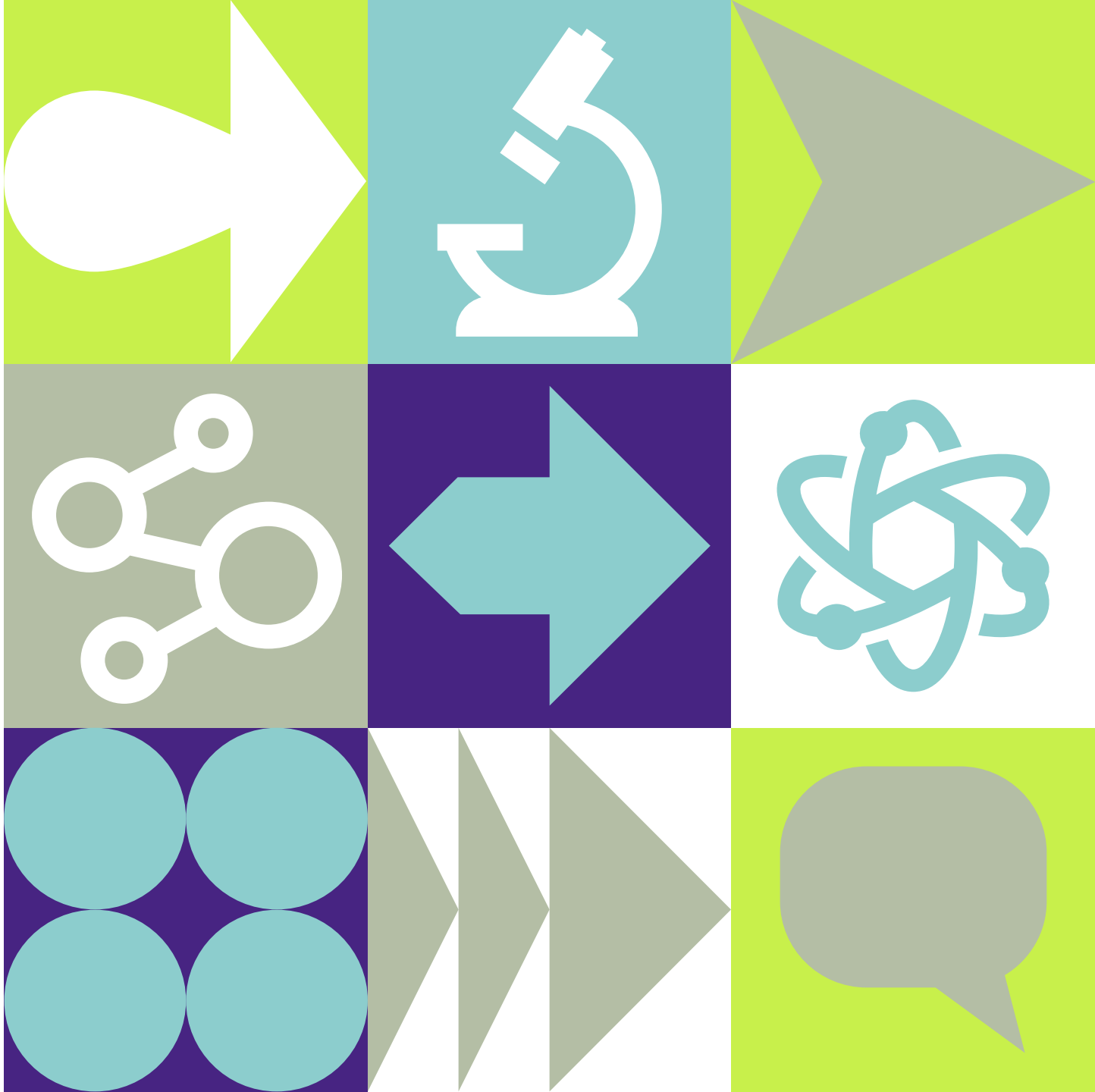
IAS 2021

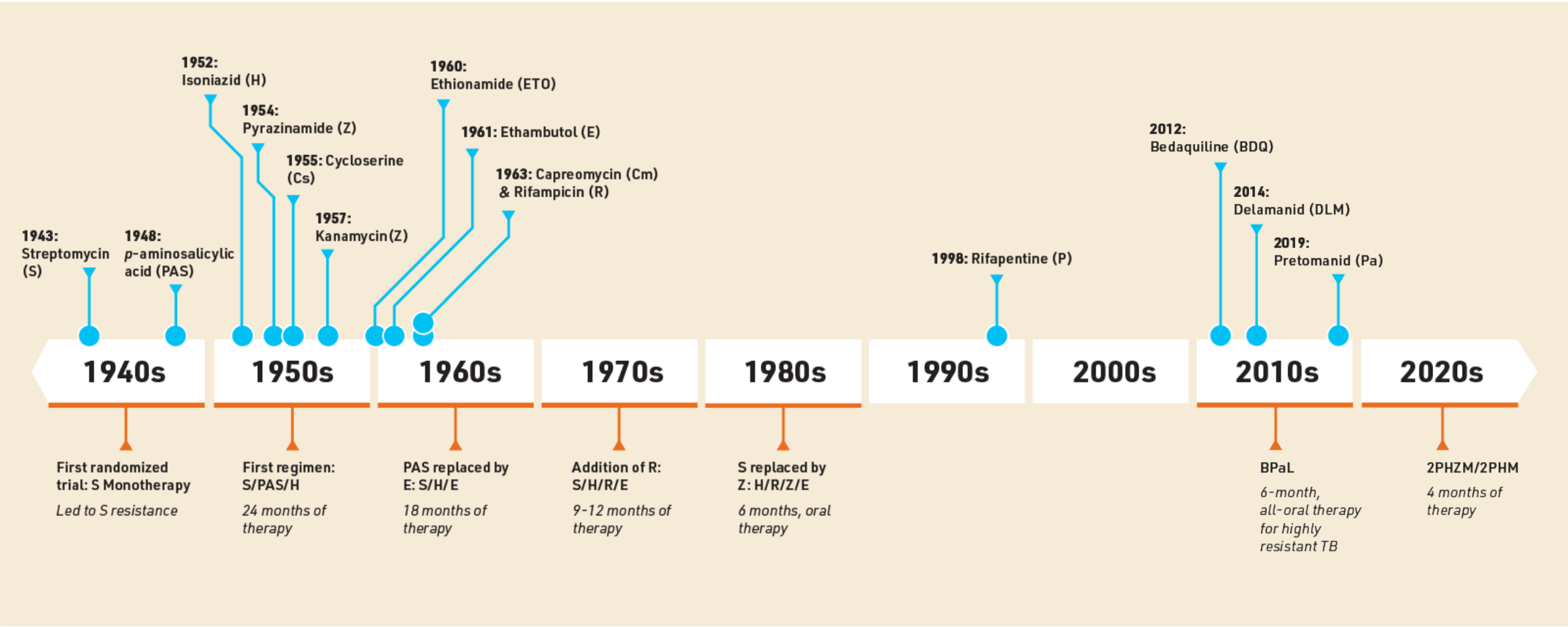
Novel Tuberculosis Drugs and Combinations

Mel Spigelman, M.D.
President and CEO
TB Alliance

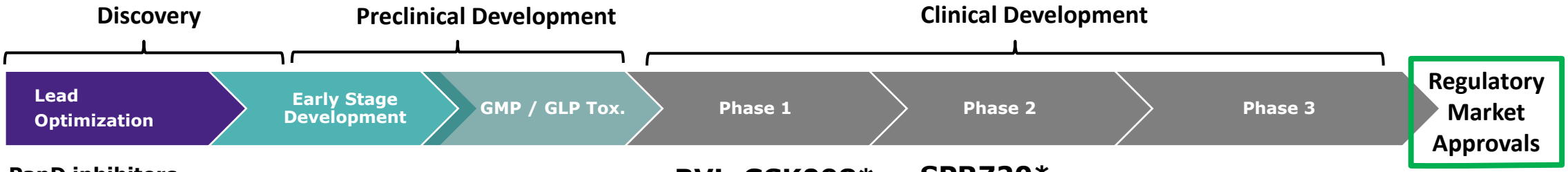
18 July 2021



Evolution of New TB Therapies



2021 Global New TB Drug Pipeline[1]



PanD inhibitors
Indazole sulfonamides
Diarylthiazoles
DprE1 Inhibitors
Direct InhA Inhibitors
Mtb energy metabolism
Macrolides
Mycobacterial Gyrase Inhibitors
Arylsulfonamides
Inhibitors of MmpL3, Translocase-1, Clp, PKS13, F-ATP synthase
Oxazolidinones

JSF-3285*
MPL-446, 447*
CPZEN-45*
NTB-3119*
TB-47*
TZY-5-84
FNDR-20081*
Spectinamide – 1810*

GSK-839*
OTB-658
Sanfetrinem

BVL-GSK098*
GSK-286*
TBAJ-587
TBAJ-876
TBI-223
Macozinone* (PBTZ-169)
TBI-166

SPR720*
BTZ-043*
TBA-7371*
GSK-656* (070)
OPC-167832*
Delpazolid
Sutezolid
Telacebec* (Q203)
SQ-109*
Macozinone*

Bedaquiline*
Delamanid*
Pretomanid*

Rifapentine / Moxifloxacin
(4-month regimen)

Underline = updates since November 2020

*New chemical class. Known chemical classes for any indication are color coded: fluoroquinolone, 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 series identified: http://www.newtbdrugs.org/pipeline/discovery

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WORKING GROUP ON NEW TB DRUGS
www.newtbdrugs.org

Updated: March 2021

Mel Spigelman, MD

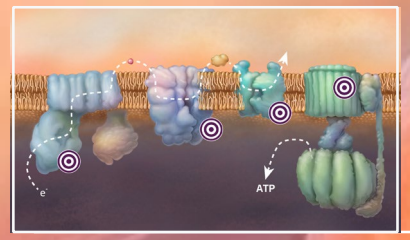
Novel Drugs and Combinations

Five Ways to Target TB

PROVEN PATHWAY

Electron Transport Chain

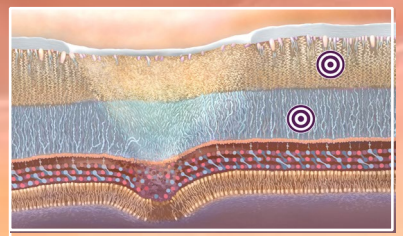
Stop the generation of cell energy so TB bacteria can't grow



PROVEN PATHWAY

Cell Wall Disruption

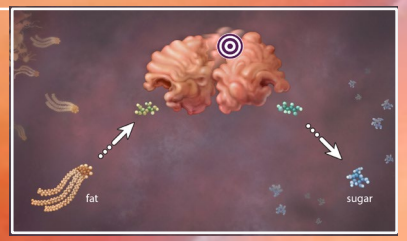
Weaken cell walls and in the process, destroy TB bacteria



NEW PATHWAY

Central Carbon Metabolism

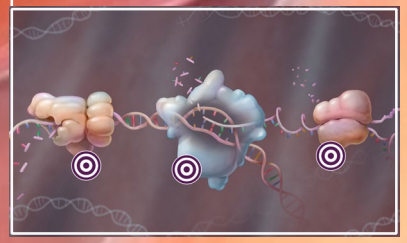
Starve TB bacteria so it can't grow



NEW PATHWAY

Protein Degradation

Poison the cell by inhibiting the ability to eliminate waste



NEW PATHWAY

Protein Synthesis

Block TB's ability to make protein necessary for its survival

Regimens, Biologics and Host Directed Therapies under Clinical Development

Phase 2

2HRZE 2HR

Bedaquiline - Delamanid with MBT for MDR

INH - RIF - PZA – MOX

CC-11050 - Auranofin - Everolimus - Vitamin D3 + Rifabutin-modified TB Therapy

Pravastatin - Rifafour & Vitamin B6

Metformin

Imatinib

Auranofin

Phase 3

2HRZE + experimental drugs

BEAT-TB

Bedaquiline - Linezolid - Levofloxacin with OBR

Bedaquiline - Pretomanid - Linezolid

Bedaquiline - Pretomanid - Linezolid - Moxifloxacin

Bedaquiline - Moxifloxacin - Linezolid - Pyrazinamide

Delamanid with OBR

Immunoxel

= Host-Directed Therapy

= Biologic

Recent Treatment Shortening Successes

Study 31

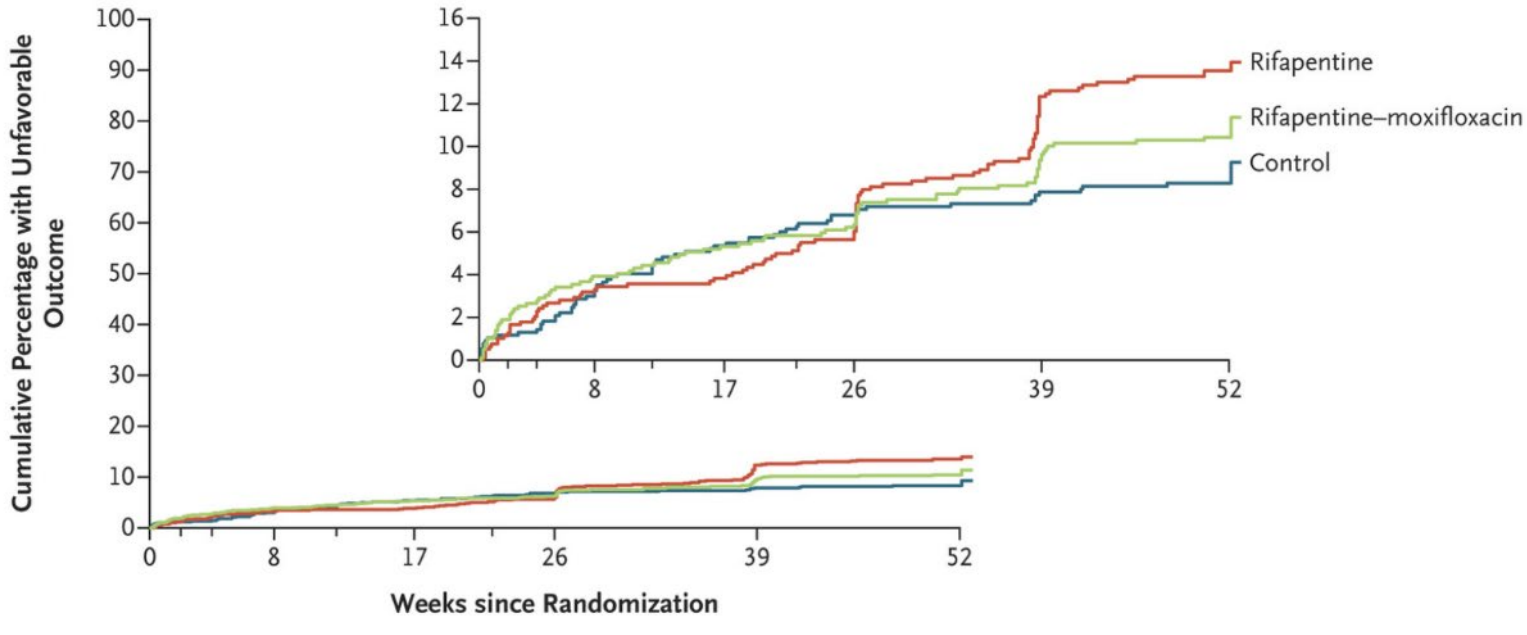
- Clinical trial of a four-month, rifapentine and moxifloxacinh-based regimen for treatment of drug-sensitive TB

Nix-TB

- Pivotal clinical trial testing the three-drug BPaL regimen (consisting of bedaquiline, pretomanid and linezolid) against highly drug-resistant TB

Shorter Four-Month Treatment Regimen

"Study 31" Results published in the *New England Journal of Medicine* show that a **four-month** daily treatment regimen is as effective as the standard daily six-month regimen in curing drug-susceptible TB



No. at Risk						
Rifapentine	784	758	749	727	660	644
Rifapentine–moxifloxacin	791	758	747	728	686	668
Control	768	742	724	711	675	658

Source: Dorman et al. Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis. *N Eng J Med* 2021; 384:1705-1718.

Nix-TB Results

New England Journal of Medicine, March 2020

PARTICIPANT STATS

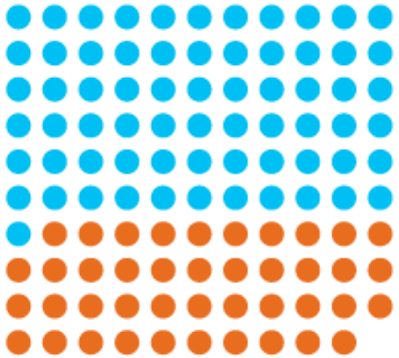
109 participants with **confirmed TB**

71 with **XDR TB***

65%

38 with **MDR TB****

34%



THE RESULTS

Favourable outcomes

with **XDR TB**

89%

79-95 (95% CI)

with **MDR TB**

92%

79-98 (95% CI)

90% of all participants had **favourable outcomes**

95% CI (83-95)

Clinical resolution
6 months after therapy

THE BPaL REGIMEN

6 months, 3 oral agents

- Bedaquiline
- Pretomanid
- Linezolid

COMPARED TO OTHER REGIMENS

Nix-TB	6 months†
Others	18+ months

†extendable to 9 months

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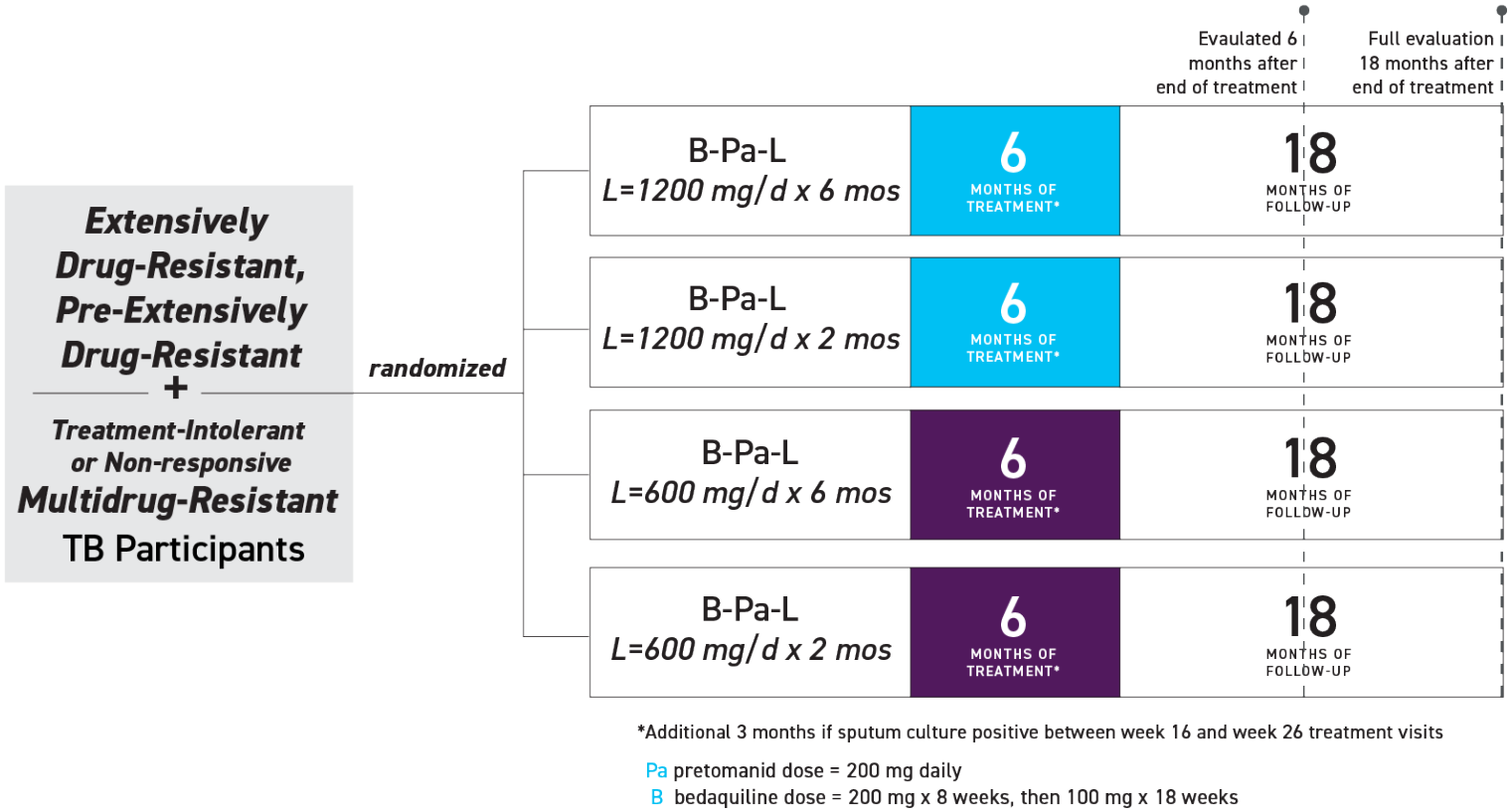
*Using definition of XDR-TB prior to 2020
**Treatment-intolerant or non-responsive MDR-TB

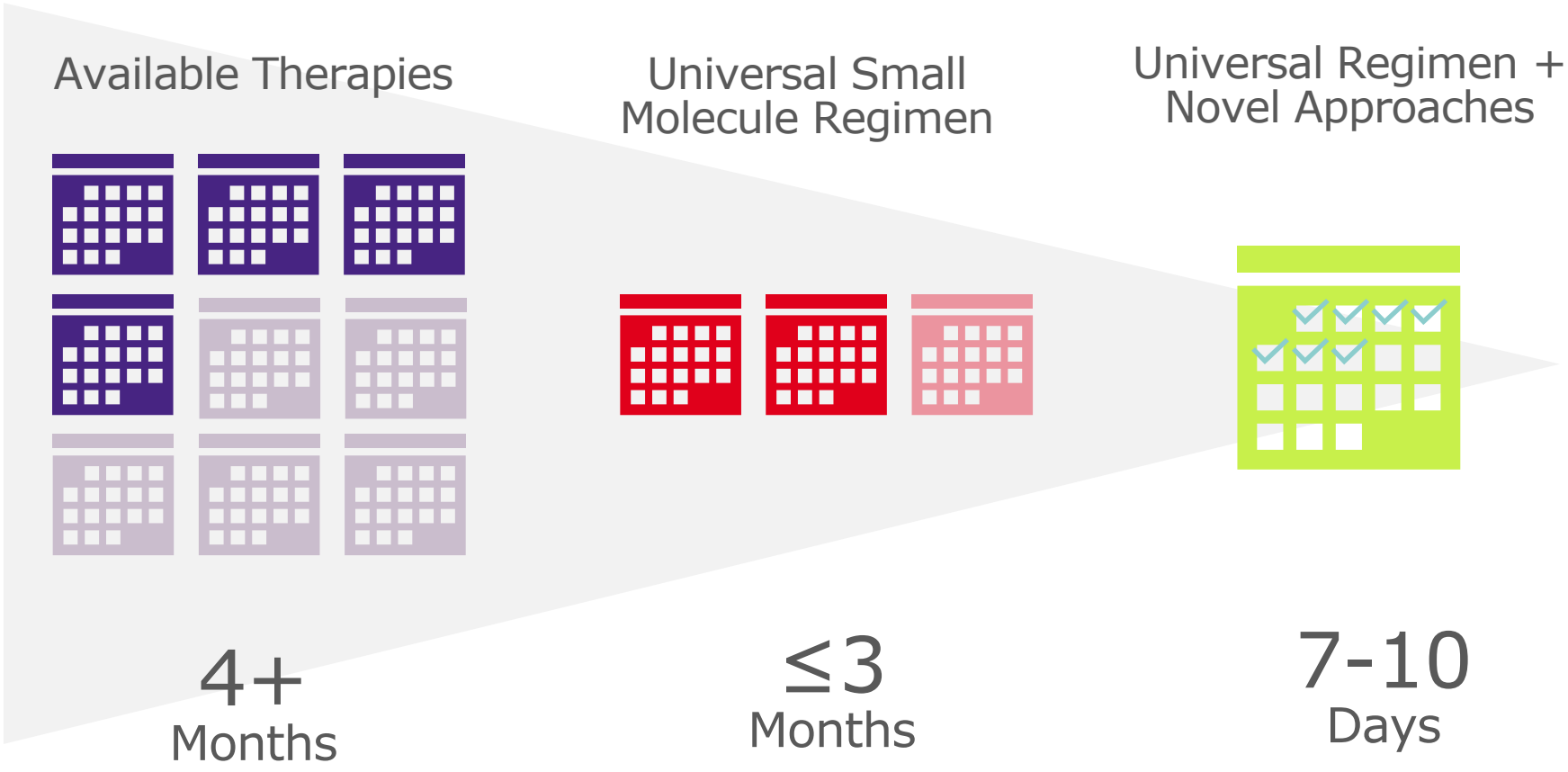
Source: Conradie et al. Bedaquiline, pretomanid and linezolid for treatment of extensively drug resistant, intolerant or non-responsive multidrug resistant pulmonary tuberculosis. *N Eng J Med* 2020;382:893-902.

ZeNix: Linezolid Optimization Trial

- The ZeNix trial seeks to optimize linezolid dosing within the BPaL regimen
- This trial:
  - Evaluates the linezolid dose
  - Evaluates the linezolid duration
- 181 patients enrolled and randomized across 5 sites in Russia, 1 site in Georgia, 1 site in Moldova and 4 sites in South Africa

Late-Breaker Oral Abstract Presentation
- Wednesday, 21 July
- 10:00-10:50am CEST



The Future of TB Treatment

Novel drug combinations enable shorter, simpler and more effective treatment