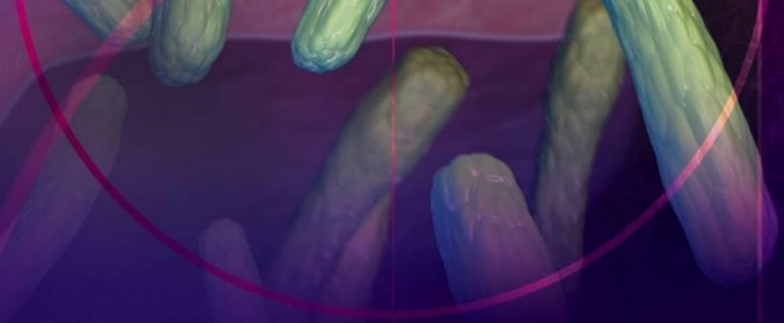
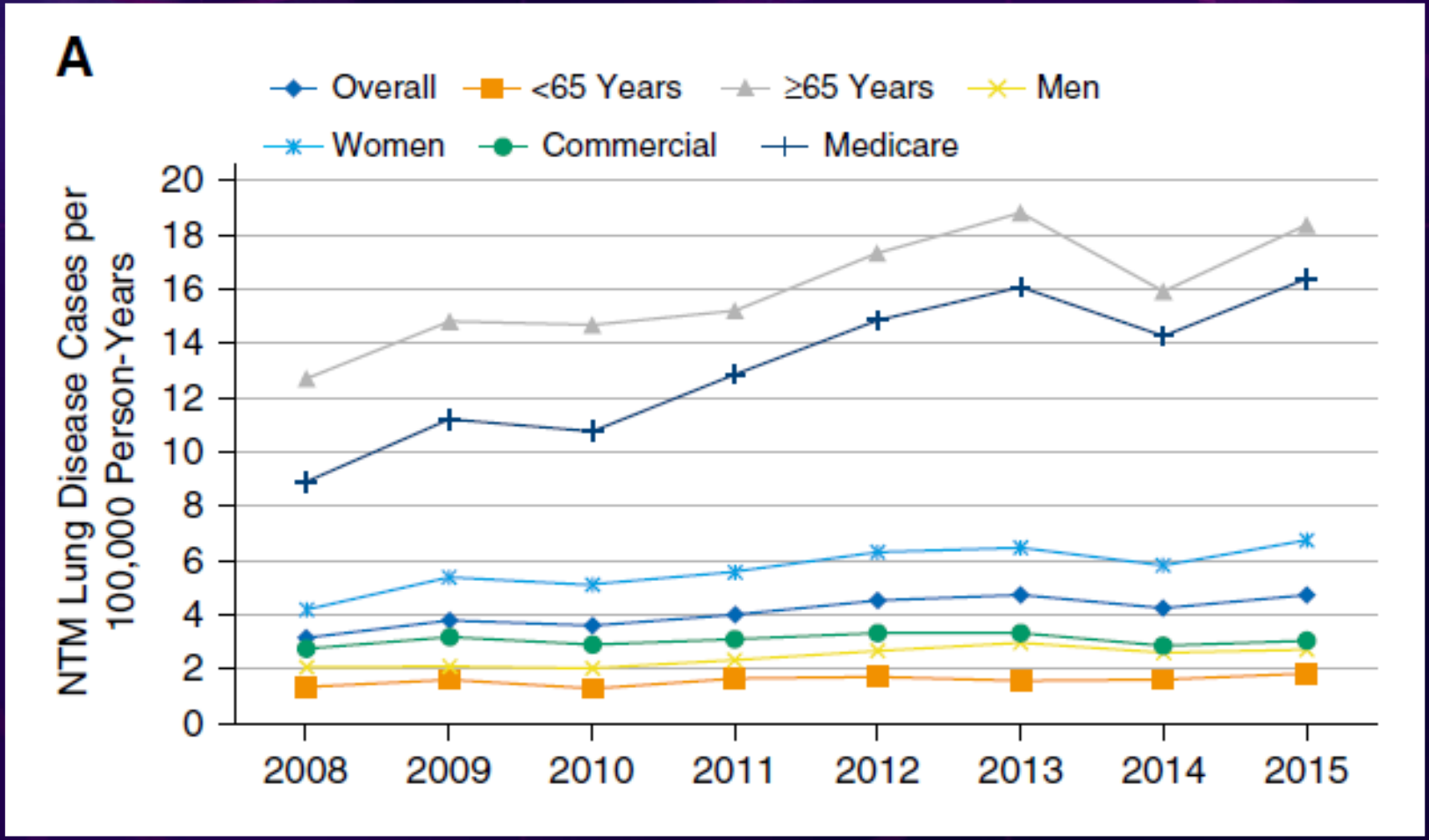


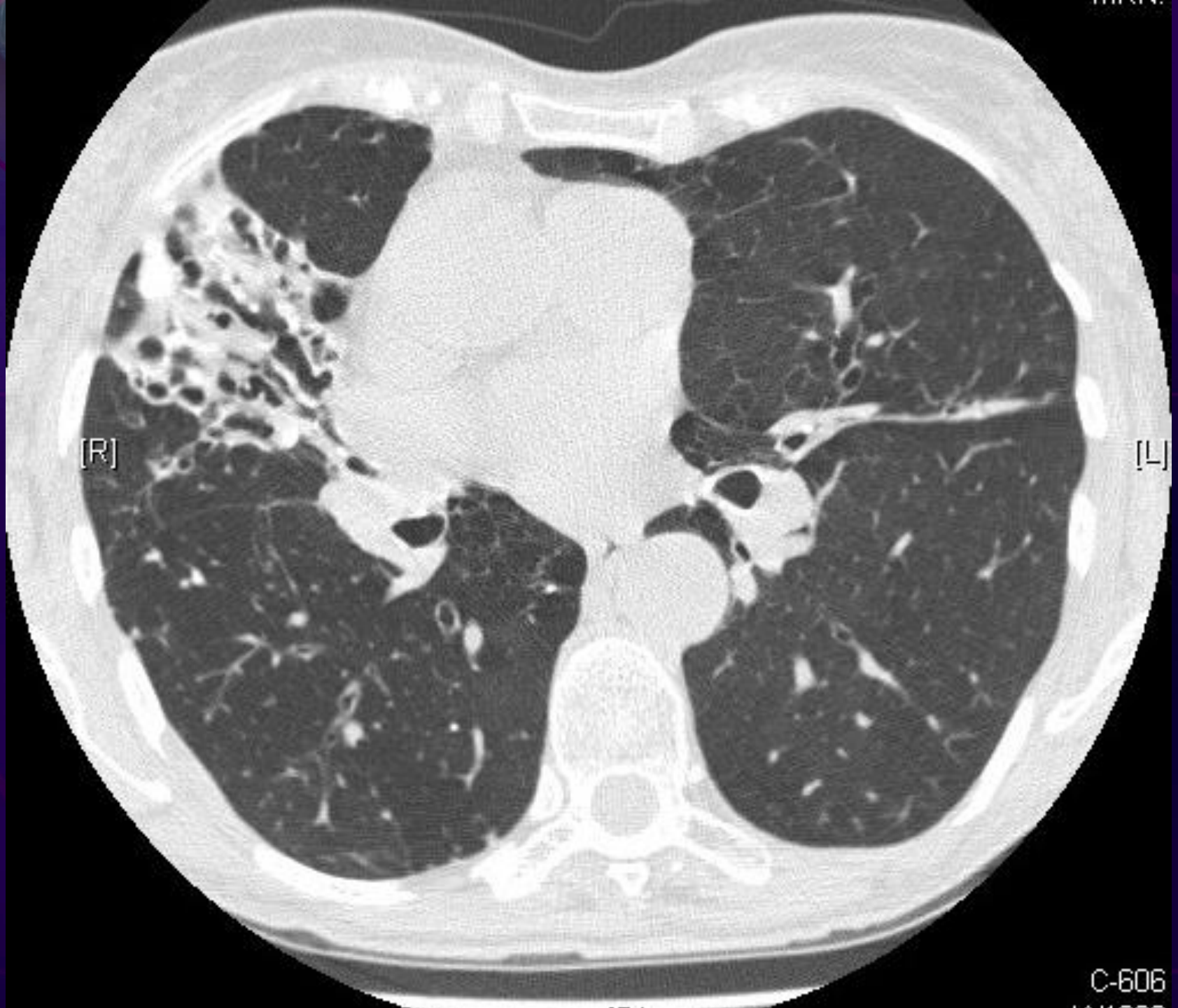
Advances in NTM Pulmonary Disease

Kevin L. Winthrop, MD, MPH
Professor, Divisions of Infectious Diseases, Epidemiology, Ophthalmology
Oregon Health & Science University

US Incidence Increasing



Winthrop KL et al. Ann ATS 2020


[R]
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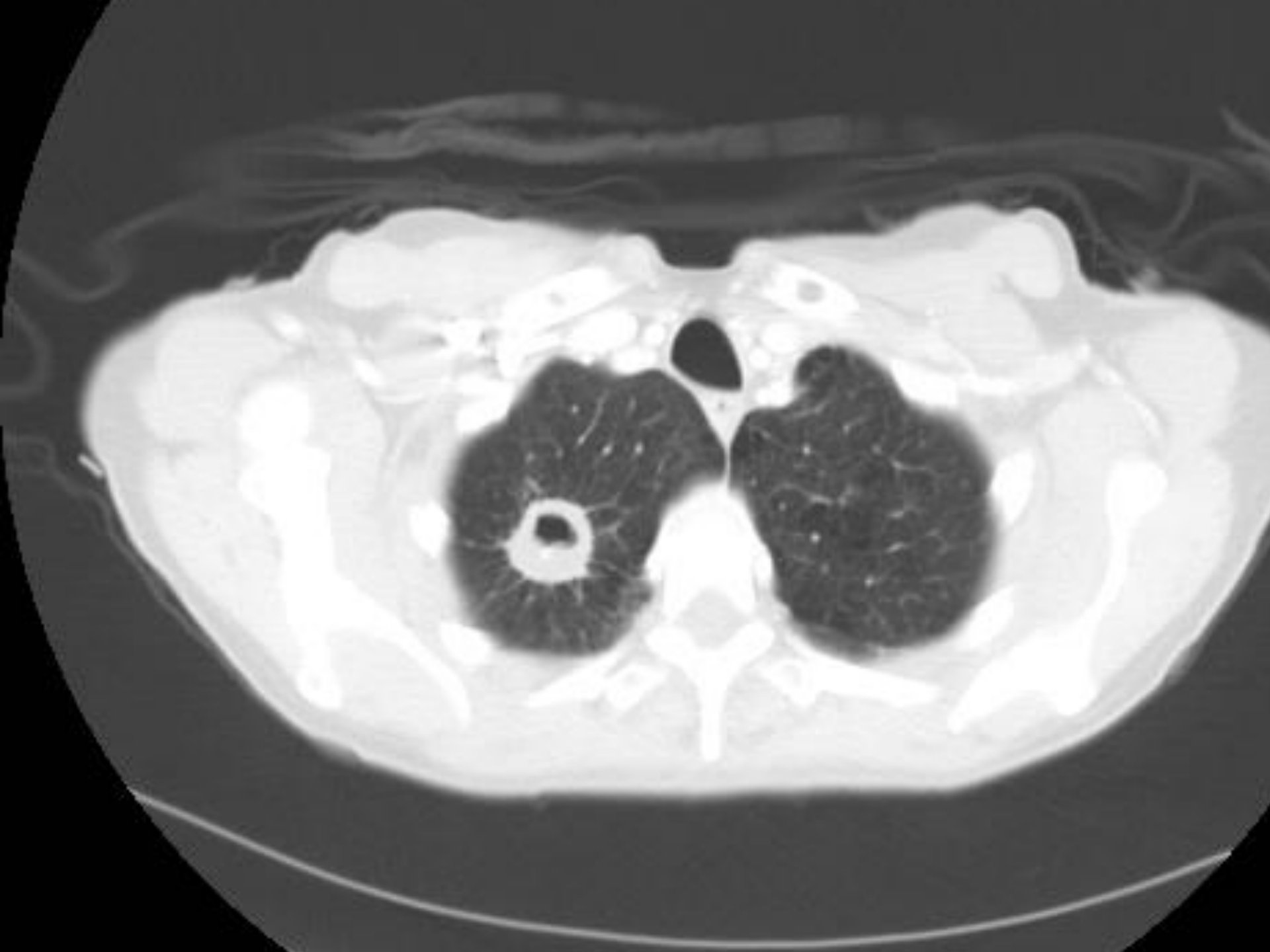
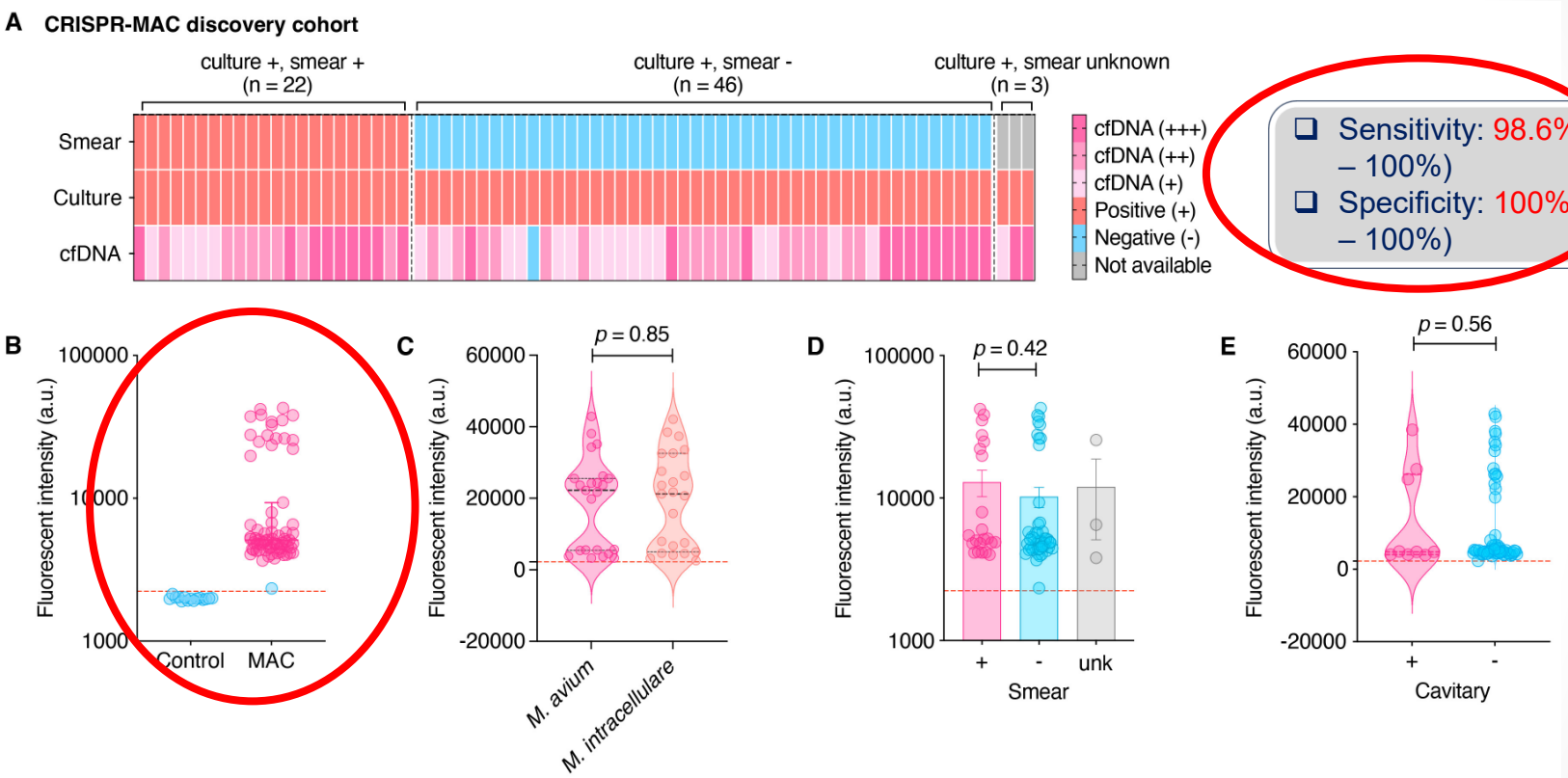


Cell-free DNA Diagnostic

CRISPR-MAC Diagnostic Performance (Discovery cohort)



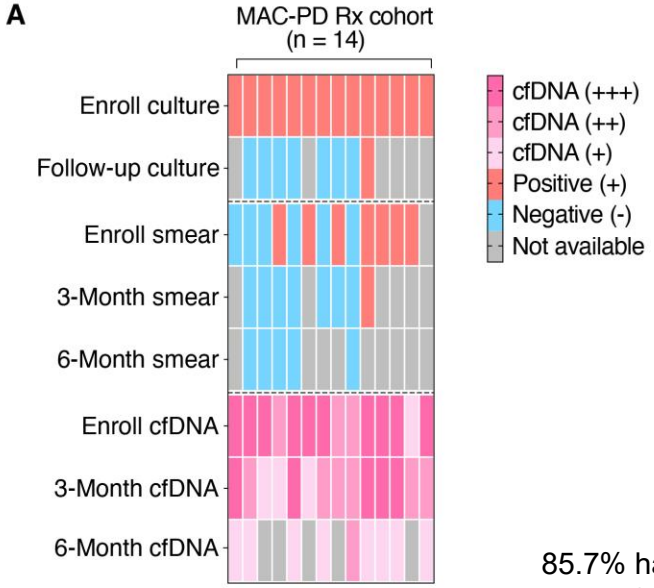
- Sensitivity: 98.6% (95%CI: 92.4 – 100%)
- Specificity: 100% (95%CI: 78.2 – 100%)

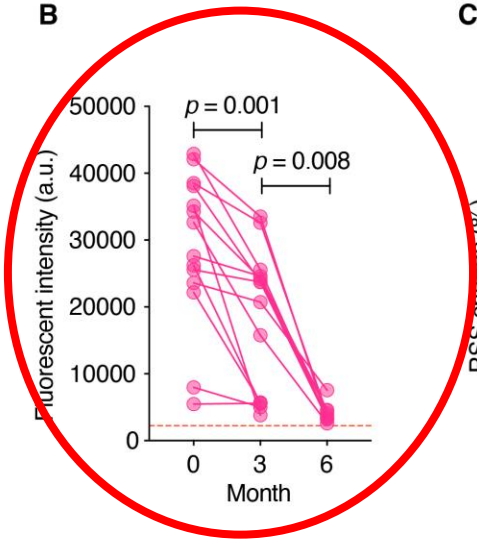
- CRISPR-MAC signal did not significantly differ with *M. avium* and *M. intracellulare* infections and either cavitary disease or smear positivity

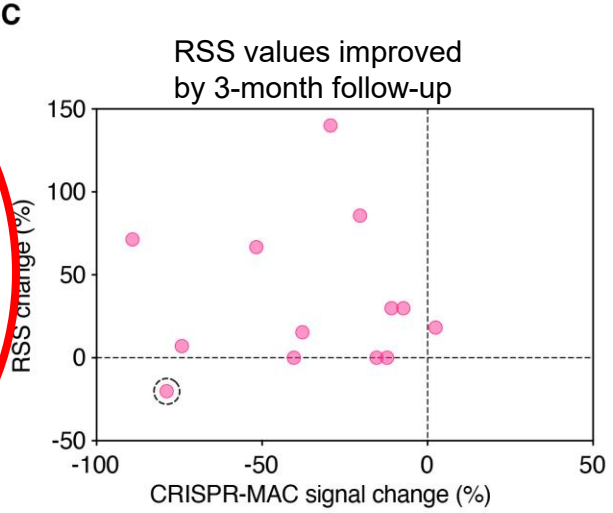
OHSU | Portland State University | SCHOOL OF PUBLIC HEALTH

Ning B et al. AJRCCM 2023

Serum MAC-cfDNA changes following treatment initiation

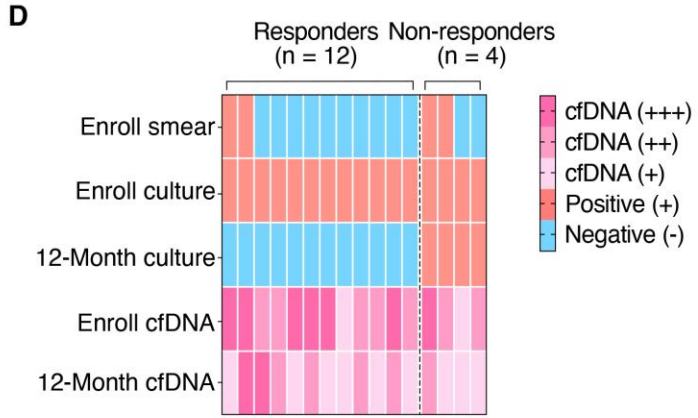


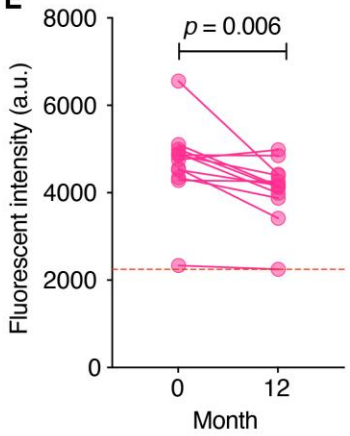


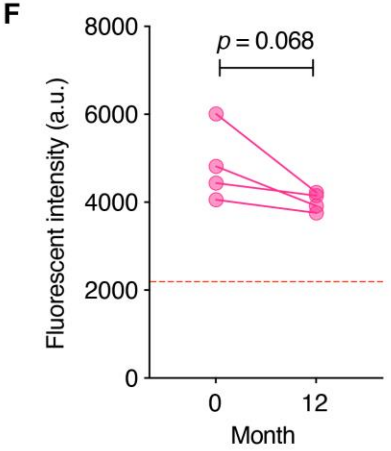


85.7% had significant MAC-cfDNA decreases at 3-month follow-up that further decreased at month 6

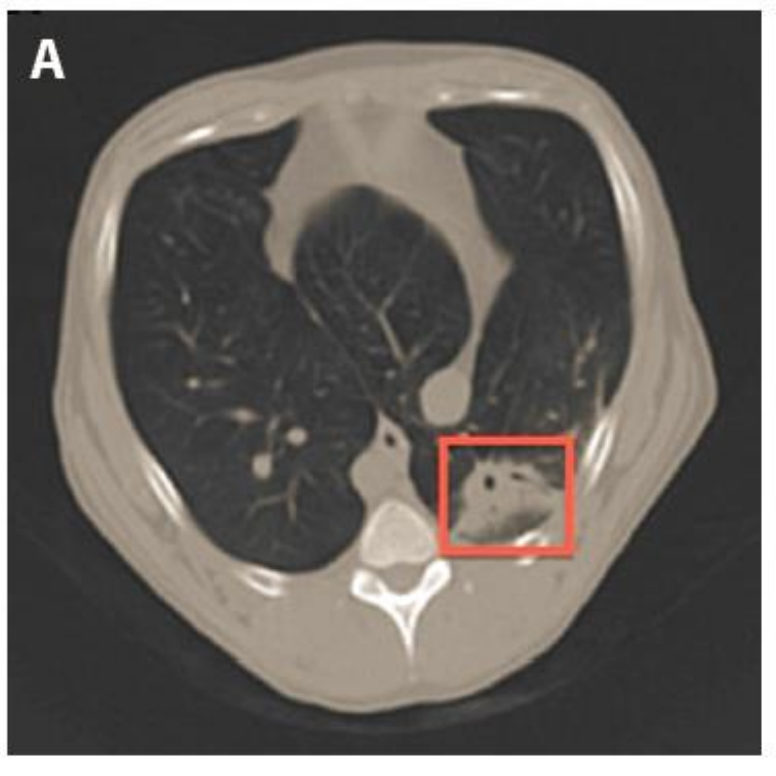
Comparison of MAC-cfDNA between responders and non-responders







Ning B et al. AJRCCM 2023



Macaque Model of Pulmonary MAC

Th1 response suppressed

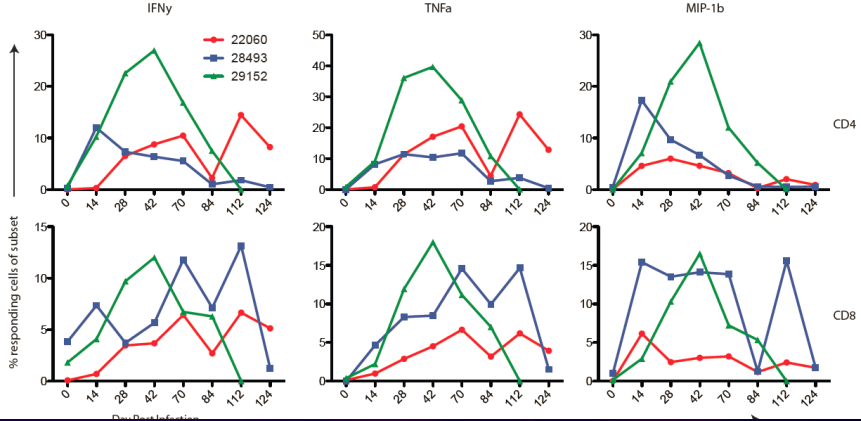
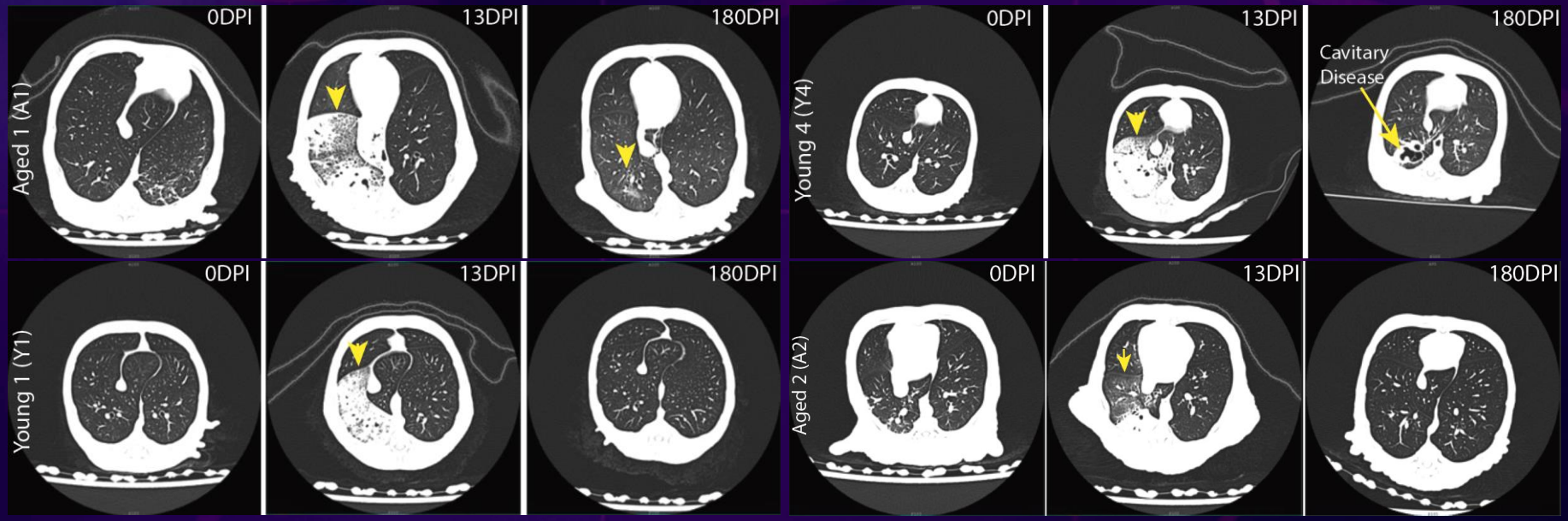
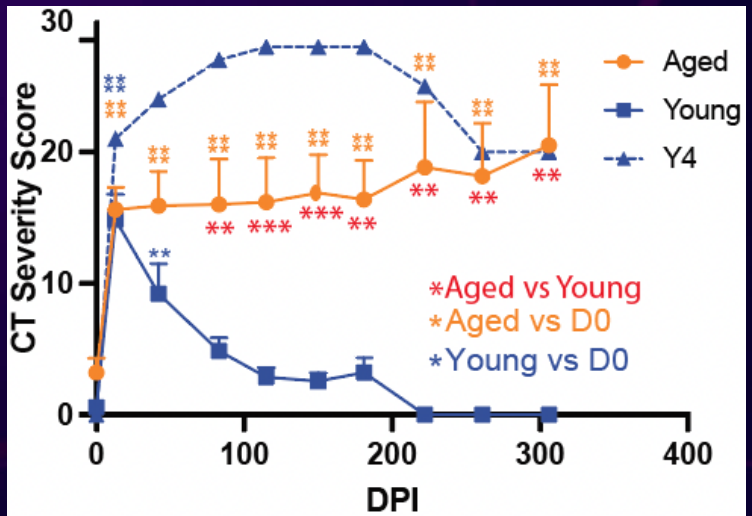


Figure 5. Frequency of *M. avium*-specific T cells. T cell responses were also assessed using intracellular staining. PBMC and BAL cells were stimulated overnight with *M. avium* lysate in the presence of brefeldin A. The cells were stained with surface markers CD4 and CD8, and then permeabilized followed by intracellular staining for IFNy, TNFa, and MIP-1b. PBMC responses were minimal with less than 1% of cells within subsets responding (data not shown). There was an inverse correlation between inoculum dose and size of the T cell response in BAL. Animal 29152 receiving the lowest infection dose showed the highest T cell response overall, whereas 22060 generated the lowest T cell response. CD4 responses were also on average larger than CD8 T cell responses.

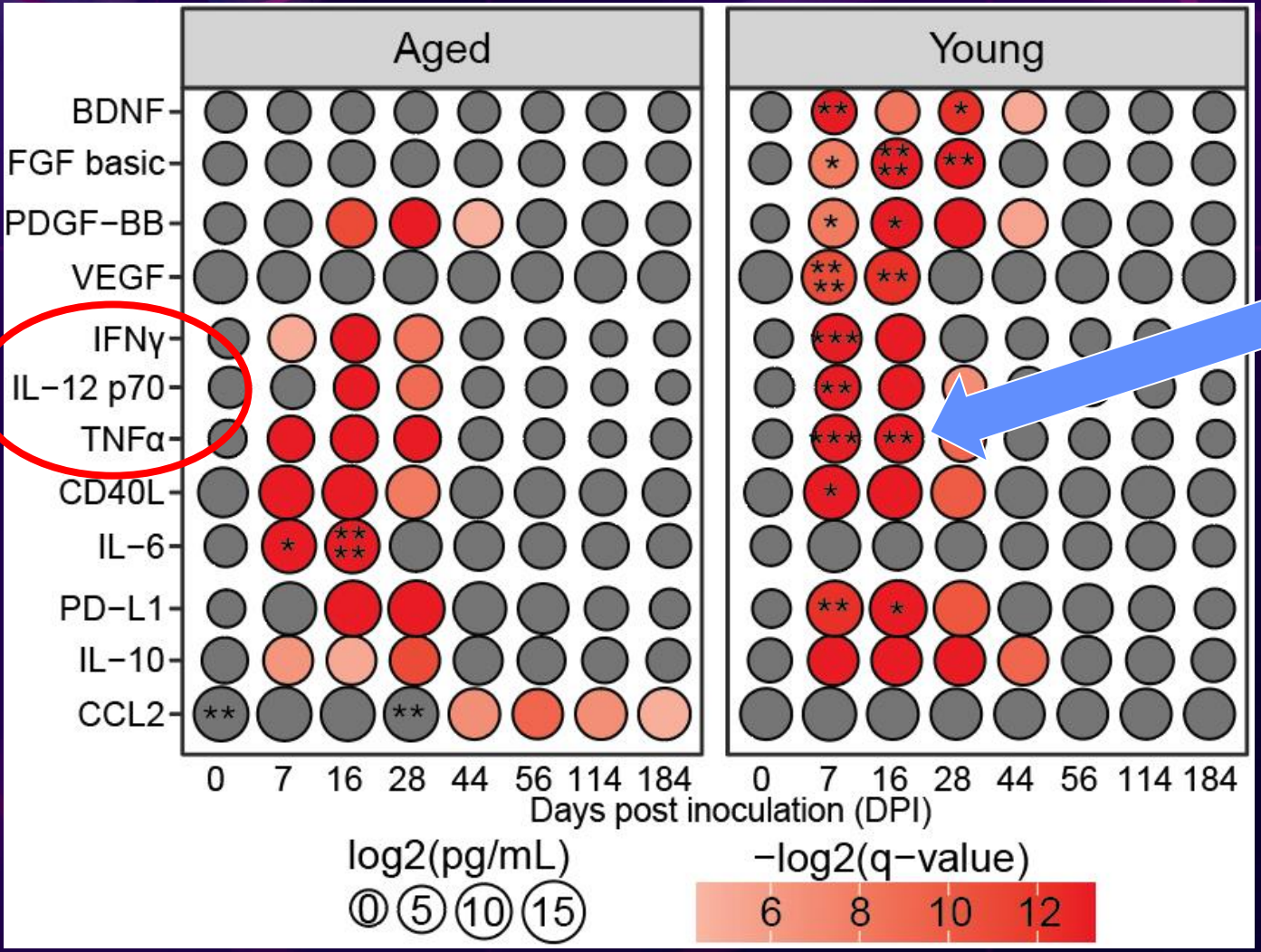
Winthrop KL et al. AJRCCM 2016

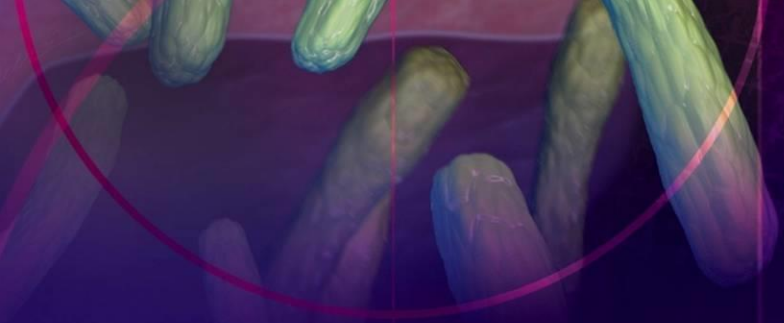
Bronchiectasis and NTM disease radiologically Aged > Young





Delayed Th1 response in Aged Animals





Current Antimicrobial Treatment

Currently Approved Therapies in NTM

- Azithromycin, clarithromycin
  - Disseminated MAC
- Liposomal amikacin
  - Refractory pulmonary MAC

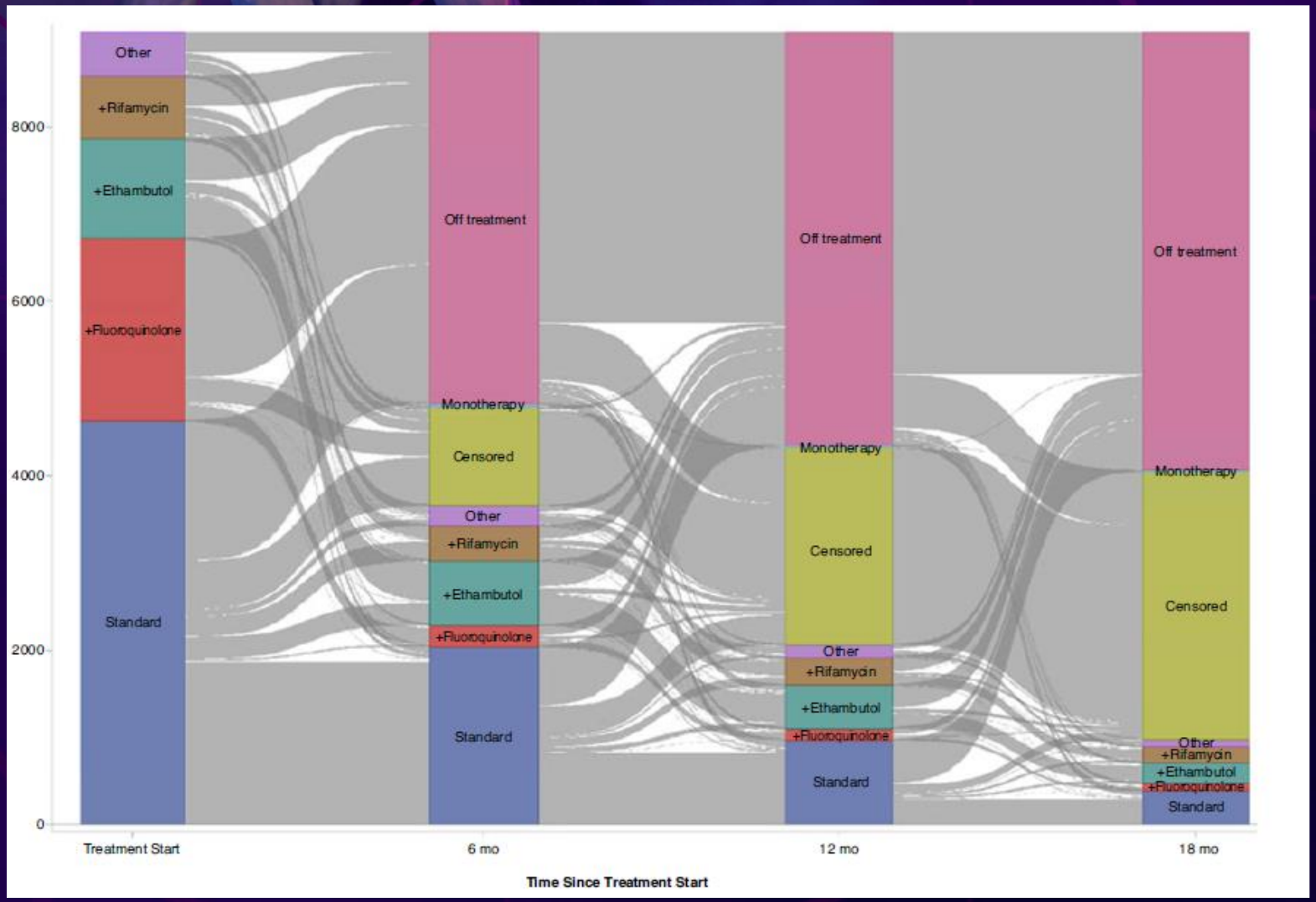
https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/050662s044s050,50698s026s030,050775s015s019lbl.pdf

MAC Therapeutic Options

- **Diagnosis ≠ decision to treat**
  - Observation vs. suppression vs. cure
- Treatment best defined for MAC
  - Macrolide, rifampin, ethambutol
  - Amikacin (parenteral or inhaled PRN)
  - 18-24 months (12 month culture negative)
  - No macrolide monotherapy
  - TIW okay if non-cavitary or not re-infection

Griffith DG, et al. AJRCCM 2007

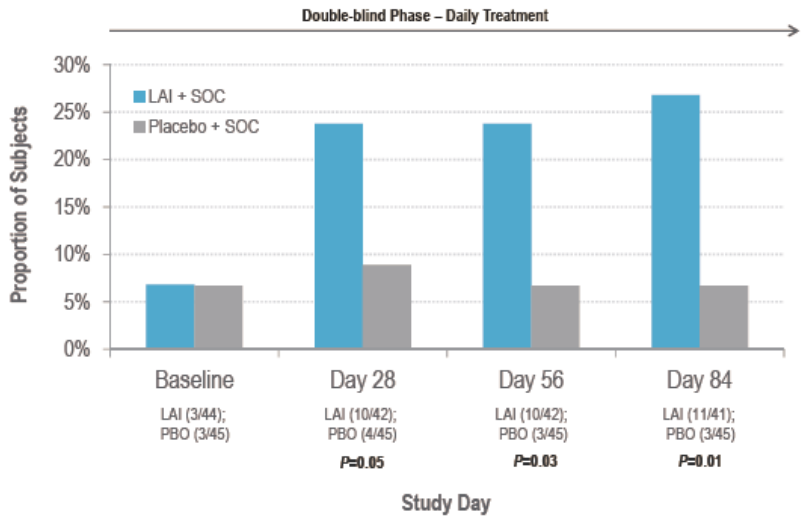
The Success of Guideline-Based Therapy



Ku J et al. CID 2022

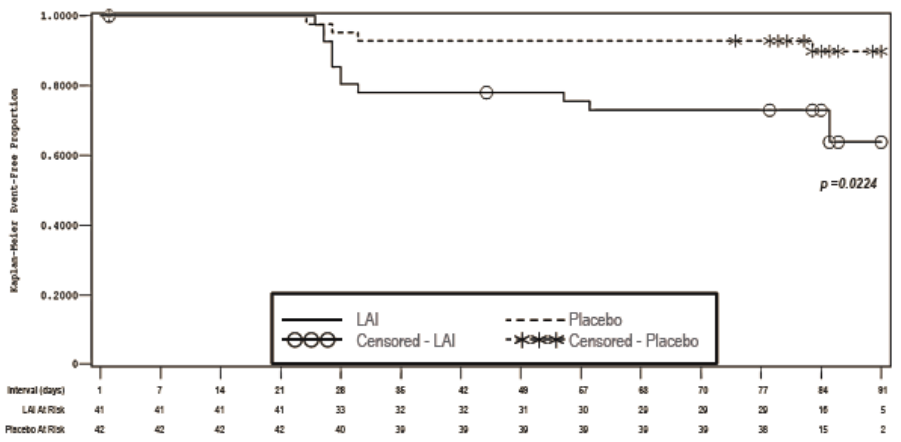
Inhaled Liposomal Amikacin

Proportion of Subjects with NTM Culture Conversion to Negative (mITT Population)



NOTE: Missing Values Excluded
P-value for stratified Cochran-Mantel-Haenszel test of treatment arm adjusting for the randomization strata

Kaplan-Meier Plot of Time from Study Baseline to NTM Culture Negative* (mITT Population)



* Censoring at Date of Last Contact or At Initiation of Open-Label LAI

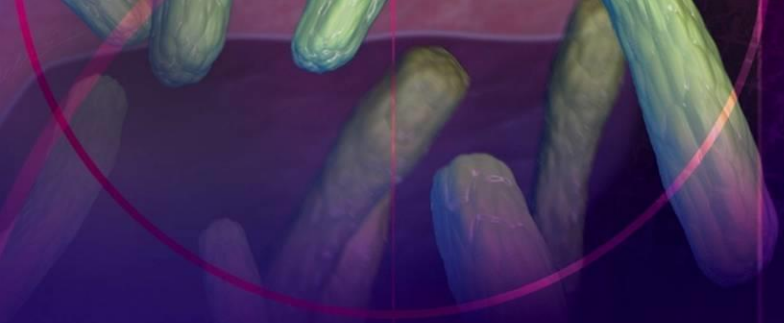
Note: Subjects without event or censoring criteria are censored at study day 91.
Number at risk is the subjects remaining at risk after the corresponding interval day.

Olivier K et al. ATS 2014

M. Abscessus "Options"

- Oral agents
  - Clofazimine 100mg, Omadacycline 300mg, 15% macrolide
- Parenteral agents
  - Omadacycline 100mg daily
  - Amikacin 12mg/kg TIW
  - Imipenam 1000mg BID
  - Tigecycline 50mg daily
  - Cefoxitin 2gm TID
  - Dual beta-lactam approach

Pick 2



Emerging Therapies and Strategies

RCTs for pNTM 2024

- MAC new treatment starts
  - Liposomal amikacin
  - Clofazimine
  - 2 v 3 (AZI/EMB Vs. AZI/EMB/RIF)
  - SPR-720
  - Inhaled 7% saline
- *M. abscessus*
  - *Omadacycline*
- Refractory MAC
  - Epetraborole
  - Inhaled clofazimine
  - Delpazolid (Korea)
  - Bedaquiline (Japan)
- M. xenopi
  - Clari/Rif/EMB vs Moxi/Rif/EMB

https://www.clinicaltrials.gov/

Clofazimine

- MOA?
  - Intracellular redox cycling
  - Disrupts bacterial membrane phospholipids to generate antimicrobial lysophospholipids
  - T cell modulation
- In-vitro and murine models
  - Broad spectrum (except gram negatives)
  - Enhanced mycobacterial killing when added to macrolide and amikacin

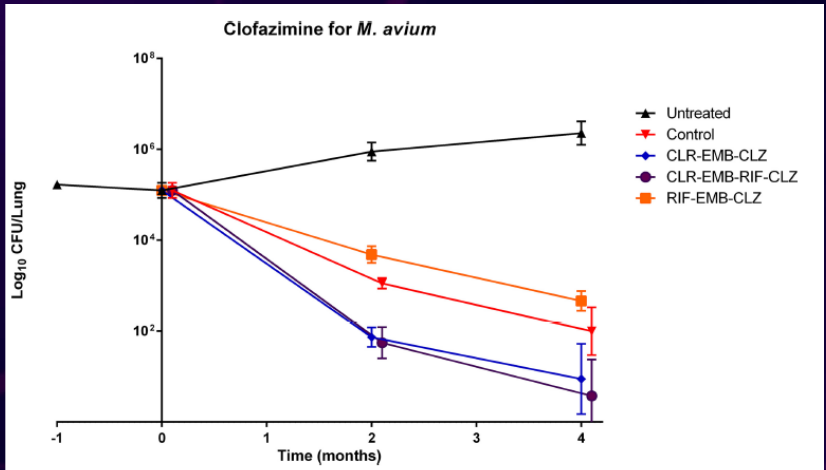
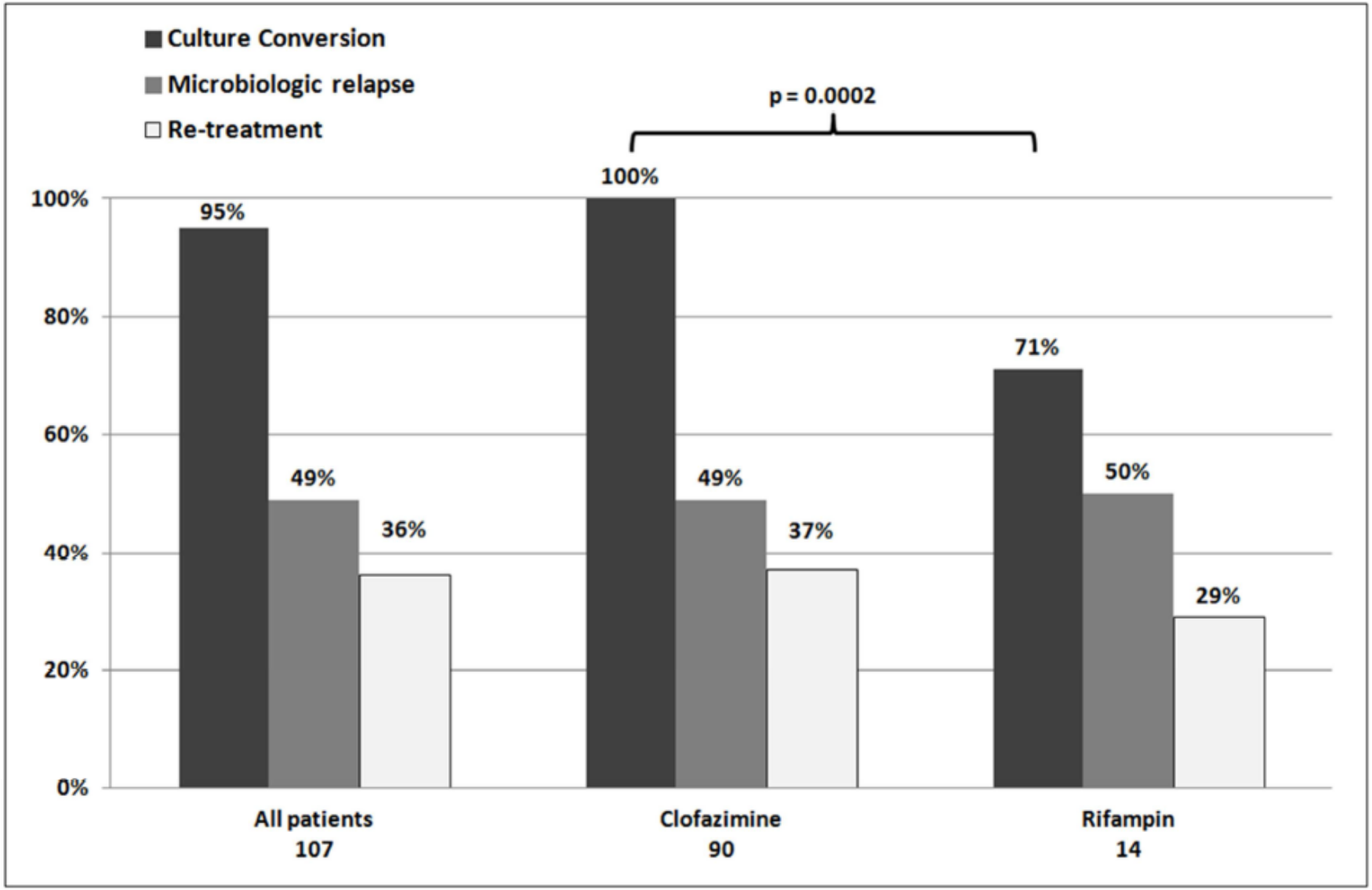


FIG 1 Lung CFU counts in BALB/c mice.

Cholo M et al. J Antimicro Chemo 2017;
Ianoix JP et al J Anti Micro Chemo Agent 2020

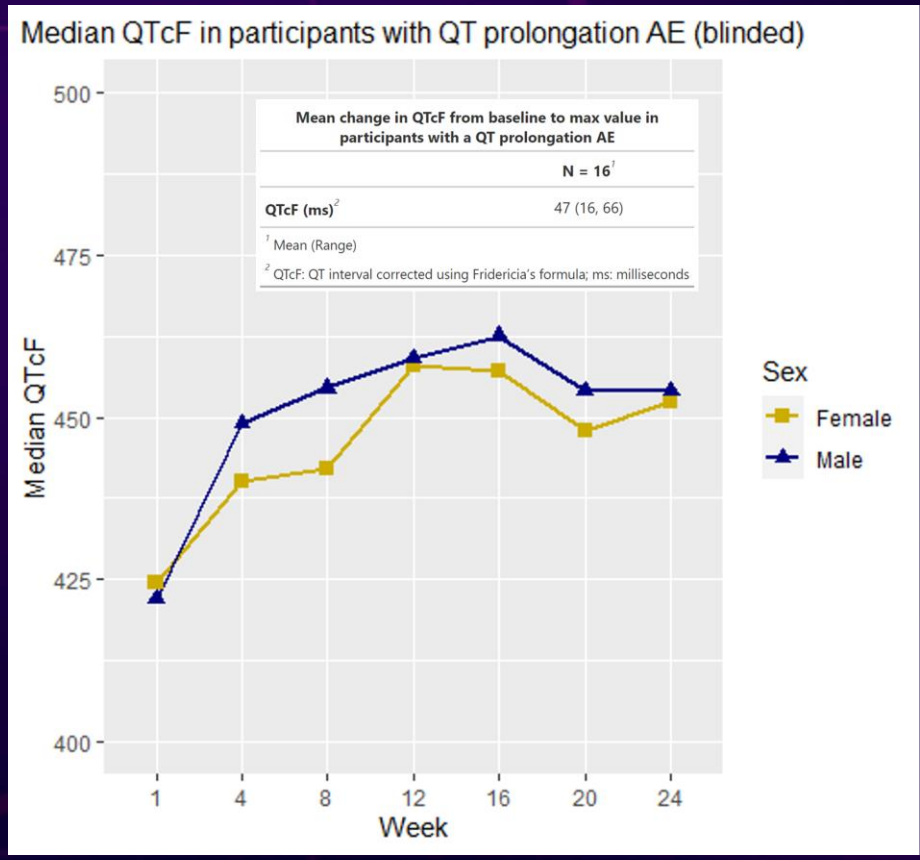
Clofazimine



Jarand J et al. Chest 2015

Clofazimine

- Phase 2 monotherapy trial (n=102)
  - 200mg daily
  - Main AE is skin tan
  - QT monitoring
- Inhaled Clofazimine trial (in refractory MAC)
  - Phase 2/3 MNKD-101



Hawkins J et al. ATS 2024 abstract

SPR-720 (Spero)

- Aminobenzimidazole
  - Targets ATPase subunits of gyrase and topoisomerase
- In-vitro with activity against MAC, M. abscessus, other mycobacteria (they all have DNA gyrase)
- Phase 2 dose-finding, monotherapy trial
  - MAC (treatment naïve)

Brown-Elliott BA et al Antimicrob Agents Chemother 2018

SPR-720 Results

Q3 2024 ending cash balance of $76.5M

CAMBRIDGE, Mass., Oct. 29, 2024 (GLOBE NEWSWIRE) -- Spero Therapeutics, Inc. (Nasdaq: SPRO), a multi-asset clinical-stage biopharmaceutical company, focused on identifying and developing novel treatments for rare diseases and multi-drug resistant (MDR) bacterial infections, today announced that a planned interim analysis of the Phase 2a proof-of-concept study of SPR720 for the treatment of NTM-PD demonstrated that the program did not meet its primary endpoint. While the data showed antimicrobial activity associated with SPR720, the interim analysis did not show sufficient separation from placebo and highlighted potential dose limiting safety issues in subjects dosed at 1,000 mg orally once daily, including three cases of reversible grade 3 hepatotoxicity. In evaluating the totality of both the efficacy and safety data, the Company has elected to suspend its current development program for SPR720 and will evaluate other potential paths forward as the remaining data are collected and analyzed.

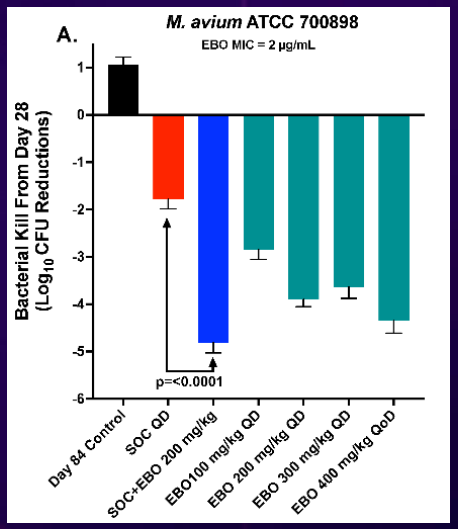
As a result of the suspension of the current SPR720 development program, Spero will undergo a restructuring and

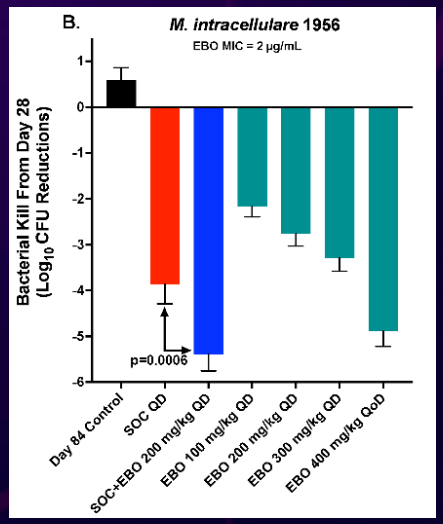
Dose-dependent hepatotoxicity

https://s3.amazonaws.com/b2icontent.irpass.cc/2748/rl139704.pdf

Epetraborole (AN2)

- Inhibits bacterial leucyl-tRNA synthetase
  - Active against variety of gram negatives
  - Low MICs to M. avium, M. abscessus
  - Pre-clinical (mouse) data suggests killing > macrolide





CFU = Colony-forming units; MAC = *Mycobacterium avium* complex; MIC = Minimum inhibitory concentration; SOC = Standard-of-care (clarithromycin, ethambutol, and rifabutin). [1] DeStefano, MS, et al. IDWeek 2022 Poster. [2] De K, et al. IDWeek 2022 Poster.

EBO Refractory MAC Failure

Phase 2/3 trail for refractory MAC with EBO added to background therapy

First oncology compound(s) from boron chemistry platform on track to advance into development in 2H25; targets best-in-class profiles with fully owned IP; novel oncology compounds target ENPP1, PI3Kα and other undisclosed targets for solid tumor indications

Company extends cash runway into 2028, implements strategic measures to optimize operations and enhance shareholder value

MENLO PARK, Calif.--(BUSINESS WIRE)--May 1, 2025-- AN2 Therapeutics, Inc. (Nasdaq: ANTX), a biopharmaceutical company focused on discovering and developing novel small molecule therapeutics derived from its boron chemistry platform, today announced topline results from the Phase 3 portion of the EBO-301 study evaluating epetraborole on top of an optimized background regimen (EBO+OBR) in treatment-refractory MAC lung disease.

The truncated Phase 3 portion of the study did not meet its primary endpoint on improvement of Quality of Life – Bronchiectasis (QOL-B) respiratory domain patient reported outcome instrument (change from baseline to month 6). The study population included patients with severe, advanced MAC lung disease with a long duration of disease, high rates of cavitary/fibrocavitary disease, and multidrug resistance to standard of care antibiotics at baseline.

Patients with long disease duration, big cavities, lots of macrolide and amikacin resistance

https://investor.an2therapeutics.com/node/8116/pdf

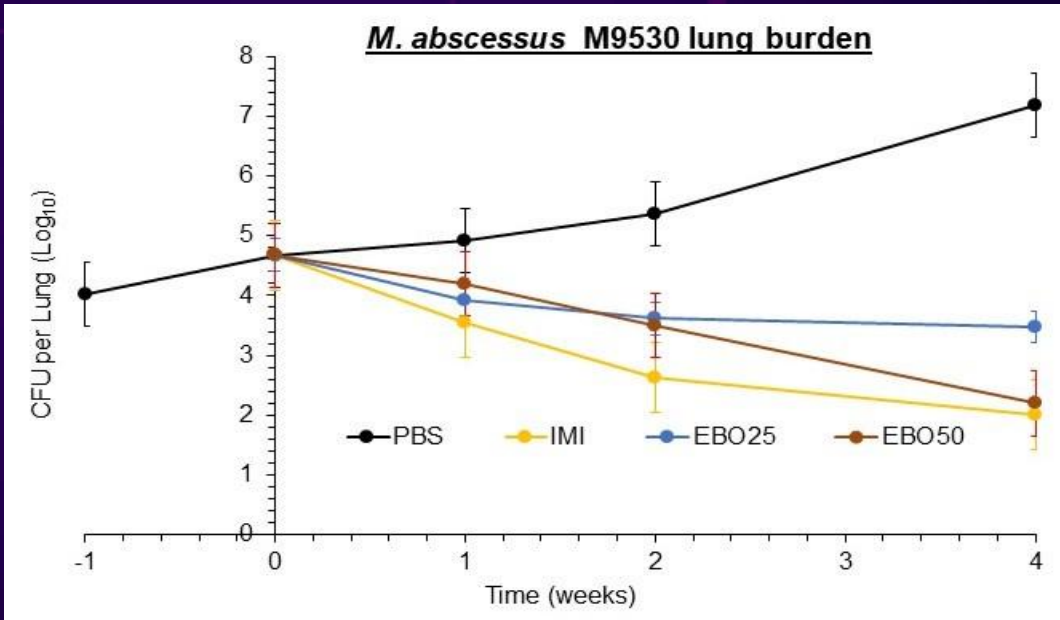
Epetraborole

In Vitro & In Vivo Activity vs. M. abscessus (Mab)

- **147 respiratory Mab isolates from U.S. & Europe**
  - MIC range 0.03–0.25 µg/ml; MIC_{90} = 0.12 µg/ml
  - Macrolide resistance, amikacin resistance, and morphology did not impact EBO activity

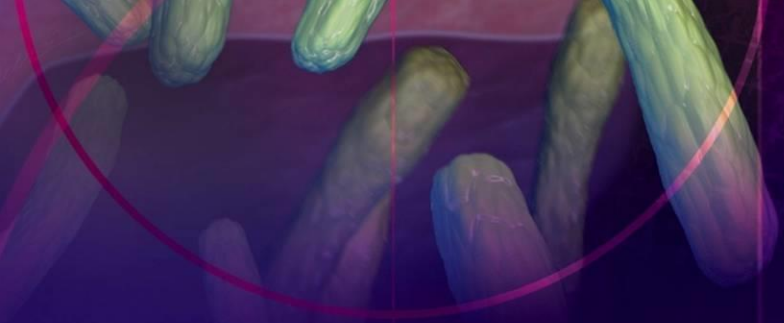
Antimicrobial	MIC (µg/mL)		
	MIC range	MIC50	MIC90
Epetraborole	0.03 - 0.25	0.06	0.125
Clarithromycin	≤0.25 - >32	>32	>32
Amikacin	4 - 64	16	64
Imipenem	≤1 - >32	8	32
Linezolid	≤0.5 - >16	16	>16
Moxifloxacin	≤0.5 - >4	4	>4
Cefoxitin	4 -128	32	64
Doxycycline	0.25 - >4	>4	>4
Tobramycin	4 - >8	>8	>8
Clofazimine	≤0.25 - 1	0.5	1
Minocycline	≤0.125 - >8	>8	>8
Tigecycline	0.25 -1	0.25	1
Rifabutin	0.5 - >4	>4	>4
Ethambutol	8 - >32	>32	>32

- **Similar to imipenem in a chronic model of Mab lung disease**



Unpublished data from Gyanu Lamichhane's Lab at Johns Hopkins University.
PBS = Phosphate-buffered saline (negative control); IMI = Imipenem 100 mg/kg SC BID; EBO25 = Epetraborole 25 mg/kg PO QD; EBO50 = Epetraborole 50 mg/kg PO QD.

CFU = Colony-forming units; Mab = *Mycobacterium abscessus*; MIC = Minimum inhibitory concentration.



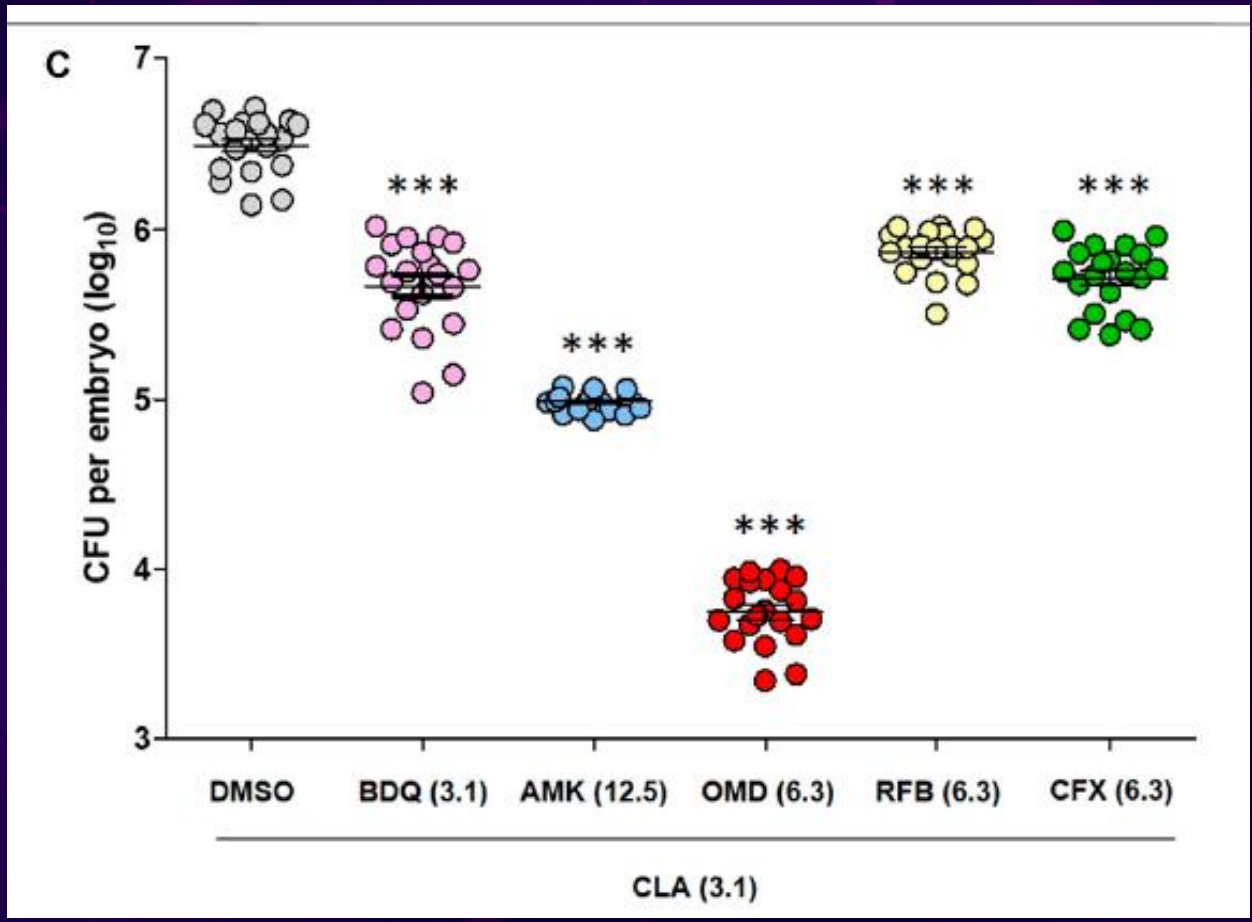
EBO *M. abscessus* Trial?

Omadacycline (Paratek)

Aminomethylcycline (tetracycline derivative)

Inhibits protein synthesis (30S Ribosomal binding)

Low MICs for M. abscessus



Zebrafish with M. abscessus

Bich Hanh BT et al. Front Pharm 2021; Nicklas DA et al Antimicro Chem 2022

Omadacycline

One Center's Experience with Omadacycline for the Treatment of *Mycobacterium Abscessus* Infections

MUSC Medical University of South Carolina

Christina M Mingora MD, Wendy Bullington PharmD, Susan E Dorman MD, Patrick A Flume MD

Medical University of South Carolina, Charleston, SC

RATIONALE

- *Mycobacterium abscessus* complex organisms are difficult to treat human pathogens that cause pulmonary and systemic disease
- Unfortunately, oral treat options are limited
- Omadacycline, an oral tetracycline analog, has been shown to demonstrate in vitro activity against *M. abscessus*
- This study sought to report efficacy, safety, and tolerability of this drug in the treatment of *M. abscessus* infections at our center

METHODS

- Retrospective chart review of all adult patients in our non-tuberculous mycobacterial disease clinic were screened
- Patients with confirmed diagnosis of *M. abscessus* infection and prescription of Omadacycline as part of directed antimicrobial regimen through December 31, 2021 were included (n = 36)
- Demographic data, relevant medical history, NTM history, and radiographic and microbiologic data (including organism subspecies and drug susceptibility testing to key antimicrobials) were recorded at time of Omadacycline initiation (baseline)
- Therapeutic drug monitoring parameters were recorded and baseline and monthly thereafter
- Descriptive statistics were performed

RESULTS

Table 1. Baseline Demographics at time of Omadacycline Initiation

Age (years), mean ± SD	61.4 ± 15.9
Sex: Female, n (%)	23 (64%)
Race, n (%) • White/Caucasian • African American • Non-white Hispanic	 31 (86%) 4 (11%) 1 (3%)
Insurance Coverage, n (%) • Private • Medicare • Medicaid	
Body Mass Index (kg/m²)	22.8 ± 5.7
Pertinent Medical History at Time of NTM Diagnosis	
Pulmonary Disease, n (%)	21 (58%)
Other Key Diagnoses • Chronic Kidney Disease, n (%) • Connective Tissue Disease, n (%) • Immune Deficiency, n (%) • Transplant Recipient, n (%)	 7 (19%) 5 (14%) 2 (6%) 6 (17%)

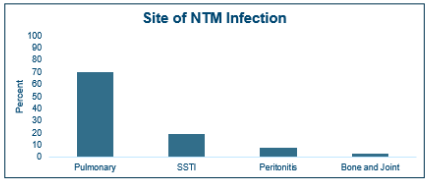


Figure X. Distribution of site of *M. abscessus* infection

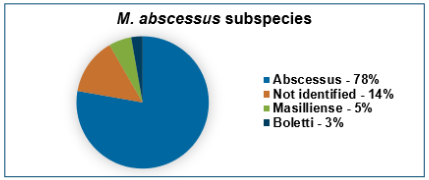


Figure X. Distribution of *M. abscessus subspecies*

Table X. Adverse Events

Any Adverse Event During Treatment Period, n (%)	15 (42%)
Adverse Events Attributed to Omadacycline	• Gastrointestinal Issue: Nausea, vomiting, diarrhea, esophagitis • Abnormal hepatic function: Transaminitis, hyperbilirubinemia • Anemia • Eosinophilia • Rash
Action Taken Related to Adverse Event	
Omadacycline Drug Cessation	8 (22%)
Prescription of Other Therapies to Mitigate AE	6 (17%)

Table X. Omadacycline History (All patients received dose 300 mg by mouth daily)

Duration of Treatment (months), mean ± SD	6.08 ± 5.29
Rationale for Use • Initial Therapy, n (%) • Transition from IV Tigecycline, n (%) • Treatment Refractory Disease, n (%) • Intolerance to Other NTM Therapy, n (%)	 3 (8%) 22 (61%) 7 (19%) 10 (28%)
Treatment Discontinued, n (%)	22 (61%)
Rationale for Therapy Discontinuation	
Microbiologic Cure, n (%)	9 (25%)
Adverse Event or Intolerance, n (%)	9 (25%)
Treatment Cost Prohibitive, n (%)	1 (3%)
Death, n (%)	3 (8%)

Table X. Microbiologic Data – *M abscessus* isolate

Susceptibility to amikacin (average MIC)	12.8
Susceptibility to tigecycline (average MIC)	1.0
Inducible macrolide resistance present, n (%)	19 (53%)

Table X. Radiographic Features – Pulmonary Disease Only

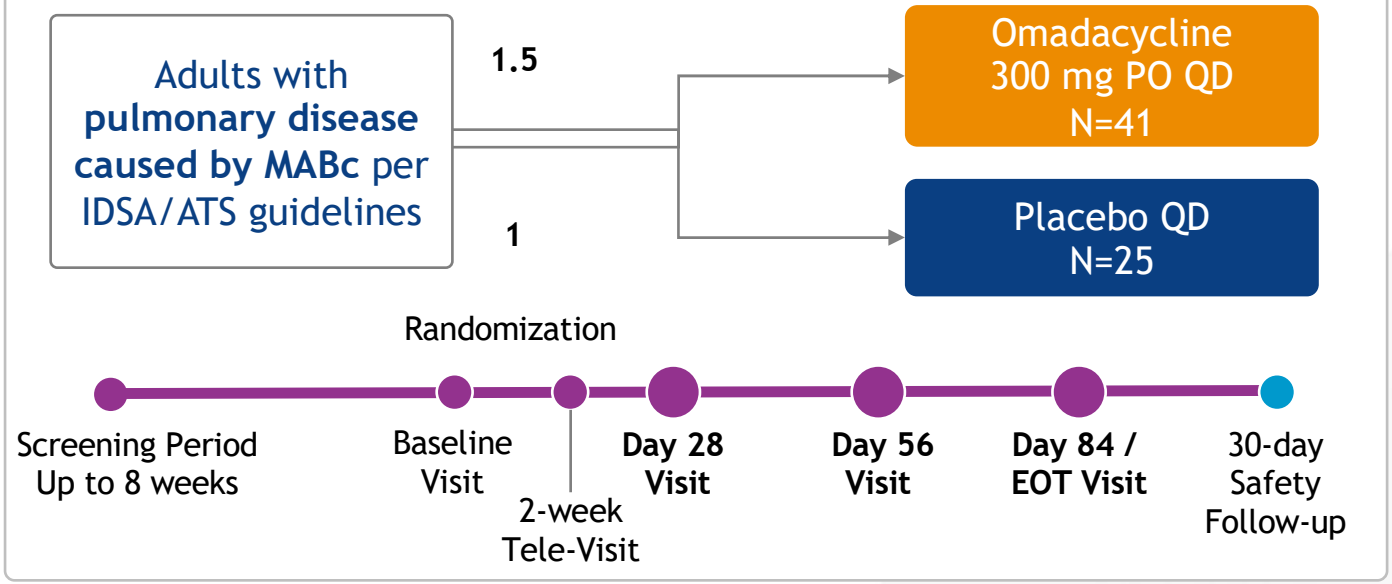
Bronchiectasis, n (%)	22 (61%)
Nodules, n (%)	25 (69%)
Cavitary Disease, n (%)	8 (22%)

CONCLUSIONS

- Omadacycline was generally well tolerated and demonstrated therapeutic efficacy with microbiologic cure in 25% of subjects and ongoing therapy in 56% of subjects
- This drug shows promise, particularly in isolates with macrolide resistance and in hosts with contraindication to other standard systemic therapies
- We are currently analyzing multi-center data collected in collaboration with NTM centers at NIH, NJH, NYU, and OHSU

Mingora C et al. ATS abstract 2022

Phase 2 Omada Trial M. abscessus



ClinicalTrials.gov NCT04922554

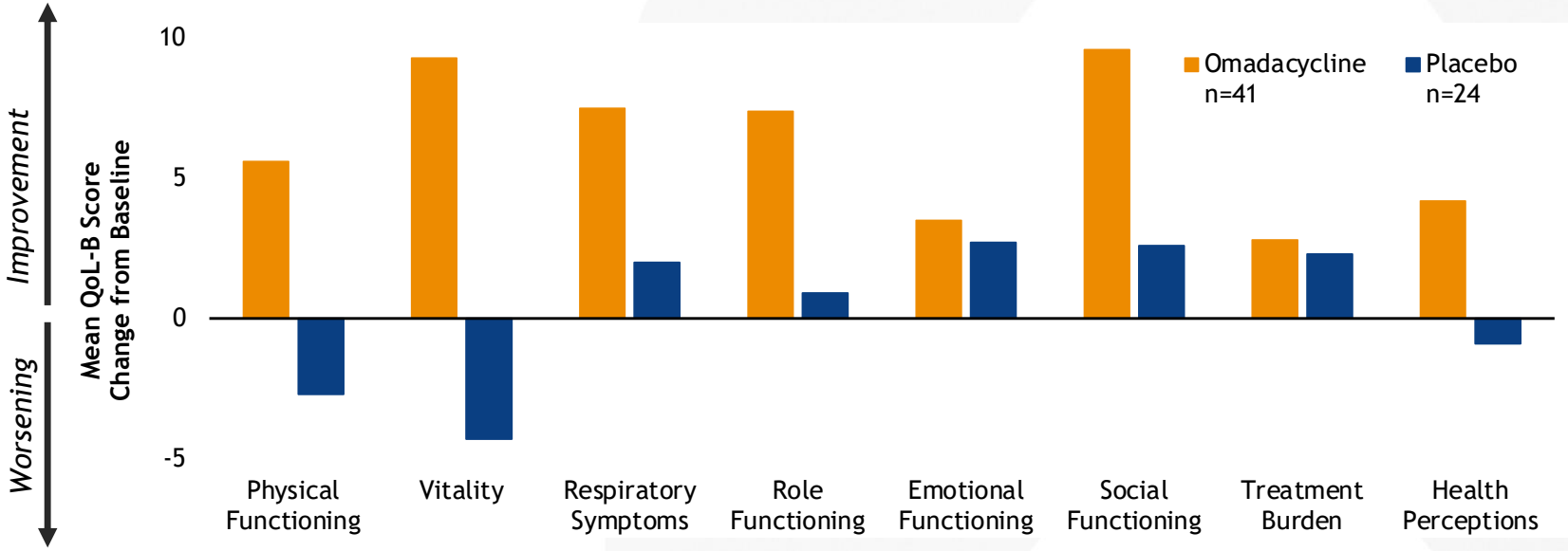
Abbreviations: EOT, end of treatment; IDSA/ATS, Infectious Diseases Society of America/American Thoracic Society; MABc PO, orally; QD, once daily; QoL, quality of life

ATS 2025

Winthrop KL et al. ATS oral presentation 2025

Mean QOL-B Domain Changes from Baseline to Day 84 / End of Treatment

Consistent Improvement Observed Across Domains with Omadacycline Treatment



Abbreviation: QoL-B, Quality of Life-Bronchiectasis

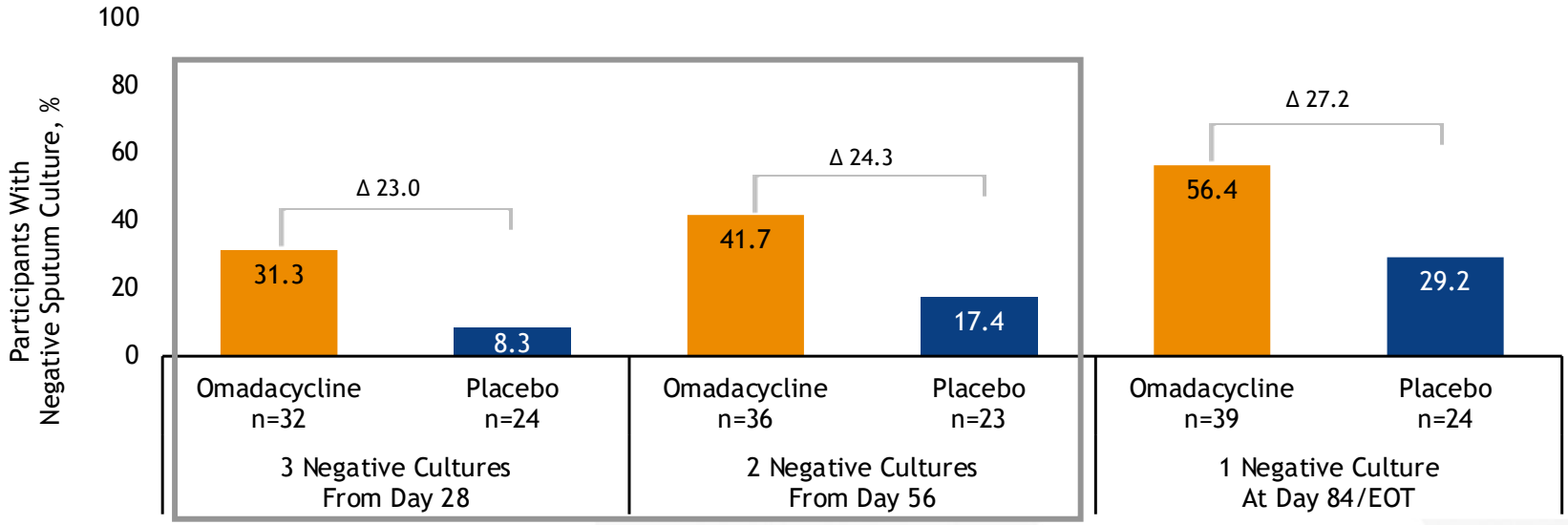
ATS 2025

San Francisco | May 16-21

Winthrop KL et al. ATS oral presentation 2025

Negative MABc Sputum Cultures

Omadacycline Had a Greater Percentage of Participants with Negative Cultures vs Placebo



Abbreviations: EOT, end of treatment; MABc, *Mycobacterium abscessus* complex

ATS 2025

San Francisco | May 16-21

Winthrop KL et al. ATS oral presentation 2025

Safety: Treatment-emergent Adverse Events

Omadacycline Was Safe and Generally Well Tolerated; Most Frequent TEAE was Nausea

Participants with, n (%)	Omadacycline (n=41)	Placebo (n=25)
Any TEAE	**35 (85.4)**	**21 (84.0)**
TEAEs in >8% omadacycline participants: Nausea*	22 (53.7)	2 (8.0)
Headache	7 (17.1)	4 (16.0)
Fatigue	7 (17.1)	1 (4.0)
Abdominal pain	6 (14.6)	1 (4.0)
Vomiting	6 (14.6)	0
Diarrhea	5 (12.2)	1 (4.0)
Alanine aminotransferase increase	4 (9.8)	0
Night sweats	4 (9.8)	0
Early treatment discontinuation for AE†	**4 (9.8)**	**0**
Serious TEAEs	**0**	**2 (8.0)**
TEAEs leading to death	**0**	**0**

*The severity of nausea associated with omadacycline was mostly mild and did not lead to treatment discontinuation
†Events leading to omadacycline discontinuation: heart failure, elevated liver enzymes, abdominal pain, parasomnia
Abbreviations: AE, adverse event; TEAE, treatment-emergent adverse event

Winthrop KL et al. ATS oral presentation 2025

Bedaquiline?

TABLE 1] Semiquantitative Monthly Sputum Cultures of 10 Patients on a Bedaquiline-Containing Regimen

Patient No.	Baseline (at the Start of Therapy)	1 mo	2 mo	3 mo	4 mo	5 mo	6 mo
1 Mab	4+	3+	1+	2+	3+	1+	2+
2 Mab	1+	3+	1+	35 colonies	37 colonies	16 colonies	3+
3 Mab	4+	28 colonies	Negative	8 colonies	Negative	Negative	32 colonies
4 Mab	4+	4+	4+	4+	4+	4+	4+
5 MAC	4+	3+	4+	4+	4+	4+	4+
6 MAC	4+	4+	Negative	Negative	2+	4+	3+
7 MAC	4+	4+	30 colonies	Negative	Negative	...[a]	...[a]
8 MAC	4+	1+	Negative	3+	4+	4+	4+
9 MAC	4+	2+	3+	1 colony	4 colonies	1+	4 colonies
10 MAC	30 colonies	8 colonies	Negative	1+	Negative	9 colonies	Negative

Solid media with countable colonies = 0-49 colonies; 1+ solid media growth = 50-99 colonies; 2+ solid media growth = 100-199 colonies; 3+ solid media growth = 200-299 colonies; 4+ solid media growth = ≥300 colonies. Negative indicates no bacterial growth. Mab = *Mycobacterium abscessus*; MAC = *Mycobacterium avium* complex. Negative = no bacterial growth.

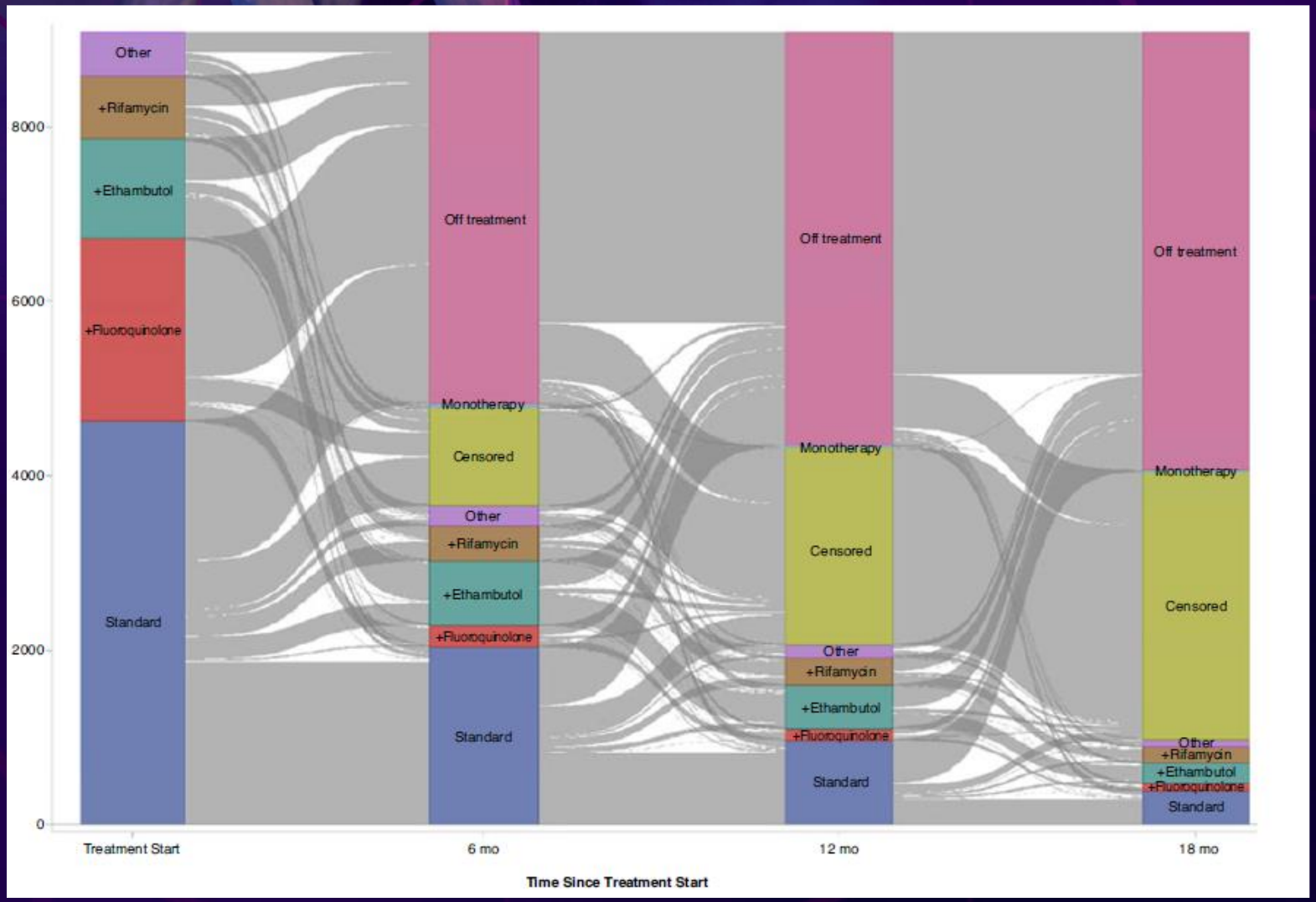
[a]Unable to produce sputum.

Philly J et al. Chest 2015

Treatment Strategy Trials

- Combination of drugs
- Length of therapy

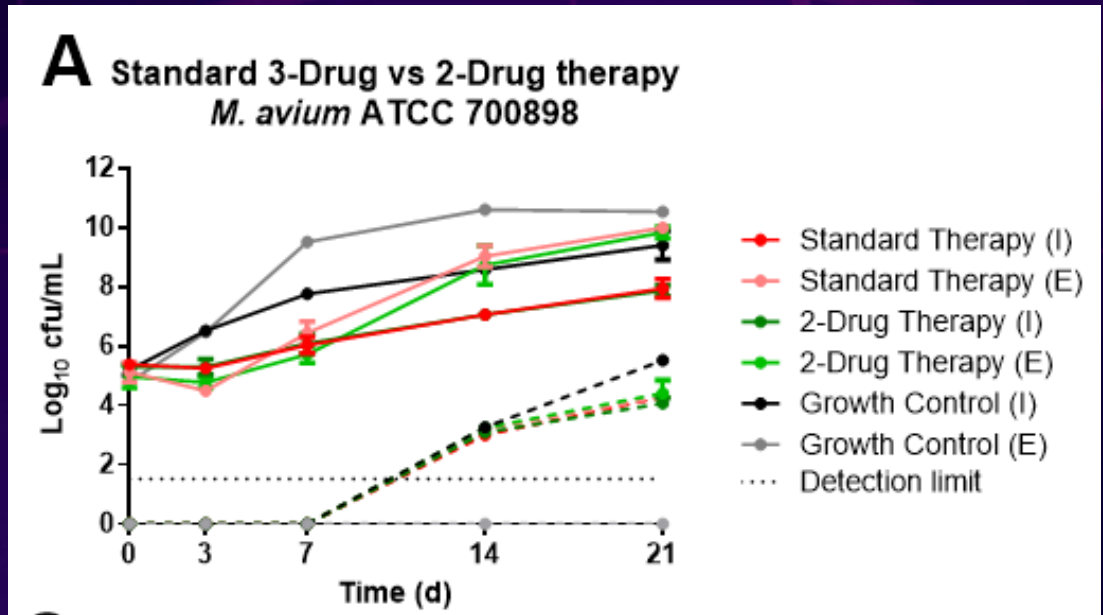
Poor Success of Guideline-Based Therapy



Ku J et al. CID 2022

2 vs 3 Drugs in the Hollow Fiber Model

- RIF-EMB-AZI vs EMB-AZI
- RIF 600mg, EMB 900mg, AZI 250mg
- Equal kill rate (intra- and extracellular)
- Equal macrolide resistance suppression
- 2 drugs not better
  - Despite 30% higher azithromycin exposure
- RNAseq: no impact of rifampicin



Jodie Schildkraut, Jelmer Raaijmakers & Jakko van Ingen – manuscript under review

MAC 2v3

- AZI/EMB Vs AZI/EMB/RIF
  - Non-cavitary MAC
  - Treatment naïve
  - 12 month duration
- Outcomes
  - Culture conversion
  - Tolerability

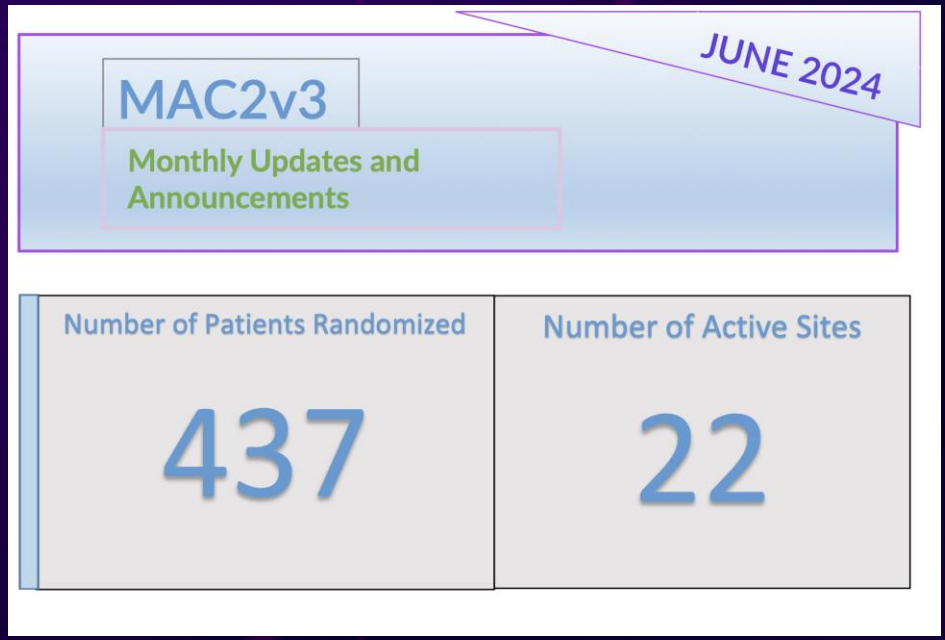


Figure 1. Comorbidities (N = 474)

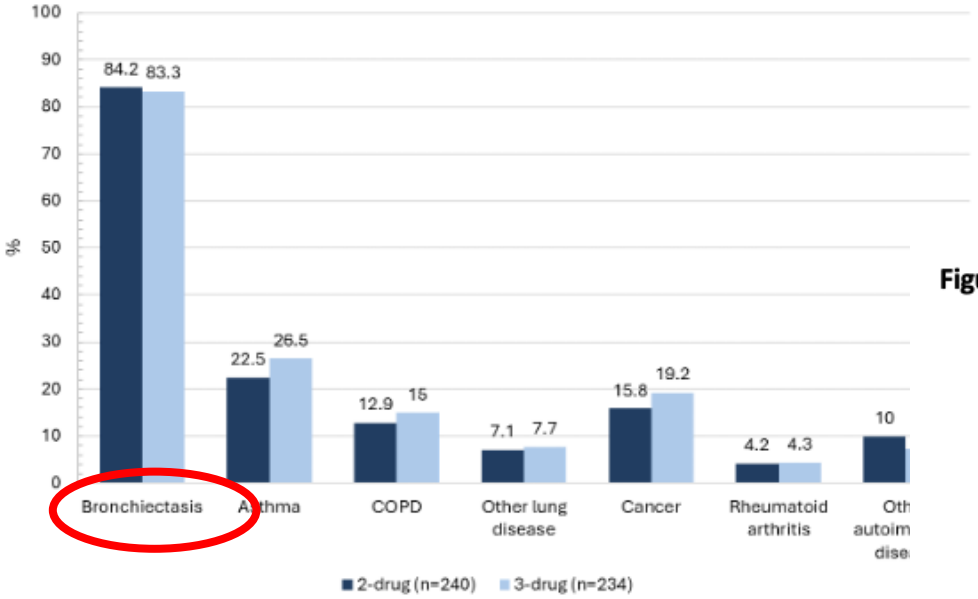


Figure 2. Most recent acid-fast bacillus culture results (n=474)

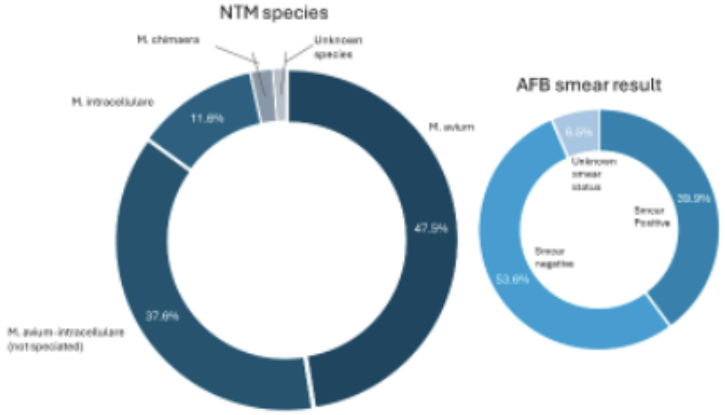
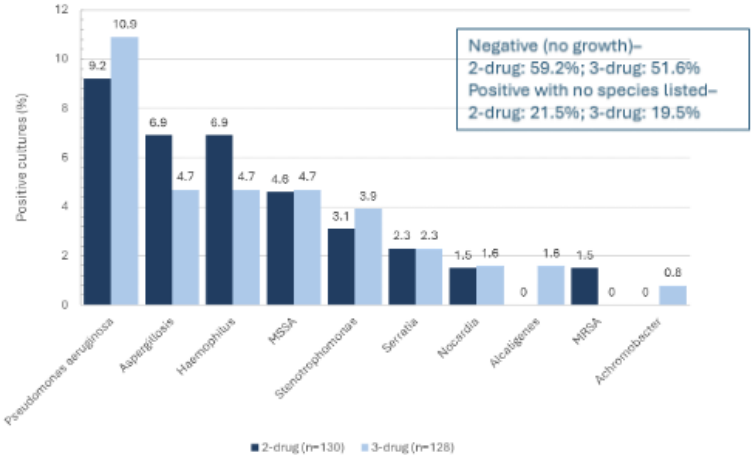


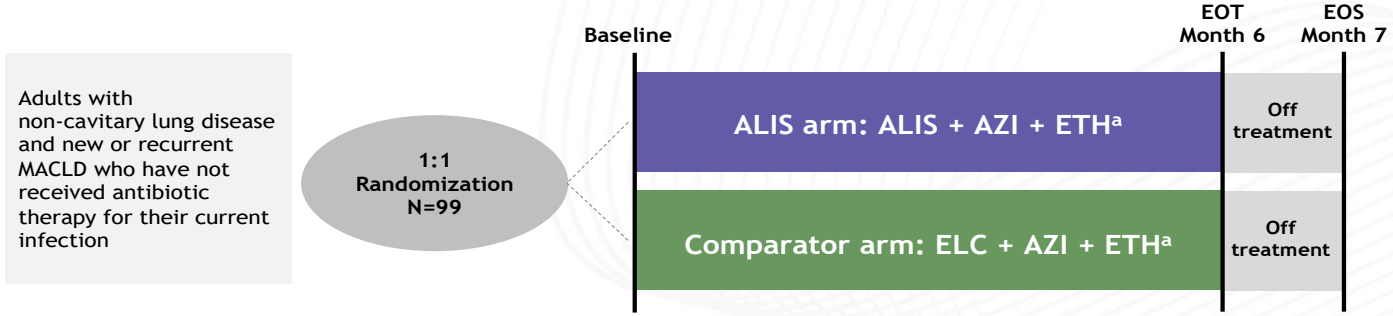
Figure 3. Other culture results (n=258 with routine or CF sputum cultures)



Henkle E et al. ATS abstract 2025

Liposomal Amikacin for Treatment Starts

Study Design



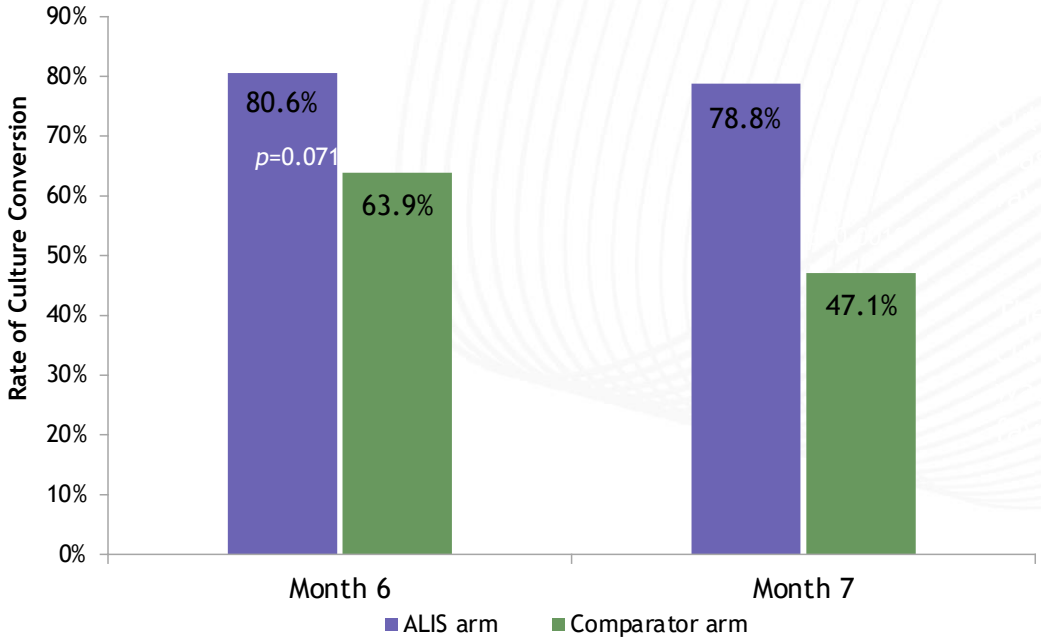
ATS 2024

San Diego, CA May 17-22

[a]ALIS 590 mg QD or placebo (ELC) QD plus AZI 250 mg QD and ETH 15 mg/kg QD PO. [b]The study was not powered to detect differences between treatment arms

Daley C et al. ATS 2024 abstract

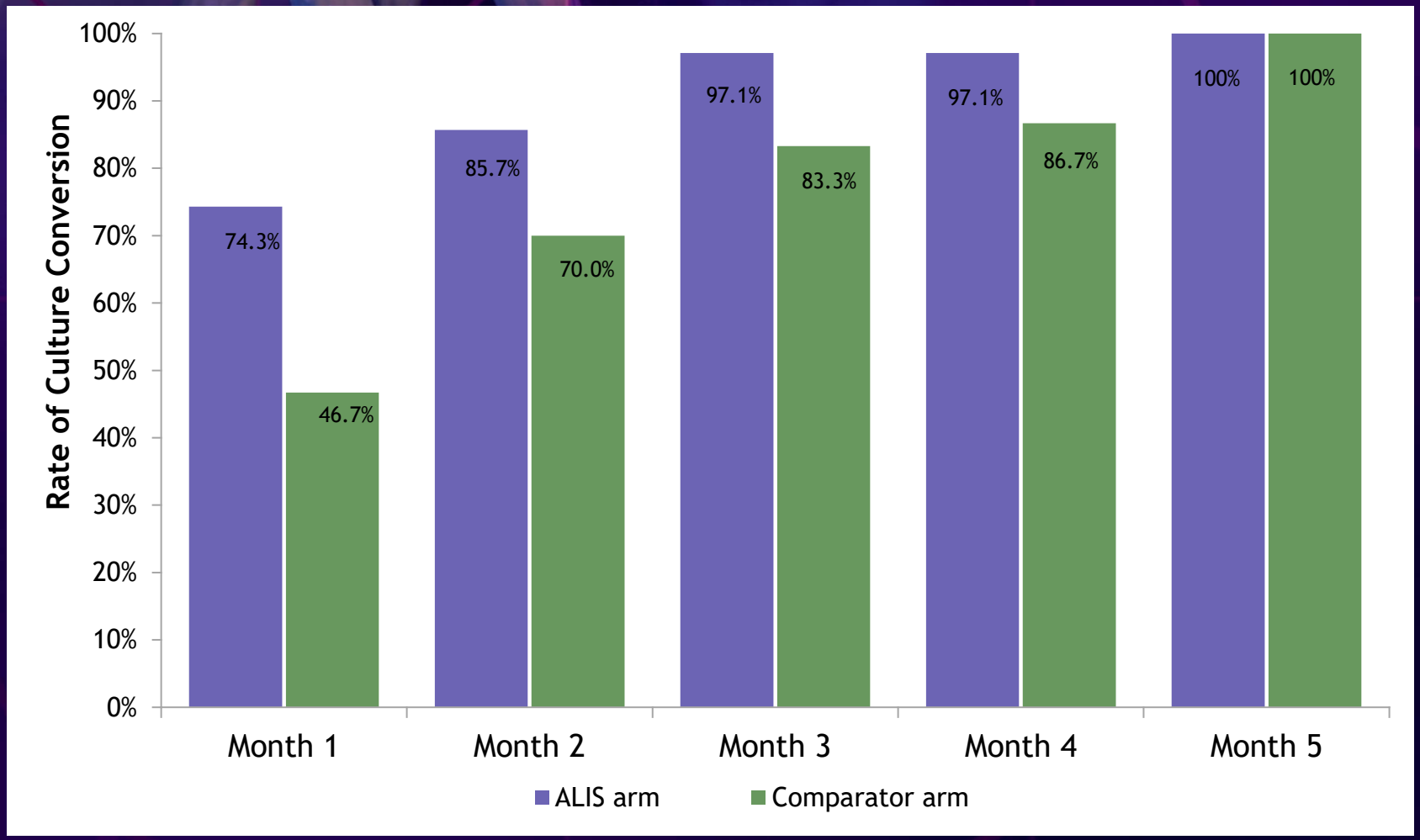
Culture Conversion at Month 6



[a]Nominally statistically significant difference between groups was observed at Month 7 (1 month off-treatment). No adjustment for multiplicity was conducted in this study.
[b]ALIS [590 mg] + azithromycin [250 mg] + ethambutol [15 mg/kg]. [c]Empty liposome control + azithromycin [250 mg] + ethambutol [15 mg/kg].
ALIS, amikacin liposome inhalation suspension; CI, confidence interval. Culture conversion by Month 6 was defined as negative cultures at Months 5 and 6. Culture conversion by Month 7 was defined as negative cultures at Months 6 and 7.

Daley C et al. ATS 2024 abstract

Among Converters: Cumulative Conversion my Month

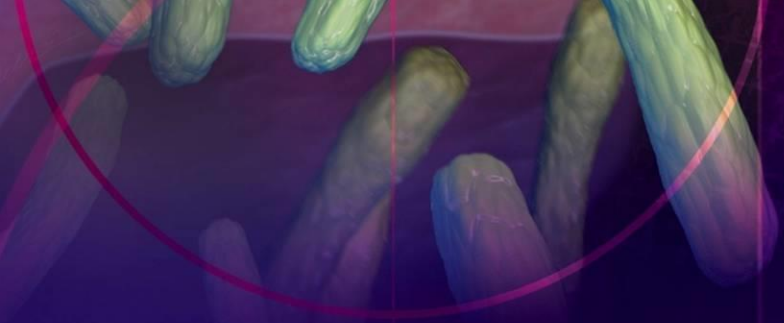


[a]ALIS [590 mg] + azithromycin [250 mg] + ethambutol [15 mg/kg]. [b]Empty liposome control + azithromycin [250 mg] + ethambutol [15 mg/kg].

Patient's status was regarded as culture converted at a specific month if both assessments at that month and the subsequent month were available and were negative after adjustment for non-productivity.

ALIS, amikacin liposome inhalation suspension; Q, quartile.

Daley C et al. ATS 2024 abstract



Non-antibiotic Approaches

Pulmonary Hygiene

7% Hypertonic Saline

- Promotes airway clearance and improved QOL in bronchiectasis
- Inhibits biofilm formation
- Antimicrobial?
- Phase 2 trial funded by NTMir
  - Treatment naïve pulmonary MAC
  - HS versus observation
  - 3 month QOL and micro outcomes

Kellet F et al. Respiratory Medicine 2011

Inhaled Glutathione/ascorbic acid/bicarb (Renovion)

- Promotes airway clearance
- Inhibits biofilm formation
- Antimicrobial?
- Phase 2 trial in Be

Early initiation – symptom improvement and delayed disease progression in broad population

✓ **ARINA-1 improves mucus symptoms after 28 days of use**

	ARINA-1	Placebo
Improvement in mucus symptoms	82.8%	27.3%
Decreases in sputum production	51.7%	18.2%

✓ **ARINA-1 stabilizes pulmonary function at day 28**

LS Mean Difference favors ARINA-1

	ARINA-1 (LS Mean)	Placebo (LS Mean)	LS Mean Difference
FEV1	-41 mL	-72 mL	31 mL
FVC	-46 mL	-93 mL	47 mL
FEF25-75%	-26 mL	-53 mL	27 mL

Soloman M et al. WBC abstract 2024

Brensocatinib in NTM?

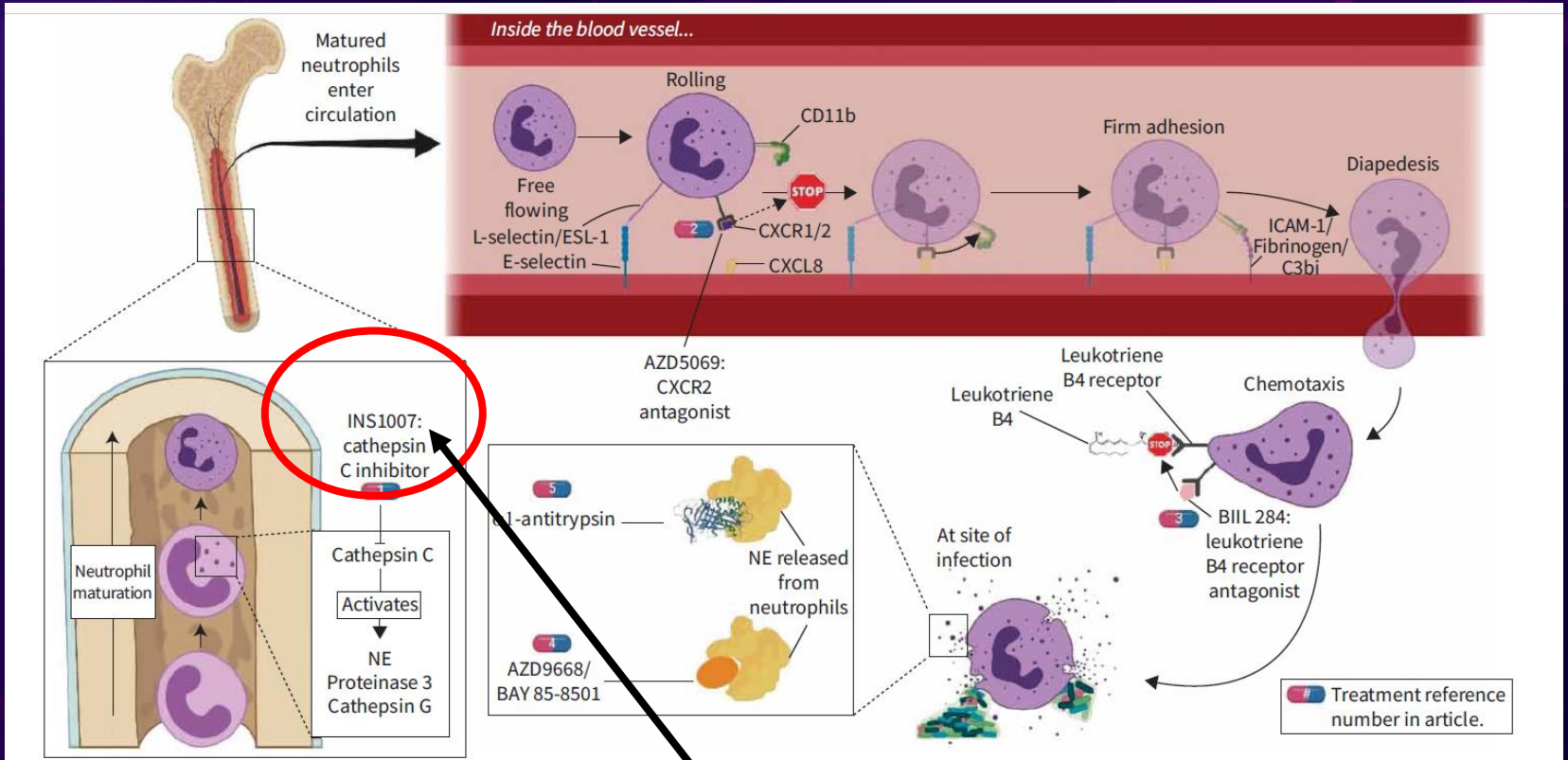


FIGURE 2 Mechanisms of current anti-inflammatory therapies in bronchiectasis in trials. NE: neutrophil elastase; ESL-1: E-selectin ligand-1; ICAM-1: intercellular adhesion molecule-1; CXCR1/2: C-X-C chemokine receptor type 1/2; CXCL8: C-X-C chemokine ligand 8.

Cathepsin C (aka dipeptidyl peptidase-1)

Giam YH et al. ERJ Rev 2021

Nitric Oxide

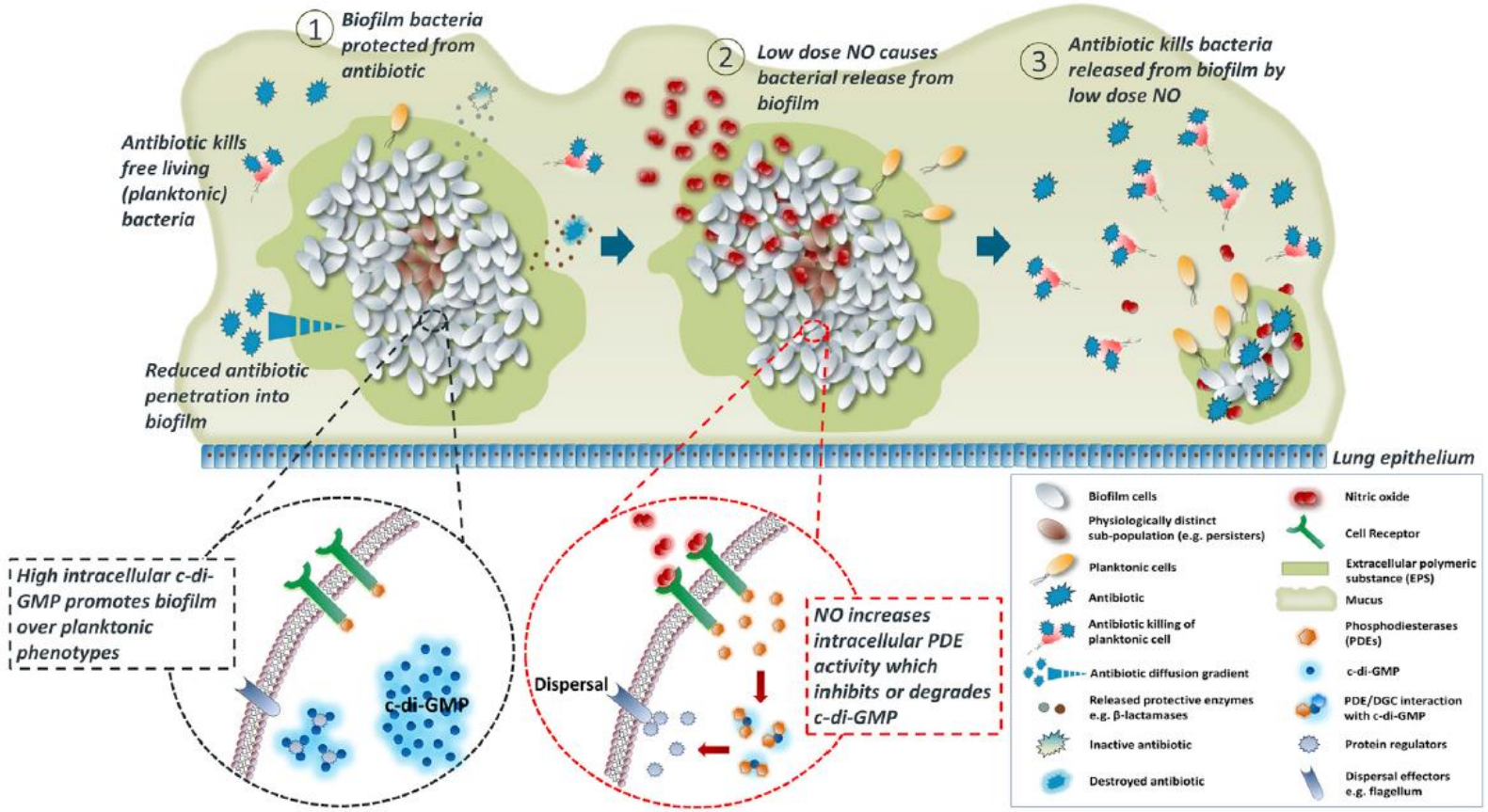


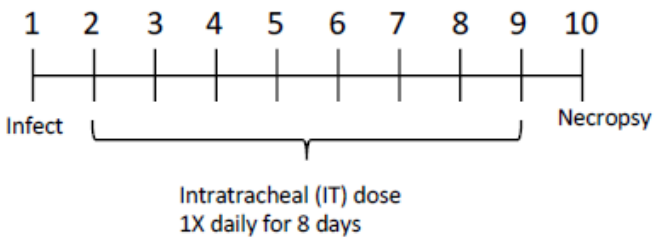
Figure 1. Role of NO in Disrupting Antibiotic Tolerance Mechanisms Associated with the Biofilm Structure

(1) Biofilm tolerance mechanisms include reduced antibiotic diffusion, release of protective enzymes capable of destroying or inactivating antibiotics in the biofilm matrix, and formation of physiologically distinct bacterial subpopulations (e.g., persister cells) resulting from nutrient and oxygen gradients. (2) Low-dose NO diffuses into the biofilm and interacts with cell receptors that upregulate cellular phosphodiesterases (PDEs), which accelerate c-di-GMP degradation. This prevents c-di-GMP from interacting with proteins at the transcriptional, translational, or post-translational level and leads to cell surface and physiological changes associated with dispersal and motility (red circle inset). (3) Dispersal is accompanied by reversion of the bacteria to a planktonic phenotype that renders them more susceptible to antibiotic-mediated killing.[18,19]

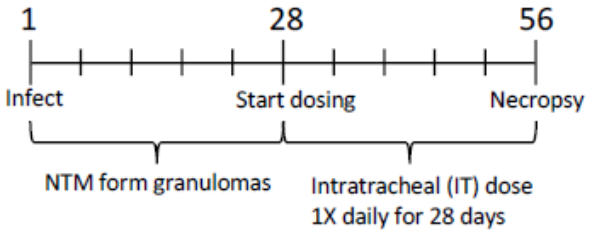
Howlin RP et al Mol Therapy 2017

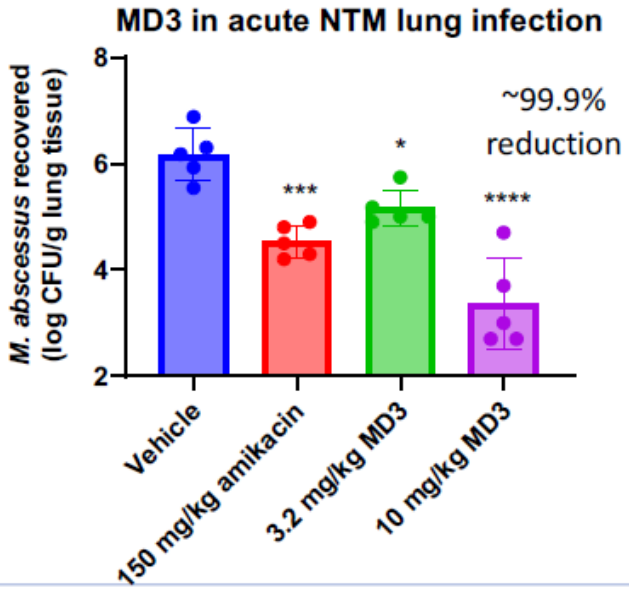
NO (ALX1) in Mouse MAC

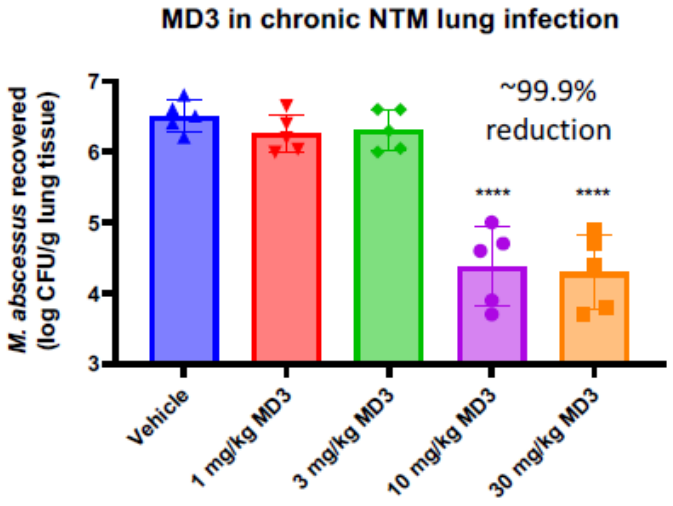
Acute NTM Infection Model



Chronic NTM Infection Model







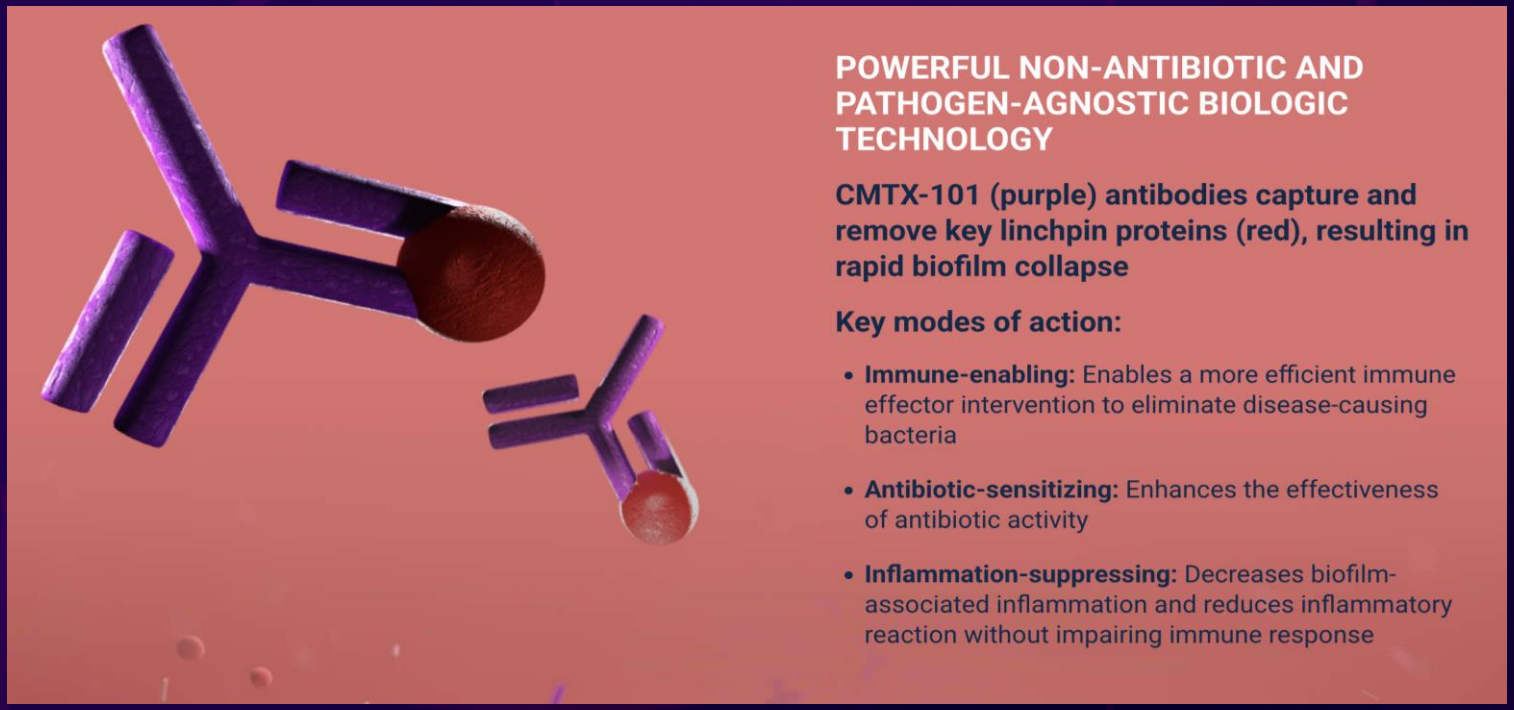
Schoenfisch M et al. WBC congress abstract 2022

Anti-Biofilm Strategies

Clarametyx Biosciences Announces Positive Interim Analysis in Phase 2a Study Evaluating CMTX-101 for Infections Associated with Cystic Fibrosis

JUNE 16, 2025 | IN NEWS

Interim data showing reduction in PsA in sputum



https://clarametyx.com/positive-interim-analysis-in-phase-2a-study/

ORIGINAL RESEARCH

OPTIMA: An Open-Label, Noncomparative Pilot Trial of Inhaled Molgramostim in Pulmonary Nontuberculous Mycobacterial Infection

Rachel M. Thomson[1,2,3], Michael R. Loebinger[4], Andrew J. Burke[1,3], Lucy C. Morgan[5], Grant W. Waterer[6], and Cecilia Ganslandt[7]

ORIGINAL RESEARCH

Subject	Species	Group	Screening	Baseline	V3 (4w)	V4 (8w)	V5 (12w)	V6 (16w)	V7 (20w)	V8 (24w)	V9 (28w)	V10 (32w)	V11 (36w)	V12 (40w)	V13 (44w)	V14 (48w EOT)	V15 (EOS)
11-101	MAC	1	+++	+	++	++	++	++	+++	++	++	+++	+++	+	++	++	++
11-102	MAC	1	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
12-102	MAC	1	+++	+	+	++	+++	++	++	+++		++	++	+++	++	+++	++
12-103	MAC	1	+	+	-	-	-	NEG	NEG	-			-	-	-	NEG	NEG
12-104	MAC	1	+	+	+	NEG	NEG	NEG	NEG	NEG	NEG	NEG	++	NEG	-	NEG	-
12-105	MAC	1	-	NEG	NEG	NEG	-	NEG	NEG	NEG	NEG	NEG	NEG	NEG	NEG	NEG	NEG
12-106	MAC	1	+	+	+	-	-	NEG	-	-							
12-110	MAC	1	+	+	+	-	-	-	-	-	NEG	-	-	-	-	NEG	NEG
13-101	MAC	1	+++	+++	+	-	+	++	++	+++							
13-102	MAC	1	+	+	+	+++	++	++	+++	++	+++	+++	+++	+++	+++	+++	++
21-101	MAC	1	++	+++	-	-	+	+	+	++	++	++	++	++	+	++	+
13-104	MAC	1	+	++	+++	+++	++										
11-103	MAC	2	+	+	-	-	-	+	-	NEG	NEG	NEG	NEG	-	-	-	+
11-105	MAC	2	+++	+++	-	-	+	-	+	+	++	++	++	++	++	++	+++
11-106	MAC	2	-	-	-	+	-	-	+	-	-	-	+	+	+	-	-
11-108	MAC	2	+	+	NEG	-	-	+	NEG	NEG	NEG	NEG	NEG	NEG	NEG	NEG	NEG
12-107	MAC	2	+	-	+		NEG	NEG	NEG	NEG	+++		+	-	+	-	-
13-103	MAC	2	+++	-	+	+	NEG	-	NEG	NEG	NEG	NEG	NEG	NEG	NEG	NEG	NEG
14-106	MAC	2	-	-	-	-	+	-	+	-	-	+	-	+	+	-	-
14-107	MAC	2	++	-	+	-	+	-	NEG	+	+	-	+	-	NEG	-	-
14-104	MAC	2	++	+	-	++	-	++	++	+	+	-	-			++	++
14-108	MAC	2	+	-	-	-	-	-	-	-	NEG	NEG	-	NEG	NEG	NEG	-
11-104	MAC	2	+++			+++											
11-107	MAC	2	+++	+++	+	+++											

Figure 2. MAC culture results. Plus signs indicate degree of smear positivity, minus sign indicates smear negative, and empty boxes indicate that no sample was submitted, usually because of patient withdrawal. EOS = end of study; EOT = end of treatment; MAC = *Mycobacterium avium* complex; NEG = smear and culture negative; V = visit; w = weeks.

29% culture conversion refractory MAC

Thomson R et al. Ann ATS 2024

NEWS | HEALTH

Viruses genetically engineered to kill bacteria rescue girl with antibiotic-resistant infection

Students helped find the viruses, called phages, that treated lung transplant patient, but strategy may be hard to repeat for other infections

8 MAY 2019 • BY ALEX FOX

Phage Therapy

- Few naturally occurring for NTM
  - Strain specific (not species specific)
- Greater numbers of pseudomonas phages
  - Phase 1b/2 trial ongoing in CF
- Case reports
  - M. abscessus
- Salvage therapy protocols

The Future

- Why is our treatment approach like that for TB?
  - Should we treat NTM like PsA flare in bronchiectasis (but for longer)?
- Can we identify a subgroup of patients where 3 month treatment is optimal?
- Strategy trials to compare treatment for those with bronchiectatic NTM
  - 3 month versus 12 months
  - 5-year outcomes
- New more potent drugs = shorter therapy
  - Eradication more likely?

Acknowledgements

- Close colleagues and friends at variety of institutions including:
  - NTMRC, NJMC, Mayo, UT Tyler, NIH, CDC, FDA, U Ontario, NYU, Georgetown, Medical Univ S. Carolina, others