Quantitative Linkage Between TTP and Time to Culture Negative Status to Optimize Drug Development Decisions

Critical Path to TB Drug Regimens 2017 Workshop
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Critical Path to TB Drug Regimens

Background

- There is currently a need to develop quantitative tools to:
  - more **accurately evaluate efficacy** in Phase II clinical trials for combination regimens for TB and
  - more **reliably predict** clinically relevant endpoints for Phase III clinical trials.

- The linkage between early biomarker measurements in Phase II and long-term clinical outcomes in Phase III may help increase efficiency of drug development for TB regimens.

- If successful, this novel approach may reduce the time required to develop an innovative regimen from decades to years.

Time to Positivity (TTP)

- With the culture-based evaluation of TB, a parameter has emerged as an alternative to solid-media cultures: time to detection (TTD), also known as time to positivity (TTP).

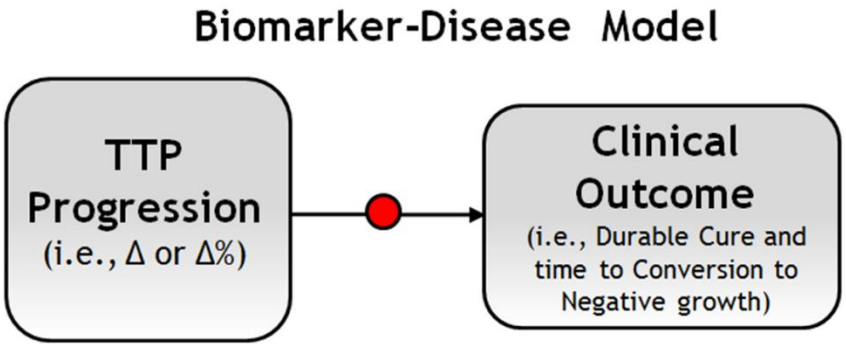
- TTP represents the time to detectable growth of *Mycobacterium tuberculosis* (Mtb) in culture.

- Potential use of TTP as an early indicator of treatment efficacy comes from some early work performed by Epstein et al., who showed that TTP of Mtb in sputum culture correlates with the response to anti-TB therapy.

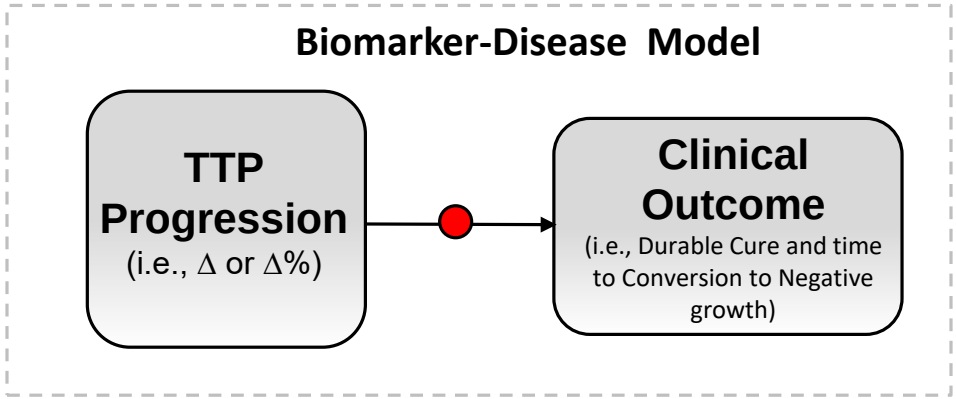
Goals

- Evaluate the relationship of TTP trajectory parameters with clinically-relevant endpoints (durable cure and relapse), based on data from 11 Phase II studies and the REMox trial.

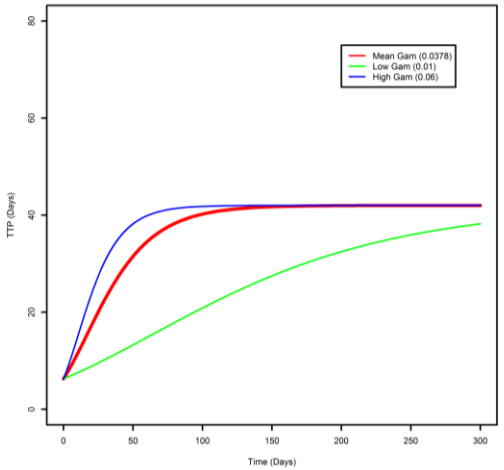
- Create Biomarker-Disease Model by Linking Above Models



Biomarker-Disease Model



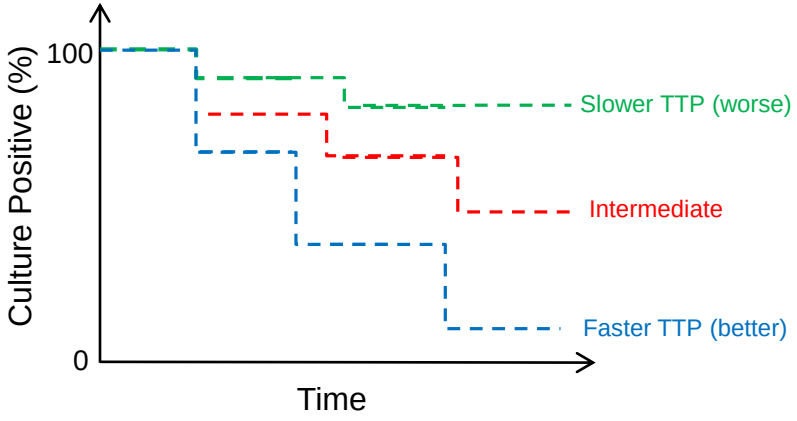
TTP-Specific Parameters



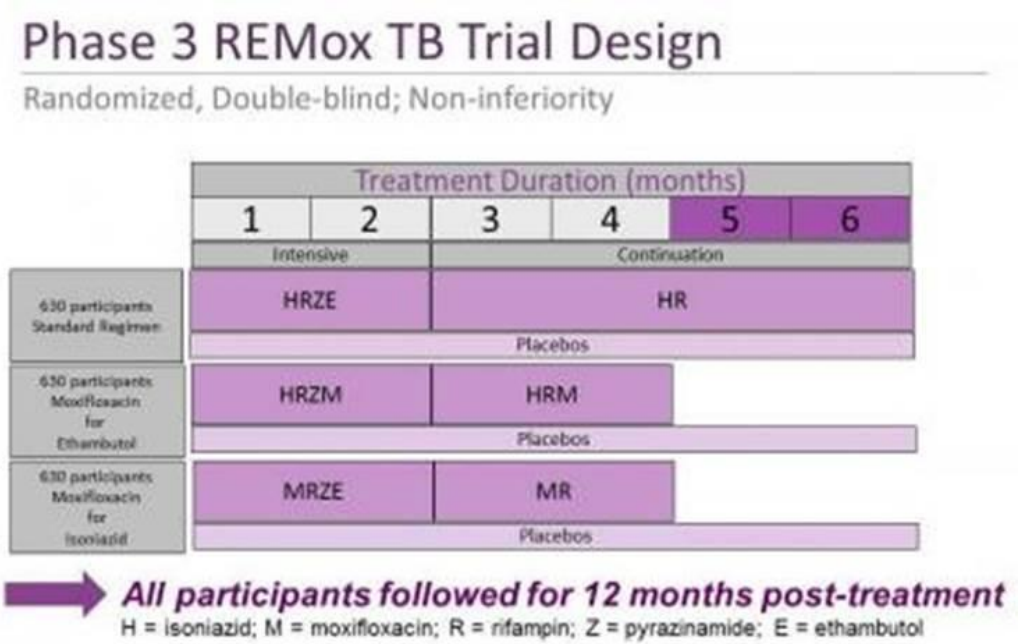
Parametric survival model driven by

TTP-specific Parameters (e.g., gamma)

Time-to-Event Model (Survival) Based on ReMOx Data



REMox TB Trial (Phase III): TTP and Clinical Response



- **Biomarker**: TTP

- **Endpoint:** Time to culture-negative status, defined as two negative-culture results at different visits without an intervening positive result. The date of culture-negative status was defined as the date of the first negative-culture result.

http://clinicaltrials.gov/ct2/show/NCT00864383

TTP Data: Gompertz Model

- A Gompertz model resulted in the best goodness-of-fit .

$$TTP(time) = Alpha * exp^{[-Beta * exp(-Gamma*Time)]}$$

Alpha: i.e. the maximum value that can be reached with the incubation time (i.e,. TTP=42 days)

Beta: TTP at the starting observation time (i.e., baseline)

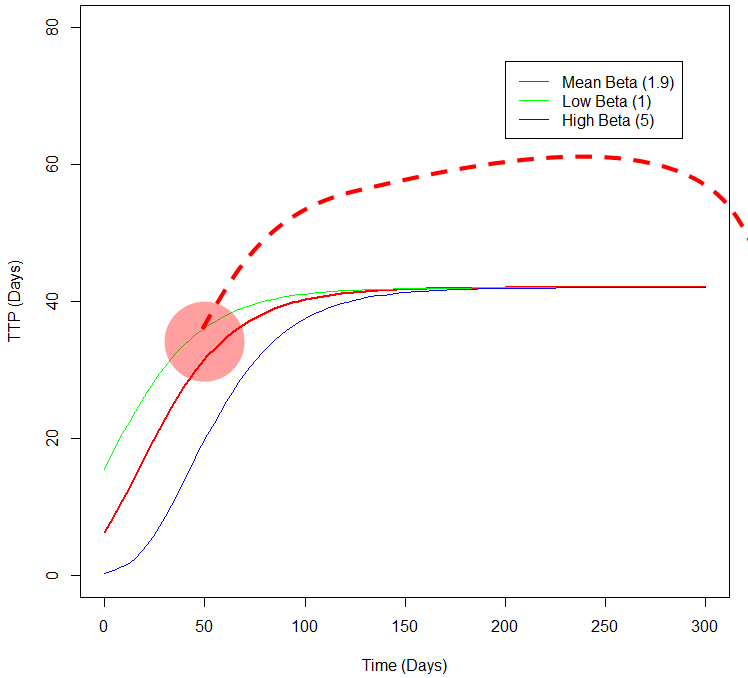
Gamma: A constant related to the proliferative ability of Mycobacterium tuberculosis (Mtb) in culture (rate of growth)

- The quantitative model describing the actual shape of TTP trajectory over time using a mixed-effects modeling approach was developed based on data collected in 11 Phase II studies.

Gompertz Function & Possible Linkage to Response

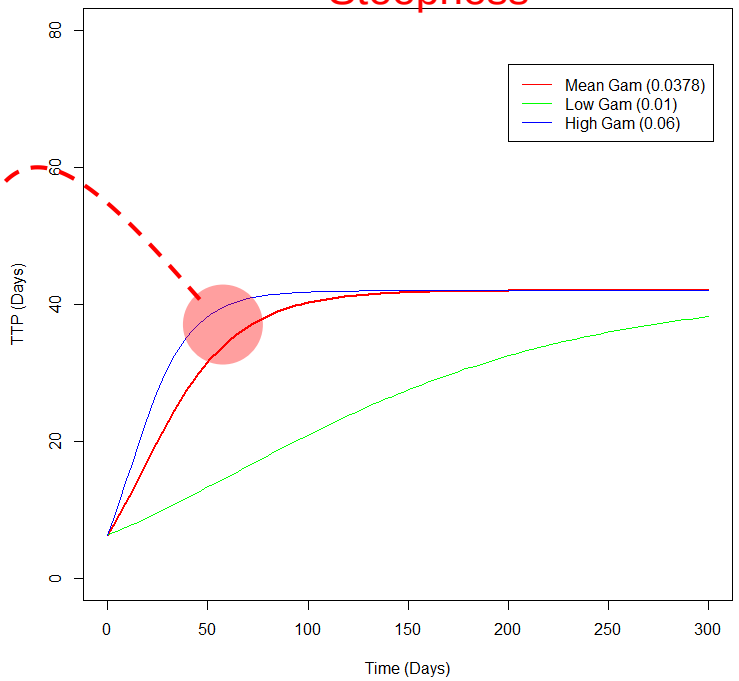
Effect of Beta (baseline parameter) on TTP Profile

Left-Right Shift, Same Steepness



Effect of Gamma (rate of growth) on TTP Profile

Steepness



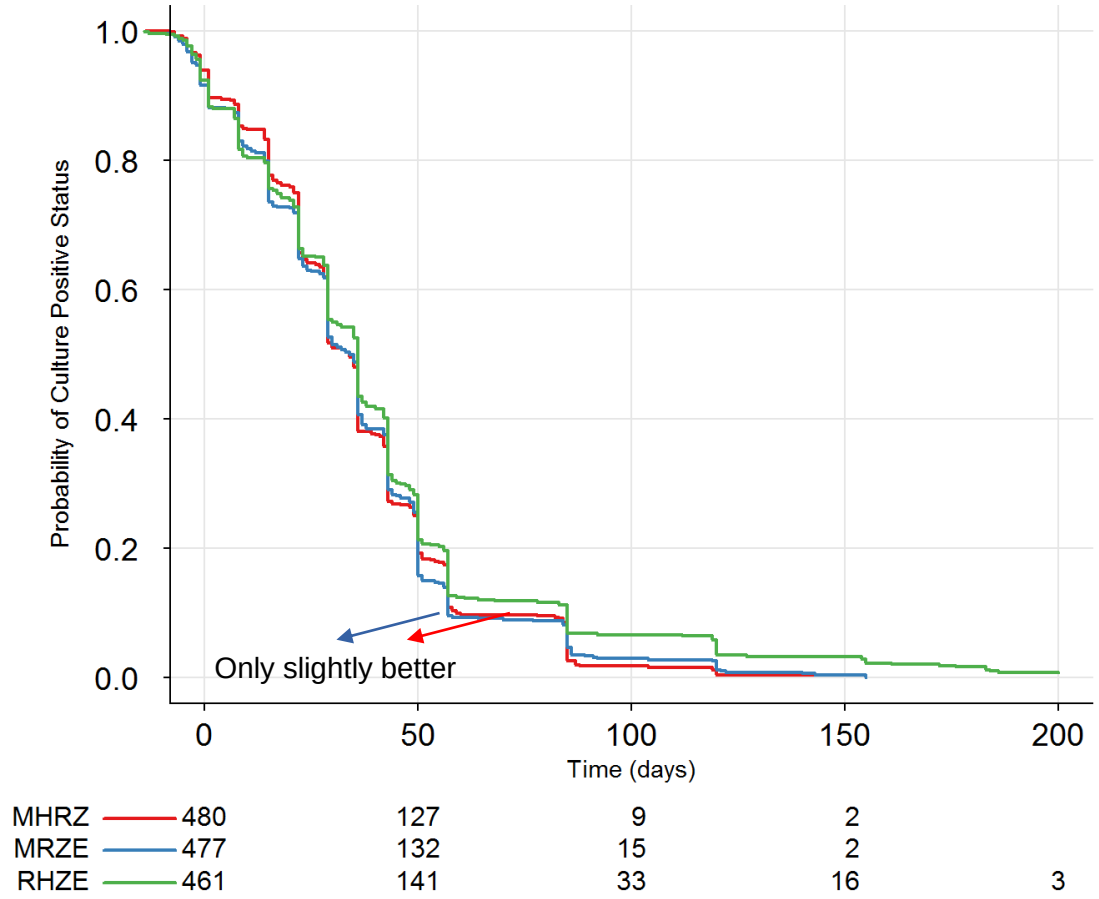
It could be hypothesized that the parameter describing these TTP profiles (sub-population) may be predictive of durable cure in a Phase III study.

REMox TB Trial (Phase III): PD Parameters of TTP

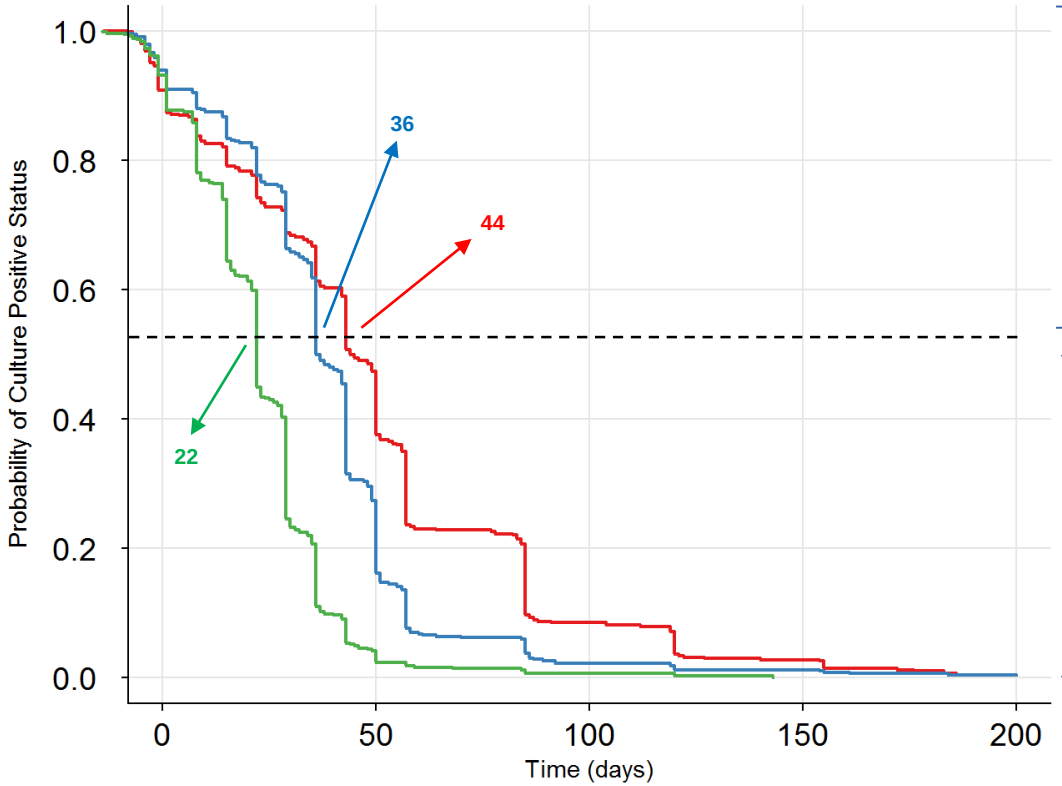
Parameters	Isoniazid (HRZM)	Ethambutol (MRZE)	Control (RHZE)
Maximum TTP (Days)	42	42	42
Baseline TTP (Day)	2.02	2.02	2.03
TTP Growth (Day^{-1})	0.0483	0.0522	0.0438

Half-Life = 14.4 days **13.3 days** **15.8 days**

Kaplan-Meier – Treatment-Response

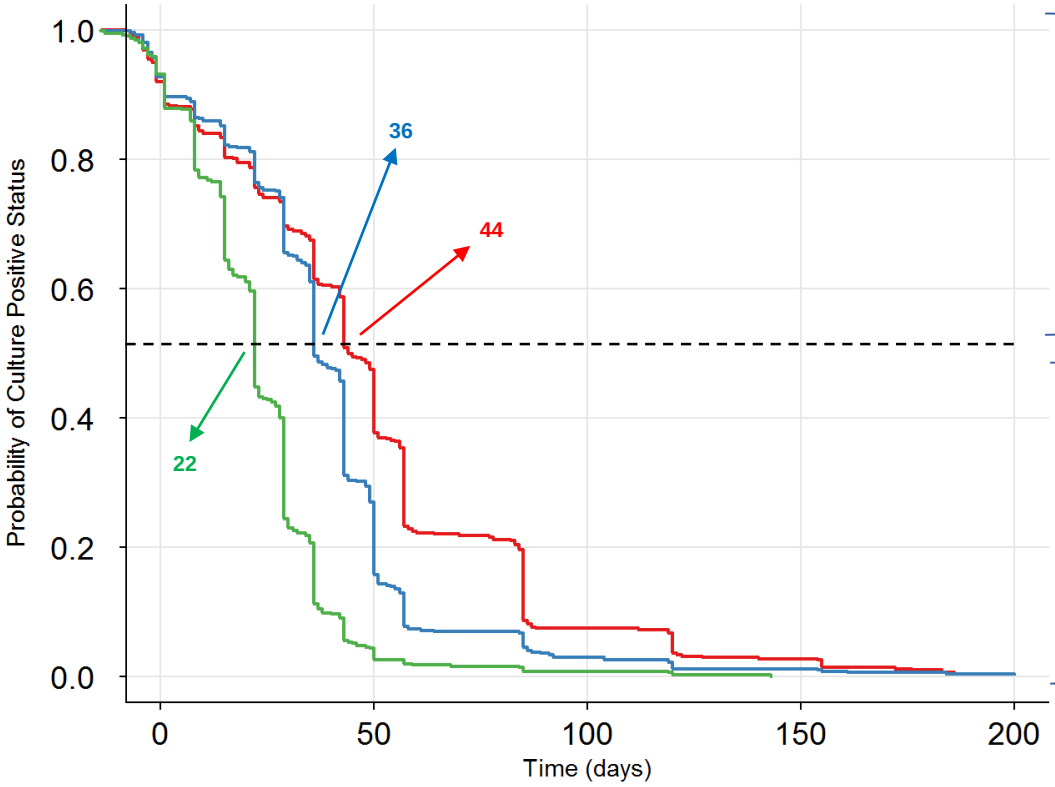


Kaplan-Meier – Response By Tertiles of Gamma (12 Months)



- The higher the Gamma (3rd tertile, green line), the shorter the time to conversion to Culture-Negative Status (all treatments combined).

Kaplan-Meier – Response By Tertiles of Gamma (TTP data from 0 to 8 weeks)

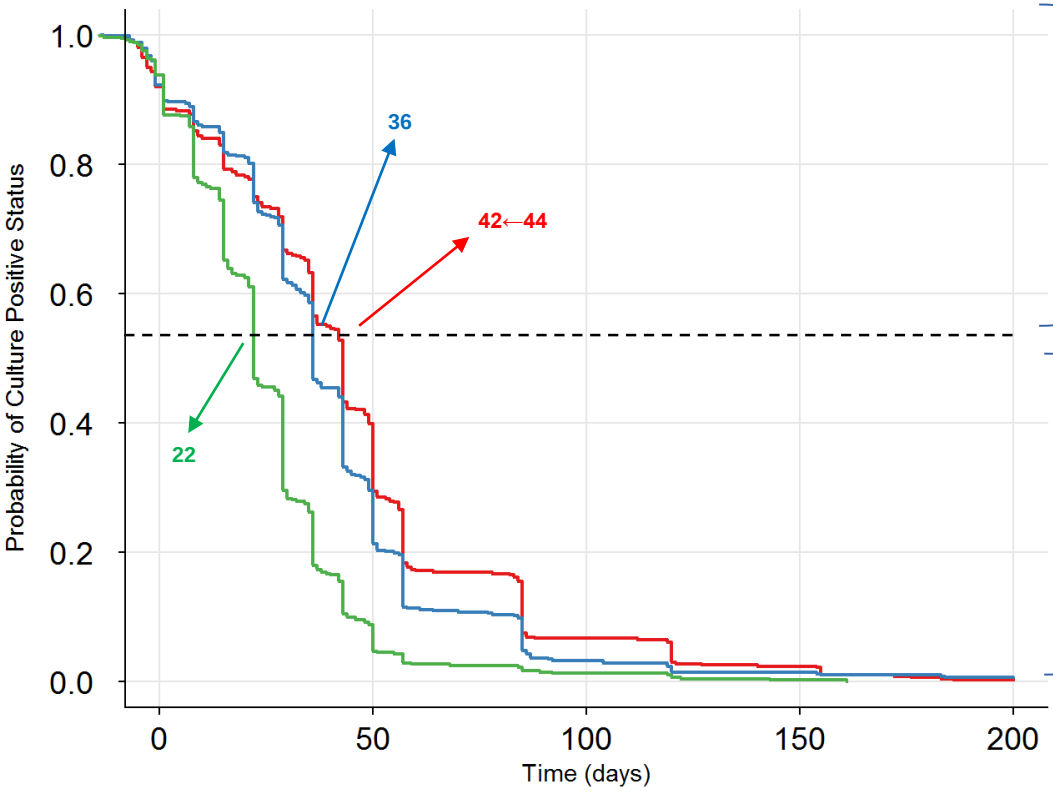


Probability Range for Non-Responders

Probability Range for Responders

The higher the Gamma (3rd tertile, green line), the shorter the time to conversion to Culture-Negative Status (all treatments combined). TTP results derived from 0-8 weeks were similar to those derived from the whole TTP duration.

Kaplan-Meier – Response By Tertiles of Gamma (TTP data from 0 to 4 weeks)

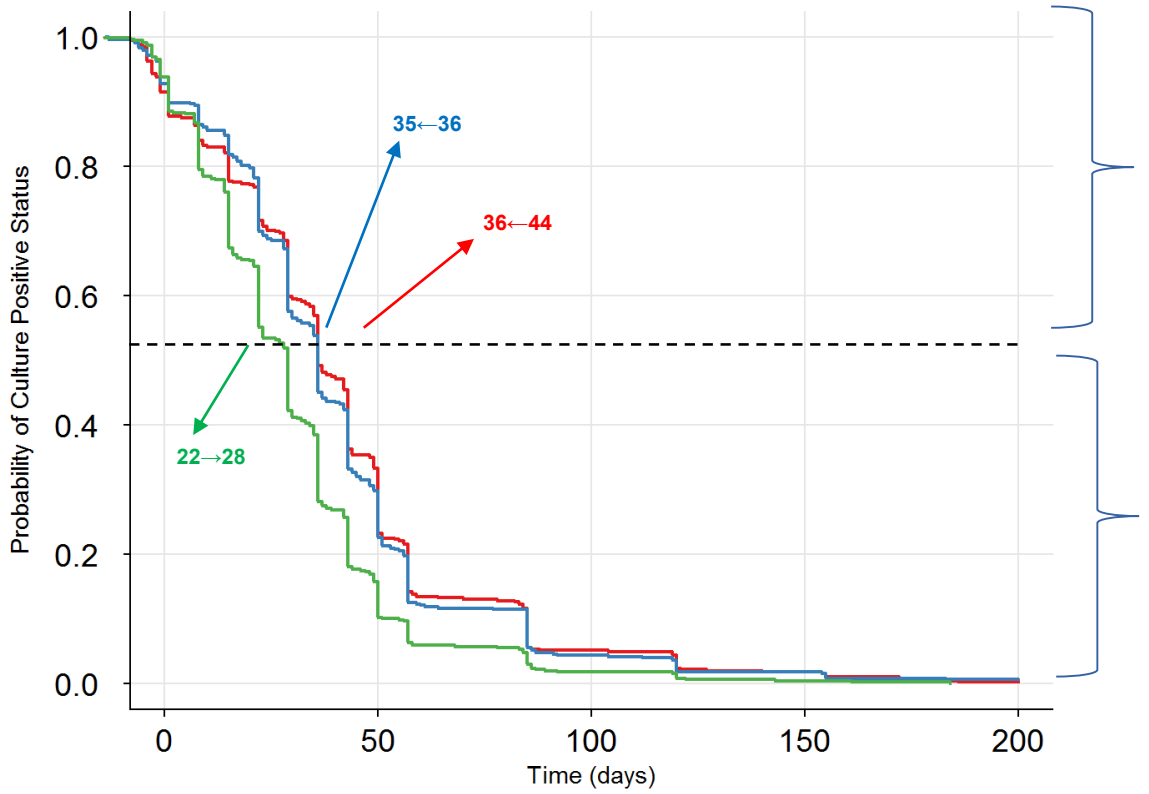


Probability Range for Non-Responders

Probability Range for Responders

The higher the Gamma (3rd tertile, green line), the shorter the time to conversion to Culture-Negative Status (all treatments combined). TTP results derived from 0-4 weeks were similar to those derived from the whole TTP duration.

Kaplan-Meier – Response By Tertiles of Gamma (TTP data from 0 to 2 weeks)



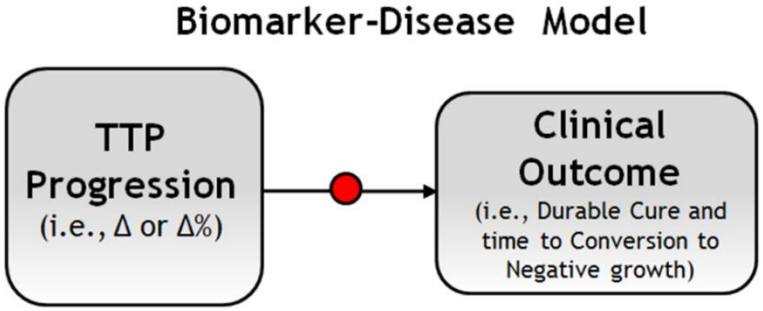
The higher the Gamma (3rd tertile, green line), the shorter the time to conversion to Culture-Negative Status (all treatments combined). Loss of resolution if TTP results are derived from 0-2 weeks.

Conclusion

The linkage between early biomarker measurements in Phase II and long-term clinical outcomes in Phase III may help increase efficiency of drug development for TB regimens.

The rate of TTP growth (as per Gompertz model) is a potential marker to use as a prognostic biomarker of response.

The early part of TTP profile is very informative (0-4 weeks).



Application/Value

- Determine early changes in TTP in Phase II (e.g., dose ranging study) and effect on long term clinical outcome in Phase III to guide decisions.
- Inform Gate decisions when considering advancing from Phase II into Phase III

Thank you!

Acknowledgments

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Appendix

Gompertz Model Development

Methodology: Datasets and Populations

- **TTP Data Collected**
  - 10 Phase II Studies
  - 1750 Subjects with TB
  - Treatments
  - Rifafour-Based (RHZE)
  - PHZE
  - Bedaquiline-Based (TMC207)
  - Pretomanid-Based (PA-824)
  - Pyrazinamide (PZ)
  - Clofazimine (CZ)

- **Baseline Characteristics**
  - Male (65.9%) ; Female (34.1%)
  - HIV (9.1%); non-HIV (90.3%)
  - CD4 Counts (cells/µL)
    - Mean(CV%): 654 (47.5)
    - Median (Range): 607 [19.0, 2952]
  - Lung Cavitation
    - Yes (58.2%)
    - No (41.8%)
  - Race
    - White (11.7%)
    - Black or AA (59.4%)
    - Asian (7.5%)
    - Hispanic (1.5%)
    - Other (17.7%), Missing (2.1%)

Methodology: Modeling Approach

- Extensive evaluation of mathematical functions to describe the non-linear and saturable behavior of TTP over time.
  - Linear Models (previously tested)
  - Emax and Gompertz (sigmoidal, asymptotic function)
  - Cubic & Quadratic Models (exponential functions)
  - Weibull Models (a stretched exponential function)

- With and without right censoring
  - Right censored data was implemented using M3 method (estimate likelihood for 42)

- Covariate Analysis (Sources of Variability)
  - HIV (Yes/No), CD4 Counts
  - Pulmonary Cavitation
  - Treatments

- Software: Phoenix NLME v1.3 (non-linear mixed effect modeling)

Results: Introducing the Gompertz Model

- A Gompertz model resulted in the best goodness-of-fit.

$$TTP(time) = Alpha * exp^{[-Beta * exp(-\mathbf{Gamma}*Time)]}$$

i.e. the maximum value that can be reached with the incubation time (i.e,. TTP=42 days)

TTP at the starting observation time (i.e., baseline)

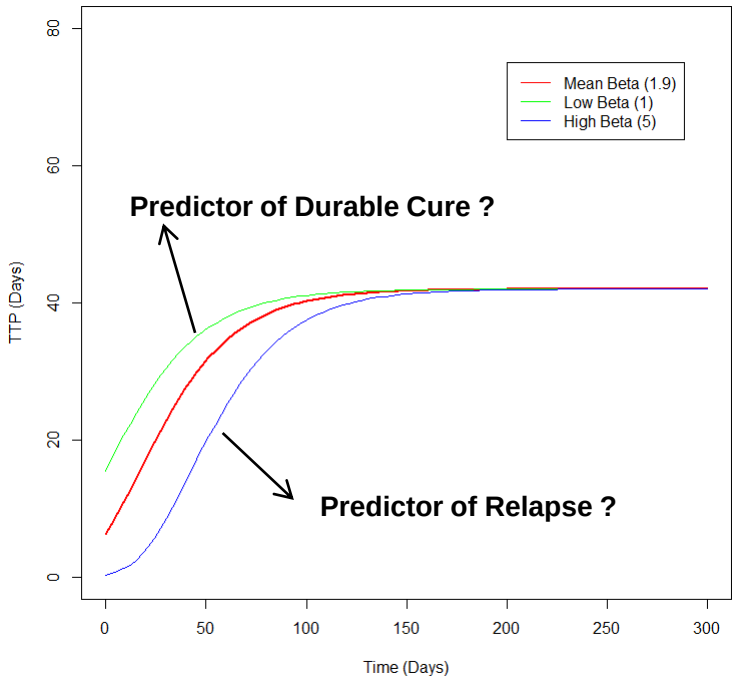
A constant related to the proliferative ability of Mycobacterium tuberculosis (Mtb) in culture (rate of growth)

- Note: Often used in oncology to model tumor size over time (to be used as a predictor of survival).

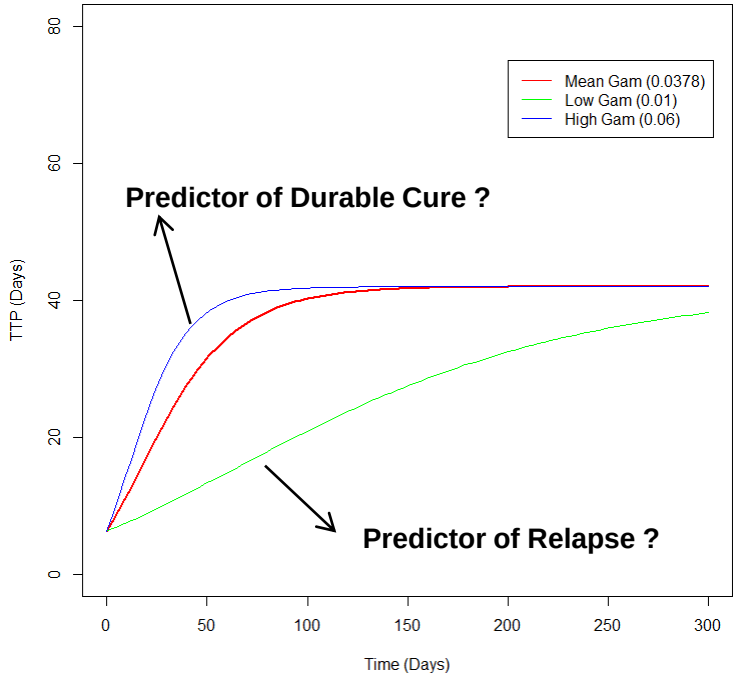
Results: Introducing the Gompertz Model

- Flexibility of a Gompertz model to characterize non-linear profiles

Effect of Beta Parameter on TTP Profiles
Left-Right Shift, Same Steepness



Effect of Gamma Parameter on TTP Profile
Steepness



Gompertz Model Parameters

Parameters	Estimate (RSE%)	Between-Subject Variability (%)
Maximum TTP (Days)	42	
Baseline TTP (Day)	1.95 (0.885)	26.8
TTP Growth (Day^{-1})	0.0378 (2.48)	93.1

Half-Life = 18.3 days

- An additional benefit of the Gompertz model is conversion of the gamma factor (rate of TTP) into a half-life i.e., ln2/gamma.
- The above results suggest that TTP doubled every 18 days.
- Residual error: 23.7%