Introduction of BPaLM and BPaLC in the context of SMARRTT operational study in Belarus

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Regional workshop on accelerated introduction of the WHO Guidelines for Prevention, Diagnosis and Treatment of Drug-Resistant Tuberculosis (DR TB)
April 28-30, 2025, Almaty, Kazakhstan

TB Practecal
Innovating MDR-TB Treatment

СТАРТ

НАЧАЛО ИССЛЕДОВАНИЯ | ЯНВ 2017 – ДЕК 2020 | НОЯ 2020 – МАР 2021 | МАР 2021

Этап 1

TB-Practecal

6-месячные курсы лечения

Только пероральные препараты

1. **Бедаквилин, претоманид и линезолид + моксифлоксацин (BPaLM)**
2. Бедаквилин, претоманид и линезолид + клофазимин (BPaLC)
3. Бедаквилин, претоманид и линезолид (BPaL)

Схема лечения BPaLM показала наибольшую эффективность и безопасность, поэтому она была выбрана для второго этапа исследования.

Этап 2

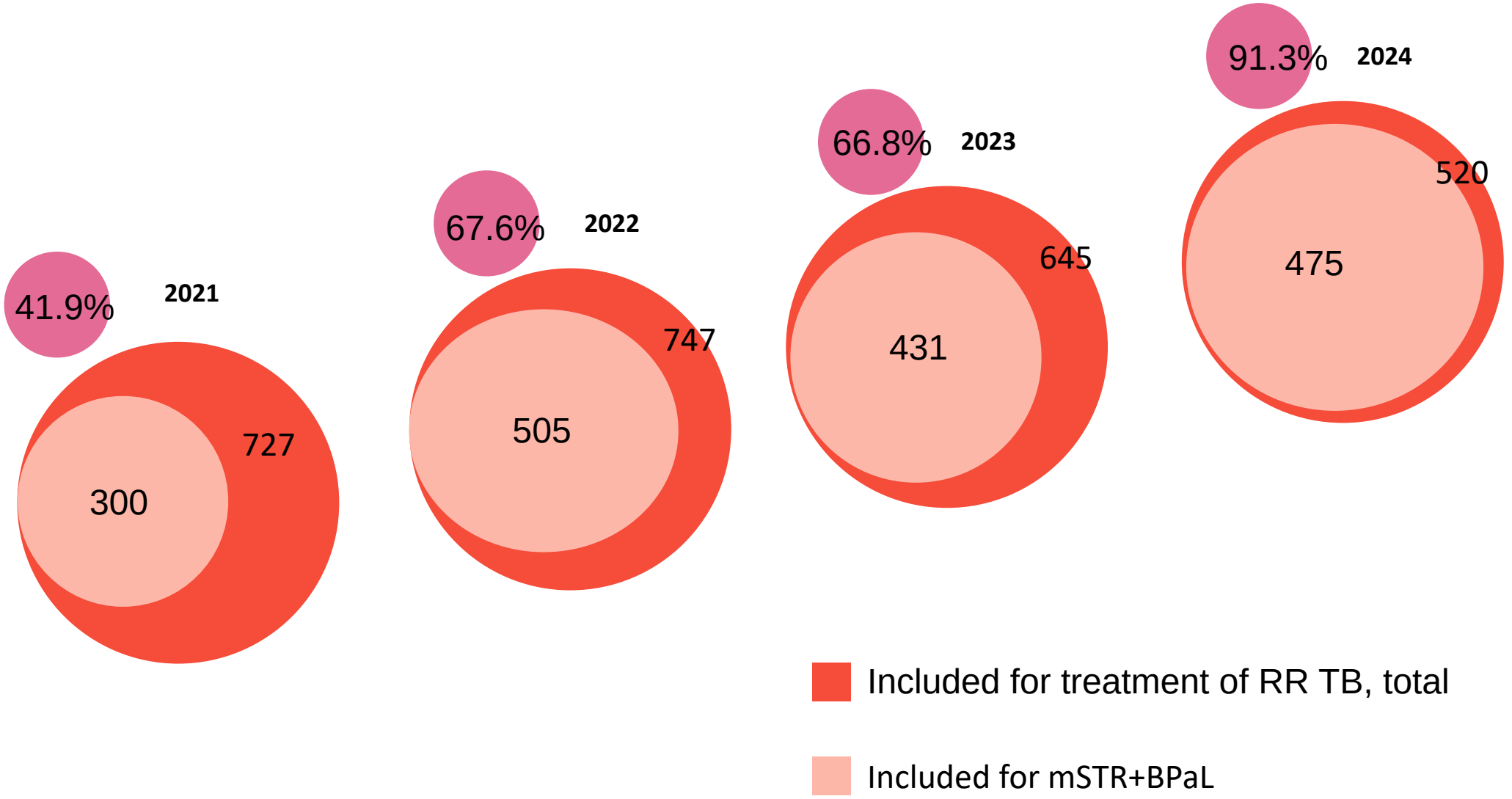
Рекомендуемое ВОЗ стандартное лечение

Курсы лечения
9-24 месяца
+/- инъекции

Набор пациентов завершен

552 пациента

Short-term treatment of RR TB, 2021-2024



Inclusion criteria:

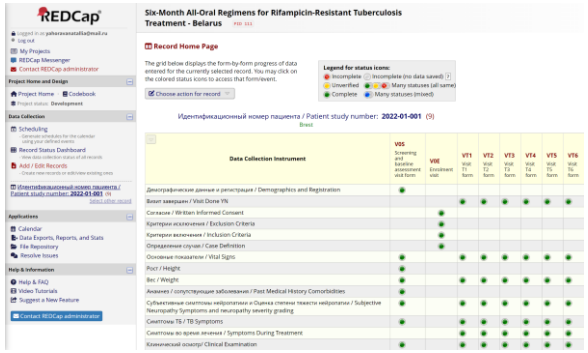
- MDR/RR TB or pre-XDR TB;
- Age 15 years and older;
- Signing the informed consent

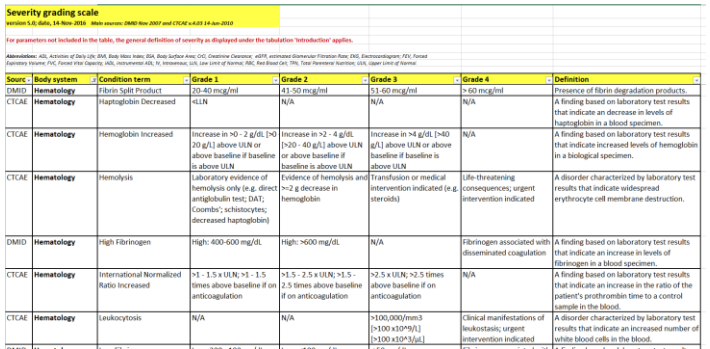
Exclusion criteria:

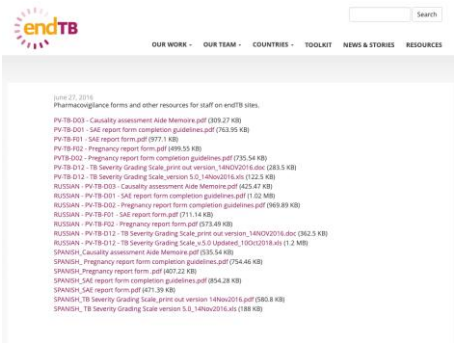
- Participation in another study
- Use of drugs included in short-term treatment > 1 month
- CNS TB, bone and joint TB
- Allergy to drugs included in the treatment
- QT adjusted against the Fridericia formula ≥ 500 ms
- MDR/RR TB treatment for more than 4 weeks with no signs of treatment failure

Monitoring of treatment

	Исследование/Обследование	Исходная оценка и скрининг	Фаза лечения (Н=Неделя)						Последующее наблюдение (М=Месяц)	
			Н л 4	Н л 8	Н л 12	Н л 16	Н л 20	Н л 24	Мп 6	Мп 12
Клиническая оценка	Письменное информированное согласие	X								
	Анкетные данные, анамнез	X								
	Клинический осмотр[1]	X	X	X	X	X	X	X	X	X
	Соблюдение лечения		X	X	X	X	X	X		
	Сопутствующая терапия		X	X	X	X	X	X	X	
	Нежелательные явления		X	X	X	X	X	X	X	
Бактериологические исследования	Мазок мокроты	X (2)	X	X	X	X (2)	X	X (2)	X	X
	Посев мокроты	X	X	X	X	X	X	X	X	X
	mWRDT (GeneXpert)[2]	X								
	Экспресс-тест на устойчивость к FQ [3]	X								
	ТЛЧ (R/FQ +/- Bdq +/- Lzd)[4]	X					(X)	(X)	(X)	(X)
	Количество гемоглобина/тромбоцитов/ лейкоцитов	X	X	X	X	X	X	X		
Лабораторные исследования	Креатинин сыворотки крови (на момент включения в исследование и при наличии клинических показаний или отклонений на ЭКГ)	X								
	Сывороточный калий (на момент включения в исследование и при наличии клинических показаний или отклонений на ЭКГ)	X								
	Липаза сыворотки крови (по клиническим показаниям)	X								
	Ферменты печени в сыворотке крови	X	X	X	X	X	X	X		
	Тест на беременность (для женщин)[5]	X								
	Анализ на ВИЧ и анализ на гепатит[6]	X								
	Глюкоза в крови /HbA1c[7]	X	X	X	X	X	X	X	X	X
Другие исследования	Рентгенография грудной клетки[8]	X						X		
	ЭКГ[9]	X	X	X	X	X	X	X		
	Скрининг на остроту зрения и обследование с использованием краткого скрининга периферической нейропатии (КСПН) [1]	X	(X)	(X)	(X)	(X)	(X)	(X)		







SMARRTT Operational Study

Prospective study:

- BPaLM: **24 weeks, Bdq-Pa-Lzd $_{600->300}$-Mfx**
- BPaLC: **24 weeks, Bdq -Pa-Lzd $_{600->300}$-Cfz***

* - Mfx resistance, Mfx intolerance

Ethics

The study has been approved

- by the Ethics Committee (EC) of MSF
- Independent EC of Belarus

02/16/2022 - inclusion of the first patient

Included into the study (n=720)
RR/MDR TB (n=381)
pre-XDR TB (n=339)

Excluded (n=8)
- Resistance to Pa (n=3)
- Resistance to Lzd (n=2)
- Refusal to participate (n=3)

completed the treatment – **712 patients (period of treatment – 16 Feb 2022 – 31 July 2024)**

Characteristics of patients

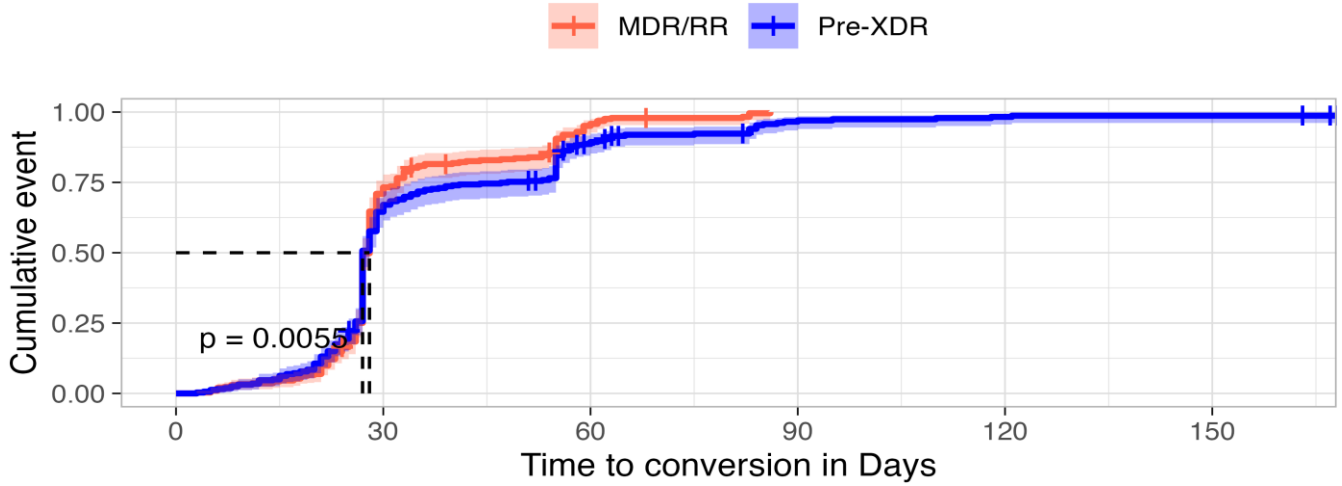
Parameters	RR/MDR TB, n=378	pre-XDR TB, n=334	Total, n=712
Age, Median (25th; 75th percentile)	48 (38, 57)	46 (38, 57)	46 (38, 57)
Women	82 (21.7%)	84 (25.1%)	166 (23.3%)
BMI, Median (25th; 75th percentile), kg/m^2	21.4 (19.6, 23.2)	21.1 (19.3, 23.1)	21.3 (19.4, 23.1)
History of TB	72 (19.0%)	106 (31.7%)	178 (25.0%)
Characteristics of the TB process			
Cavity of destruction in the lungs	128 (34.3%)	136 (41.3%)	264 (37.6%)
Positive sputum smear	83 (22.0%)	93 (27.8%)	176 (24.7%)

Characteristics of patients

Co-existing diseases	RR/MDR TB, n=378	pre-XDR TB, n=334	Total, n=712
Hepatitis B	9 (2.38%)	9 (2.69%)	18 (2.53%)
Hepatitis C	36 (9.52%)	61 (18.3%)	97 (13.6%)
HIV infection	25 (6.61%)	37 (11.1%)	62 (8.71%)
Diabetes mellitus	24 (6.35%)	19 (5.69%)	43 (6.04%)
Alcohol	110 (29.1%)	125 (37.4%)	235 (33.0%)
BMI < 18.5 kg/m2	62 (16.4%)	55 (16.5%)	117 (16.4%)

Deliverables

Time to culture conversion – 27 (26, 34) days



Culture conversion period	RR/MDR TB	pre-XDR TB	Total
1	249 (83.3%)	235 (76.8%)	484 (80.0%)
2	44 (14.7%)	55 (18.0%)	99 (16.4%)
3	6 (2.0%)	13 (4.3%)	19 (3.1%)
4	0 (0%)	3 (1.0%)	3 (0.5%)

Evaluation of treatment results

Treatment failure	Treatment has been discontinued or at least two anti-tuberculosis drugs administration should be changed for the reasons as follows: • positive seeding of each of two separate samples taken with at least four weeks interval, starting at week 16 (+/- 2 weeks) or later, or • there are signs of additionally acquired resistance to the drugs used in the study, or • serious adverse events (SAE) (at least two anti-tuberculosis drugs should be replaced in the treatment regimen)

Results

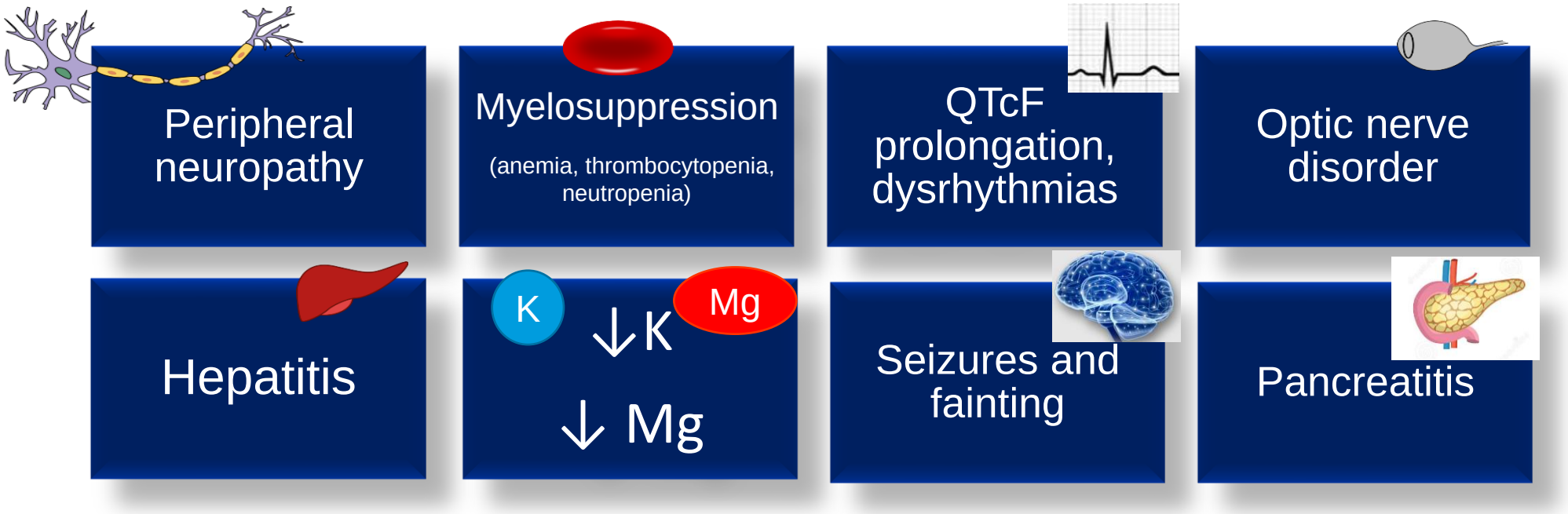
Treatment success – 93.1%

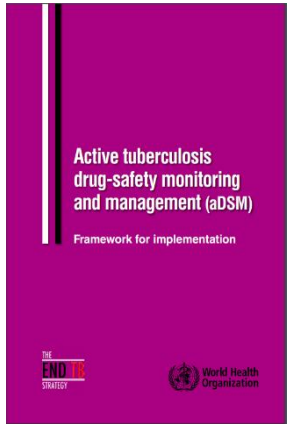
*** p > 0.05**

RR/MDR TB,
n=378

pre-XDR TB,
n=334

Active drug safety monitoring and management (aMBL), n=720



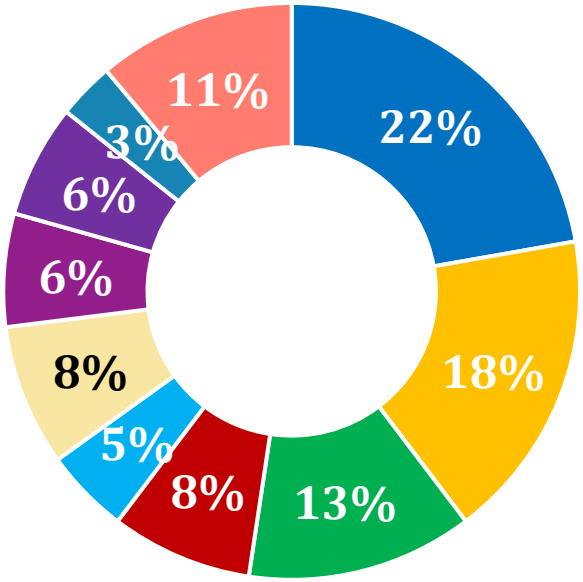


"Intermediate package":

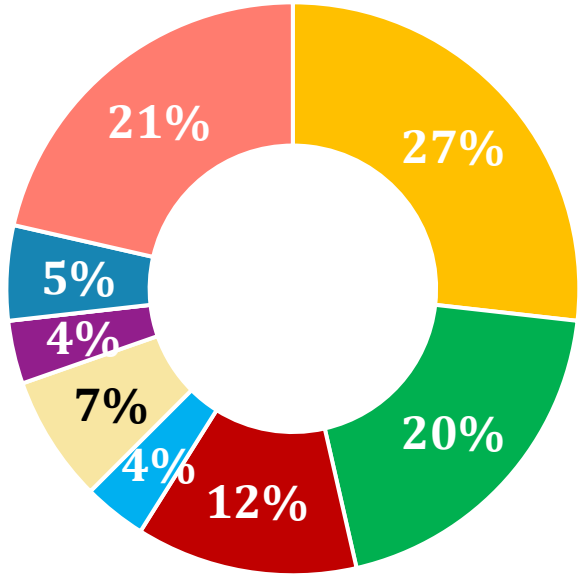
- Serious adverse events – 119 in 82 patients
- Adverse events of particular interest – 8 in 8 patients

Safety profile of BPaLM/C, n=720

Serious adverse events (SAE)



- Cl. difficile infection
- Impaired liver function
- Myelosuppression
- Acute kidney injury
- Elevated amylase level
- QTcF prolongation or ventricular premature beats
- Acute heart failure
- Toxic-allegric reaction
- Progression of cancer
- Other



RR/MDR TB,
63 SAEs in 46 patients

pre-XDR TB,
56 SAEs in 36 patients

Serious adverse events were detected **in 82 (11.4%)** patients.

Safety profile of BPaLM/C, n=720

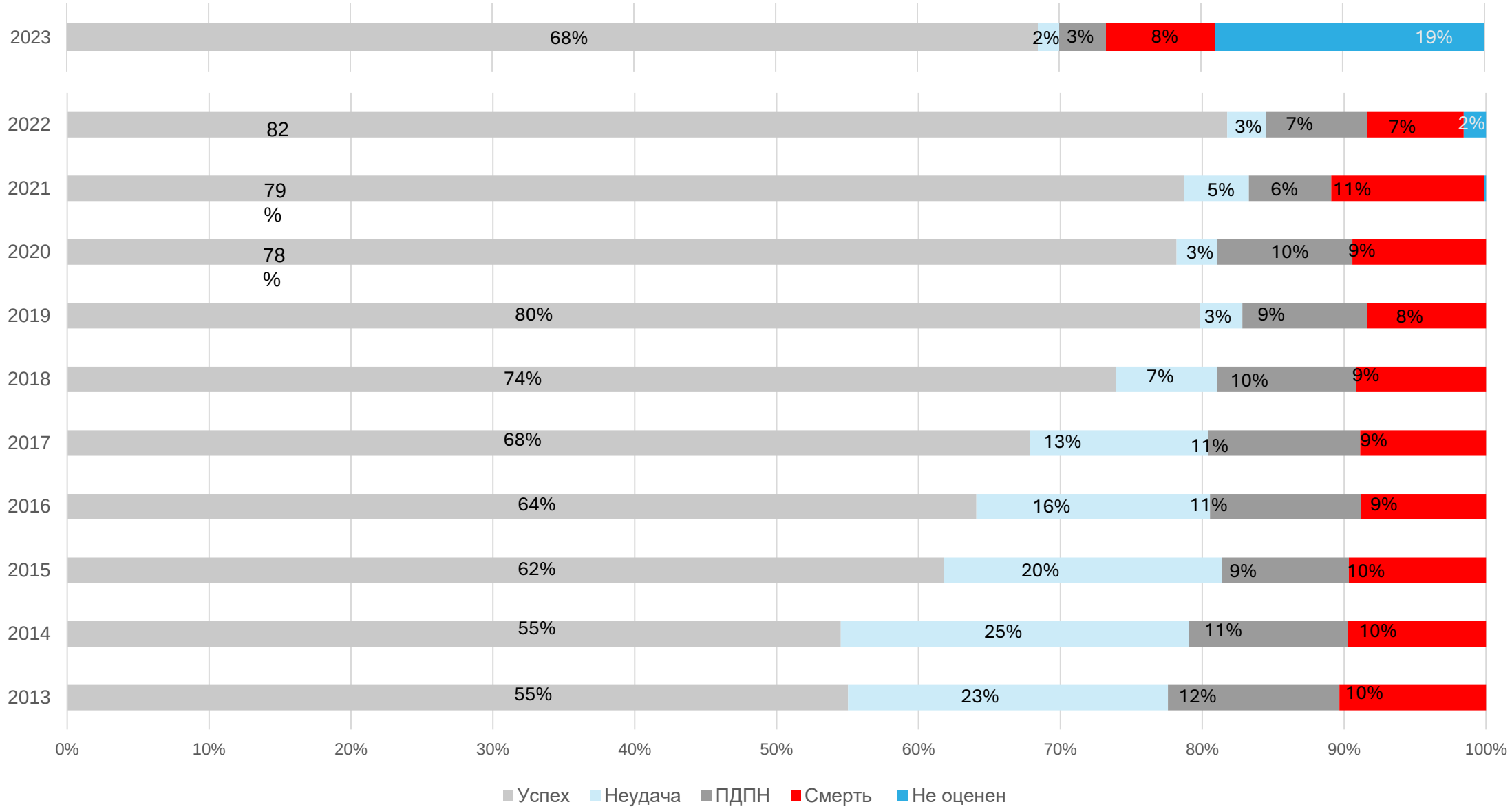
Outcomes of serious adverse events

Resolved	81 (68%)
Resolved with consequences	6 (5%)
Waiting resolution	5 (4%)
Not resolved	1 (1%)
Died	15 (13%)
Unknown	11 (9%)

Actions for management of serious adverse events

Interruption of treatment – 59 (49.6%)
Lzd dose reduction – 8 (6.7%)
Withdrawal of 1 drug – 15 (12,6%)
Withdrawal of treatment – 3 (2.5%)

Results of RR TB treatment



Follow-up, n=449

Follow-up period

RR/MDR TB – 9 patients died,
1 recurrent case with unknown status

pre-XDR TB – 10 patients died,
3 recurrent case with unknown status

Success of follow-up

RR/MDR TB – 90.0%

pre-XDR TB – 84.0%

Follow-up period

Cause of death:

CHD/acute heart failure	6 (32%)
Oncological disease	3 (16%)
Acute cerebrovascular accident	3 (16%)
Atrial fibrillation	1 (5%)
Alcohol	1 (5%)
Covid-19	1 (5%)
HIV infection	1 (5%)
Failed to identify	3 (16%)

Conclusions

- Success of treatment and follow-up — RR/MDR TB – 95.0% and 90.0%; pre-XDR TB – 91.2% and 84.0%, respectively
- Good safety profile
    - Low incidence of serious adverse events during treatment – 11.4%
- Monitoring and management of adverse events is an important component of Good Clinical Practice