PNU-100480 (sutezolid) Update

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Pfizer

Sutezolid: Preclinical and Clinical

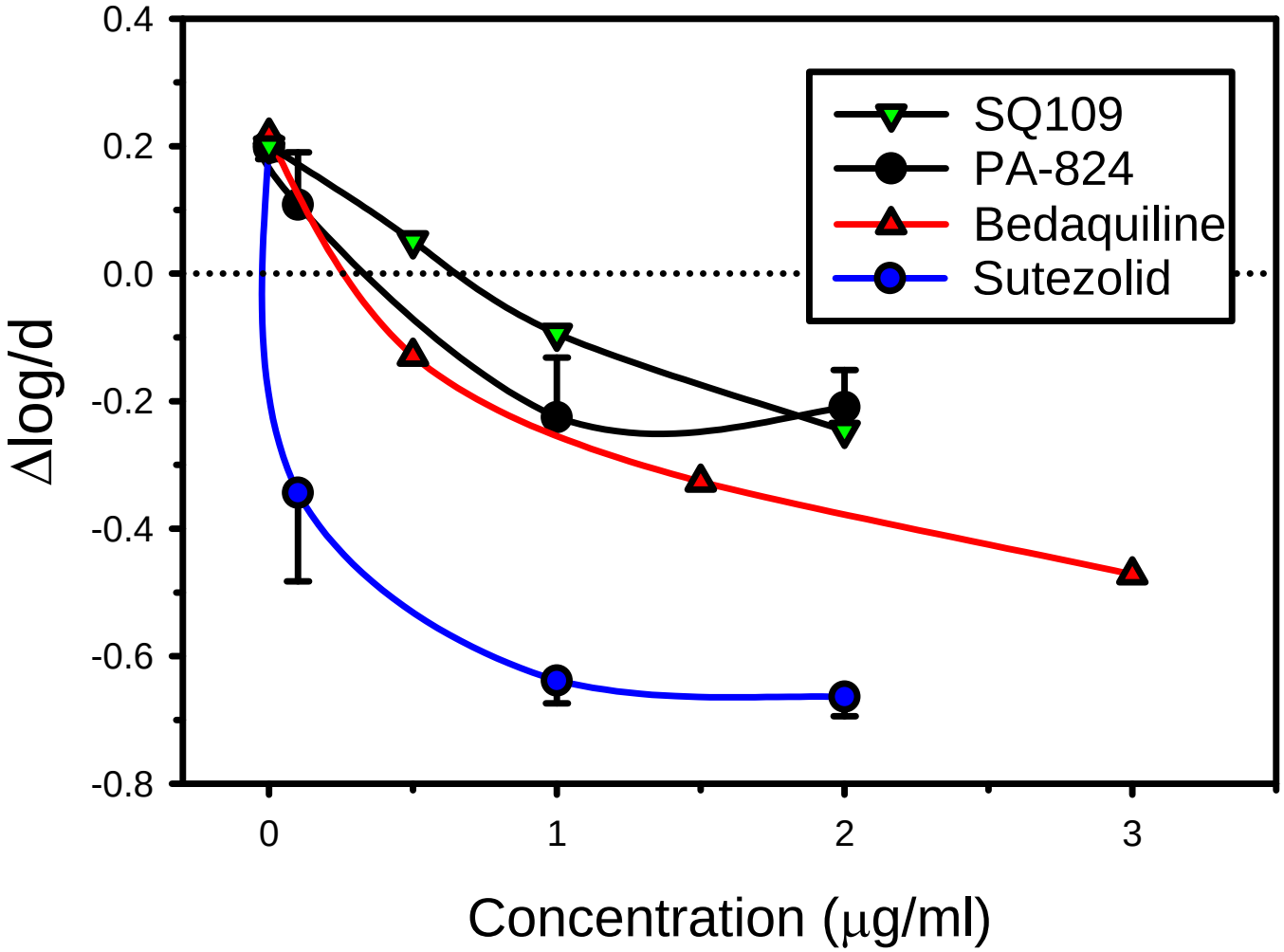
- Preclinical
  - Superior bactericidal activity vs. LZD regardless of LZD dose
  - Earlier sterlization (1-2) with standard drugs
- Phase 1: SAD, MAD
  - Doses to 600 mg BID reasonably well absorbed and tolerated to 28d
  - No safety signals, incl. hematology
  - Superior bactericidal activity *ex vivo* in whole blood culture (WBA) regardless of LZD dose or concentration
  - Killing linked to T > MIC
- Phase 2: EBA trial (nearly complete)
  - Sutezolid 600 mg BID, 1200 mg QD, HREZ
  - 14 days, Sputum (CFU and TTP) and WBA endpoints
  - Goal is to show activity in lung and assist in dose selection

Innovative development strategy

- Universal regimen
  - No cross-resistance to current TB drugs (*excl*. FQs, PZA)
  - Effective in DS, M/XDR-TB, HIV-TB
- Parallel studies in DS and M/XDR-TB
  - Larger DS-TB trial to inform M/XDR
- Adaptive licensing based on 2-month sputum culture
  - Also described as accelerated or provisional licensing
  - Initially in M/XDR, HIV-TB, later in DS-TB
- Global TB outcome registry during adaptive licensing
  - Report safety and effectiveness outcomes

Candidates for universal regimen

concentration-activity relationship in whole blood culture



UJ: additive

whole blood culture

A **Combined bactericidal activity (Δlog/d)**

TMC207 mg/L \ PNU-100480 mg/L	0	0.1	1	2
0	0.216	-0.442	-0.664	-0.642
0.5	-0.129	-0.502	-0.884	-0.897
1.5	-0.327	-0.778	-0.973	-1.133
3	-0.472	-0.715	-1.036	-1.150

Difference from sum of individual activities

TMC207 mg/L \ PNU-100480 mg/L	0	0.1	1	2
0				
0.5		0.069	-0.091	-0.125
1.5		-0.010	0.017	-0.164
3		0.199	0.099	-0.035

mean= -0.004±0.116

P= 0.912

Activity of novel combinations

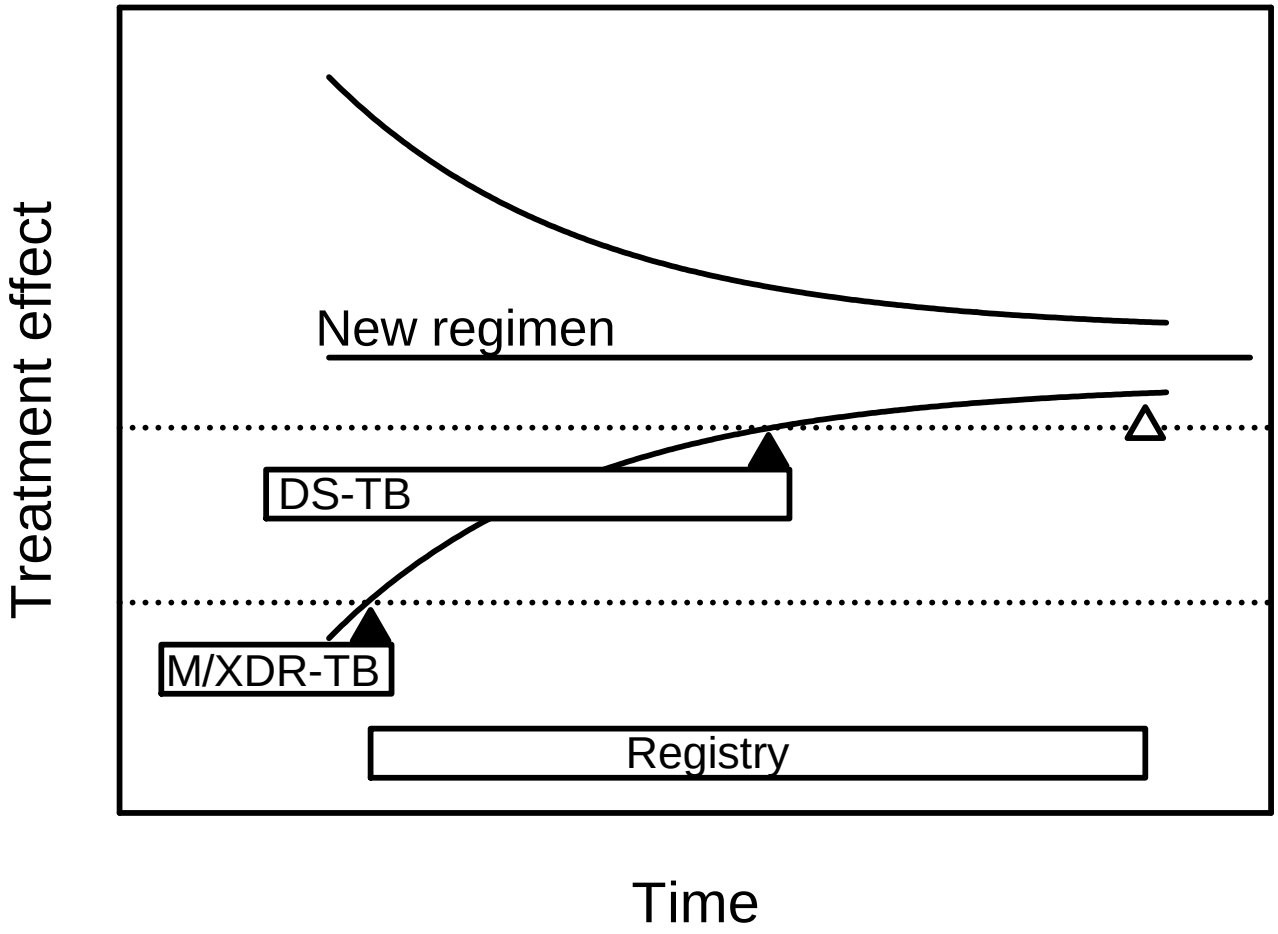
Drug combo	Overall effect	Difference from sum	P	Predicted cWBA at standard doses
USq	additive	-0.017	0.5	-
UJ	additive	-0.004	0.9	-0.41
JPa	< additive	0.179	**0.03**	0.01
UPa	≤ additive	0.628	0.2	-0.34
UJPa	antagonistic	0.493	**0.03**	0

Nitroimidazole antagonism: NO?

- In hypoxic, non-replicating cultures, nitroimidazoles-derived NO poisons the respiratory chain, resulting in depletion of ATP
  - Combinations of nitroimidazoles and TMC207 may be less than fully additive if they share a common mechanism of action.
- Whole blood cultures (and likely most *in vivo* conditions) are neither hypoxic nor fully replicating
- Under non-hypoxic conditions, NO triggers a dormancy response in *Mtb* through activation of DosR
  - This may reduce the activity of other drugs
- Nitroimidazoles are unlikely to become part of a UJ-containing universal regimen

Adaptive licensing

based on 2-mo culture status



Summary

- Early clinical findings support superior efficacy and safety of sutezolid *vs*. linezolid
- Combinations including sutezolid, bedaquiline, SQ109 appear likely as candidates for a new universal regimen
- Innovative development strategies for sustainable TB drug development can enhance value to patients, physicians, and sponsors, yet address regulatory concerns regarding the approval of medicines that are safe and effective

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