

Belarus' experience in implementing and scaling up the use of BPaL(M)

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**The 20th meeting of WHO BPaLM Accelerator Platform &
The 30th webinar of European Virtual Medical Consilium**

31 October 2024

Prerequisites for the implementation of BPaL(M)

National TB policy, based on WHO guidelines

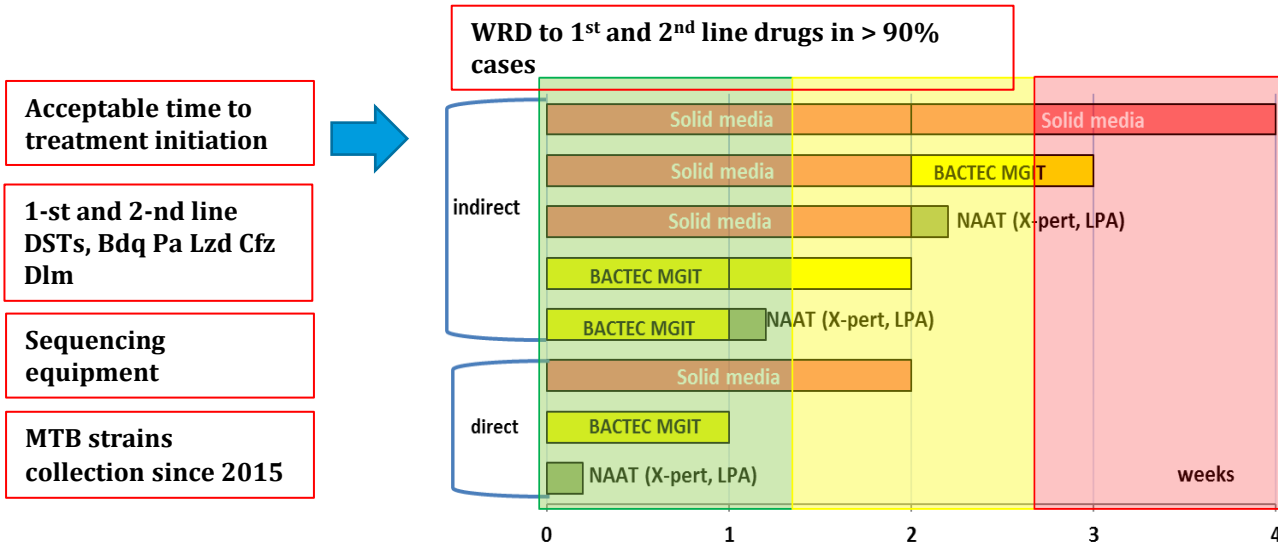


Regulatory framework

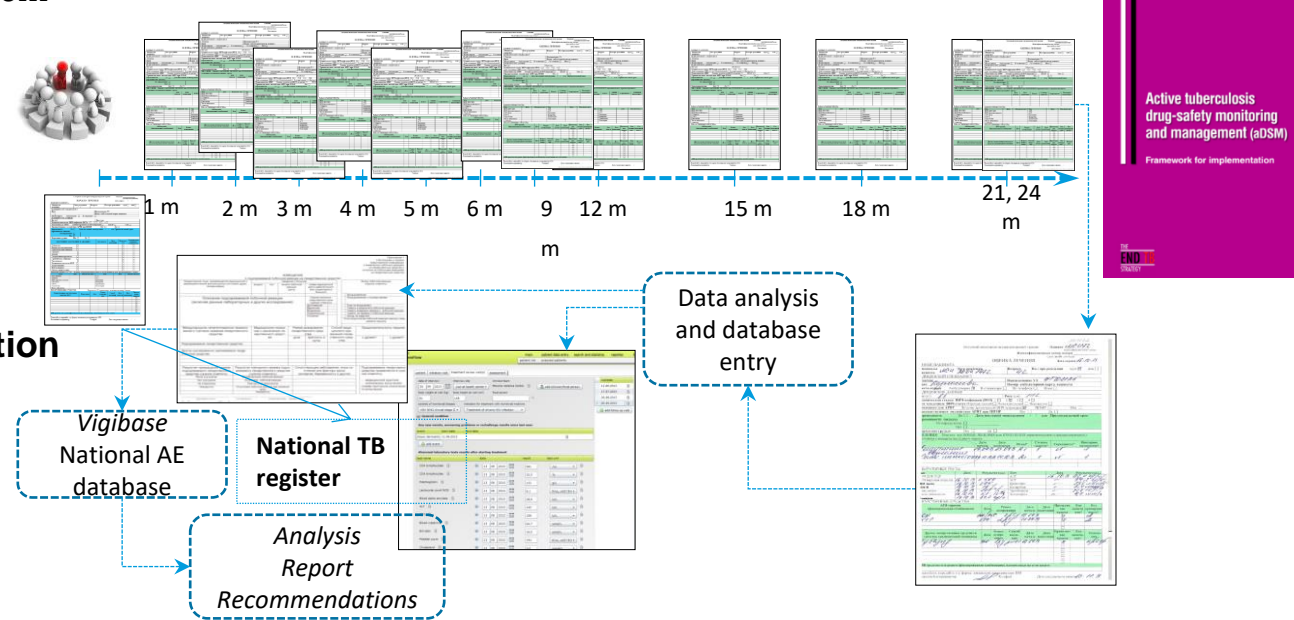


**Start of programme implementation
BPaL: December 2022**

Lab. and diagnostic potential



Active Drug Safety Monitoring (aDSM), Interaction with the Pharmacovigilance System



National PV system

National PV policy, based on WHO guidelines

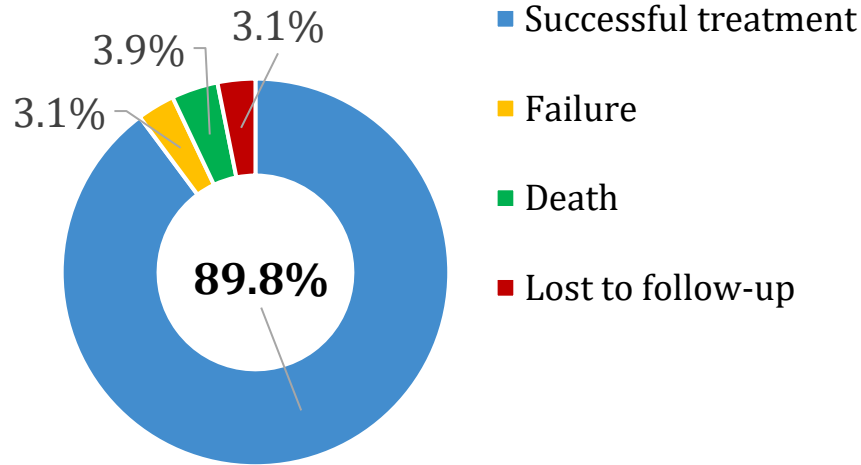
Spontaneous reporting: 5,4 per 100 000

- CM - HIV, 2012
- CM - HIV M/XDR-TB, 2013
- CM - LZD, 2014
- CM - BDQ, 2015
- CM - DLM, 2016
- CM - BDQ+DLM, 2016
- aDSM - mSTR, 2018

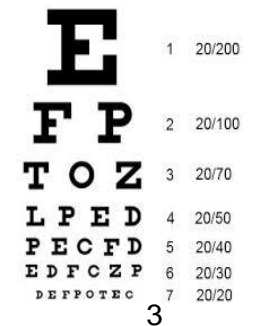
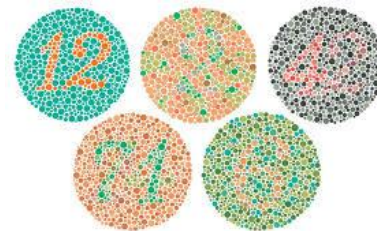
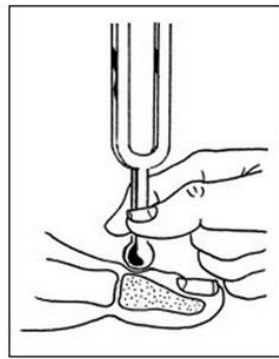
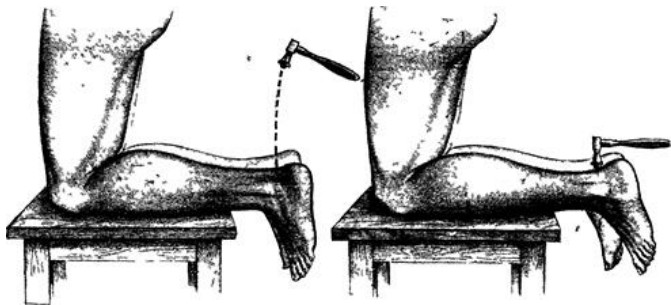
RR-TB Consilium. Experience of the implementation of mSTR OR

- RR-TB Concilium - since 2010, online – III 2020
- Regular monitoring visits

Regional cohort
n=540



- aDSM skills, tools and assessment of neurological status, visual acuity and color perception
- quality check «Monitoring template»

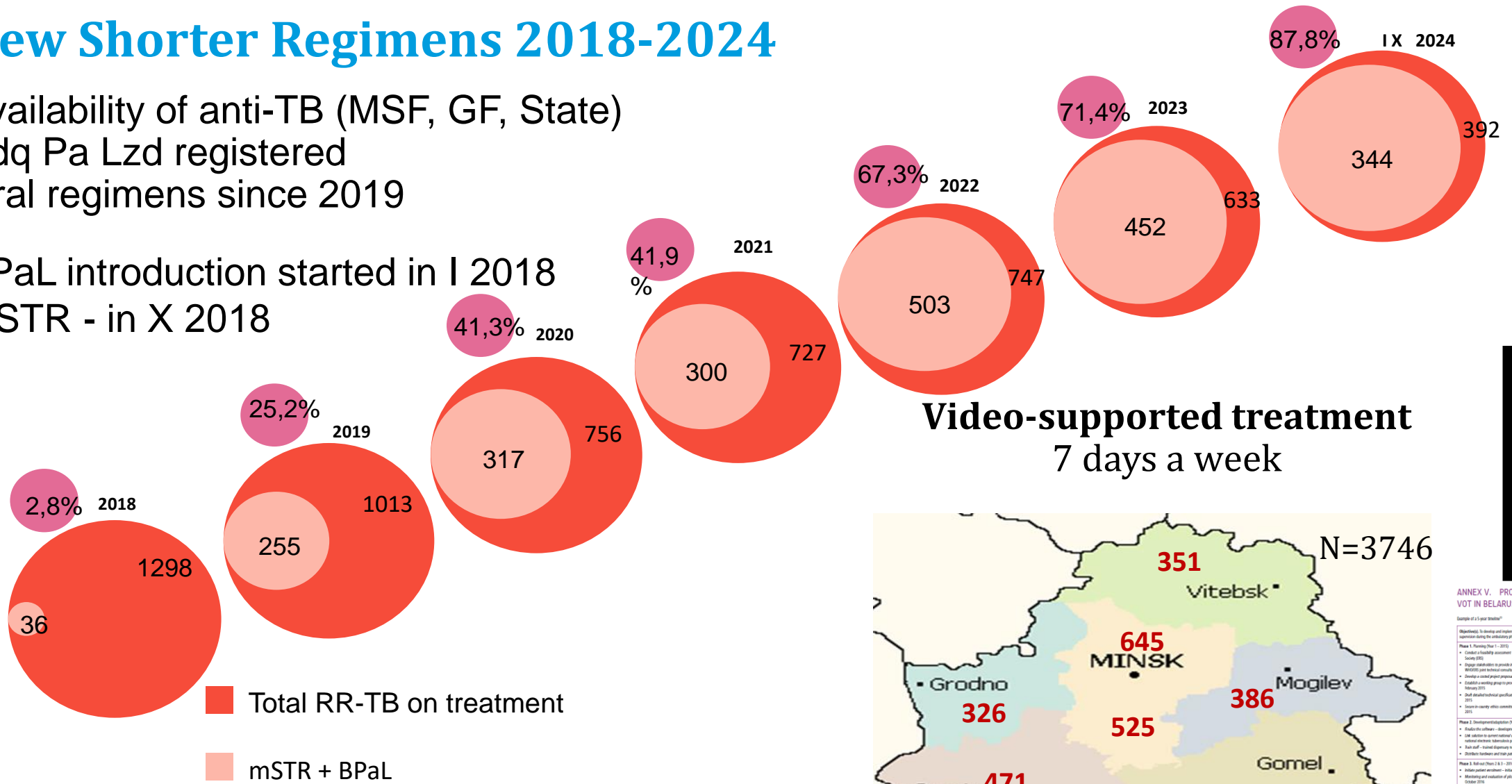


Drug supply

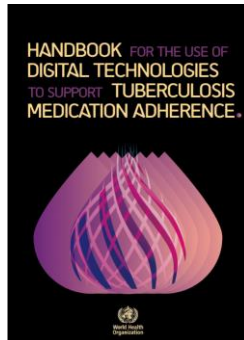
New Shorter Regimens 2018-2024

Availability of anti-TB (MSF, GF, State)
Bdq Pa Lzd registered
Oral regimens since 2019

BPaL introduction started in I 2018
mSTR - in X 2018



Video-supported treatment 7 days a week



ANNEX V. PROGRAMMATIC IMPLEMENTATION OF VOT IN BELARUS

Example of a 5-year timeline*

Phase 1: Planning (Year 1 - 2018)

- Conduct feasibility assessment - conducted by WHO in January 2018 with support of the European Respiratory Society (ERS)
- Organize stakeholder to provide input on solution - WHO survey of public views on priority areas in early 2018, WHO/ERS joint technical consultation to develop detailed technical VOT for VOT in February 2018
- Formulate a national action plan - developed by the Global Fund in February 2018
- Establish a working group to provide oversight and guidance - established by the Ministry of Health of Belarus in February 2018
- Staff educational qualification - drafted by local Belarusian company "BelarusPharm" for VOT app in May 2018
- Secure in-country ethics committee approval for pilot project - secured through Ministry of Health in September 2018

Phase 2: Development/Implementation (Year 2 - 2019)

- Develop the software - development finalized by BelarusPharm in January 2019
- Conduct a software - development finalized by BelarusPharm in January 2019
- Conduct a software - development finalized by BelarusPharm in January 2019
- Conduct a software - development finalized by BelarusPharm in January 2019
- Conduct a software - development finalized by BelarusPharm in January 2019

Phase 3: Roll-out (Year 3 & 4 - 2019-2021)

- Initial patient enrollment - initiated single site preliminary pilot in Minsk in January and February 2019
- Monitoring and evaluation of pilot study results - monitoring by ERS/Ministry of Health of Belarus from January to October 2019
- Additional pilot study results - pilot findings published in European Respiratory Journal in March 2020

Phase 4: Mainstreaming (Year 5 - late 2019-2021)

- Expansion of patient enrollment - expansion to all seven country regions with planned recruitment of 600 patients (200 each with Belarus, 400 each with the Global Fund) from October 2019 to 2020, 200 patients from all regions of the country were on VOT by 1 September 2021

The designations employed and the presentation of this material do not imply the expression of any opinion whatsoever concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of frontiers and boundaries

BPaL(M/C) Experience : Clinical trial – TB-PRACTECAL

Jan 2018 – Aug 2021 – 70 patients from Minsk and Minsk region

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A 24-Week, All-Oral Regimen for Rifampin-Resistant Tuberculosis

Bern-Thomas Nyang'wa, M.B., B.S., Catherine Berry, B.Med.,
 Emil Kazounis, M.Med.Sci., Ilaria Motta, Ph.D., Nargiza Parpieva, Sc.D.,
 Zinaida Tigay, M.D., Varvara Solodovnikova, M.D., Irina Liverko, Sc.D.,
 Ronelle Moodliar, M.B., B.S., Matthew Dodd, M.Sc.,
 Nosipho Ngubane, M.B., B.Ch., Mohammed Rassool, M.B., B.Ch.,
 Timothy D. McHugh, Ph.D., Melvin Spigelman, M.D., David A.J. Moore, M.D.,
 Koert Ritmeijer, Ph.D., Philipp du Cros, M.B., B.S., and Katherine Fielding, Ph.D.,
 for the TB-PRACTECAL Study Collaborators*

ABSTRACT

BACKGROUND

In patients with rifampin-resistant tuberculosis, all-oral treatment regimens that are more effective, shorter, and have a more acceptable side-effect profile than current regimens are needed.

From the Public Health Department, Operational Center Amsterdam (OCA), Médecins sans Frontières, Amsterdam (B.-T.N., K.R.); the Public Health Department,

Outcome	n	%
Successful treatment	60	85,7
Excluded from the study	10	14,3

The NEW ENGLAND JOURNAL of MEDICINE

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Standard-Care Group	BPaLM Group	BPaLC Group	BPaL Group
Intention-to-treat population				
No. of patients	152	151	126	123
Geographic distribution — no. (%)				
Belarus	29 (19.1)	28 (18.5)	21 (16.7)	21 (17.1)



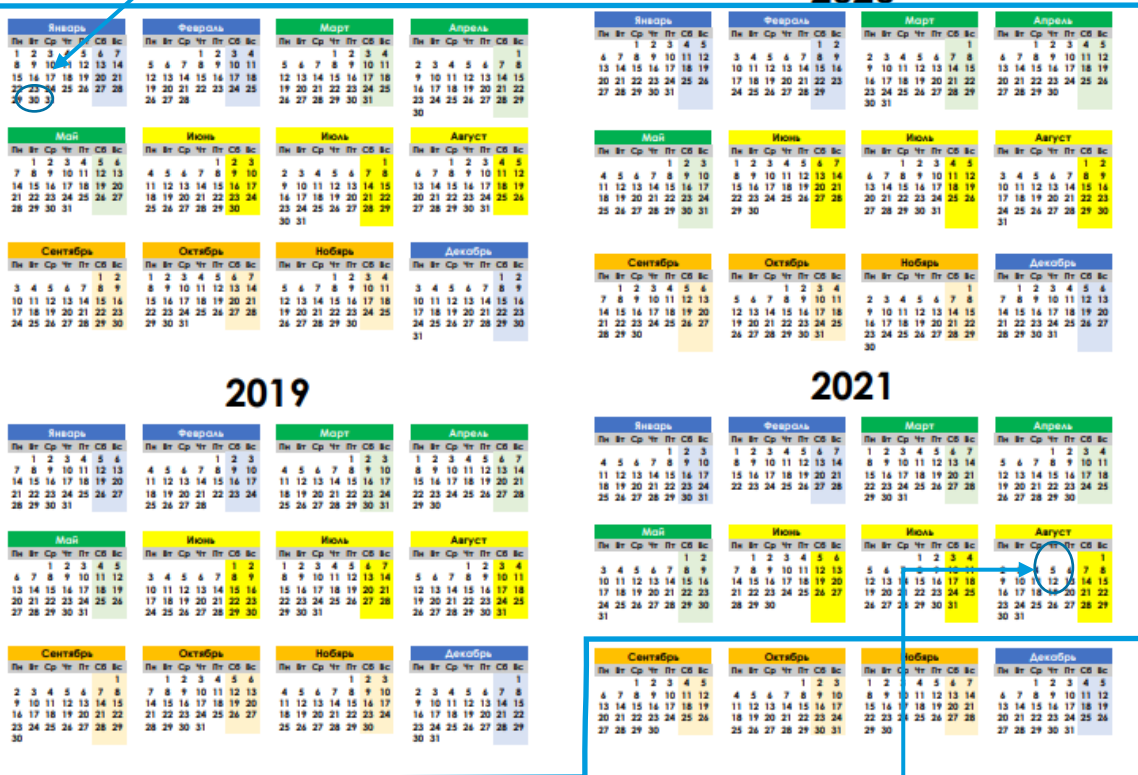
Nov 2021 – Jan 2022 - Ethics OR SMARRTT was approved by

- the MSF Ethics Committee (EC)**
- Independent EC of Belarus.**

BPaL(M) Experience: Clinical Trial (CT) and Operational Research (OR)

1st patient CT

2018

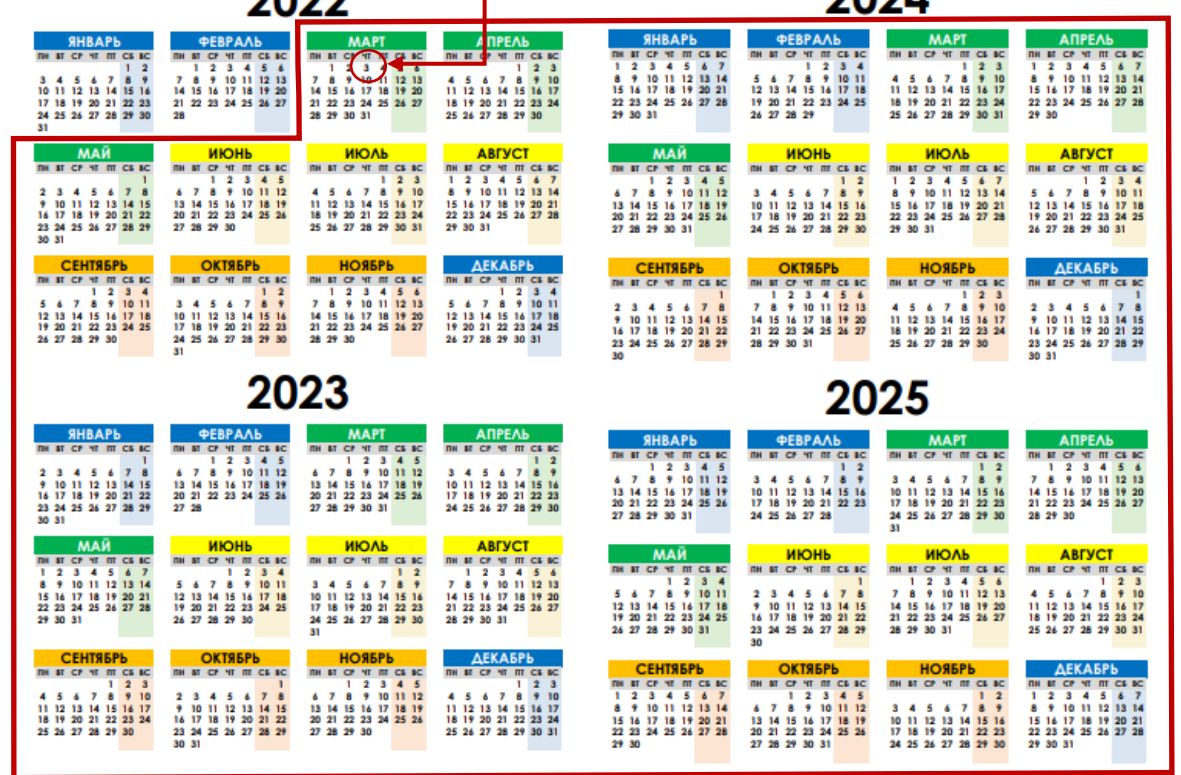


End of CT

1st patient OR

2022

2024



BPaLM Treatment Monitoring

	Investigation/Observation	Baseline assessment & Screening	Treatment Phase (W=Week)						Follow-Up (M=Month)												
			W _T 4	W _T 8	W _T 12	W _T 16	W _T 20	W _T 24	M _F 6	M _F 12											
Clinical evaluation	Written informed consent	X																			
	Demographics, Medical History	X																			
	Clinical Examination ¹	X	X	X	X	X	X	X	X	X											
	Treatment adherence		X	X	X	X	X	X													
	Concomitant treatment		X	X	X	X	X	X	X												
	Adverse events		X	X	X	X	X	X	X	X											
	Bacteriology	Sputum smear	X (2)	X	X	X	X (2)	X	X (2)	X	X										
Sputum culture		X	X	X	X	X	X	X	X	X											
mWRDT (GeneXpert) ²		X																			
Laboratory tests	Rapid test for FQ resistance ³								X												
	DST (R/FQ +/- Bdq +/- Lzd) ⁴										X							(X)	(X)	(X)	(X)
	Haemoglobin/platelets count / white blood count		X								X	X	X	X	X	X	X	X			
	Serum creatinine (at baseline and if clinically indicated or ECG abnormalities)		X								X										
	Serum potassium (at baseline and if clinically indicated or ECG abnormalities)		X								X										
	Serum lipase (if clinically indicated)		X								X										
	Serum liver enzymes		X								X	X	X	X	X	X	X	X	X		
	Pregnancy test (female) ⁵		X								X										
	HIV and hepatitis test ⁶		X								X										
	Other	Blood glucose/HbA1c ⁷		X							X	X	X	X	X	X	X	X	X	X	X
Chest X-ray ⁸			X							X										X	
ECG ⁹			X							X	X	X	X	X	X	X	X	X	X		
Visual acuity & BPNS ¹			X							X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)		

The screenshot shows the REDCap data entry interface. The main content area displays a table for 'Data Collection Instrument' with columns for V01 (Baseline), V02 (W4), V03 (W8), V04 (W12), V05 (W16), V06 (W20), and V07 (W24). The table contains rows for 'Demographics and Registration', 'Clinical Examination', 'Treatment Adherence', 'Concomitant Treatment', 'Adverse Events', and 'Laboratory Tests'. The 'Laboratory Tests' row shows 'X' marks in the V01, V02, V03, V04, V05, V06, and V07 columns, indicating data collection at all time points.

Severity grading scale
version 5.0, 06/14 Nov 2016. Main version: 04/01 Nov 2007 and CTCAE v4.03 14 Jun 2007

For parameters not included in the table, the general definition of severity as displayed under the tabulation 'Introductions' applies.

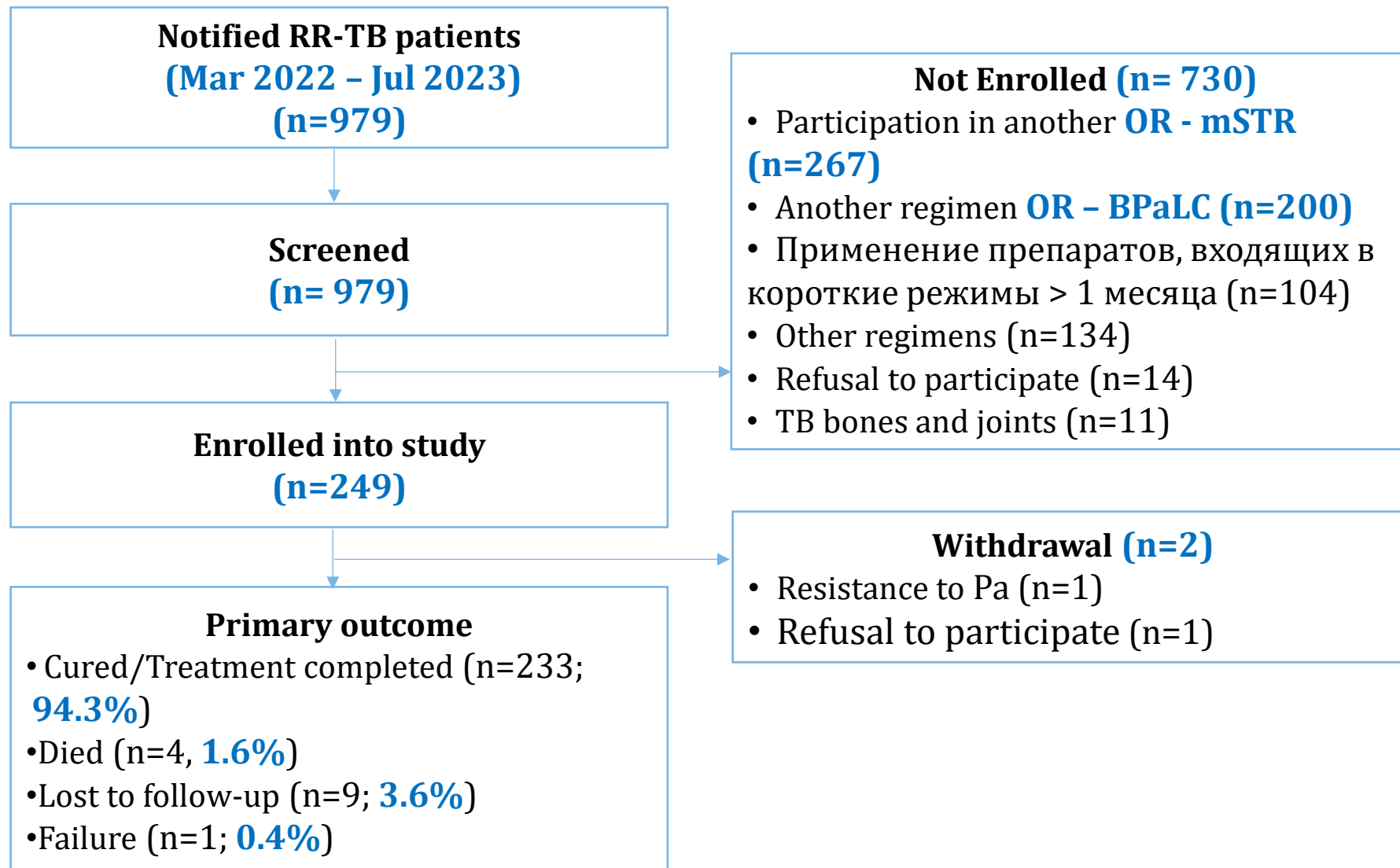
Source	Body system	Condition term	Grade 1	Grade 2	Grade 3	Grade 4	Definition
CTCAE	Hematology	Fibrin Split Product	>140 mg/ml	>150 mg/ml	>160 mg/ml	>170 mg/ml	Presence of fibrin degradation products.
CTCAE	Hematology	Haptoglobin Decreased	<LN	N/A	N/A	N/A	A finding based on laboratory test results that indicate a decrease in levels of haptoglobin in a blood specimen.
CTCAE	Hematology	Hemoglobin Increased	Increase in >0 - 2 g/dL (>20 g/L) above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 g/dL (>20 - 40 g/L) above ULN or above baseline if baseline is above ULN	Increase in >4 g/dL (>40 g/L) above ULN or above baseline if baseline is above ULN	N/A	A finding based on laboratory test results that indicate increased levels of hemoglobin in a biological specimen.
CTCAE	Hematology	Hemolysis	Laboratory evidence of hemolysis only (e.g. direct antiglobulin test, DAT, Coombs), schistocytes, increased haptoglobin	Evidence of hemolysis and >2 g decrease in hemoglobin	Transfusion or medical intervention indicated (e.g. steroids)	Life-threatening consequences; urgent intervention indicated	A disorder characterized by laboratory test results that indicate widespread erythrocyte cell membrane destruction.
DMID	Hematology	High Fibrinogen	High: 400-600 mg/dL	High: >600 mg/dL	N/A	N/A	Fibrinogen associated with disseminated coagulation
CTCAE	Hematology	International Normalized Ratio Increased	>1.15 x ULN; >1.15 - 2.5 times above baseline if on anticoagulation	>1.5 - 2.5 x ULN; >1.5 - 2.5 times above baseline if on anticoagulation	>2.5 x ULN; >2.5 times above baseline if on anticoagulation	N/A	A finding based on laboratory test results that indicate an increase in the ratio of the patient's prothrombin time to a control sample in the blood.
CTCAE	Hematology	Leukocytosis	N/A	N/A	>100,000/mm ³ (>100 x10 ⁹ /L) (>100 x10 ⁹ /L)	N/A	Clinical manifestations of leukostasis; urgent intervention indicated

The screenshot shows the endTB website search results page. The search bar contains the text 'Pharmacokinetics forms and other resources for staff on endTB sites'. The results list several documents, including 'PV18-003 - Causality assessment Aide Memoire.pdf (309.27 KB)', 'PV18-001 - SAE report form completion guidelines.pdf (763.95 KB)', 'PV18-002 - SAE report form.pdf (977.1 KB)', 'PV18-F02 - Pregnancy report form completion guidelines.pdf (775.54 KB)', 'PV18-D12 - TB Severity Grading Scale, print out version, 14NOV2016.doc (283.5 KB)', 'PV18-D12 - TB Severity Grading Scale, version 5.0, 14Nov2016.xls (122.5 KB)', 'RUSSIAN - PV18-D03 - Causality assessment Aide Memoire.pdf (652.47 KB)', 'RUSSIAN - PV18-D01 - SAE report form completion guidelines.pdf (1.02 MB)', 'RUSSIAN - PV18-D02 - Pregnancy report form completion guidelines.pdf (969.89 KB)', 'RUSSIAN - PV18-F01 - SAE report form.pdf (711.14 KB)', 'RUSSIAN - PV18-F02 - Pregnancy report form.pdf (573.49 KB)', 'RUSSIAN - PV18-D12 - TB Severity Grading Scale, print out version, 14NOV2016.doc (283.5 KB)', 'SPANISH - Causality assessment Aide Memoire.pdf (535.14 KB)', 'SPANISH - Pregnancy report form completion guidelines.pdf (754.46 KB)', 'SPANISH - SAE report form completion guidelines.pdf (854.28 KB)', 'SPANISH - SAE report form.pdf (471.39 KB)', 'SPANISH - TB Severity Grading Scale, print out version, 14Nov2016.pdf (268.1 KB)', and 'SPANISH - TB Severity Grading Scale version 5.0, 14Nov2016.xls (188 KB)'. The page also includes a search bar and navigation links like 'OUR WORK', 'OUR TEAM', 'COUNTRIES', 'TOOLKIT', 'NEWS & STORES', and 'RESOURCES'.

Enrolment flow diagram

247 patients
completed the treatment
(treatment start date
Март 2022 - Июль 2023)

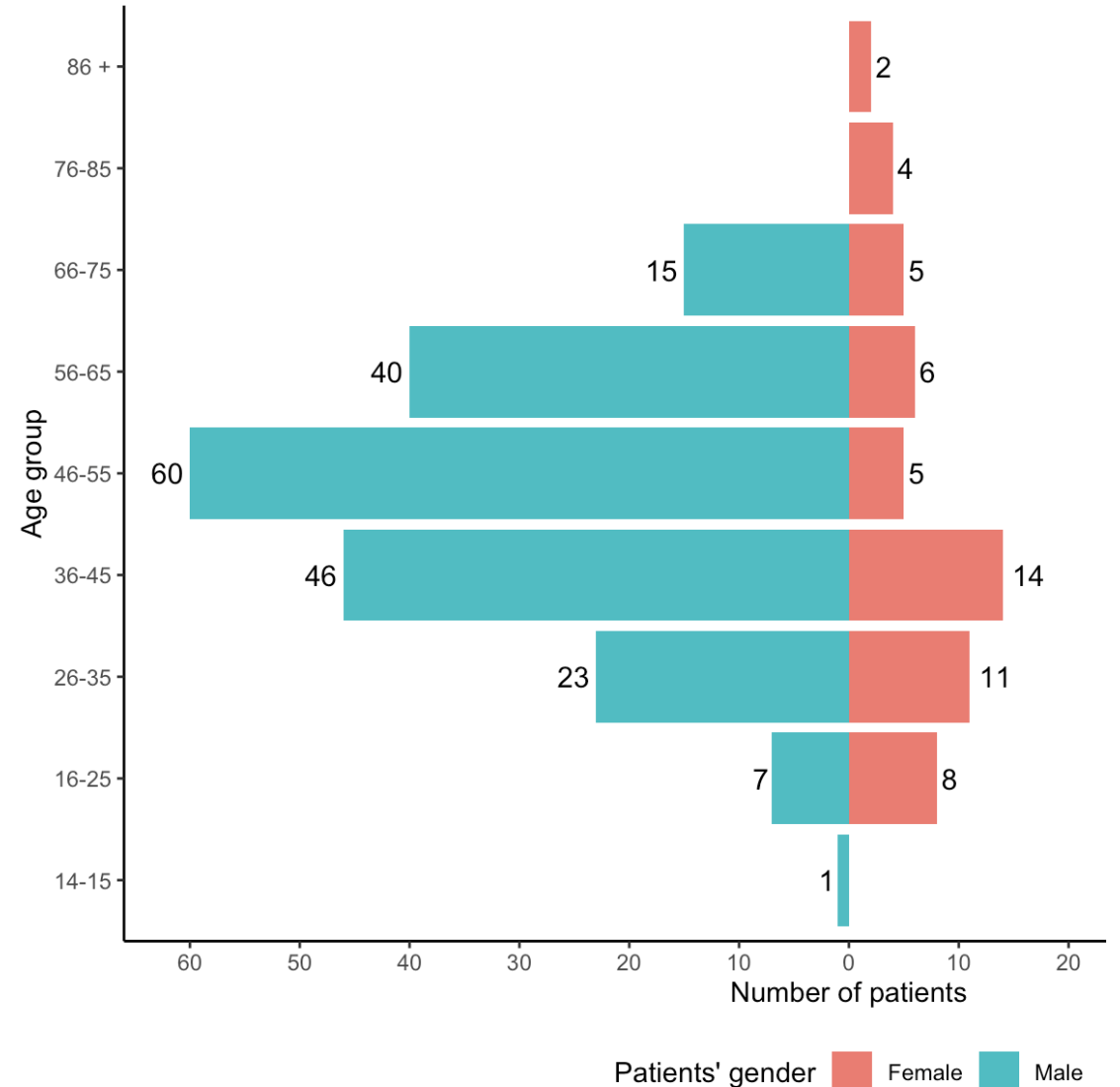
Total number of enrolled patients:
Feb 2022 - Aug 2024 -
722 patients



Experience with use of BPaLM

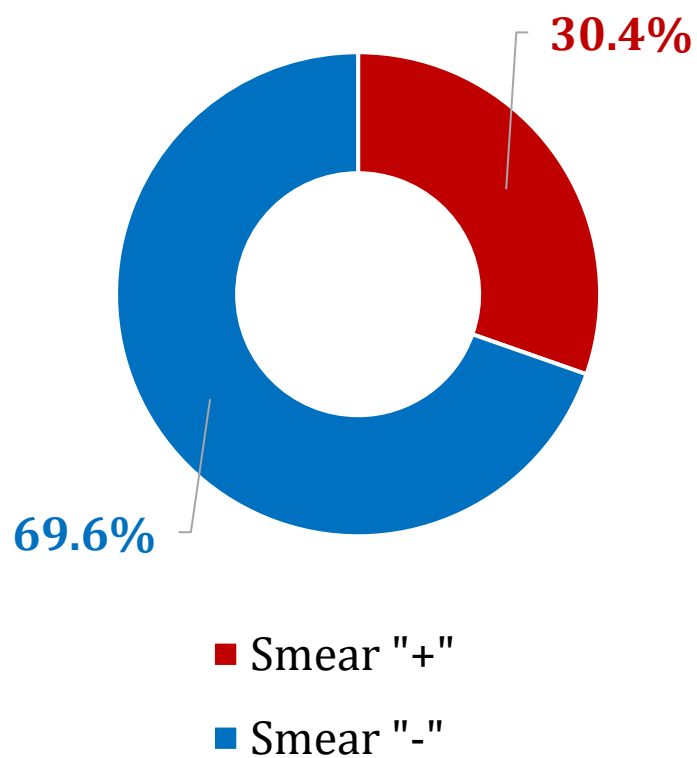
02.03.2022 - first patient enrolled,
247 patients
completed the treatment
(treatment start date
Mar 2022 – Jul 2023)

History of TB	- 52 (21,1%)
BMI<18.5 kg/m2	- 47 (19,0%)
Homeless	- 4 (1,6%)
In the penitentiary system.	- 14 (5,7%)
Psychoactive substances	- 5 (2,0%)

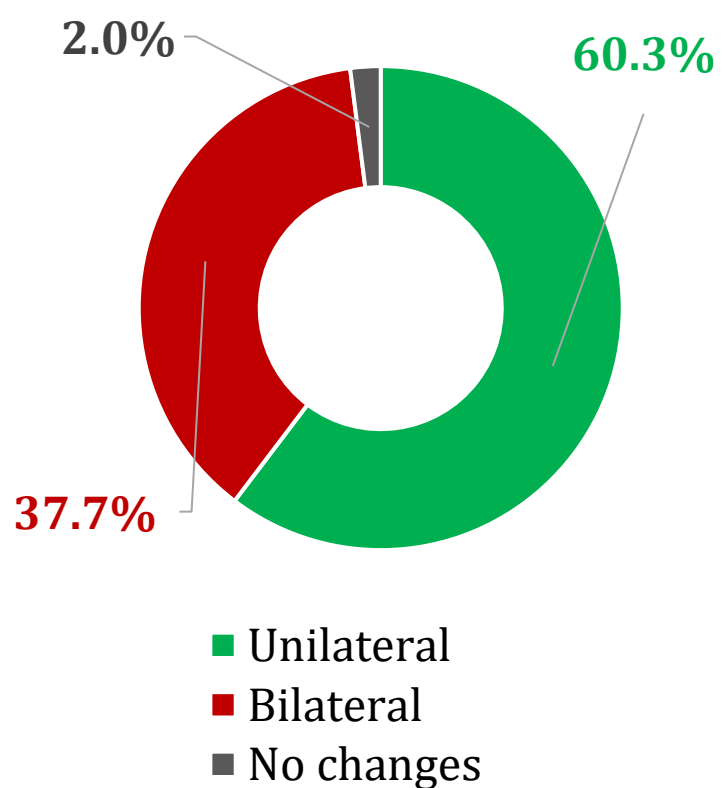


ВРaLM, характеристика ТБ процесса, n=247

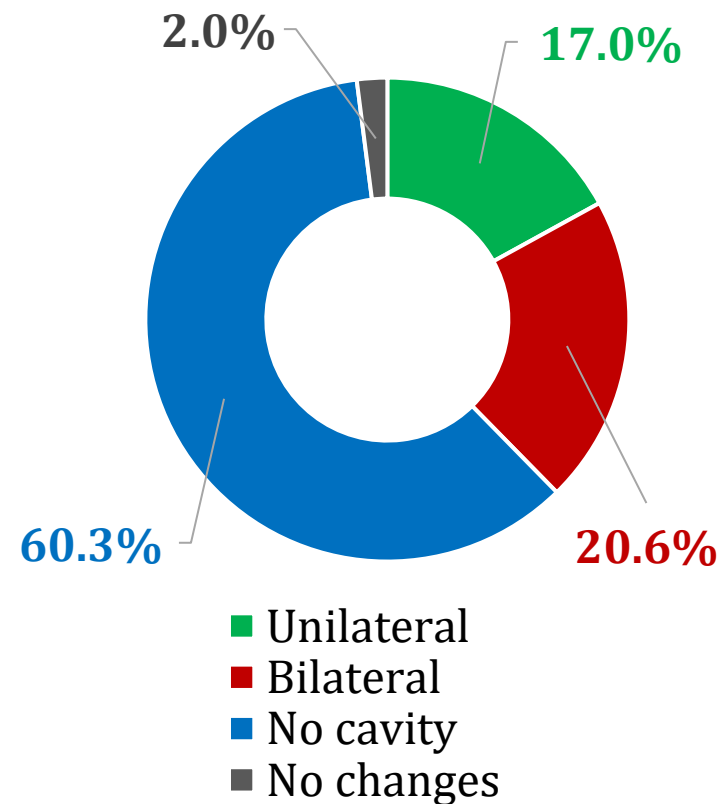
Sputum smear



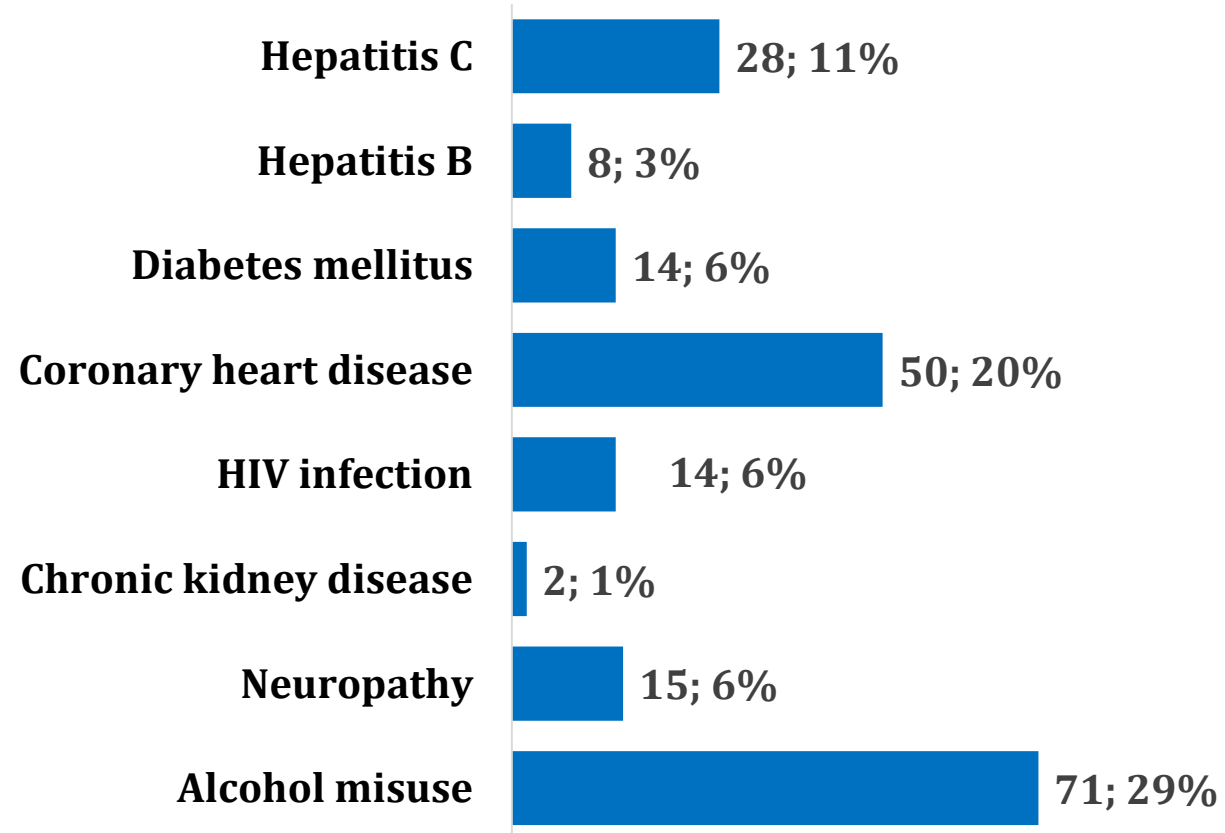
Changes in chest X-ray



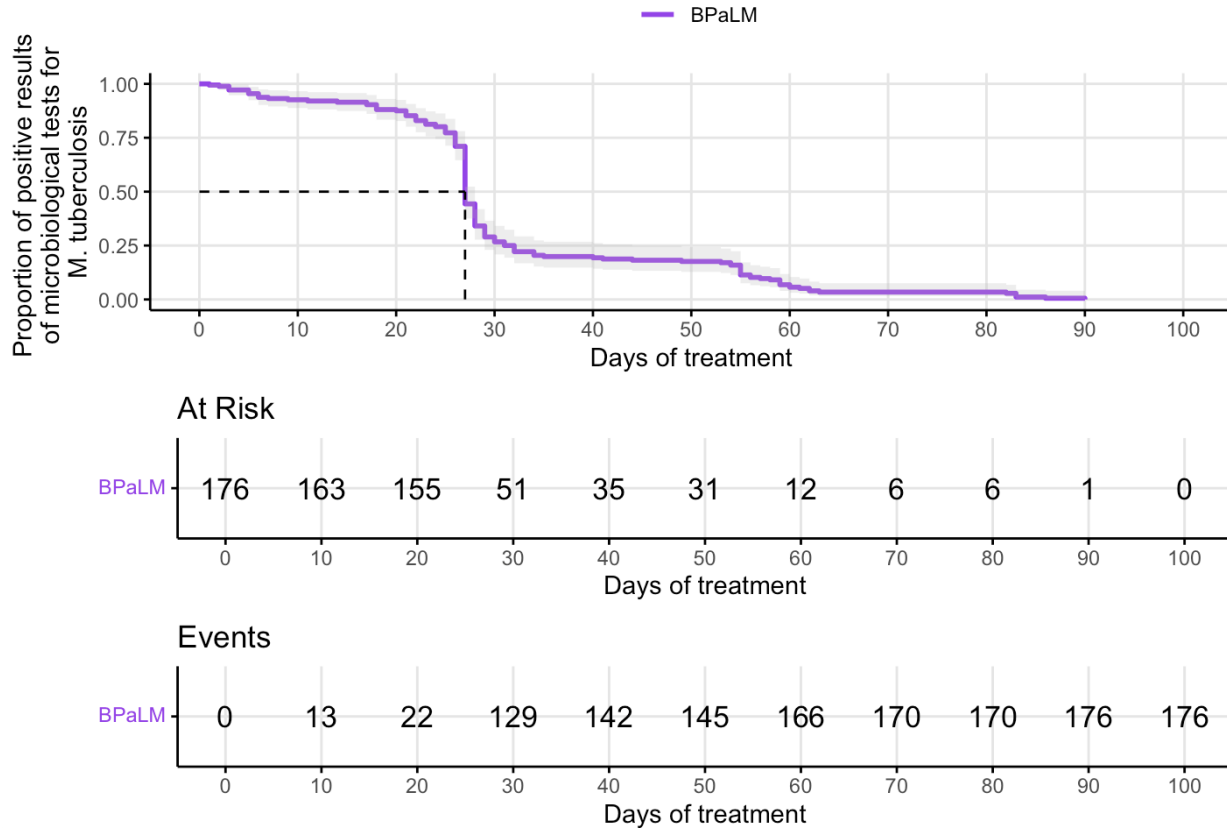
Presence of a cavity



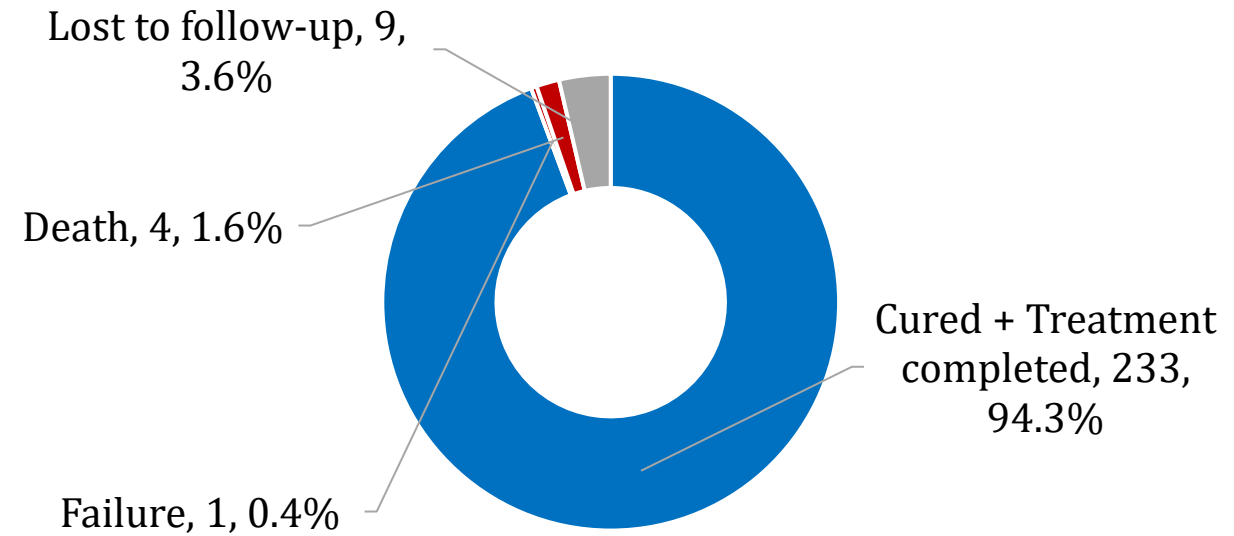
BPaLM, Patient' characteristics, n=247



Results

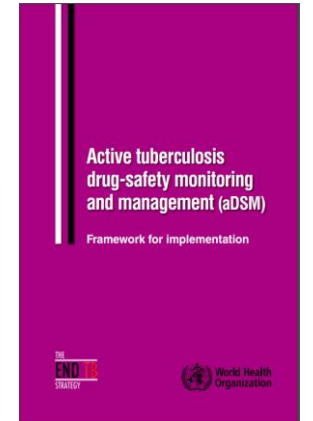
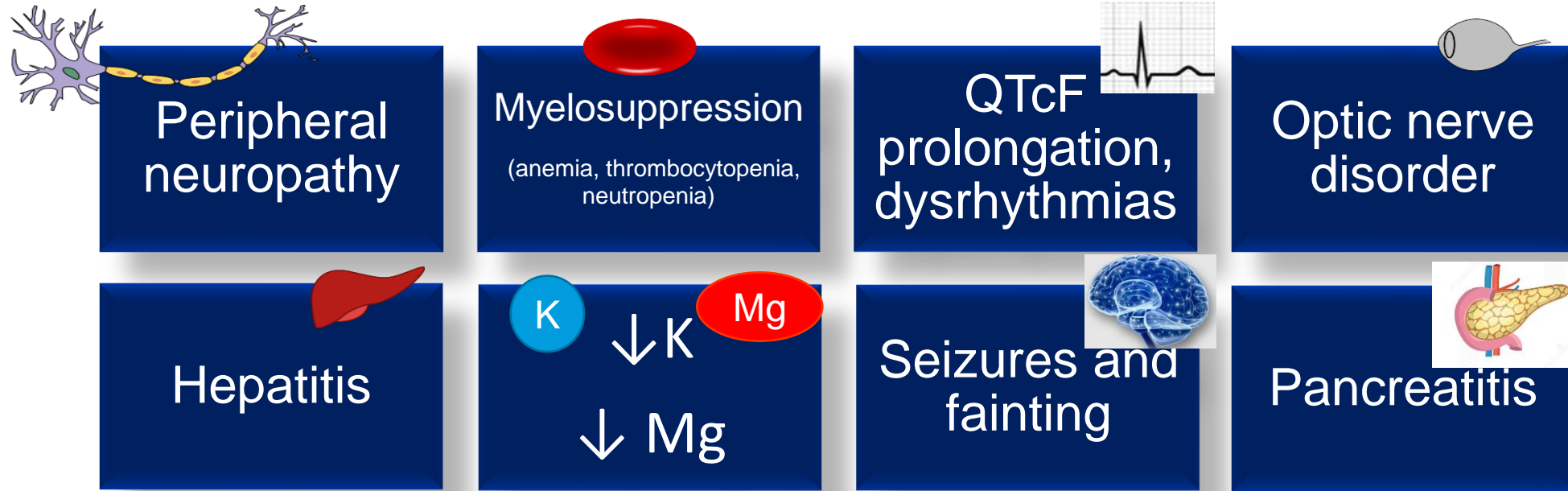


Treatment success – 94.3%



Median (IQR) time to culture conversion was 27 (26-31) days

Active Drug Safety Monitoring and Management (aDSM), BPaLM n=249

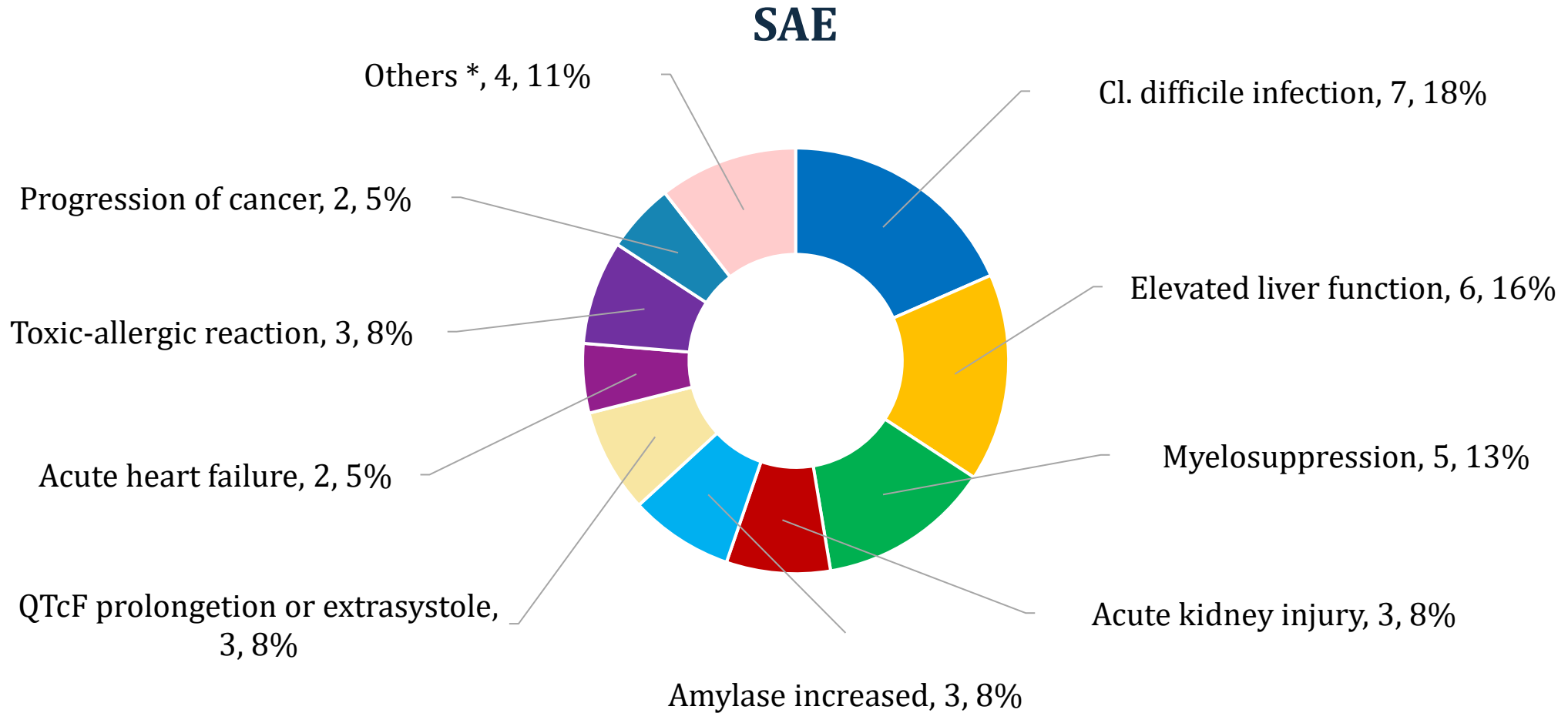


«Intermediate package»:

Serious adverse events - 38 у 29 пациентов

Adverse events of special interest – 3 у 3 пациентов

BPaLM safety profile, n=249

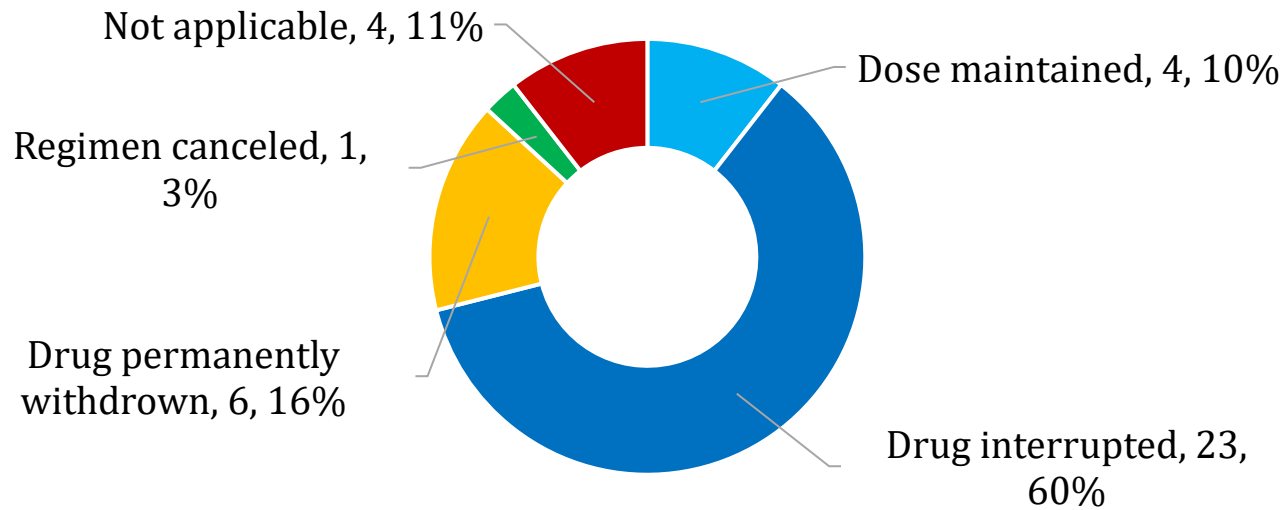


11.6 % of patients had SAEs

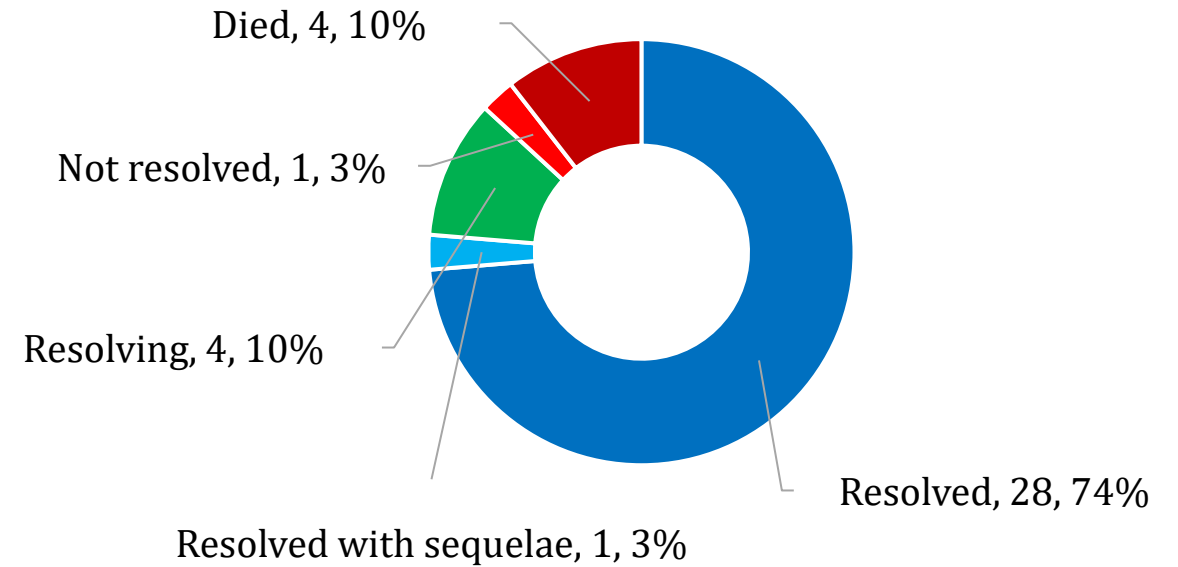
* Others: fracture - 1, intestinal bleeding - 1, intestinal ischemia - 1, intestinal motility disorder - 1

BPaLM safety profile, n=249

Actions to manage SAE

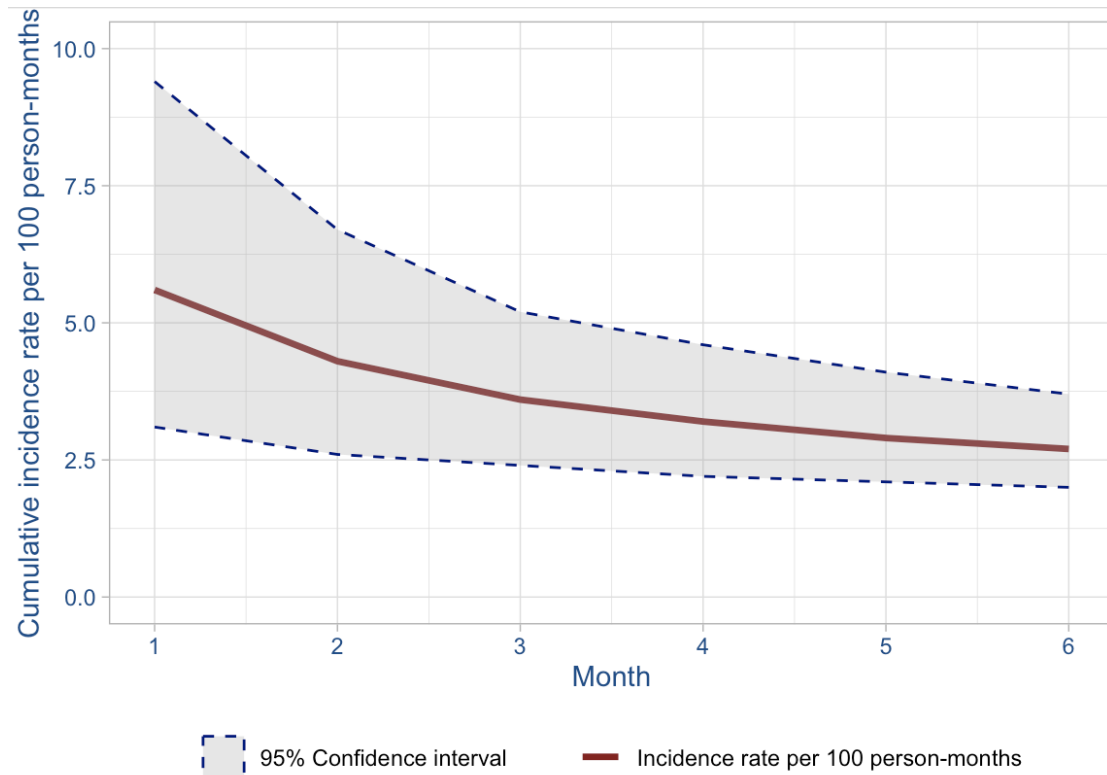


SAE outcomes

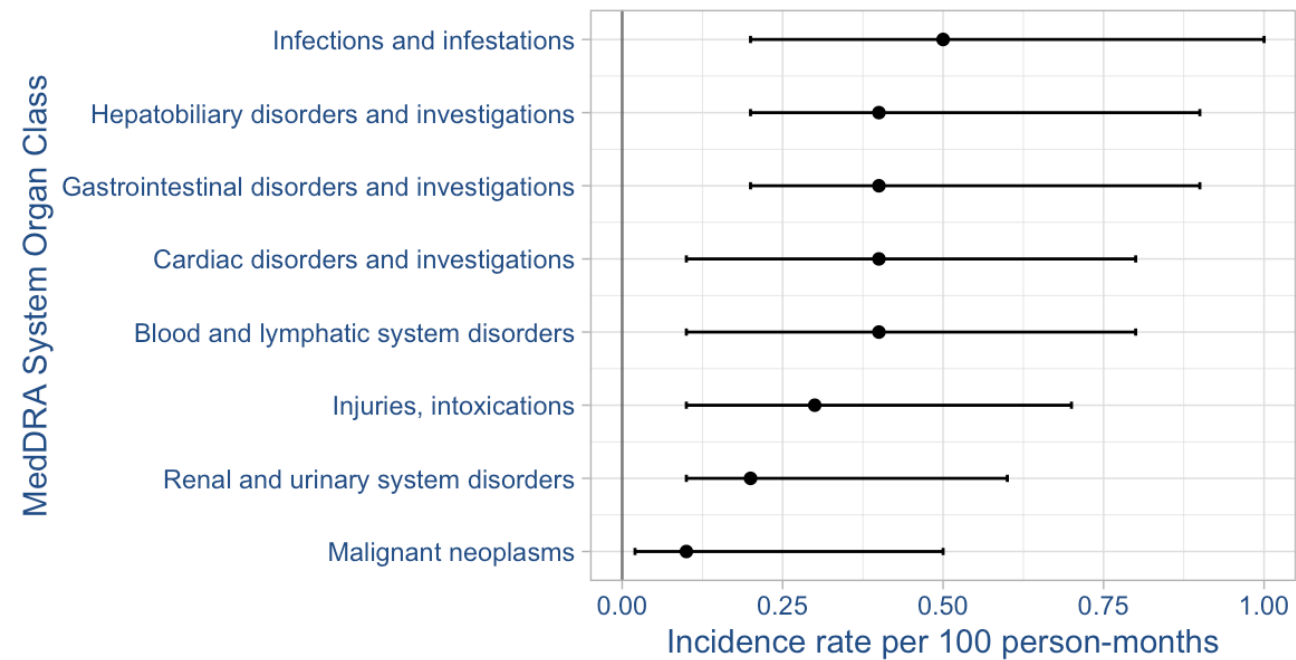


BPaLM safety profile, n=249

Cumulative incidence rate of SAE



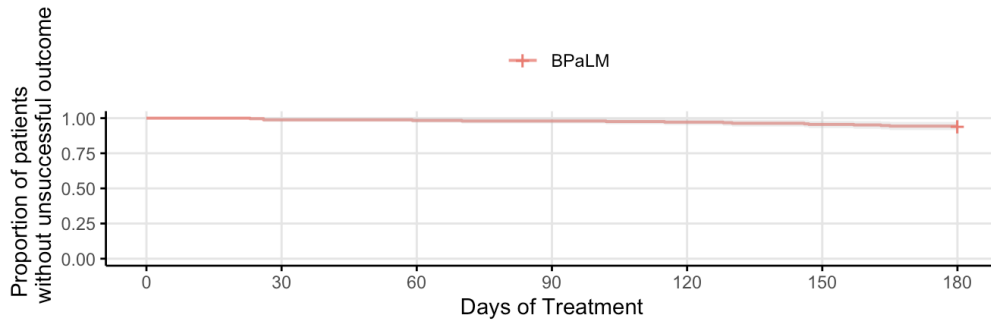
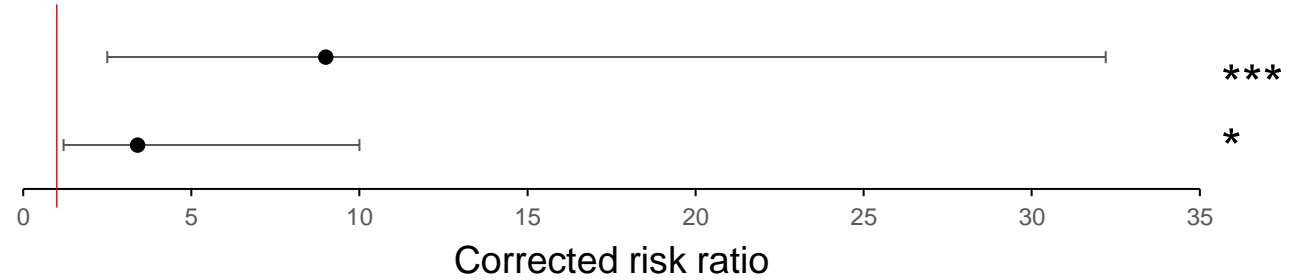
Incidence rate of SAE



Median time to AE occurrence was 75 (26-119) days

Predictors of unfavourable treatment outcomes, BPaLM, n=247

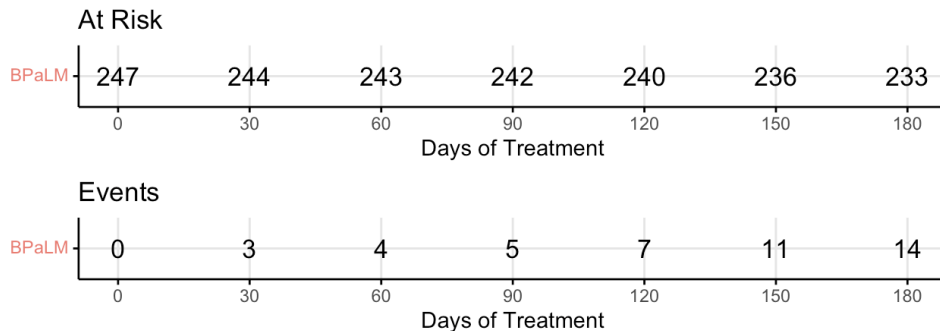
Sputum smear positive result at treatment start
Alcohol misuse



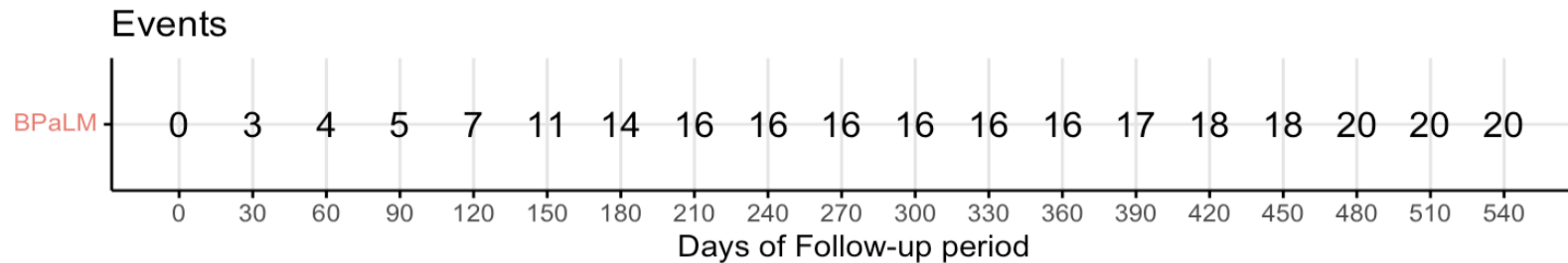
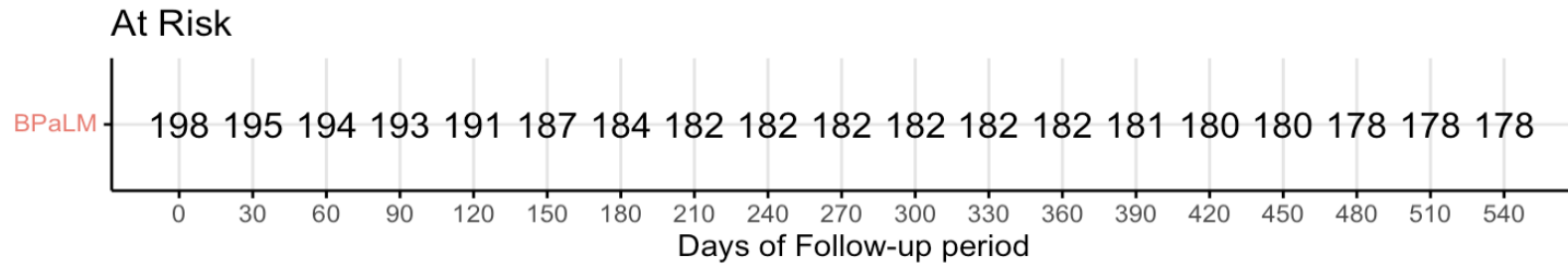
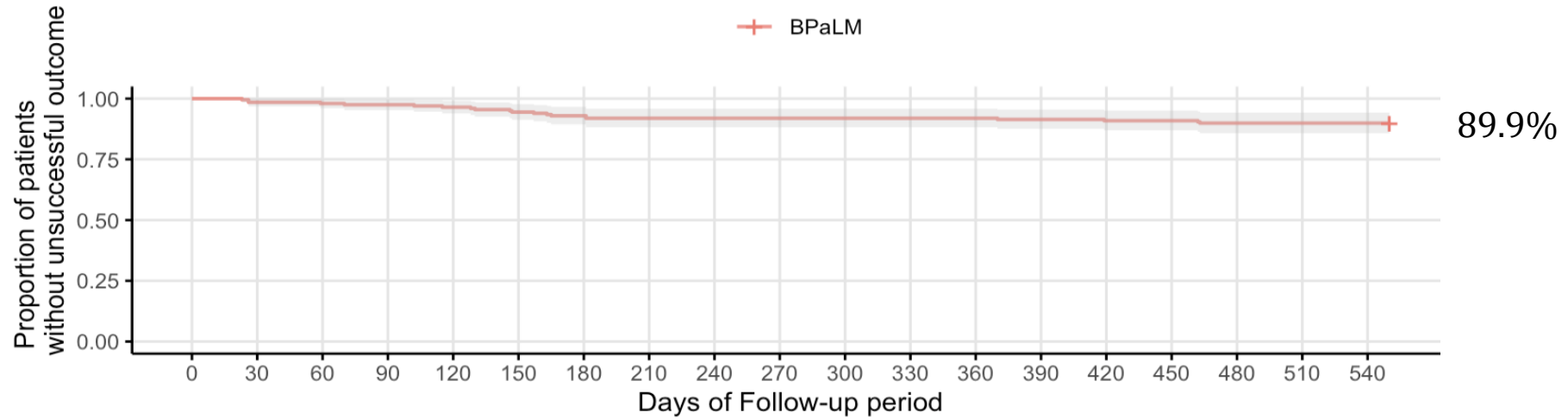
*** - $p = 0,00076$

* - $p = 0,022$

Multivariate regression analysis by Cox proportional Hazards method



Follow-up, BPaLM, n=198



Внедрение ВРaL/М в Беларуси - 2025

ВРaL/М – 80%

МКРЛ *

10%

+BEAT-TB

BDLL/C

Длинные режимы **

10%

* mSTR – 10%: children < 14 years of age, pregnant, lactating women

** Longer regimens - 10%:

- severe extrapulmonary TB (CNS, miliary, bone and joint)
- resistance to Bdq, Lzd, Pa, Lfx, Cfz, Dlm
- treatment failure due to lack of conversion, clinical response, additional resistance
- loss to follow-up
- intolerance to ВРaL or mSTR drugs
- conditions that require a personalized approach

Acknowledgements

- **Thanks to all operational research participants,**
- **Doctors Without Borders (Médecins Sans Frontières (MSF),**
- **WHO regional office for Europe,**
- **Global Fund to Fight AIDS, Tuberculosis and Malaria,**
- **NTP, regional monitors,**
- **Staff of the Republican Scientific and Practical Center for Pulmonology and Tuberculosis, Minsk,**
- **Staff of all TB facilities in Belarus.**