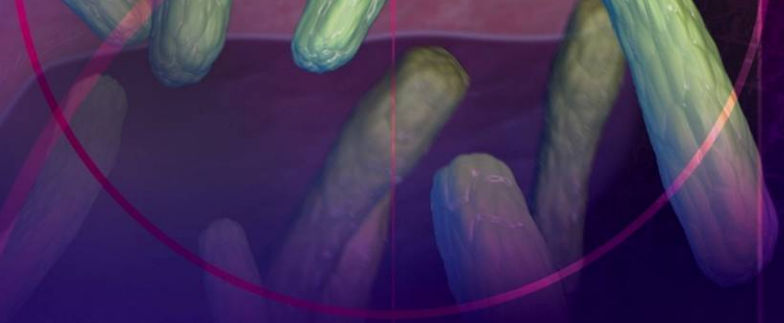


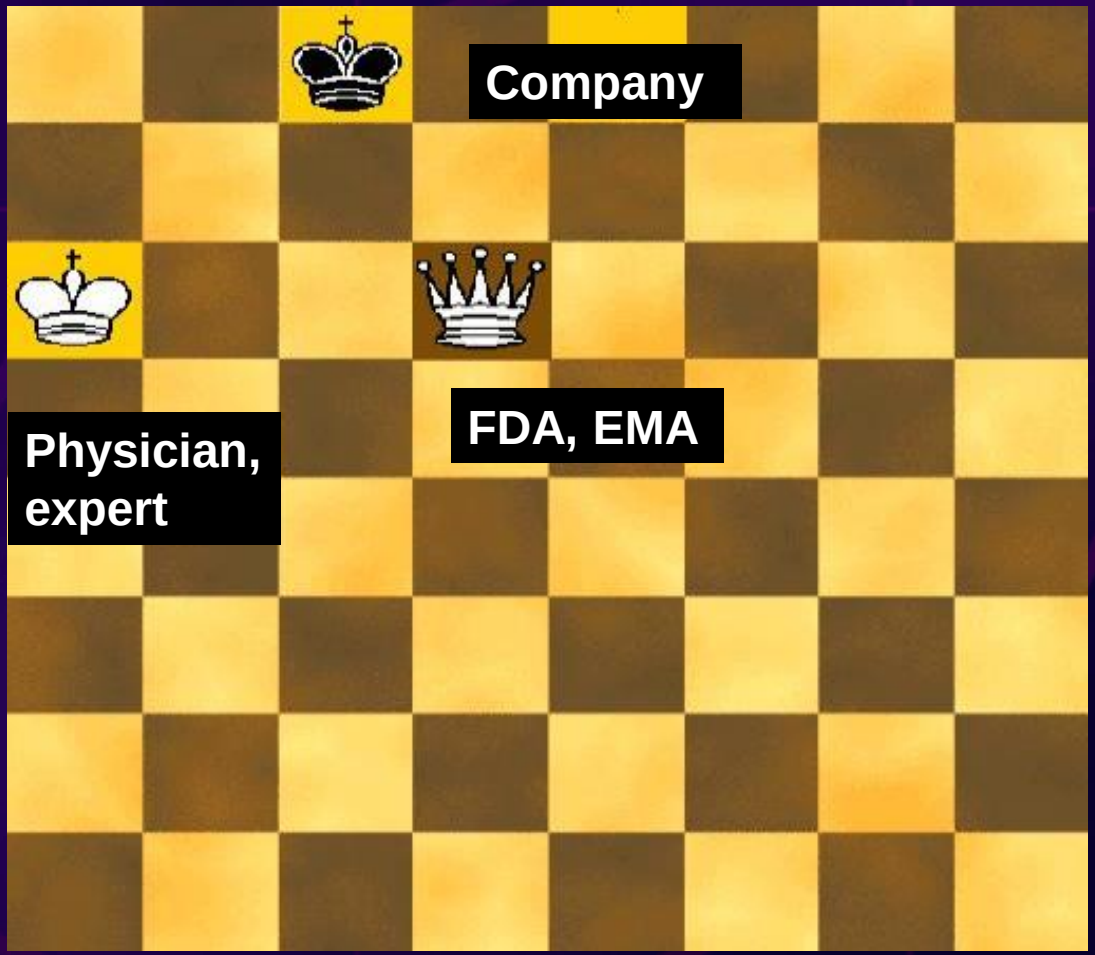
NTM Trial Design Considerations and Examples

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

Disclosures

- Research support
  - FDA, PCORI, NTMir, COPD Foundation, Insmed
- Consulting honorarium
  - Insmed, Red hills, Paratek, Johnson and Johnson, Horizon

Stalemate (black to move)



Currently Approved Therapies in NTM

- Azithromycin
  - Disseminated MAC in patients with HIV
  - “in combination with ethambutol”
- Clarithromycin
  - Disseminated MAC in patients with HIV
  - no mention of companion drugs needed

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

Current NTM RCTs

- *MAC*
  - Liposomal amikacin
  - Clofazimine
  - GM-CSF
  - NO
  - 2 v 3: AZI/EMB versus AZI/EMB/RIF
  - CLARI/RIF/EMB vs AZI/RIF/EMB
- *M xenopi*: CLARI/RIF/EMB vs MOXI/RIF/EMB
- *M. abscessus*
  - Liposomal amikacin
  - NO

https://www.clinicaltrials.gov/

Considerations and Examples

- Patient selection/disease state
- Treatment exposure groups
- Outcome measures
- Trial Length

Patients/Disease State

- Goal = enroll patients with capacity to change
  - Will respond to therapy
  - Can measure difference with therapy
- Measuring safety/efficacy
  - 1 drug much easier than 4 drugs
- Sick versus not-sick (or at least not very)
  - Non-active comparator

Pulmonary NTM (MAC)

- Standard of care is generally not treating with ABX first
  - Takes months to “sort out”’
  - Clearance, hygiene, exercise, education first
  - ABX after 3-6 months or more is common
  - Exception is cavitary disease or those with severe symptoms

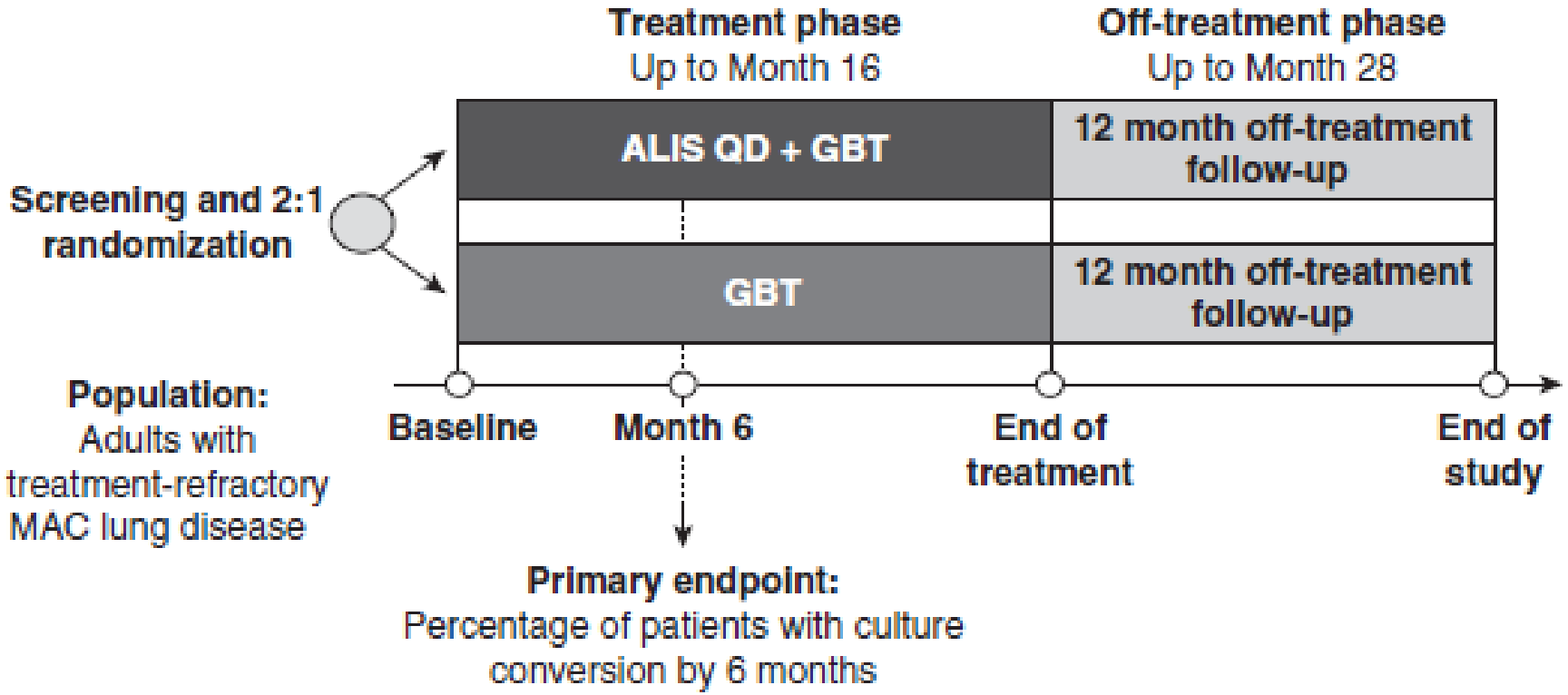
Natural History

- Roughly 50% of those meeting criteria start therapy after diagnosis
  - Reasons multifactorial
- 10-15% patients convert to negative spontaneously
- 20-25% remain stable for years
  - Bronchial hygiene/clearance helps?
  - Cavitary disease, lower BMI make less likely

Henkle E et al. Ann Am Thor Soc 2017; Hwang JA, et al. *Eur Respir J* 2017;49:1600537; Ahn CH, et al. *Am Rev Respir Dis.* 1982

“Refractory” disease

- Arbitrary definition (but with some basis)
  - 10-20% of patients do not convert
- <u>Benefit</u>
  - Can power study with patients taking background multi-drug therapy
  - Because placebo group changes little to none
- <u>Con</u>
  - But measurable change in new therapy group could be minimal
  - *M. abscessus* as example



Griffith D, et al. Am J Respir Crit Care Med. 2018

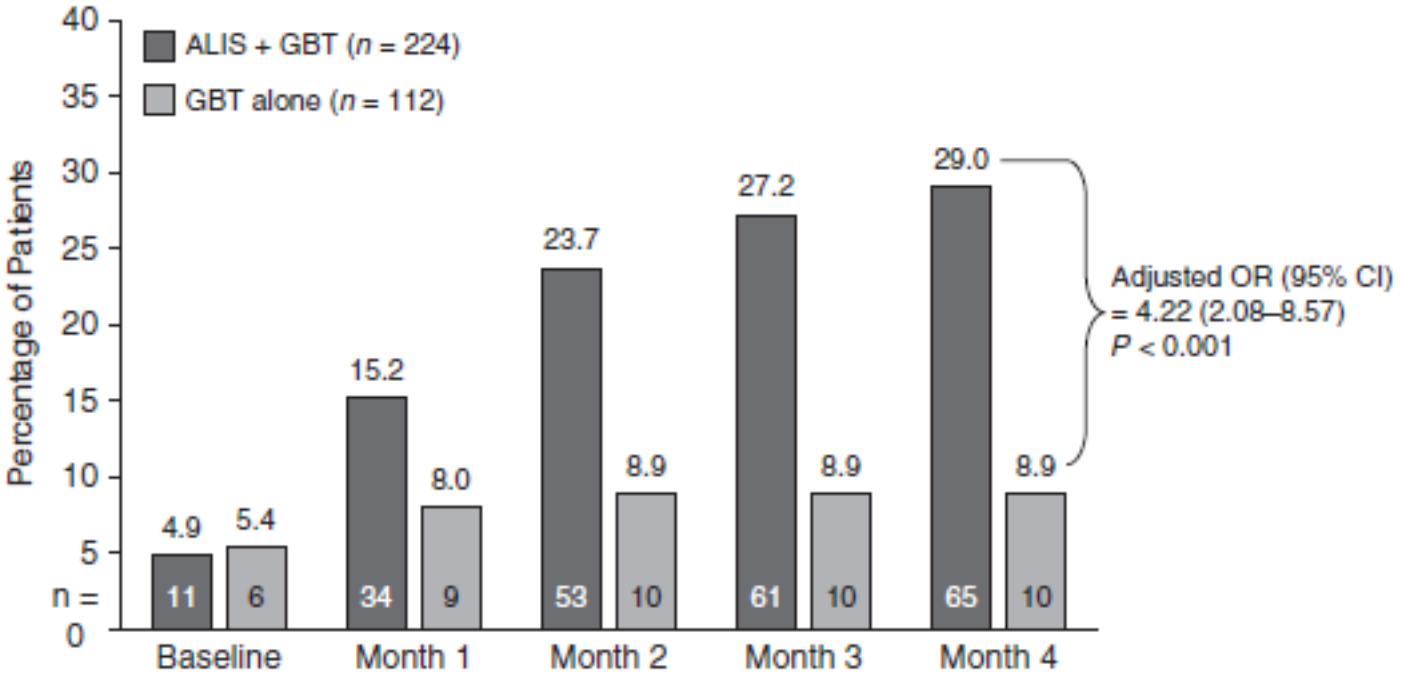


Figure 3. Proportion of patients achieving culture conversion, shown by the first month of conversion: intention-to-treat population. The cumulative proportion of patients achieving culture conversion is displayed by the first month at which sputum cultures were *Mycobacterium avium* complex negative. Month 4 was the latest time point at which a patient could achieve the first of three consecutive negative sputum cultures and be considered a converter in the primary endpoint analysis at Month 6. Patients with positive cultures during screening and negative cultures at baseline and Months 1 and 2 were considered converters at baseline. ALIS = amikacin liposome inhalation suspension; CI = confidence interval; GBT = guideline-based therapy; OR = odds ratio.

Griffith D, et al. Am J Respir Crit Care Med. 2018

Treatment Naïve Patients

- Benefit
  - Group has greatest capacity to change
  - Easier to measure
  - Can power study versus placebo
- Con
  - Difficult to power study with active comparator (at least one that is effective)

FDA-sponsored Clofazimine Monotherapy Trial

- Phase 2, Randomized, placebo-controlled
  - 24 weeks clofazimine monotherapy
- Inclusion criteria
  - Non-cavitary, “Stable” pulmonary MAC patients
- Outcomes
  - Culture conversion at 24 weeks (primary)
  - Semi-quantitative cultures
- Power assumptions
  - 35% conversion CFZ, 10% in placebo
  - N=102

https://www.clinicaltrials.gov/

Multi-Drug Active Comparator Trial

- Large, multi-site pragmatic trial
  - NTM Consortium and Trials network (35 sites)
- RCT comparing 2- vs 3-drugs for pulmonary MAC
  - AZI/EMB vs AZI/EMB/RIF
  - Non-cavitary disease
- Co-primary outcomes at 12 months
  - Culture conversion and tolerability
  - Non-inferiority
- Power considerations
  - Assumed 85% conversion in each group
  - 10% NI margin
  - N= 500

https://www.clinicaltrials.gov/

Outcomes

- Efficacy
  - Microbiologic
  - Patient reported (QOL)
  - Patient function (6MWT?)
  - Clinical Outcome Measure?
- Safety
  - Tolerability
  - SAEs

Treatment outcome definitions in nontuberculous mycobacterial pulmonary disease: an NTM-NET consensus statement

Jakko van Ingen[1], Timothy Aksamit[2], Claire Andrejak[3,4], Erik C. Böttger[5], Emmanuelle Cambau[6], Charles L. Daley[7], David E. Griffith[8], Lorenzo Guglielmetti[9,10], Steven M. Holland[11], Gwen A. Huitt[7], Won-Jung Koh[12], Christoph Lange[13,14,15,16], Philip Leitman[17], Theodore K. Marras[18], Kozo Morimoto[19], Kenneth N. Olivier[20], Miguel Santin[21], Jason E. Stout[22], Rachel Thomson[23,24], Enrico Tortoli[25], Richard J. Wallace Jr[26], Kevin L. Winthrop[27] and Dirk Wagner[28] for NTM-NET

TABLE 1 List of definitions

Version#	Outcome parameter	Votes¶	Agreed+
	Culture conversion		
1	The finding of at least two consecutive negative mycobacterial cultures from respiratory samples during antimycobacterial treatment (the sampling date of the first negative culture is then the date of culture conversion)	0	
2	The finding of at least two consecutive negative mycobacterial cultures from respiratory samples, collected at least 4 weeks apart, during antimycobacterial treatment (the sampling date of the first negative culture is then the date of culture conversion)	6	
3	The finding of at least two consecutive negative mycobacterial cultures from respiratory samples, collected at least a day apart, during antimycobacterial treatment (the sampling date of the first negative culture is then the date of culture conversion)	2	
4	The finding of at least three consecutive negative mycobacterial cultures from respiratory samples during antimycobacterial treatment (the sampling date of the first negative culture is then the date of culture conversion)	6	
5	***The finding of at least three consecutive negative mycobacterial cultures from respiratory samples, collected at least 4 weeks apart, during antimycobacterial treatment (the sampling date of the first negative culture is then the date of culture conversion)***	9	22/23 (96%)

Definition of Culture Conversion

TUBERCULOSIS CULTURE CONVERSION WITH BEDAQUILINE

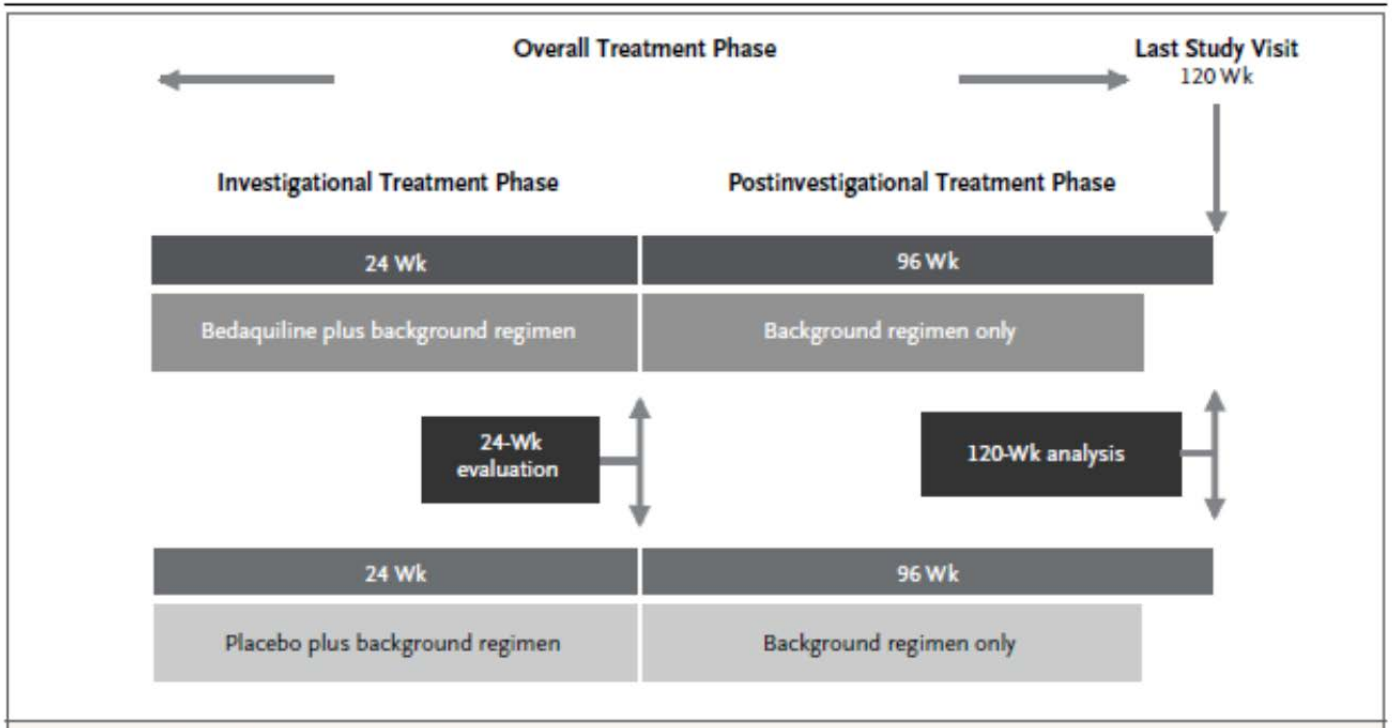


Figure 1. Study Design and Drug Regimens.

Patients with multidrug-resistant tuberculosis were assigned in a 1:1 ratio to receive either bedaquiline (400 mg once daily for 2 weeks, followed by 200 mg three times a week for 22 weeks) or placebo, plus a preferred five-drug, second-line antituberculosis background regimen. The total treatment period was 18 to 24 months, during which bedaquiline was administered for 6 months. The total trial duration was 120 weeks (30 months), which included an anticipated 6-month period after the completion of treatment.

Diacon A et al. NEJM 2016

Culture Conversion

- Do 2 consecutive negatives predict 3?
- "Sustainability" while on treatment important
  - Do 2 consecutive negatives predict sustained negativity?
- "Durability" off treatment
  - Clinical relevance when comparing regimens?
  - Environmental re-infection rate is high no matter what group patient came from
  - Utility in defining optimal treatment duration for a particular regimen (what is the minimum?)
- Semi-Quantitative predicts conversion
- Time to conversion

Griffith DE et al. AJRCCM 2015

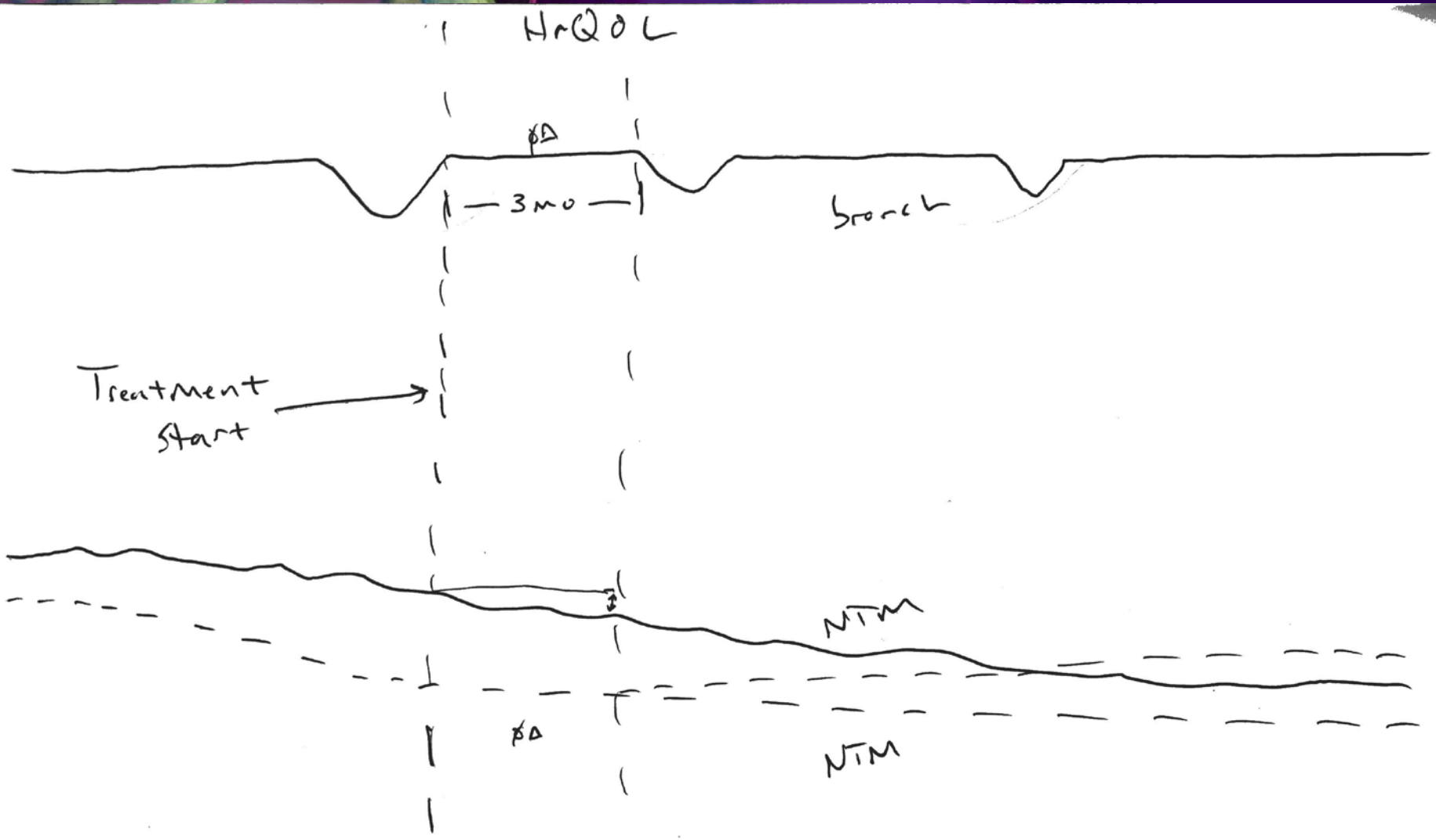
QOL-B and NTM Module

- RSS of QOL-B
  - 9 questions
  - Good internal consistency, test-retest reliability, convergent validity, and some responsivity in bronchiectasis
  - Needs some refinement, minimal important difference
  - Useful in NTM bronchiectasis?
- Question of when to measure
  - issue of inhaled therapies versus oral
- NTM module
  - Developed specifically for pulmonary NTM in general
  - Incorporate fatigue and other factors
  - Needs longitudinal evaluation

QOL-B in NTM

- Prospective Cohort (OHSU Biobank)
- Enrolled at treatment start (n=21)
  - At 12 months, increased QOL-B-RSS (+9, p=0.04)
  - Driven by those with poor scores (<70) at enrollment
- Enrolled already on therapy >90 days (n=16)
  - At 12 months, no change

Henkle E et al. ATS abstract 2018


HrQOL
ΔΔ
3mo
Treatment
start
NTM
ΔΔ
NTM

Function

- PFTs
  - Generally show no change during therapy
  - Most with fixed underlying lung damage
- 6MWT
  - Maybe correlates with sputum conversion
  - Meaningful? Huge SDs and heterogeneity
  - Operator dependent
- Exercise capacity
  - Steps via fitbit?

NTM is not TB

- TB is curable
  - Culture conversion is surrogate for cure
  - Cure has a definition
  - Contagious (you must treat it!)

NTM is not TB

- NTM is infectious disease but…
  - Not contagious
  - Chronic inflammatory disease
  - Treatment guided by disease activity
  - Generally not curable, although usually suppressable
  - Relapse/re-infection common after therapy stop

Griffith D et al. AMJRCC 2007; Henkle E et al Ann Am Thor Soc 2017, Wallce RJ Jr et al Chest 2014

NTM is not TB

- Culture conversion is only part of story
  - Does not always correlate with how patient feels or functions
  - Does not always correlate with radiographic change
- Clinical meaningfulness
  - We all agree yes
  - Need to more data correlating with other measures to prove

Combined Outcome Measures

- Need a disease activity index
  - Objective signs
  - Subjective feelings
  - Physician and patient input
  - Clinical meaningfulness to patient and physician

ACR20

- Improvement of 20% in number of tender and number of swollen joints, and;
- Twenty percent (20%) improvement in 3 of the 5 criteria:
  - Patient Global Assessment;
  - Physician Global Assessment;
  - Functional ability measure [HAQ];
  - Visual analog pain scale;
  - Erythroctye sedimentation rate or C-reaction protein.

NTM-DAS scoring

Measure	Data	Coding
CRP	Numeric result	0=normal (<10?) 1=10-<40 2=>=40
Most recent AFB culture result	Negative Positive/Smear negative Positive/Smear positive	0=negative 1=positive 2=smear positive
NTM Symptoms score	Numeric result	0=>=85 1=>=60 2=<60
QOL-B Respiratory Symptoms score	Numeric result	0=>=80 1=>=50 2=<50
CT scan cavitary disease	No cavitary disease Cavitary disease	0=no cavities 2=cavities
CT scan extent of tree-in-bud	None Unilateral Bilateral	0=no tree-in-bud 1=unilateral 2=bilateral
Physician Visual Analog Scale, disease activity	*0----------10* *0=not active at all 10=most active*	*0=0-4* *1=5-7* *2=8-10*
Patient Visual Analog Scale, "how active was your NTM disease during the past week"	*0----------10* *0=not active at all 10=most active*	*0=0-4* *1=5-7* *2=8-10*

ANNALS ATS SUPPLEMENT

Patient-Centered Research Priorities for Pulmonary Nontuberculous Mycobacteria (NTM) Infection

An NTM Research Consortium Workshop Report

Emily Henkle[1], Timothy Aksamit[2], Alan Barker[3], Charles L. Daley[4], David Griffith[5], Philip Leitman[6], Amy Leitman[6], Elisha Malanga[7], Theodore K. Marras[8], Kenneth N. Olivier[9], D. Rebecca Prevots[10], Delia Prieto[7], Alexandra L. Quittner[11], William Skach[12], John W. Walsh[7], Kevin L. Winthrop[13], and the NTMRC Patient Advisory Panel

Patient Advisory Panel Members
Cynthia Flora
Marge Gustafson
Bob Gustafson
Matthew Pozsgai
Mary Pozsgai
Margery Stalch
Sue Tsang

Treatment	**Reduce the burden of antibiotic treatment for NTM disease**	**Develop and evaluate alternative delivery systems for IV antibiotics** **Repurpose existing therapies** **Develop new, more effective drugs with a shorter therapy duration**
	Improve understanding of who needs or benefits from antibiotic therapy.	**Role of therapy in mild cases to prevent disease progression** **Predictors of treatment response**
Clinical outcomes	**Develop a composite measure of disease activity or severity.**	**Develop a composite index of disease activity or severity that include microbiological, chest imaging, and quality of life measures.**
	Identify and validate biomarkers associated with disease risk, prognosis, and treatment response	**Identify biomarkers associated with disease risk, prognosis, or treatment response**

NTM Trials

- Placebo controlled trials
  - Can power
  - Ethical if non-cavitary disease
  - Monotherapy Vs. Multi-drug therapy
  - Can show efficacy in 3-4 months
- Outcome measures
  - Disease activity
  - Goal for therapy should be low or no disease activity (needs a definition)

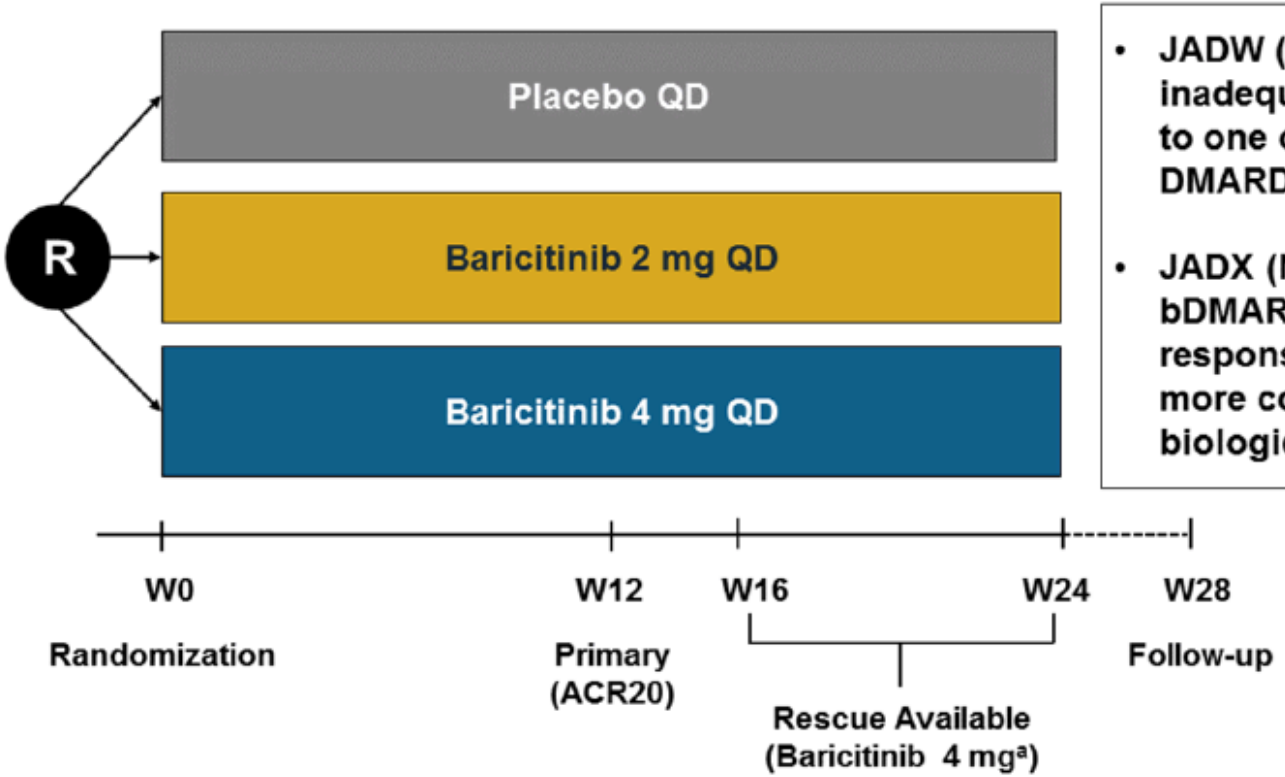
Monotherapy Vs. Multi-drug therapy

"Figure out a drug's safety/efficacy first, approve it, and then figure out how best to use it"

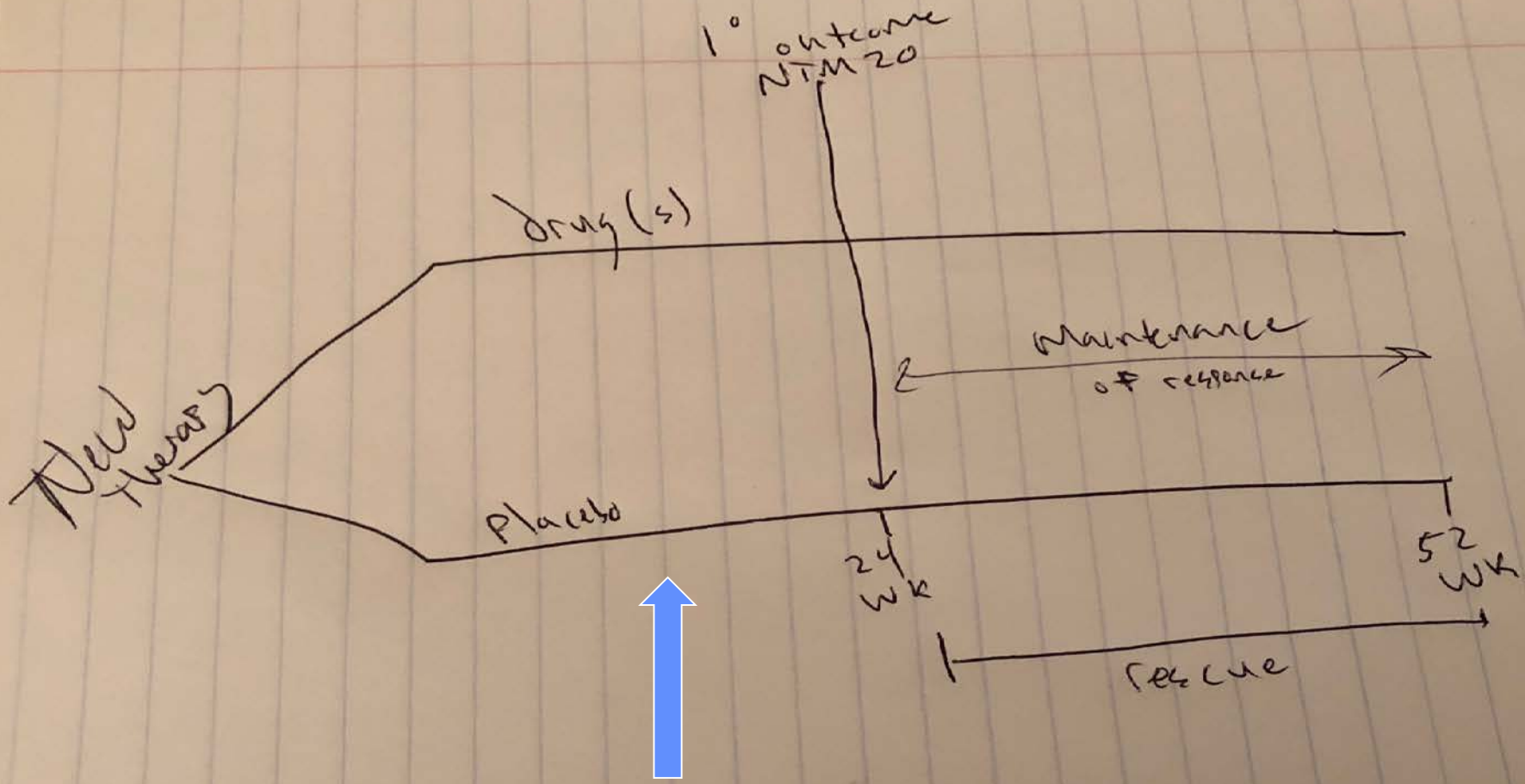
- **Design should reflect scientific question**
  - **Combination therapy must be justified**
  - **Easier to figure out a drug in monotherapy**
- **Phase 3 trials**
  - **Generally should reflect how you think drug should be used post-approval**
  - **Acquired drug resistance an issue, but not for all drugs**
- **Strategy trials**
  - **step up, step down, combinations, versus other drugs**

Winthrop K. Alaska Air, seat 10F, 4/7/2019

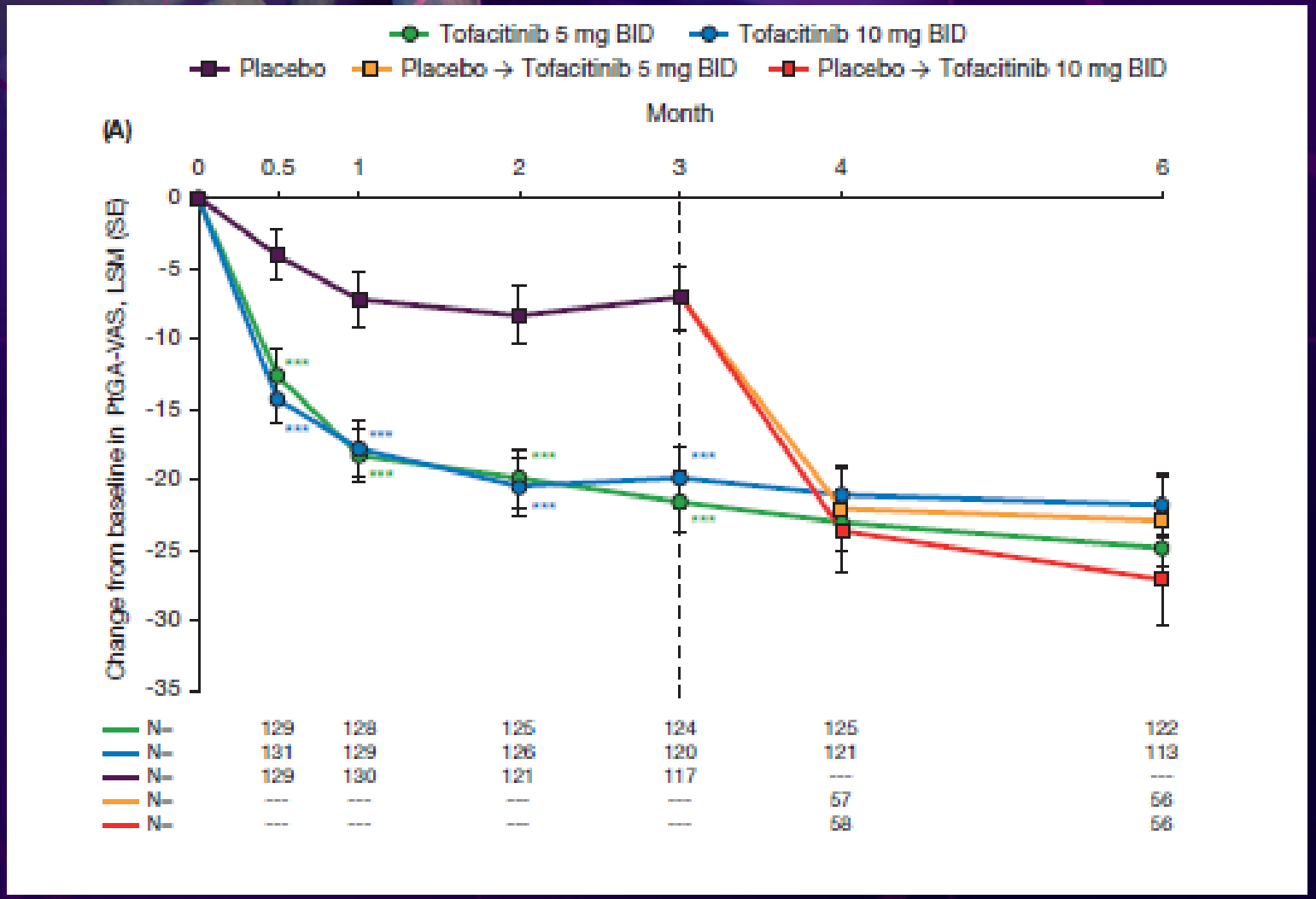
Figure 5: Study Design for JADW and JADX



- JADW (N = 527 bDMARD-IR): inadequate response or intolerance to one or more injectable, biologic DMARDs
- JADX (N = 684 cDMARD-IR, bDMARD-naïve): inadequate response or intolerance to one or more conventional DMARDs, and biologic DMARD naïve


1° outcome
NTM20
drug(s)
Maintenance
of response
New therapy
Placebo
24 WK
52 WK
rescue

12-16 weeks



Strand V et al. RMD Open 2019

A small trial to prove efficacy

- Focussed patient population
- Small, tight groups of clinicians who are closely involved with, and ”invested in”, the trial
- A good drug

Plus a larger trial to prove safety

- Larger patient population
- Simple data-collection: meds, AEs – not much else!

Acknowledgements

- Close colleagues and friends at variety of institutions including:
  - OHSU, NJMC, Mayo, UT Tyler, NIH, PCORI, Univ. Ontario, U Florida, CDC, ATS/IDSA, OHSU, OHA, ACR, EULAR, and ERS
  - FDA and industry partners