Cours d'Automne en Chimiothérapie Infectieuse et Vaccinologie

Infections à Mycobactéries

Update sur les nouveaux antibiotiques anti-TB: bedaquiline, delamanid, pretonamid

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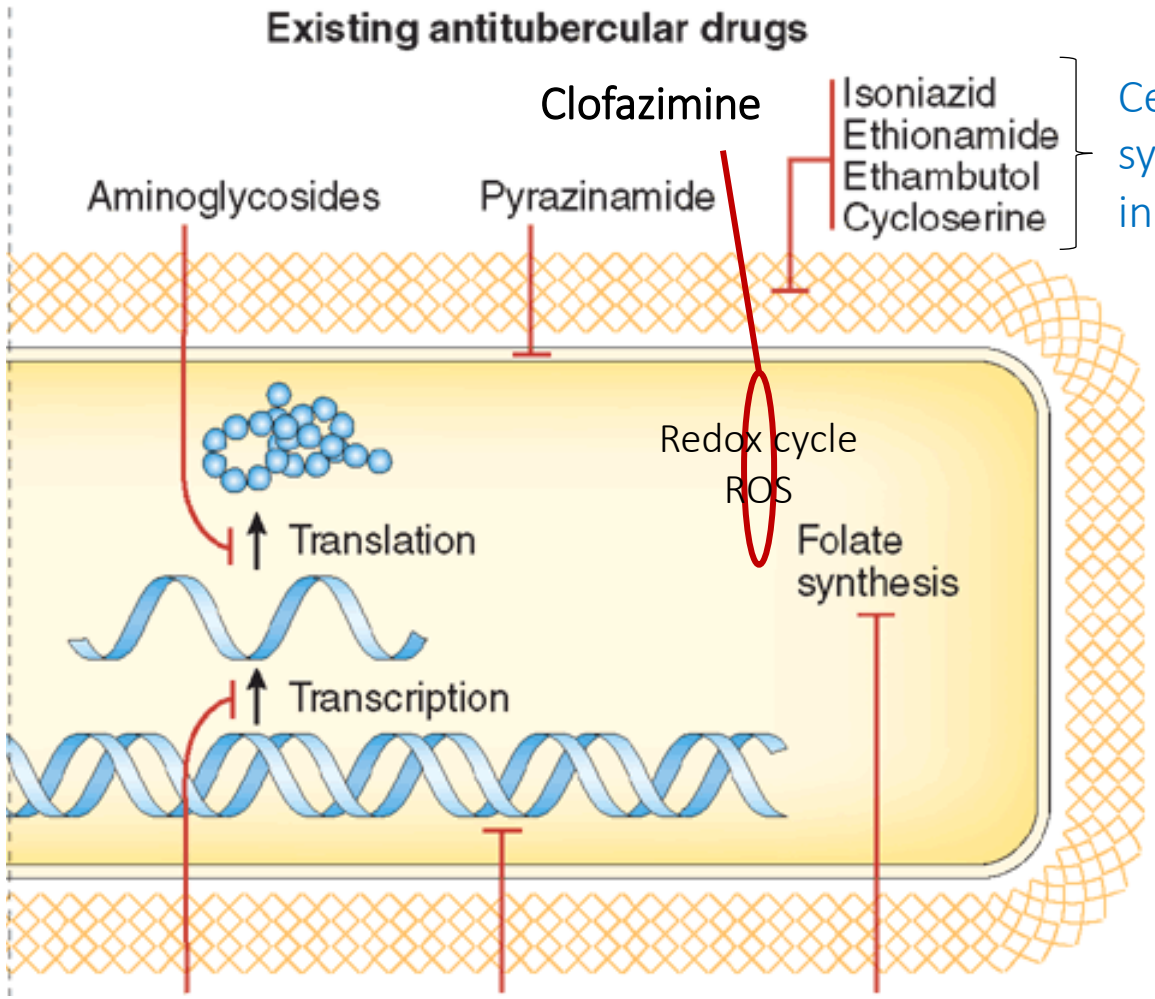
Lyon TB study group



Adapted from Sassetti & Rubin, Nature Medicine 13, 279 - 280 (2007)

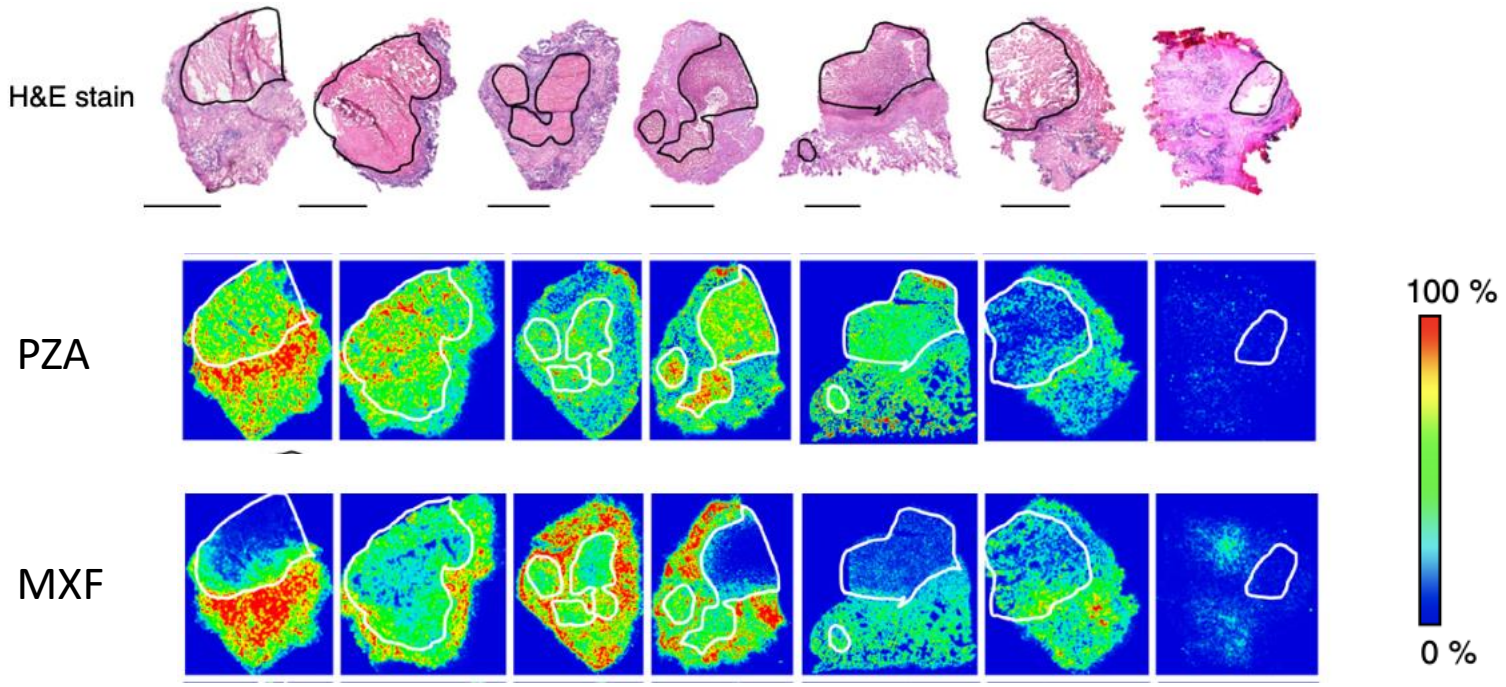
lipophilicity, activity in acidic pH

Drug-drug interactions

Bactericidal and « sterilizing » activity

Safety and tolerability considerations

Drug diffusion: association between sterilizing activity and drug distribution into TB lesions *in vivo*



MALDI mass spectrometry imaging of small molecules in TB-infected lung tissue
Ion maps of PZA and MXF in representative (selected from more than 200 lesions) lung lesions.
Outlines highlight the **necrotic center** of each lesion. Scale bars, 5 mm.

Prideaux B et al., Nature Medicine 2015

2020 Global New TB Drug Pipeline [1]

Preclinical Development | **Clinical Development**

Early Stage	GMP / GLP Tox.	Phase 1	Phase 2	Phase 3	Regulatory Market Approvals
GSK-724* (DG167)	GSK-286*	SPR720*	TBA-7371*		
GSK-839*	OTB-658	TBI-223	GSK-656*		Bedaquiline*
Caprazene nucleoside CPZEN-45*	Sanfetrinem	BTZ-043*	OPC-167832*		Delamanid*
Benzopyranone NTB-3119	TBAJ-587	TBI-166	Telacebec		Pretomanid*
Spectinamide 1810*	TBAJ-876	Macozinone* (PBTZ-169)	Delpazolid		
PM181108A quinoline oxazole			Sutezolid		
Pyrazolopyridine carboxamide TB-47*			SQ-109*		
			Macozinone*		

New chemical class* Known chemical classes for any indication are color coded: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide, beta-lactam.

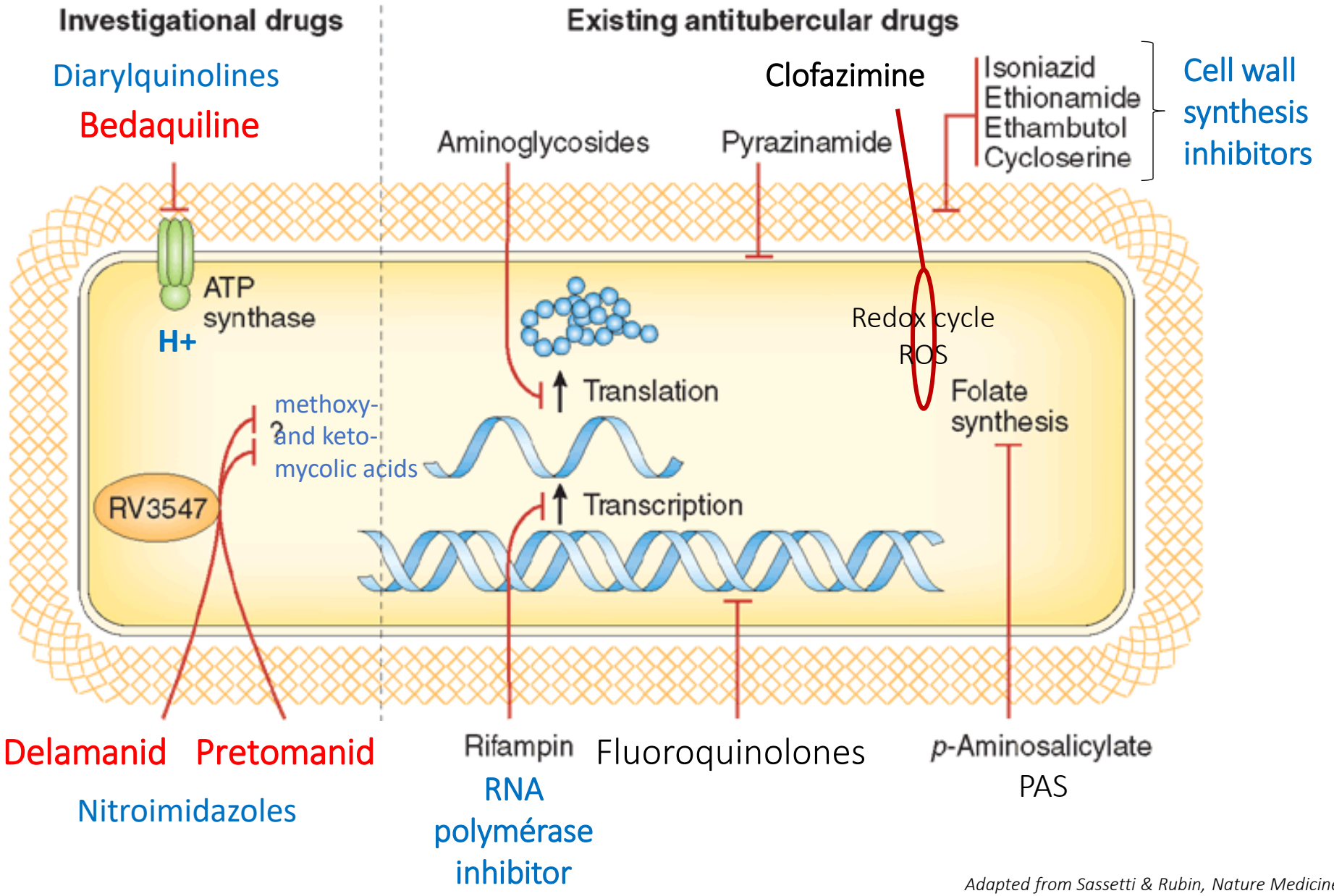
[1] New Molecular Entities not yet approved, being developed for TB or only conditionally approved for TB. Showing most advanced stage reported for each. Details for projects listed can be found at http://www.newtbdrugs.org/pipeline/clinical Underline = new to Phase since October 2019

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

WORKING GROUP ON NEW TB DRUGS

www.newtbdrugs.org

Updated: March 2020



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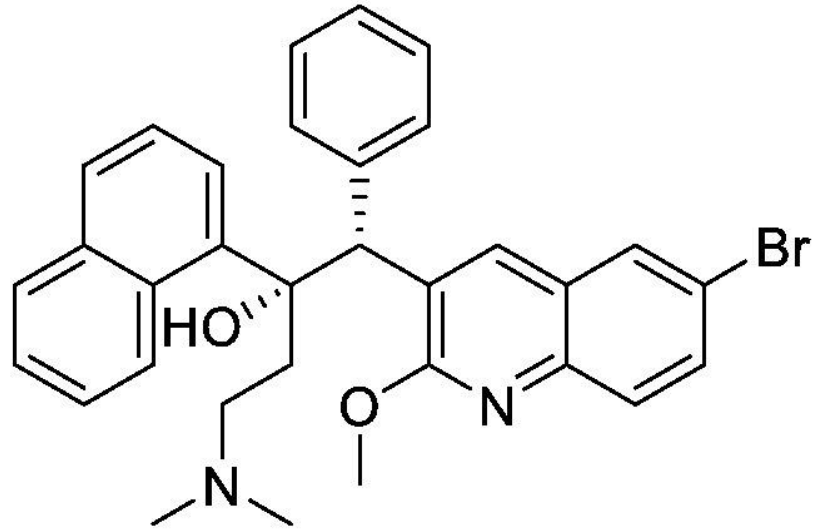
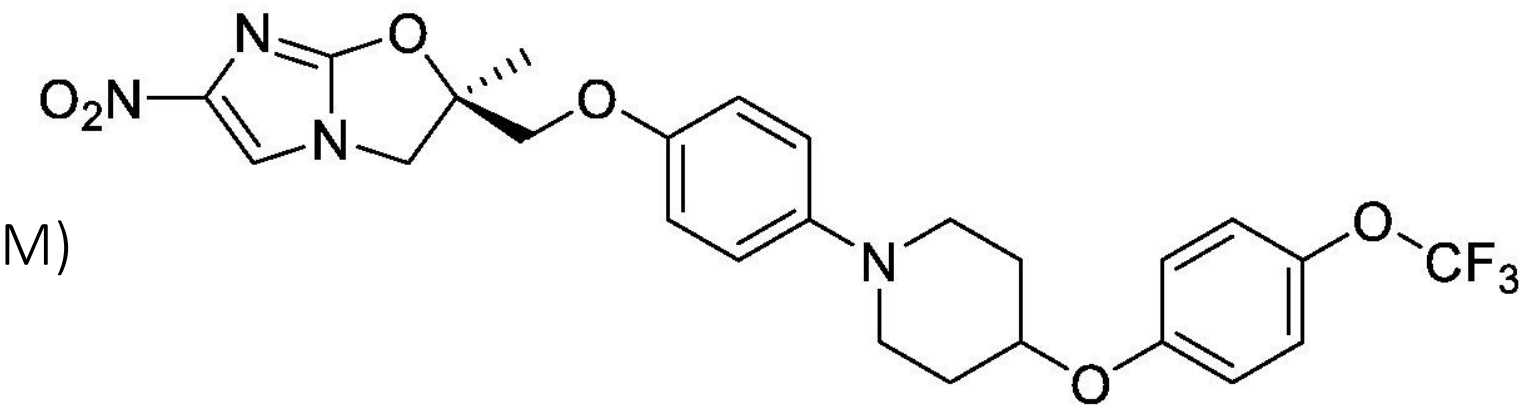
Bedaquiline (BDQ)



Bedaquiline (TMC207)

Delamanid (DLM)



Delamanid (OPC-67683)

BDQ efficacy outcomes of the 3 prospective phase IIb trials

Study (authors)	Time of end point (weeks)	Arm	mITT population (N)	Result	Ref.
C208 stage 1 (Diacon *et al.*)	8	Bedaquiline	23	Cult Conv: 48%	[31,32]
		Placebo	24	Cult Conv: 9%	
C208 stage 2 (Diacon *et al.*)	24	Bedaquiline	79	TCC: 83 days Cult Conv: 79%	[31,32]
		Placebo	81	TCC: 125 days Cult Conv: 58%	
	120	Bedaquiline	66	Favorable outcome: 58%	
		Placebo	66	Favorable outcome: 32%	
C209 (Pym *et al.*) **Open trial**	24	Bedaquiline	233	TCC: 57 days Cult Conv: 79%	[33]
	120	Bedaquiline	205	Favorable outcome: 61%	

Cult Conv: Rate of culture conversion at the end point; mITT: Modified intention-to-treat; TCC: Median time to sputum culture conversion.

Observational studies, n=18 – meta-analysis, n=1, no phase III

Diacon AH, Pym A, Grobusch MP et al. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. N. Engl. J. Med. 371(8), 723–732 (2014).
Diacon AH, Pym A, Grobusch M et al. The diarylquinoline TMC207 for multidrug-resistant tuberculosis. N. Engl. J. Med. 360(23), 2397–2405 (2009)
Pym AS, Diacon AH, Tang S-J et al. Bedaquiline in the treatment of multidrug- and extensively drug-resistant tuberculosis. Eur. Respir. J. 47(2), 564–574 (2016).
Guglielmetti L et al. Future Microbiol 2020

BDQ PK

		Remark	
Bioavailibilty	**> 90%**	⇢ Food intake	TDM Education/Follow-up
Half-life	**24h**	Loading dose **2w** Terminal half life **5.5 months**	Mutant selection can occur after stopping the drug
Compound	**Lipophilic**	Good tissular diffusion Bactericidal	Probable neutralizing activity
Biotransformation	**Liver (2 metabolites)** **CYP3A4**	Strong interactions with inducers/inhibitors CYP450	**RFP**/EFV = ↘ RTV/Triazoles/MLD = ↖
Renal clearance	**Negligeable**	/	/

BDQ Safety

Trial (authors)	Trial arm	Patients with AE, %		Patients stopping treatment, %	Deaths, % (TB-related deaths, %)		
		Total	SAE		Total	During the trial	After the end of the trial
C208 Phases I and II (Diacon *et al.*)	Bedaquiline	96	7	4	12 (6)	7 (2)	5 (4)
	Placebo	95	2	5	4 (3)	1 (0)	3 (3)
C209 (Pym *et al.*)	Bedaquiline	89	6	3	7 (3)	5 (2)	2 (1)

AE: Adverse event; SAE: Serious adverse event; TB: Tuberculosis.

Cardiotoxicity : QTc interval > 500 msec (5 to 19%) EKG monitoring (FQ, MXF > LVF)
Hepatotoxicity : liver enzyme monitoring
Functional signs (nausea, arthro-myalgia, headache…)
Under-reported safety

Diacon AH, Pym A, Grobusch MP et al. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. N. Engl. J. Med. 371(8), 723–732 (2014).
Diacon AH, Pym A, Grobusch M et al. The diarylquinoline TMC207 for multidrug-resistant tuberculosis. N. Engl. J. Med. 360(23), 2397–2405 (2009)
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BDQ Resistance

		Remark
Emergence	**Selection of spontaneous chromosomal mutants**	
Mutation rate	**10^{-7}**	
Mechanism	**Efflux pump**	
Target genes	*atpE*	Rare, high-resistance
	rv0678	Cross-resistance with clofazimine 2 to 6.3% MDR-TB 0.7% DS-TB Can occur after BDQ interruption
	pepQ, rv1979c	
Detection	Phenotypic, genotypic, WGS/NGS	Association with bactericidal and neutralizing drugs

DLM efficacy outcomes of the prospective phase IIb and III trials

Study (authors)	Efficacy				Ref.
	End point (weeks)	Arm	mITT population (N)	Result	
Trial 204 (Gler *et al.*)	8	Dlm 100 mg	141	Cult conv: 45%	[72]
		Dlm 200 mg	136	Cult conv: 42%	
		Placebo	125	Cult conv: 30%	
Trial 208 and observational study 116 (Skripconoka *et al.*; Wells *et al.*; Gupta *et al.*)	120	Dlm ≥6 months	192	Favorable outcome: 75%	[73–75]
		No Dlm or Dlm ≤2 months	229	Favorable outcome: 55%	
Trial 213 (von Groote-Bidlingmaier *et al.*)	8	Dlm	226	Cult conv: 58%	[76]
		Placebo	101	Cult conv: 54%	
	24	Dlm	226	TCC: 52 days Cult conv: 88%	
		Placebo	101	TCC: 60 days Cult conv: 86%	
	120	Dlm	339	Favorable outcome: 81%	
		Placebo	170	Favorable outcome: 81%	

Cult Conv: Rate of sputum culture conversion; Dlm: Delamanid; mITT: Modified intention-to-treat; TCC: Time to sputum culture conversion.

Large multinational, double-blind, placebo-controlled Phase III trial failing to demonstrate superiority in time to sputum conversion and favorable outcomes by the addition of delamanid to an optimized background regimen.

Etudes observationelles, n=11

Gler MT, Skripconoka V, Sanchez-Garavito E et al. Delamanid for multidrug-resistant pulmonary tuberculosis. N. Engl. J. Med. 366(23), 2151–2160 (2012).
Skripconoka V, Danilovits M, Pehme L et al. Delamanid improves outcomes and reduces mortality in multidrug-resistant tuberculosis. Eur. Respir. J. 41(6), 1393–1400 (2013).
on Groote-Bidlingmaier F, Patientia R, Sanchez E et al. Efficacy and safety of delamanid in combination with an optimised background regimen for treatment of multidrug-resistant tuberculosis: a multicentre, randomised, double-blind, placebo-controlled, parallel group Phase III trial. Lancet Respir. Med. 7(3), 249–259 (2019).

DLM PK

		Remark	
Characteristic	**Prodrug**, activated by mycobacterial nitroreductase		
Bioavailibilty	**Good but saturable**	⇢ BID ⇢ Food intake (x2.7)	TDM Education/Follow-up
Half-life	**30-38h**	Terminal half life **> 6 months**	
Compound	**Highly lipophilic**	Good tissular diffusion Bactericidal	Neutralizing activity ?
Biotransformation	**Albumin** **Liver CYP3A4**	Caution hypaoAlb Interactions with inducers/inhibitors CYP450	Malnutrition factor **RFP** = ↘ 45% DLM+Ethb =↖25% Ethb RTV/Triazoles/MLD = ↖
Renal clearance	**Negligeable**	/	/

Summary based on Guglielmetti L. et al. Future Microbiol 2020

DLM Safety

Study (authors)	Trial arm	Patients with AE, %		Patients stopping treatment, %	Deaths, %			Ref.
		Total	SAE		Total	During the trial	After the end of the trial	
Trial 204 (Gler *et al.*)	Dlm 100 mg	91	10	3	0.2	0.2	0	[72]
	Dlm 200 mg	94	13	4				
	Placebo	93	11	3				
Trial 208 and observational study 116 (Skripconoka *et al.*; Wells *et al.*; Gupta *et al.*)	Dlm ≥6 months	N.A.	N.A.	N.A.	1	N.A.	N.A.	[64,66]
	No Dlm or Dlm ≤2 months	N.A.	N.A.	N.A.	8	N.A.	N.A.	
Trial 213 (von Groote-Bidlingmaier *et al.*)	Dlm	99	26	2	4	N.A.	N.A.	
	Placebo	97	28	2	4	N.A.	N.A.	

AE: Adverse event; Dlm: Delamanid; N.A.: Not available; SAE: Serious adverse event; TB: Tuberculosis.

Cardiotoxicity : QTc interval > 500 msec EKG monitoring (FQ)
Hepatotoxicity : liver enzyme monitoring
Electrolyte unbalance
Functional signs (nausea, arthro-myalgia, headache…)
Under-reported safety

Gler MT, Skripconoka V, Sanchez-Garavito E et al. Delamanid for multidrug-resistant pulmonary tuberculosis. N. Engl. J. Med. 366(23), 2151–2160 (2012).
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DLM Resistance

		Remark
Emergence	**Selection of spontaneous chromosomal mutants**	4.4 to 9.7% in MDR, XDR-TB
Mutation rate	**10^{-5} -10^{-6}**	
Mechanism	**Activation of delamanid (prodrug)**	
Target genes	*fbiA, B, C*	
	ddn	
	fgd1	
Detection	Phenotypic, genotypic, WGS/NGS	Association with bactericidal and neutralizing drugs

Multiple heterogenous *M. Tb* populations

Summary based on Guglielmetti L. et al. Future Microbiol 2020
Anh Nguyen VT et al. Clin Infect Dis 2020

Breakthrough

Culture Conversion in Patients Treated with Bedaquiline (63%) or Delamanid (27%) or both (10%): a prospective multi-country study

Interim analysis : among 1,106 patients treated programmatically in one of 16 countries on five continents, we found that 85% of patients experienced a favorable interim outcome (i.e., conversion of sputum from positive to negative) within 6 months.

Franck MF et al. Clin Infect Dis 2020

BUT….

Multi-drug resistant tuberculosis with simultaneously acquired-drug resistance to bedaquiline and delamanid

Simultaneously acquired resistance

Rv0678 and fbiC

Yoshiyama T et al. Clin Infect Dis 2020

☢ Heteroresistant infections/intra-patient variant strains ☢

Bedaquiline (BDQ)

- diarylquinoline that targets the mycobacterial ATP synthase
- Multiple preclinical studies confirm the bactericidal and sterilizing activity on *M. tuberculosis*, both *in vitro* and in animal models.
- Phase II clinical trials have shown that bedaquiline exerts delayed bactericidal activity and improves treatment outcomes
- Reassuring safety profile; caution drug-drug interactions; CYP3A4/liver; EKG/QTc prolongation.

Delamanid (DLM)

- nitroimidazole that inhibits the synthesis of the mycobacterial cell wall
- Preclinical evidence of the efficacy of delamanid is scarce.
- Evidence from clinical trials on the efficacy of delamanid is controversial, with findings from a Phase II trial,
- showing reduced time to culture conversion in the delamanid arm, not replicated by a larger Phase III trial
- Reassuring safety profile; caution drug-drug interactions; CYP3A4/liver; EKG/QTc prolongation.