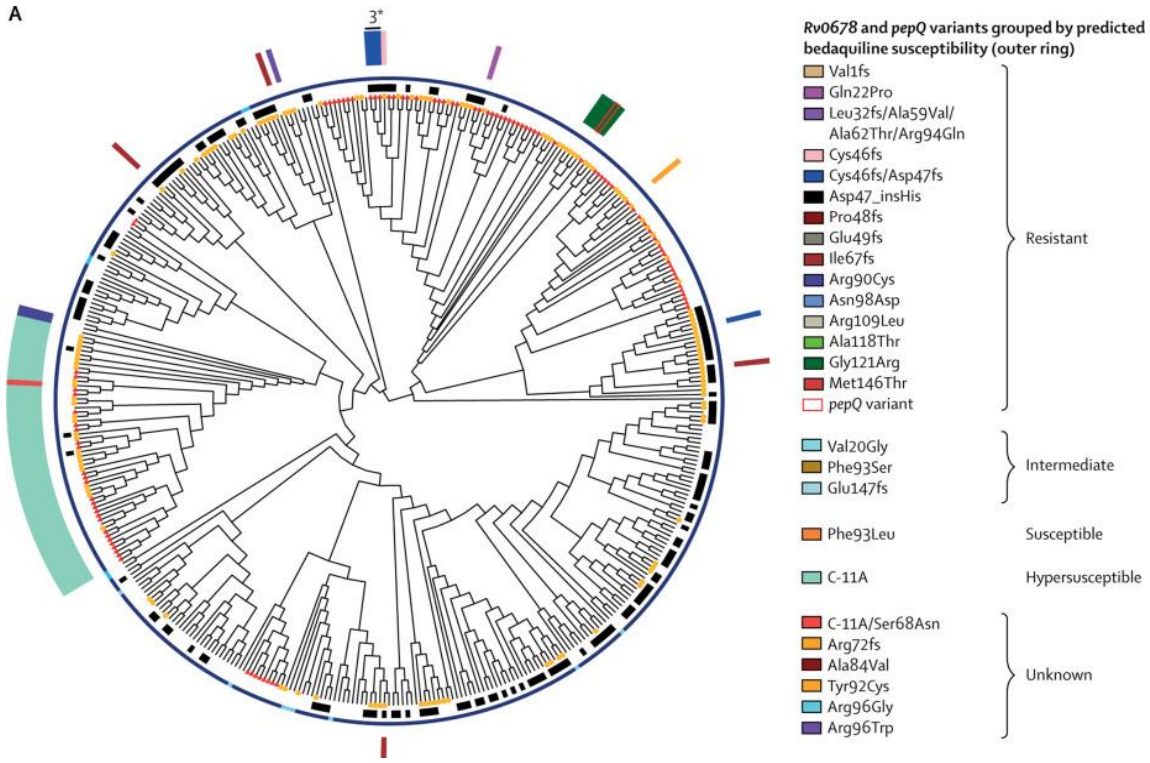
*Go/No-go decision to proceed to Stage 2 based on unfavorable outcome trajectory of DBOS & PBOS vs. HRZE through 4, and 6 months of treatment, respectively.

- Stage 1 patients will be followed for 12 months post randomization
- DBOS or PBOS considered for Stage 2

D – delamanid, P – pretomanid, B – bedaquiline, **O – OPC-167832, S – sutezolid**

n.b. No NCEs (in clinical development), to my knowledge, have sterilizing potency equal to or better than rifamycins or diarylquinolines

Back to the Bug



Population-level emergence of bedaquiline and clofazimine resistance-associated variants among patients with drug-resistant tuberculosis in southern Africa
Nimmo Lancet Microbe 2020

<u>BDQ-resistant M. tuberculosis is typically resistant to:</u>
Rifampicin
Isoniazid
Pyrazinamide
Ethambutol
Clofazimine
+/- Fluoroquinolones

n.b. Rv0678 mutations may affect intra-bacterial concentrations of companion drugs (which may or may not be clinically important)

We don't know the impact of different mutations on BDQ's contributions to clinical cure

Is DR-*M.tb* = DS-*M.tb*?

'off-target' effects of resistance mutations
Increased susceptibility to ROS and DNA damage
Remodeling of transcriptional programs
Metabolic repression of folate biosynthesis
Altered siderophores
Remodeling of cell wall lipids
Increased cell wall permeability
Differences in expression of peptidoglycan synthesis genes
Upregulation of efflux pumps

What are the effects of these changes in cell wall composition, energy use, metabolism, pumps on drug activity for drugs with different mechanisms of action than the drug identified in the molecular assay?

Will a simple MIC answer that question? MIC against what strain(s), under what conditions?

Lahiri PMID 27226566 J Biol Chem 2016; Patel mBio 2023 PMID 36779708;
Ofori-Anyinam bioRxiv PMID 37905073; Campodonico PMID 29616007 2017

Treatment of BDQ-R/RR-TB (Rx: 12-24 months)(if BPaLL cannot be used)

Group	Medicine	
A	Levofloxacin or moxifloxacin*	Generally well-tolerated
	~~Bedaquiline*~~	
	Linezolid*	Bone marrow suppression, peripheral neuropathy
B	~~Clofazimine§~~	
	Cycloserine or terizidone§	(Common) CNS toxicity
C‡	~~Ethambutol~~	
	Delamanid	(Rare) CNS side effects
	~~Pyrazinamide~~	
	Imipenem-cilastin or meropenem (+ clavulanic acid)	IV formulation
	Amikacin	Deafness, vestibular dysfunction, kidney toxicity
	Ethionamide or prothionamide	Nausea and vomiting
	p-aminosalicylic acid	GI toxicity, hypersensitivity, drug-induced lupus

*Use all 3; §Add both; ‡Add these, as needed

Lancet (2018) Menzies group; WHO Guidelines 2019

Back to the Pipeline-- Strategies

A.

Diarylquinoline-containing
TBAJ-876
TBAJ-587
Sudapyridine
BDQ (adjust dose)

B.

Diarylquinoline-free

+

Oxazolidinones
Delpazolid
Sutezolid
TBI-223
MK-7762

DprE1 inhibitors
BTZ-043
TBA-7371
Quabodepistat (OPC-167832)

+

Unique NCE
Ganfeborole (GSK-656)
GSK-286*
Sanfetrinem
Telacebec (Q203)
Alpibectir (BVL-GSK098)/Eth

Existing drugs likely to have activity against a majority of BDQ/RR-TB strains

How to Design Regimens? Note: No mouse study will recapitulate the range of clinical BDQ-R strains

Need for collaborative approach

A.

Diarylquinoline-containing
TBAJ-876
TBAJ-587
Sudapyridine
BDQ (adjust dose)

B.

Diarylquinoline-free

Can we have:

- Harmonized protocol
- Smart diagnostic strategy
- Multitude of global sites
- Multiple funding streams
- Synthesis/integration of data

Oxazolidinones
Delpazolid
Sutezolid
TBI-223
MK-7762

DprE1 inhibitors
BTZ-043
TBA-7371
Quabodepistat (OPC-167832)

Unique NCE
Ganfeborole (GSK-656)
GSK-286*
Sanfetrinem
Telacebec (Q203)
Alpibectir (BVL-GSK098)/Eth

Existing drugs likely to have activity against a majority of BDQ/RR-TB strains

Considerations

- Whom to include (& how to diagnose them)?
  - Rv0678 mutations (all? only?); genotypic/phenotypic R?; new dx vs. on-treatment failures; companion drug R?
- Standard of care
  - We don’t know how it performs; composition will change over time (parallel to endTB, at its inception)
- We don’t know BDQ genotypic-phenotypic-clinical correlations
  - How active is B against ‘B-resistant’ strains?
- Many NCE are likely to fail to progress over next 3-5 years
  - Trials must be flexible, nimble
- AI/ML-driven predictions of mouse model results & clinical response
  - Increasingly used in TB regimen development (like in other disease areas)
- Outcomes
  - Measure *benefits* more smartly
- Geography

Outcomes (to debate)- from CLOBbeR-TB proposal

Co-Primary Endpoints:

(1) Time to sputum culture conversion in liquid media, defined as the time from the start of treatment until the first negative sputum culture, over 24 weeks

(2) Incidence of bacteriologic failure or relapse or clinical failure through 104 weeks of follow-up

Secondary Endpoints:

(1) Proportion of participants with a Grade 3 or higher adverse event through 52 weeks

(2) All-cause mortality

(3) Proportion of participants with sputum culture conversion at 8 weeks or at 24 weeks

(4) The rate of change in time to sputum culture positivity (TTP) through 24 weeks in the Mycobacterial Growth Indicator Tube (Bactec MGIT960) system

Exploratory Endpoints:

(1) Composite efficacy / safety: The proportion of participants without an unfavorable outcome and no grade 3 or higher adverse events during treatment or follow-up

(2) EQ-5D-5L Quality of Life questionnaire

(3) FACIT-TB, Functional Assessment of Chronic Illness Therapy – Tuberculosis, for persons with TB

(4) St. George's Respiratory Questionnaire

(5) Time until cessation of TB symptoms

(6) Home-time: The number of days alive with without in-person healthcare.

(7) Pharmacokinetics (PK) and pharmacodynamics (PD)

Summary

- Post-BDQ era = post-antibiotic era
- BDQ resistance is emerging at alarming rates, and we do not have a regimen to treat patients with BDQ/RIF-R TB
  - Returning to the days of injectables and 18-24 months of treatment
  - Molecular/phenotypic DST-clinical correlations still unknown
  - **Patients with BDQ resistant TB need access to effective treatment under safe conditions**
- Diagnostics work needs to progress alongside trials work, to allow for early identification of patients for trials
- Several NCE in the pipeline--all-oral, once-daily, synergistic regimens with good safety profiles are in reach (but are unlikely to be < 6 months, unless new diarylquinolines are effective against broad range of BDQ-R strains (and robust to further resistance))
- Work to do to build preclinical-clinical knowledge base, to allow for modeling work that can accurately predict regimens' activities for the broad range of patients with BDQ-R/RR-TB
- **Need for strong, coordinated approach & transparency**

Thank you.