Patients and TB: Improving treatment outcomes through a patient centred approach and access to new treatments

5th TB Symposium – Eastern Europe and Central Asia
Ministry of Labour, Health and Social Affairs of Georgia
and Médecins Sans Frontières

22- 23 March , 2016 , TBILISI , GEORGIA

Off label use – Bedaquilline beyond 24 weeks

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Bedaquiline: available evidence

- Bedaquiline (Bdq) is approved for the treatment of multidrug-resistant tuberculosis (MDR-TB)
- Bdq efficacy and safety have been shown in two Phase II trials, C208[1] and C209[2]
- In both trials, Bdq was given for 24 weeks

1. Diacon et al, NEJM 2014
2. Pym et al, ERJ 2015

Recommendations for Bdq use

janssen | PHARMACEUTICAL COMPANIES OF Johnson&Johnson

“ The total duration of treatment with SIRTURO© is 24 weeks ”

“ Bedaquiline should be used strictly at the dose recommended by the manufacturer, (…) for a total maximum duration of 24 weeks ”

“ Bedaquiline may be used on a case-by-case basis for durations longer than 24 weeks when an effective treatment regimen cannot be provided otherwise ”

Compassionate Use / Expanded Access framework in France

Doctors ask for the drug for a specific duration / indication

The French MDR-TB Consilium supports the request

The French National Drug Regulatory Agency (ANSM) approves and takes responsibility for off-label use

Lack of direct liability for the company…

Methods

- Retrospective cohort study
- Multicentric, national
- All MDR-TB patients having started Bdq treatment between 2011 and 2013
- Objective: evaluate safety and efficacy in the whole cohort and compare standard/ prolonged Bdq use

Cohort characteristics

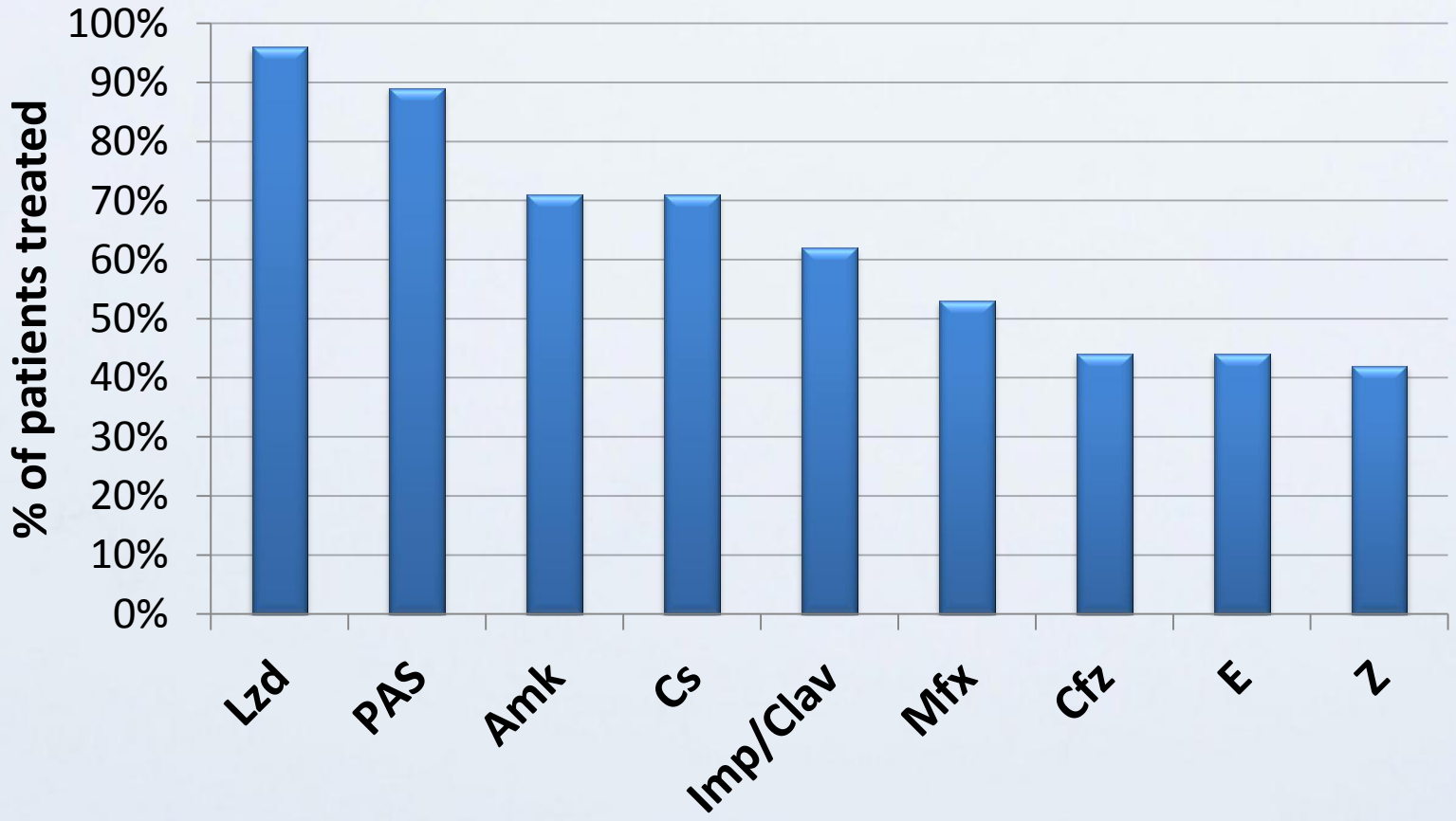
Sample = 45 patients

Sex, male	80 %
Foreign-born	98 %
HIV infection	4 %
HCV infection	47 %
Previously treated for TB	76 %
Bilateral lung involvement (N=44)	82 %
Cavities on chest radiography (N=44)	89 %
Smear-positive at treatment start	93 %
Age at admission, years (median, IQR)	38 (30 – 42)

Resistance profile

MDR	9 %
Pre-XDR Fq	24 %
Pre-XDR SLI	13 %
XDR	54 %
N. of resistant drugs on DST, median (IQR)	9 (7 – 11)

Treatment regimens

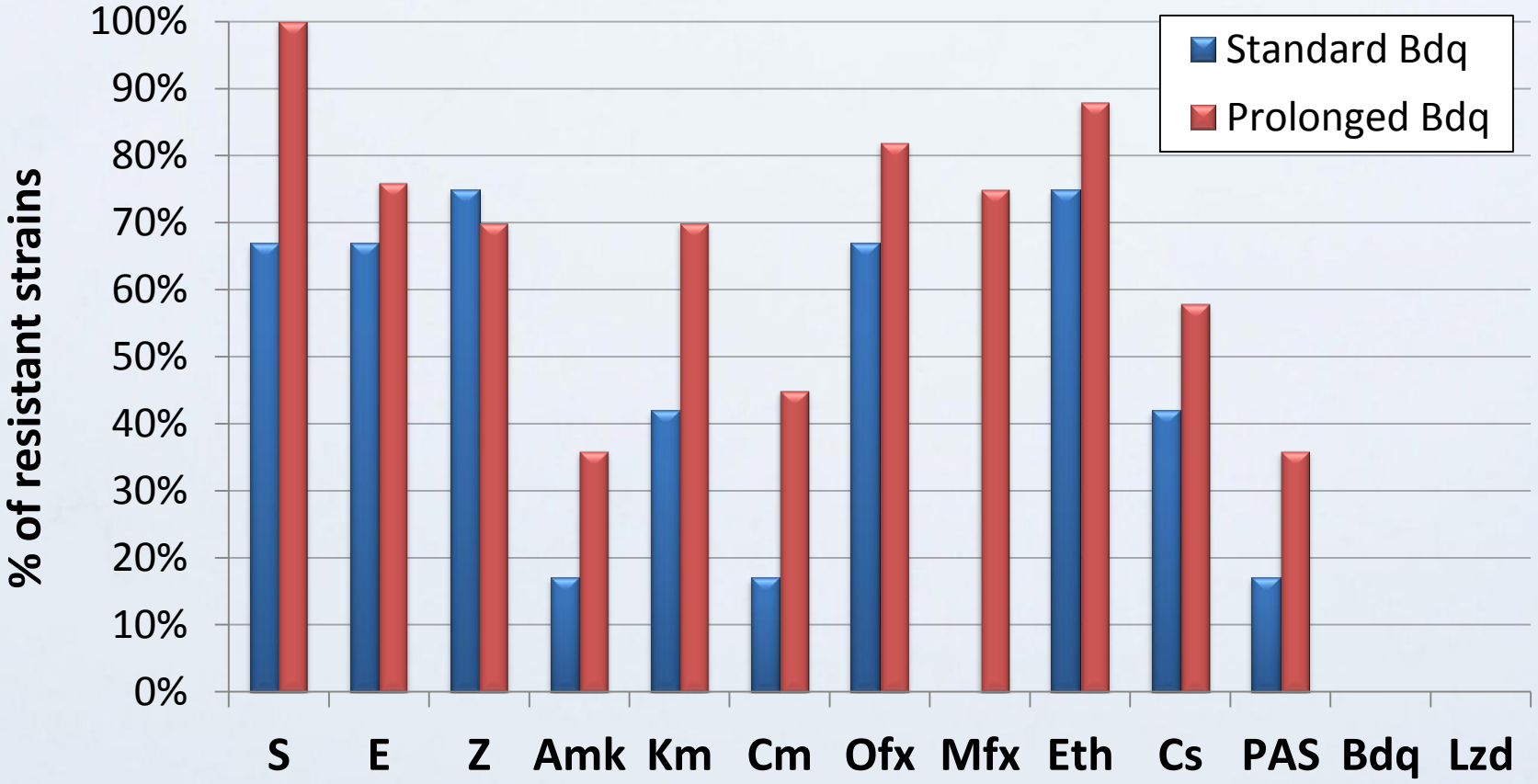


Bedaquiline treatment

Bdq treatment duration: 360 (range, 31-768)

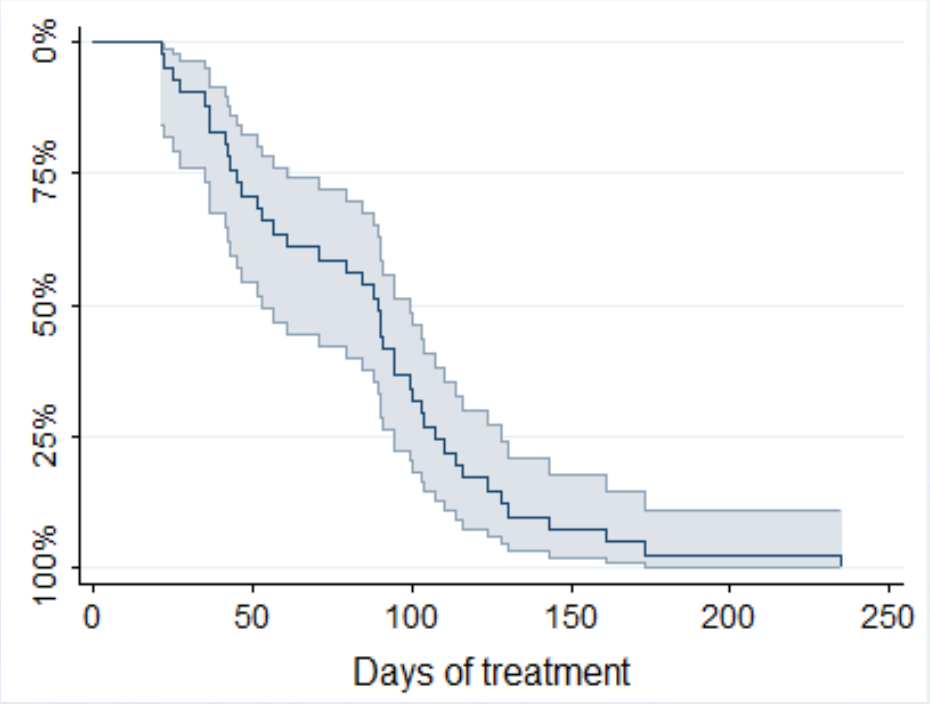
	Standard Bdq (n=12)	Prolonged Bdq (n=33)	p-value
HCV infection	17 %	58%	0.020
Previously treated for TB	25 %	94%	<0.001
Bilateral pulmonary TB	64 %	88%	NS
Cavitary pulmonary TB	82 %	91%	NS
Sputum culture-positive	75%	97%	0.048
XDR-TB	33 %	61%	NS

Comparison of resistance pattern

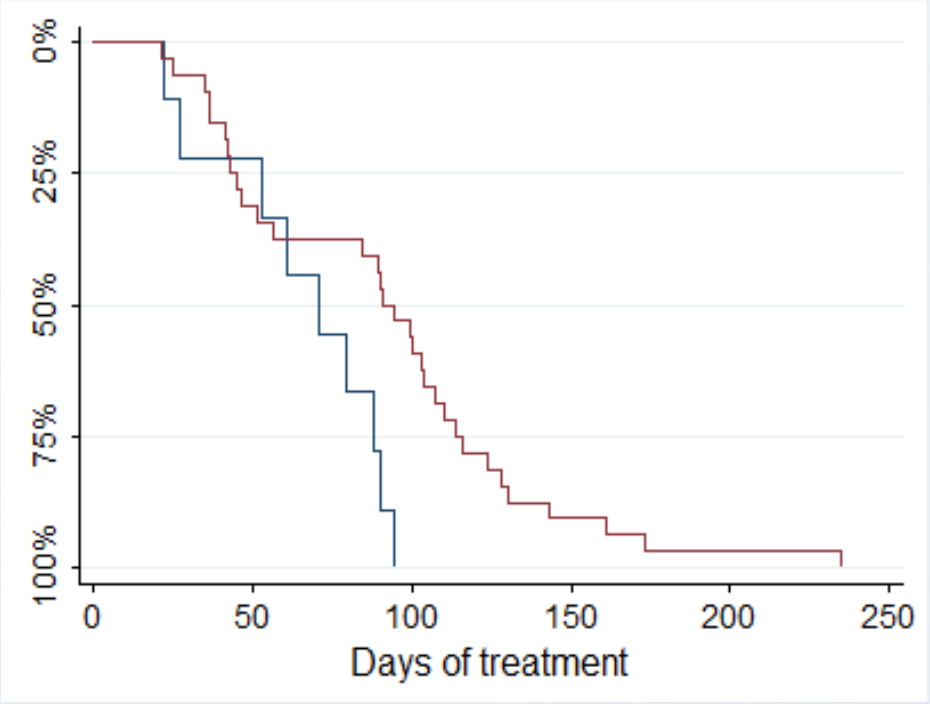


Efficacy: culture conversion

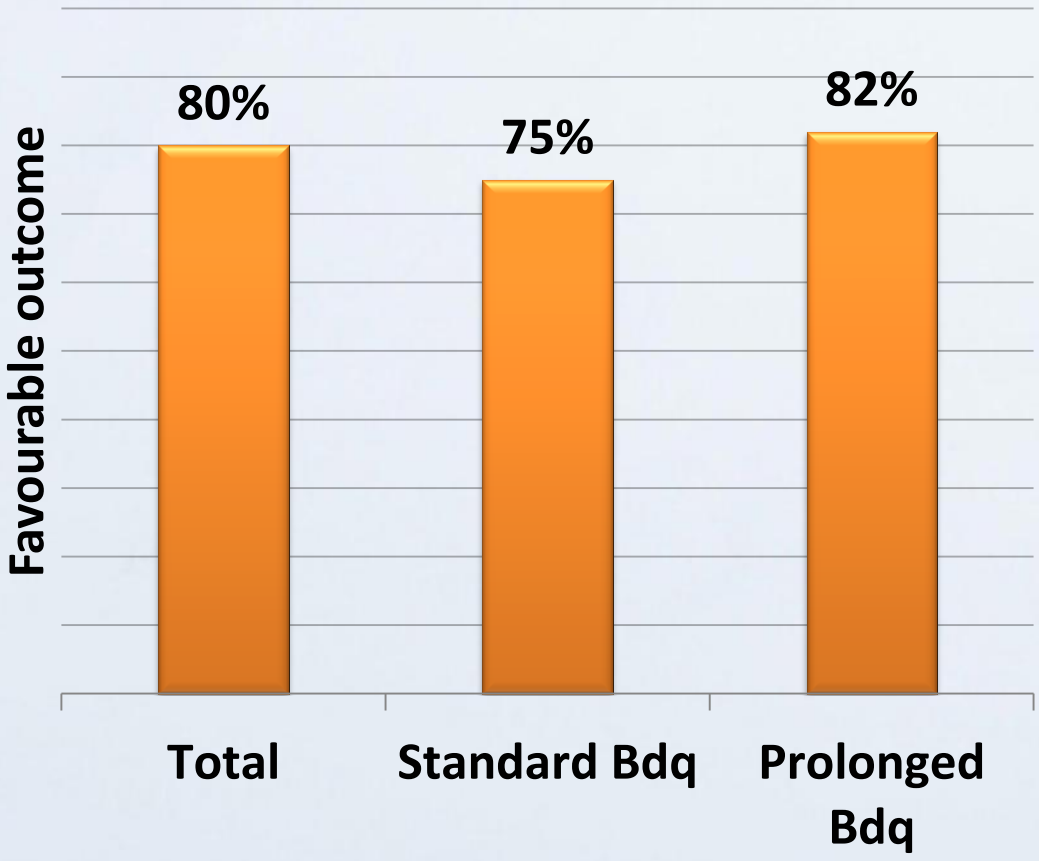
All cohort



Standard (blue) and prolonged Bdq (red)



Efficacy: treatment outcomes



Unfavourable outcome : 20%

- Lost to follow-up (N=5)
- Death (N=3)
- Failure (N=1)

Safety profile

	Standard Bdq (n=12)	Prolonged Bdq (n=33)	p-value
Any adverse event (AE)	100 %	97 %	NS
Severe AE	42 %	70 %	NS
Serious AE	8 %	21 %	NS
Liver enzymes elevation	50 %	33 %	NS
QTcB >500ms	17 %	18 %	NS
Bdq stopped due to AE	8 %	6 %	NS

Conclusions

- Prolonged Bdq use was well tolerated in this cohort
- Good outcomes of the cohort may be partially explained by the extension of Bdq treatment in selected, difficult-to-treat patients
- We advocate for prolonged Bdq treatment in specific cases through both CU/EA and programmatic use

For discussion: criteria for Bdq extension

Pre-requisites: pharmacovigilance, expert opinion (consilium), close monitoring, patient consent, observance

1. Weak treatment regimen if Bdq stopped (ie. less than 4 effective drugs left)
2. Delayed microbiological response (ie. 4-months sputum culture positive)
3. Risk factors for poor outcome (ie. extended lung disease, low BMI, smear 2+/3+, HIV)

ACKNOWLEDGEMENTS

Mathilde JACHYM
Damien LE DU
Dhiba MARIGOT-OUTTANDY
Bénédicte LEMAIRE
Dominique SMIZGIEL

Nicolas VEZIRIS
Jérôme ROBERT
Christine BERNARD

Marie JASPARD
Eric CAUMES

Marie LACHATRE
Yazdan YAZDANPANAH

Didi madloba…