

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**

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)

Рекомендуемое
ВОЗ стандартное
лечение

Курсы лечения
9-24 месяца
+/- инъекции

Этап 2



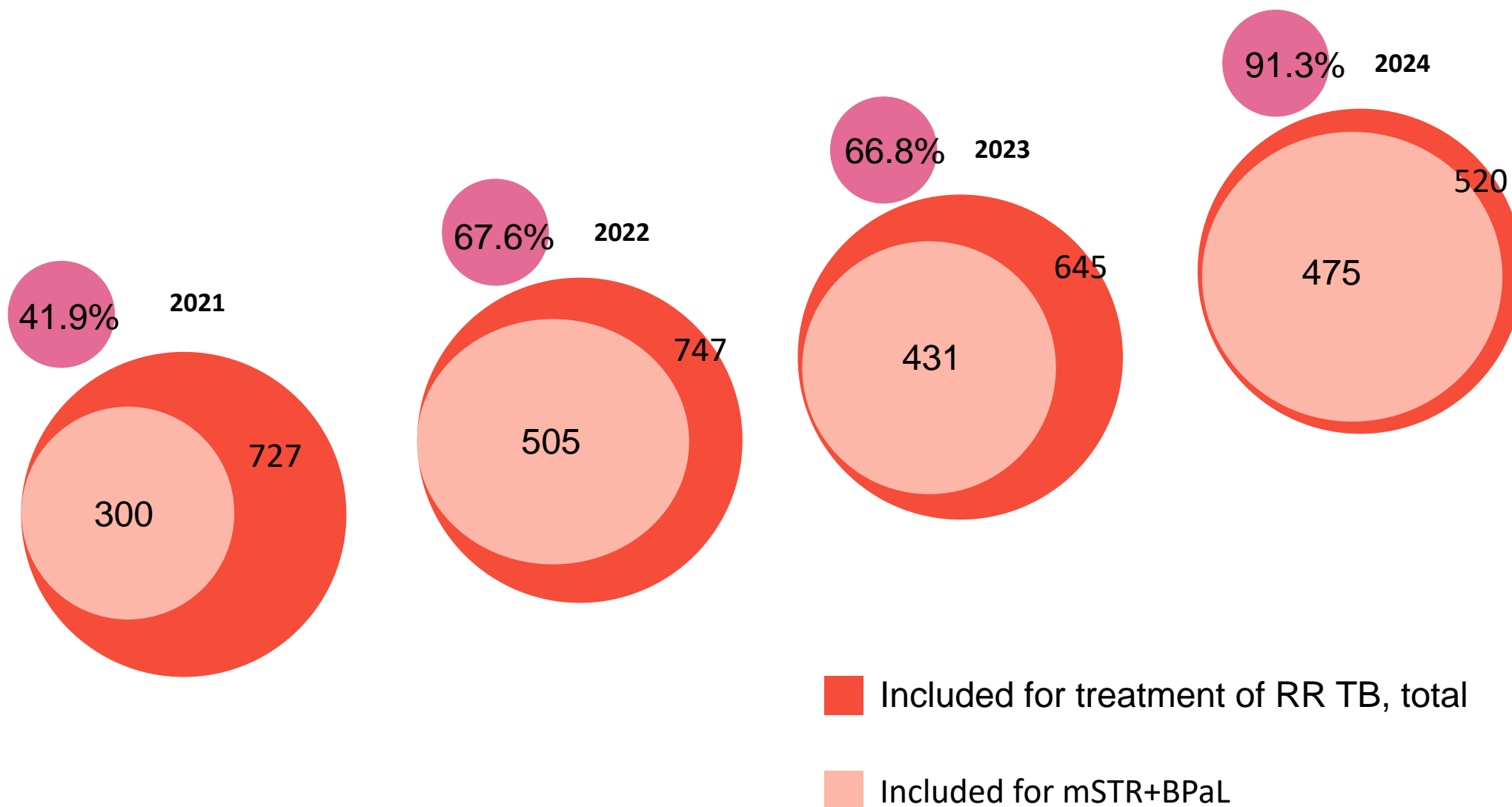
Схема лечения BPaLM показала наибольшую эффективность и безопасность, поэтому она была выбрана для второго этапа исследования.



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

SMARTT Operational Study

ИЗУЧЕНИЕ
БЕЗОПАСНОСТИ И
ЭФФЕКТИВНОСТИ



6

-ТИ МЕСЯЧНОГО
КУРСА ЛЕЧЕНИЯ
МЛУ/ШЛУ ТБ

ИССЛЕДУЕМЫЕ
РЕЖИМЫ



бедаквилин, претоманид,
линезолид
+ клофазимин
+ моксифлоксацин



Evaluation of results

ГИБКИЙ ДИЗАЙН
ИССЛЕДОВАНИЯ ДЛЯ УСКОРЕНИЯ ПРОГРЕССА




ИССЛЕДОВАНИЕ ПРОВОДИТСЯ
В НЕСКОЛЬКИХ СТРАНАХ

Monitoring of treatment

| | Исследование/Обследование | Исходная оценка и скрининг | Фаза лечения (Н=Неделя) | | | | | | Последующее наблюдение (М=Месяц) | |
|---------------------------------|---|----------------------------------|-------------------------|-------|--------|--------|--------|--------|--|--------|
| | | | Н д 4 | Н д 8 | Н д 12 | Н д 16 | Н д 20 | Н д 24 | М п 6 | М п 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 |
| | Рентгенография грудной клетки ⁸ | X | | | | | | | X | |
| Другие исследования | 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) | | |



Month All-Order Forms for Rifampicin-Resistant Tuberculosis Treatment - Belarus

2022-01-01

- Project Home
- REDCap Messageboard
- Connect REDCap to administrator
- Project Home
- Checkbook
- Project Info
- Development

Record Home Page

The list below displays the form-by-form progress of data entered for the currently selected subject. You can click on the colored status icons to access the form(s) viewed.

☒ Choose entries to delete

Legend for status icons



- Incomplete (no data saved)
- Incomplete (data saved)
- Complete
- Many statuses (all saved)
- Many statuses (all saved)

Rifampicin-resistant TB treatment - Belarus

PatIENT study number: 2022-01-001 (1)

| Data Collection Instrument | | V05 | V06 | V07 | V08 | V09 | V10 | V11 | V12 | V13 | V14 | V15 | V16 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Demographic and personal information and form | Demographic and personal information and form | Demographic and personal information and form | Demographic and personal information and form | Demographic and personal information and form | Demographic and personal information and form | Demographic and personal information and form | Demographic and personal information and form | Demographic and personal information and form | Demographic and personal information and form | Demographic and personal information and form | Demographic and personal information and form |
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| HOME | ABOUT |
| OUR WORK | OUR TEAM |
| COUNTRIES | TOOLKIT |
| NEWS & STORES | RESEARCH |
| <hr/> | |
| June 27, 2016 | |
| Pharmacokinetics and other resources for staff on endTB sites. | |
| Pv178-003 - Causality assessment Aile Memoire.pdf (209.2 KB) | |
| Pv178-001 - SAE report form completion guideline.pdf (763.9 KB) | |
| Pv178-011 - SAE report form.pdf (97.1 KB) | |
| Pv178-002 - Pregnancy report form.pdf (895.5 KB) | |
| Pv178-002 - Pregnancy report form completion guideline.pdf (735.54 KB) | |
| Pv178-012 - TB severity grading Scale, print out version 1.0b (203.5 KB) | |
| Pv178-012 - TB severity grading Scale, print out version 1.0, 14Nov2016.xls (122.8 KB) | |
| RUS000 - Pv178-003 - Causality assessment Aile Memoire.pdf (625.47 KB) | |
| RUS000 - Pv178-001 - SAE report form completion guideline.pdf (11.52 MB) | |
| RUS000 - Pv178-002 - Pregnancy report form completion guideline.pdf (696.89 KB) | |
| RUS000 - Pv178-001 - SAE report form.pdf (271.14 KB) | |
| RUS000 - Pv178-002 - Pregnancy report form.pdf (573.49 KB) | |
| RUS000 - Pv178-012 - TB severity grading Scale, print out version 1.0b (203.5 KB) | |
| RUS000 - Pv178-012 - TB severity Grading Scale, v5.0 Updated, 13NOV2016.xls (182.5 KB) | |
| SPAIN01_Causality assessment aile Memoire.pdf (335.54 KB) | |
| SPAIN01_Pregnancy report form completion guideline.pdf (734.46 KB) | |
| SPAIN01_SAE report form completion guidelines.pdf (405.26 KB) | |
| SPAIN01_SAE report form.pdf (471.39 KB) | |
| SPAIN01_TB Severity Grading Scale, print out version 14Nov2016.pdf (860.8 KB) | |
| SPAIN01_TB Severity Grading Scale version 5.1, 14Nov2016.xls (198 KB) | |

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

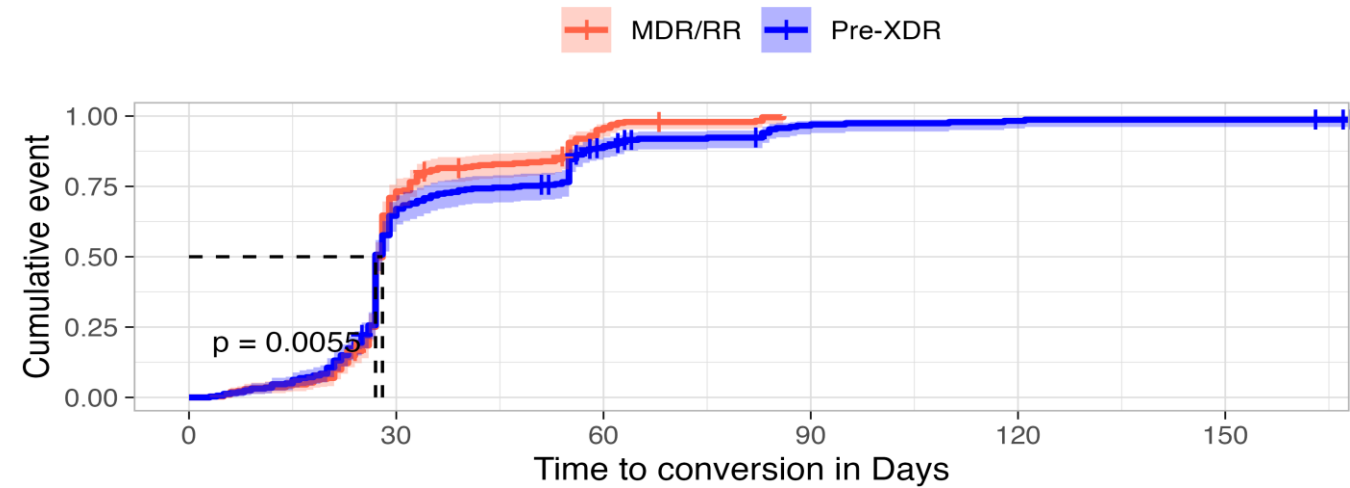
| Parameters | RR/MDR TB, n=378 | pre-XDR TB, n=334 | Total, n=712 |
|--|---------------------|----------------------|-------------------|
| Age, Median (25th; 75th percentile) | 48 (38, 57) | 46 (38, 57) | 46 (38, 57) |
| Women | 82 (21.7%) | 84 (25.1%) | 166 (23.3%) |
| BMI, Median (25th; 75th percentile), 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/m ² | 62 (16.4%) | 55 (16.5%) | 117 (16.4%) |

Deliverables

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



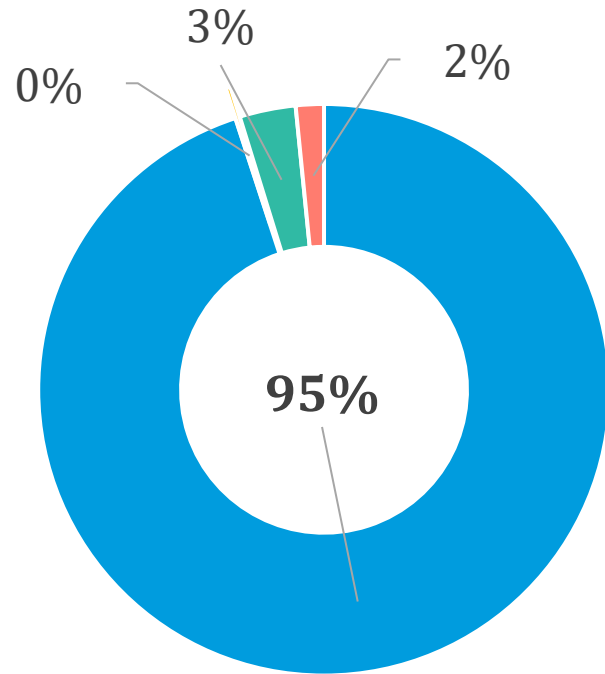
| Culture conversion period | RR/MDR TB | pre-XDR TB | Total |
|---------------------------|-------------|-------------|-------------|
| 1 | 249 (83.3%) | 235 (76.8%) | 484 (80.0%) |
| 2 | 44 (14.7%) | 55 (18.0%) | 99 (16.4%) |
| 3 | 6 (2.0%) | 13 (4.3%) | 19 (3.1%) |
| 4 | 0 (0%) | 3 (1.0%) | 3 (0.5%)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

Evaluation of treatment results

| | |
|--------------------------|---|
| Treatment failure | <p>Treatment has been discontinued or at least two anti-tuberculosis drugs administration should be changed for the reasons as follows:</p> <ul style="list-style-type: none">• 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

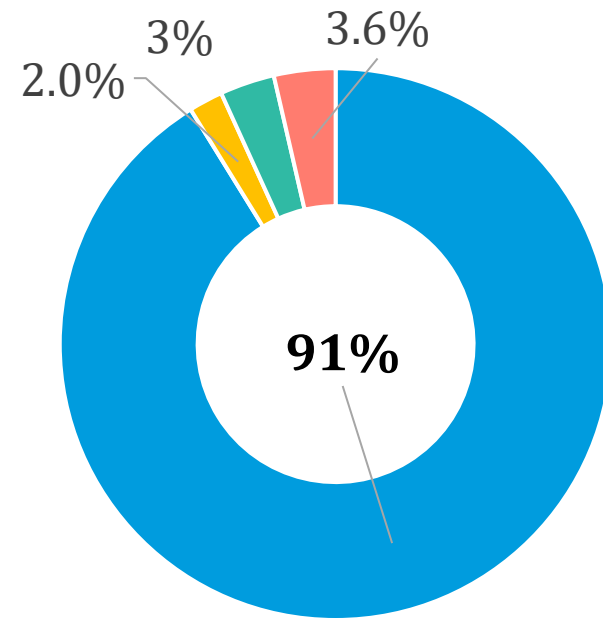
Treatment success – 93.1%



**RR/MDR TB,
n=378**

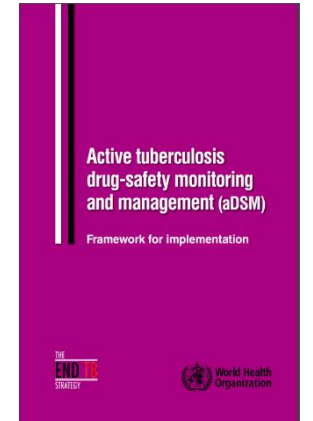
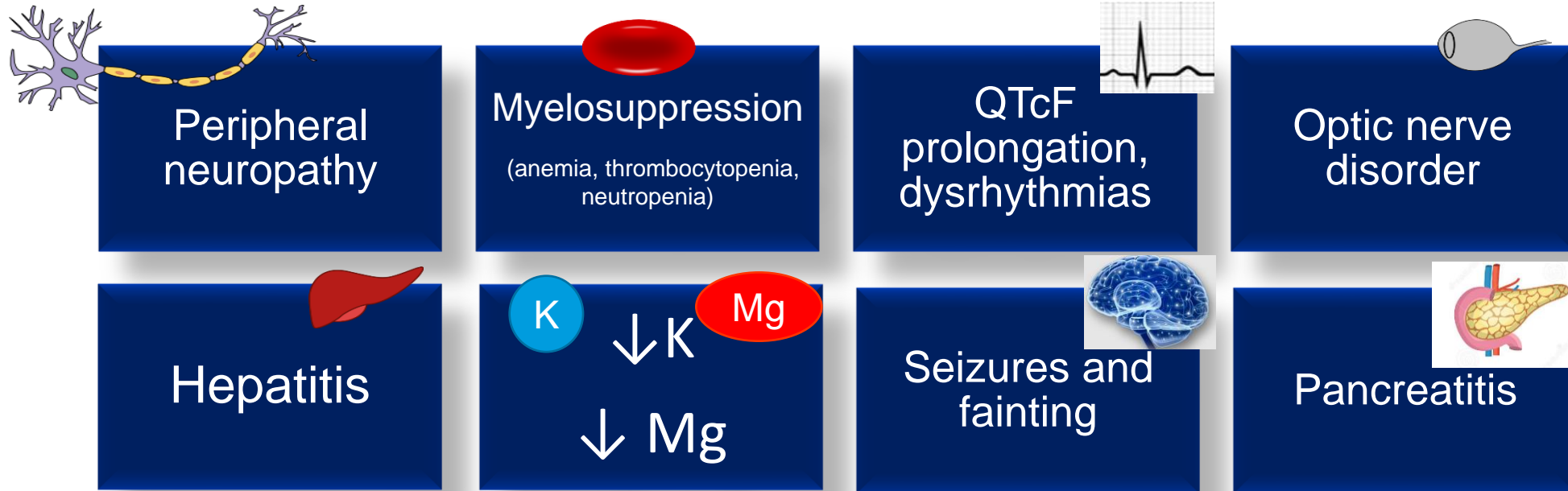
- Cured + Treatment completed*
- Failure*
- Lost to follow-up*
- Death*

* p > 0.05



**pre-XDR TB,
n=334**

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



"Intermediate package":

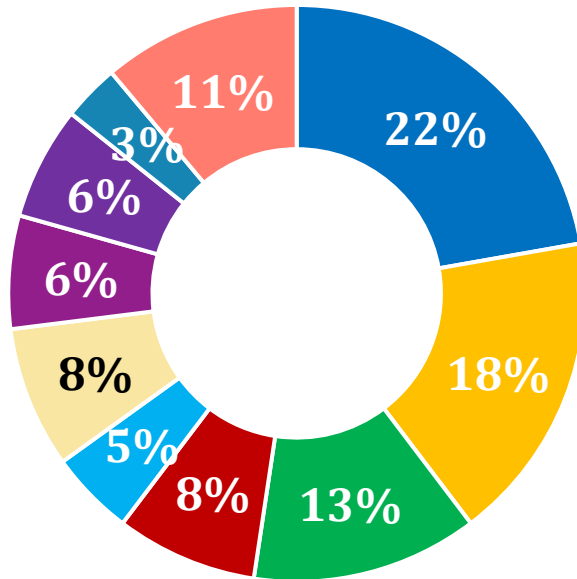
Serious adverse events – 119 in 82 patients

Adverse events of particular interest – 8 in 8 patients

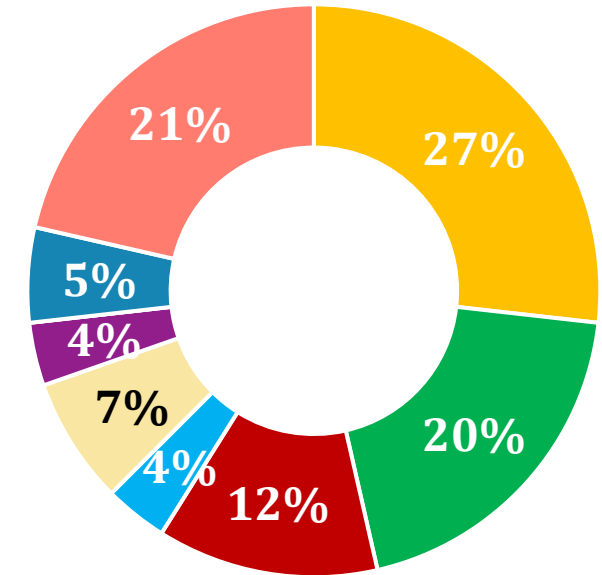
Safety profile of BPaLM/C, n=720

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-allergic 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

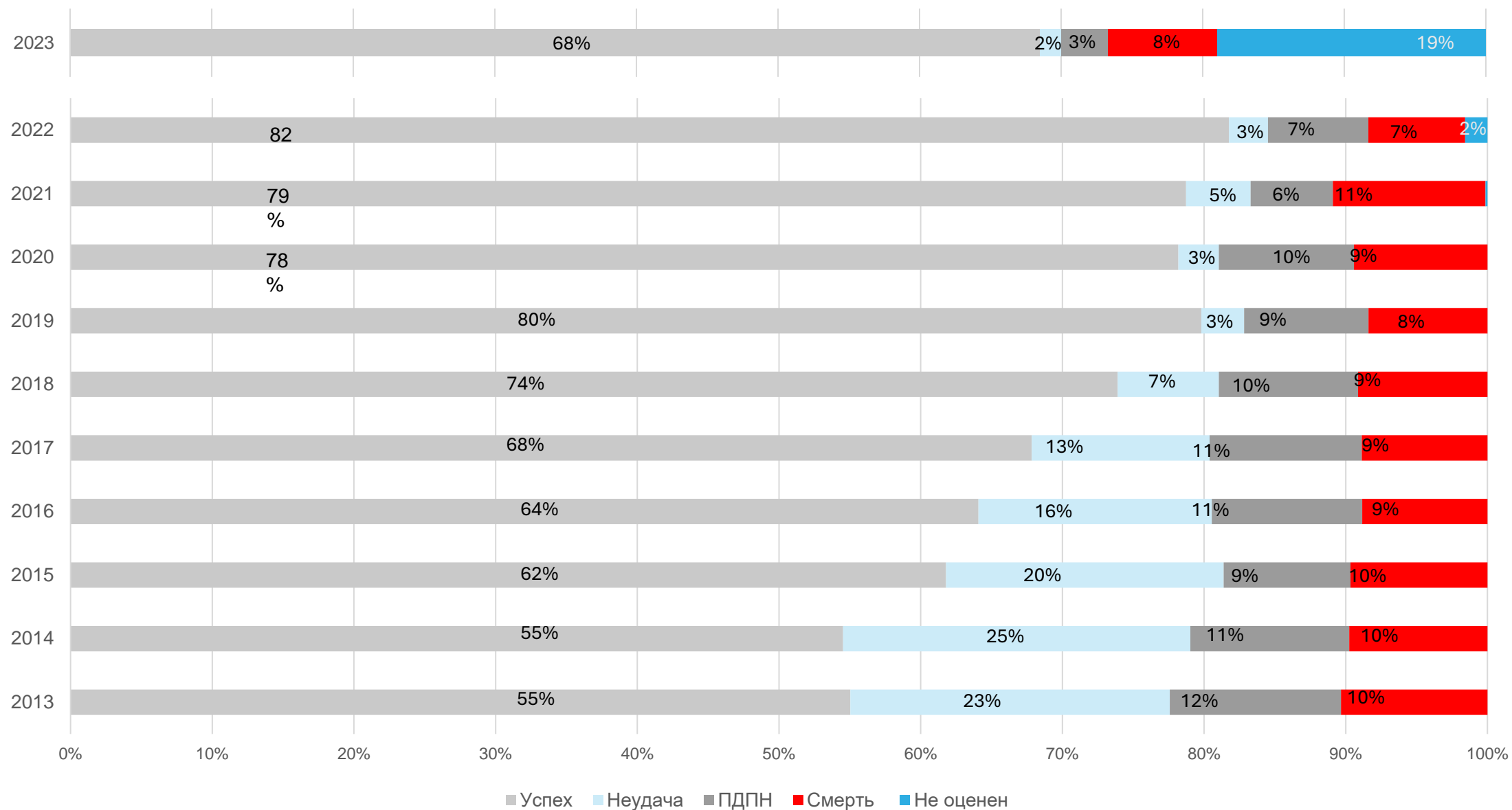
Interruption of treatment – 59 (49.6%)

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