

Evaluating the trade-off between quantity and quality of life through quality-adjusted survival analysis



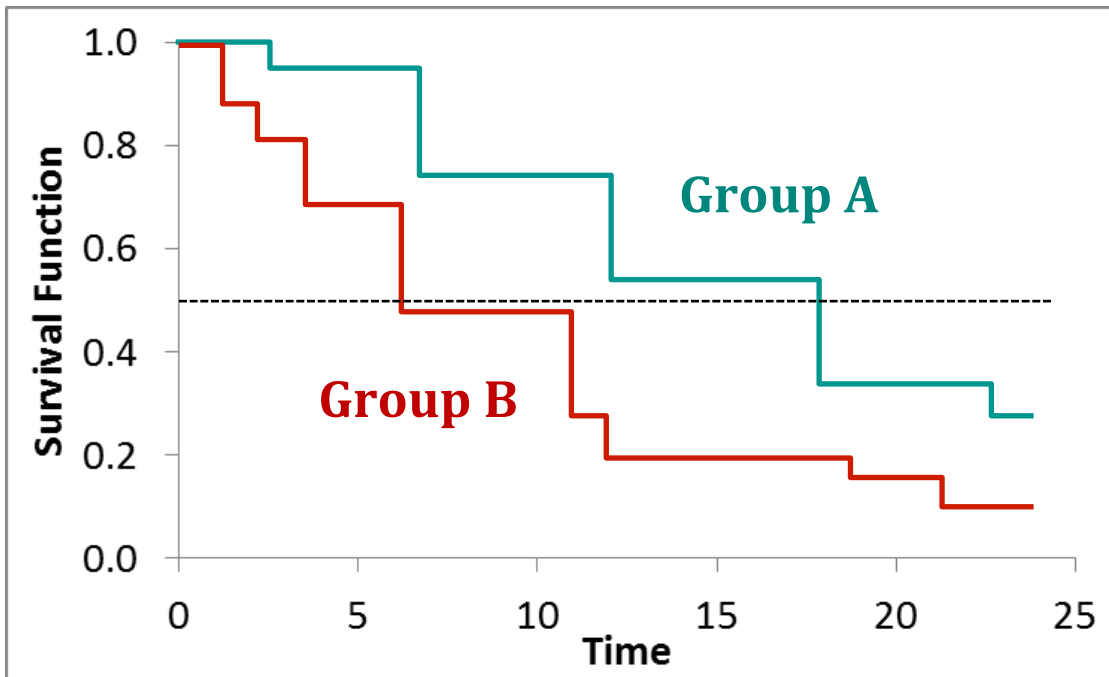
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**ICON Biostatistics & Programming
Medical Affairs Statistical Analysis**



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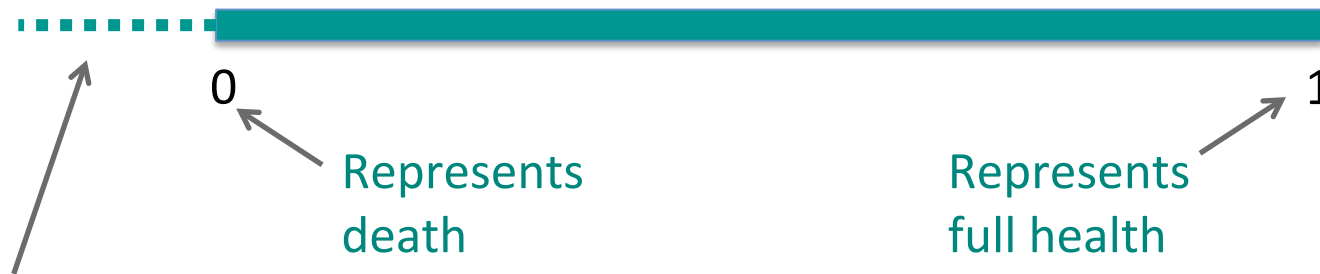
- Therapies involve trade-offs → Benefits vs Risks
- In diseases with poor survival, question of quantity versus quality of life:
 - Benefit of prolonged survival → Quantity of life
 - Risk of toxicity → Quality of life
- Endpoints reported separately
- Sometimes the treatment choice is clear
- What if treatment choice is not clear?
 - Treatment A has better survival outcomes than Treatment B
 - Treatment A has poorer quality of life profile than Treatment B
- Helpful to calculate a summary measure → QASA



- **Median survival:** Where $S(t) = 0.5 \rightarrow$ Main outcome of RCTs
- **Mean survival:** Area under $S(t) \rightarrow$ Of interest in HEOR studies
 - Never fully defined unless you observe death in every patient
 - Restricted to time point of interest (restricted mean)
 - $Mean[S(t)] \downarrow L = \int_0^L S(t) dt$

Crash course: Health-related quality of life (HR-QoL)

- Perceived attribute of well-being as it relates to health status
- Commonly used instrument is EuroQol (EQ-5D)
- EQ-5D is an example of a *health utility*
 - 0 = Death
 - 1 = Full Health



Negative values:
Health states worse
than death

- QASA combines these two techniques → Survival analysis weighted by HR-QoL
- Multiply survival function by HR-QoL over time
- QALY = Quality-Adjusted Life Year
 - [Years of life in health state] x [HR-QoL weight of health state]
 - 1 QALY = 1 year of life in full health = 2 years of life in 50% health
 - Analogous to **quality-adjusted mean** survival (area under curve)

$$Mean[S(t)] \downarrow L = \int_0^L S(t) dt \qquad QALY \downarrow L = \int_0^L S(t) Q(t) dt$$

where

S(t) = survival function, L = restricted time

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Case Study Example – Oncology Clinical Trial

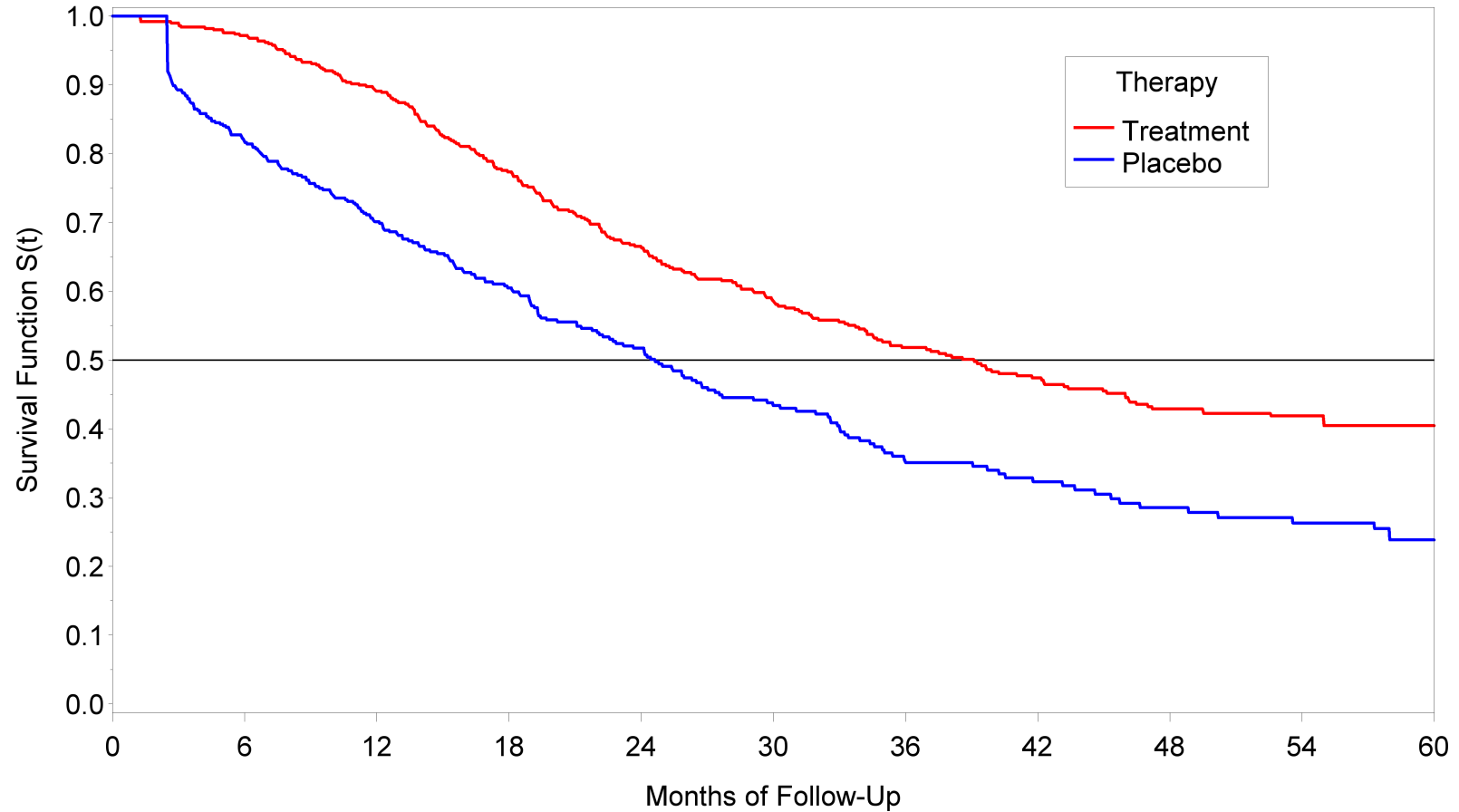
- Oncology trial data were simulated to mimic the overall attributes of actual clinical trial (i.e., I can speak freely)
- Disease = Generic term “Cancer”
- Two possible randomly assigned regimens:
 - **Treatment:** “**Red pill**” (n = 500) → Better survival, poorer QoL
 - **Placebo:** “**Blue pill**” (n = 500) → Poorer survival, better QoL
- Patients followed for 60 months or until censoring
- HR-QoL assessed at Baseline, M1, M6, M12, M18, ..., M60
- **Objective:** To assess the survival advantage of Treatment and whether this advantage still holds after adjusting for HR-QoL

- PROC LIFETEST can be used to generate Kaplan-Meier estimates and plots along with associated statistics (i.e., survival time estimates):

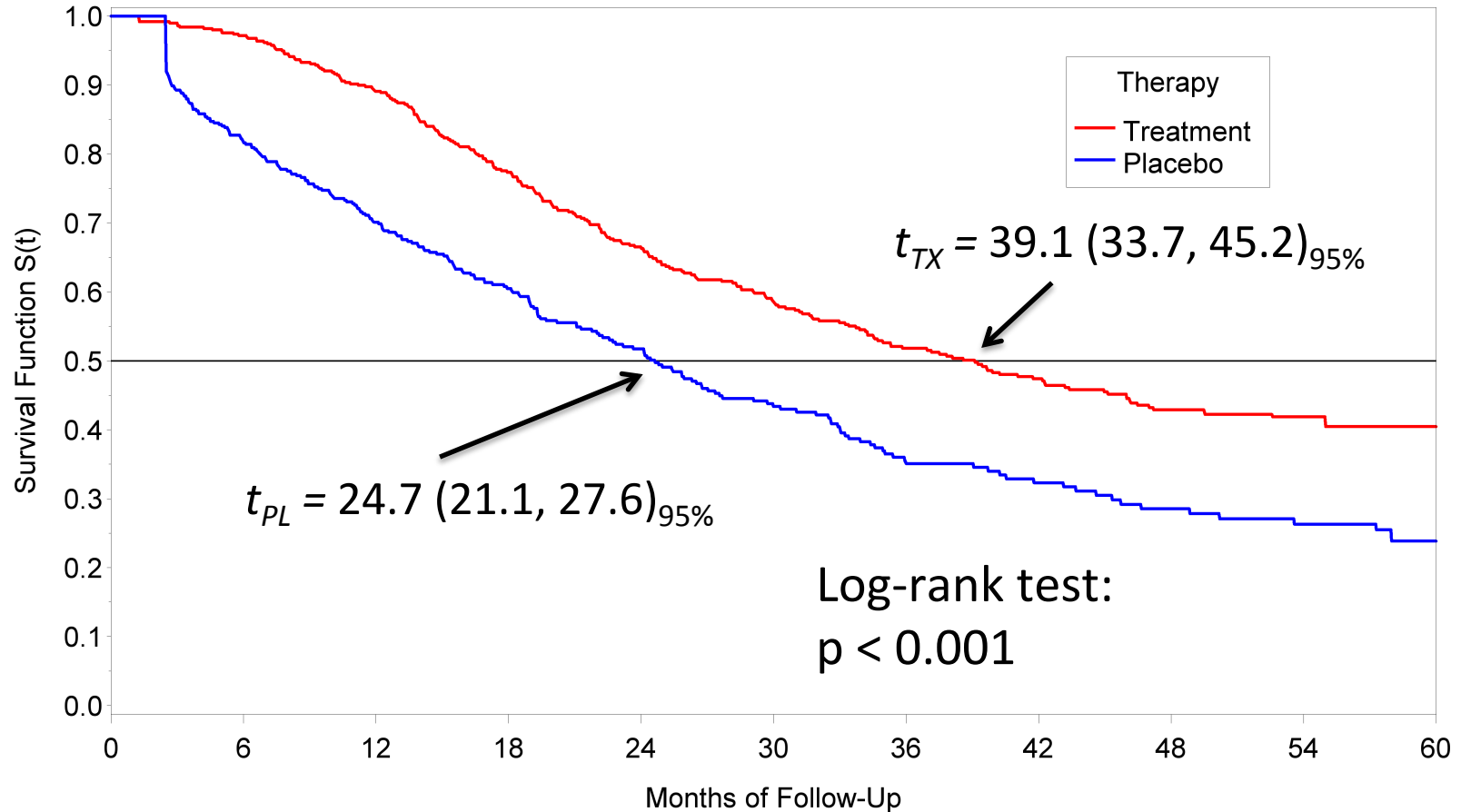
```
proc lifetest data=surv01 method=km;  
  strata tx;  
  time t_mo*death(0);  
run;
```

- Where
 - tx = Treatment group (1=Treatment, 2=Placebo)
 - t_mo = Follow-up time in months
 - death = Indicator for death (1=died, 0=censored)
- Mean HR-QoL scores plotted over time by treatment group using PROC GPLOT.

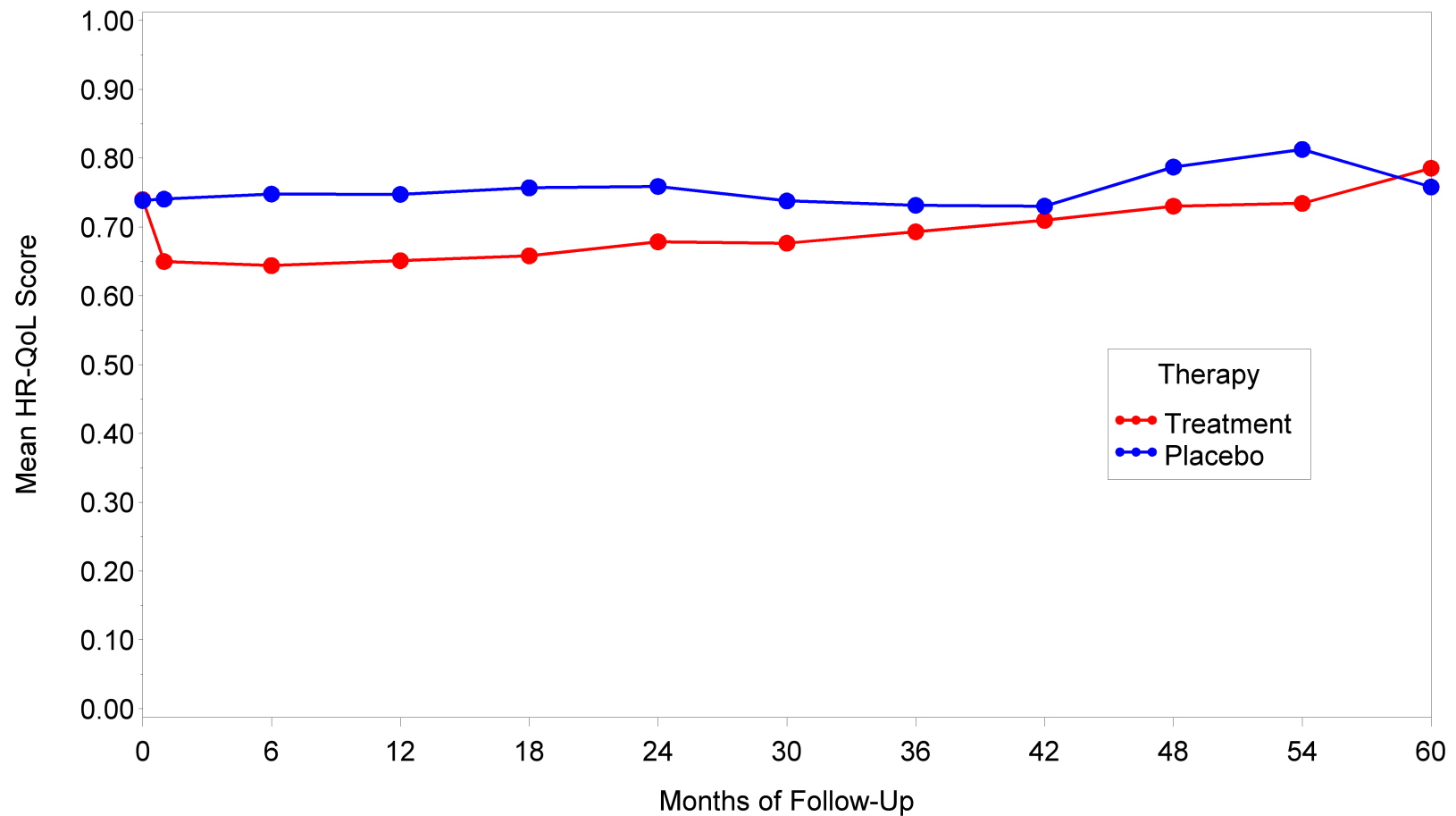
Kaplan-Meier plots of overall survival for study population



Kaplan-Meier plots of overall survival for study population

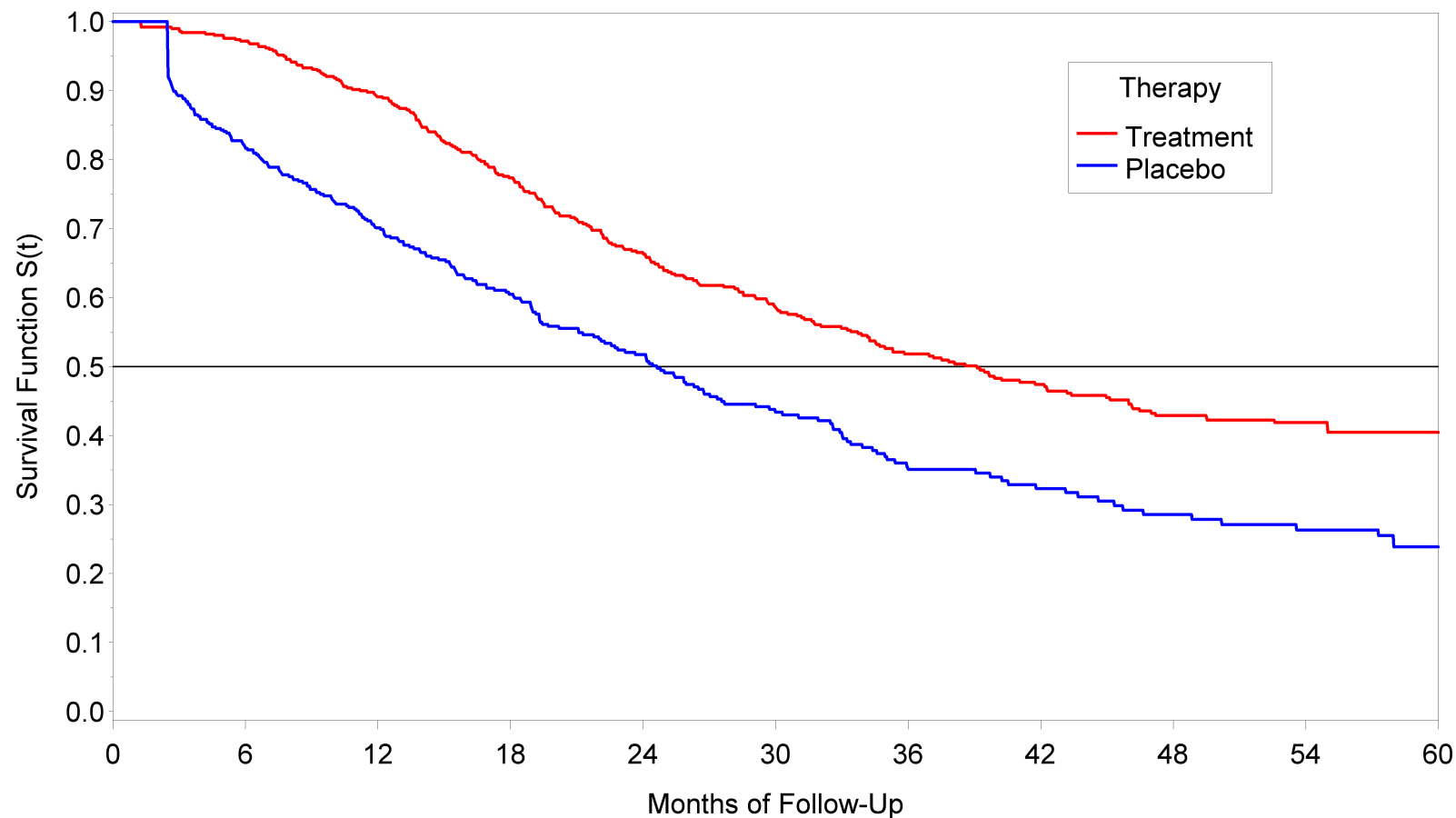


Health-related quality of life over time by treatment group



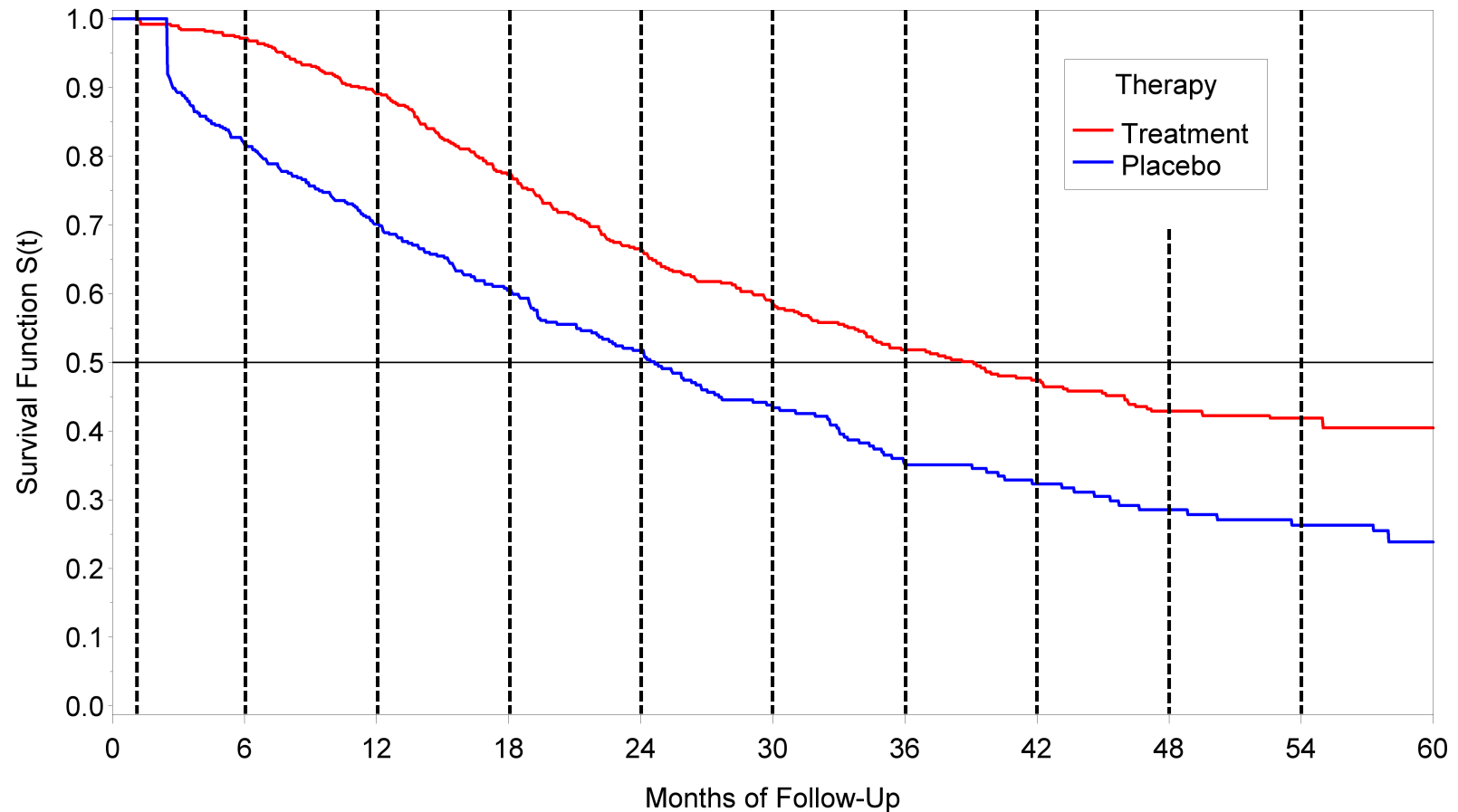
Put them together: Back to the K-M Plot

Kaplan-Meier plots of overall survival for study population



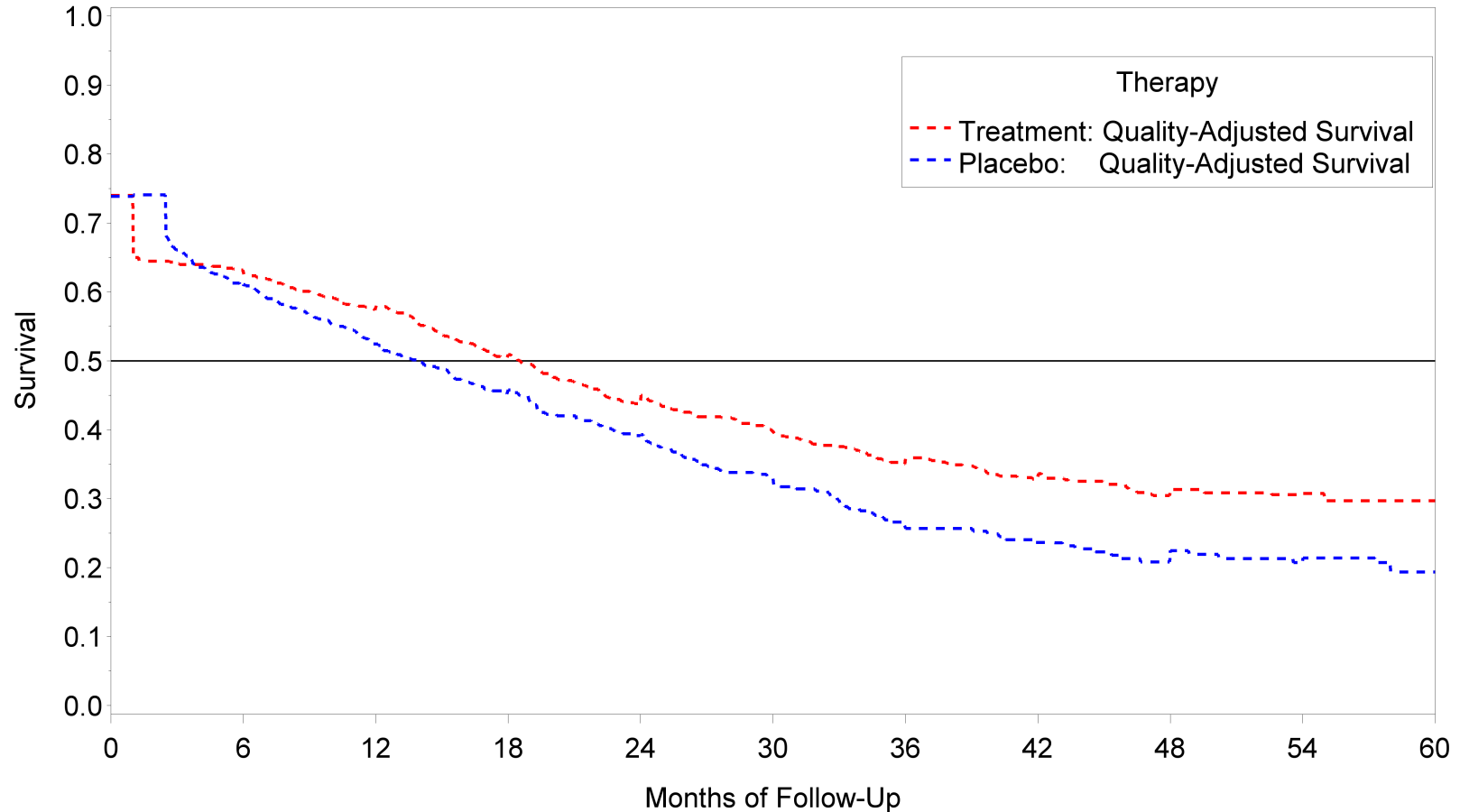
Partitioned Kaplan-Meier Plot at HR-QoL Assessments

Partitioned Kaplan-Meier plots of overall survival for study population



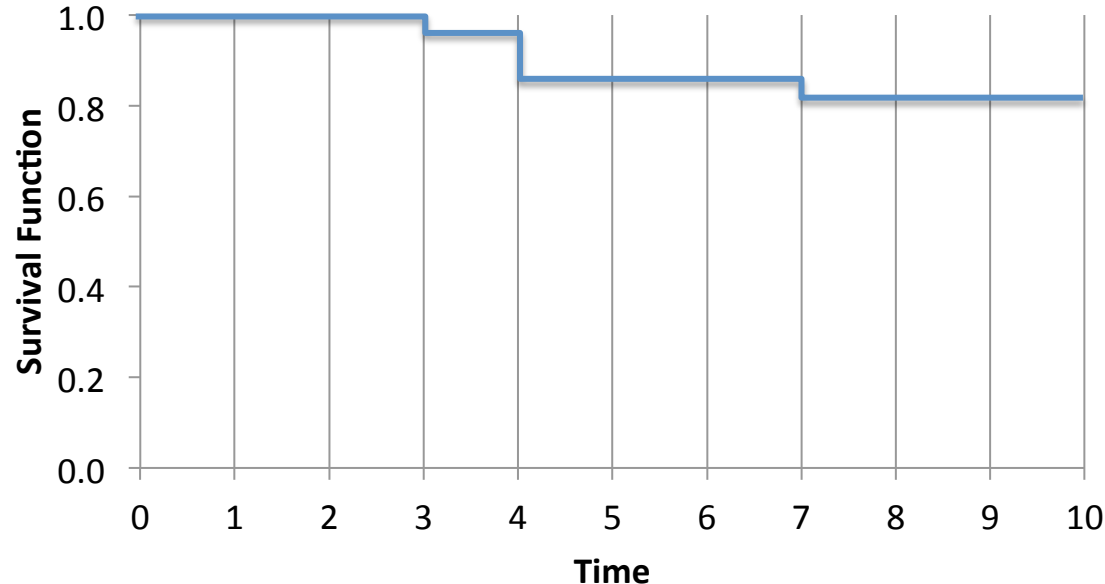
QASA Results: Kaplan-Meier Plots

Quality-adjusted Kaplan-Meier plots of survival



To calculate AUCs by treatment group

- Create a dataset at the study day-level
- Each observation will have the study day, survival function value, and quality-adjusted survival function value
- AUC is the sum of the daily survival function values between the time points of interest. [Trapezoidal method]



SAS macro to calculate AUCs using trapezoidal method

```
%let conv = 30.4368499;

%macro auc (indat=, Ldays=);
ods output summary=_mac01;
proc means data=&indat. sum;
  where (0 lt t_dy le &Ldays.);
  class tx;
  var surv qasurv;
run;

data auc_&Ldays.;
  set _mac01;
  area_surv_mo = (surv_sum / &conv.);
  area_qasurv_mo = (qasurv_sum / &conv.);
run;
%mend auc;

* AUC at overall median follow-up time (20.7 months = 631 days);
%auc (indat=daylevel01, Ldays=631);
* AUC at study end (60 months = 1826 days);
%auc (indat=daylevel01, Ldays=1826);
```

- Then confidence intervals calculated through bootstrap methods

Quality-adjusted (and unadjusted) mean survival at restricted time points

Restricted time point	Group	Unadjusted mean survival in months (95% CI)	Quality-adjusted mean survival in months (95% CI)
Median follow-up (20.7 months)	Treatment (TX)	18.5 (18.1, 18.9)	12.1 (11.8, 12.4)
	Placebo (PL)	15.5 (14.9, 16.1)	11.6 (11.1, 12.1)
	Difference (TX - PL)	3.0 (2.3, 3.8)	0.5 (-0.0, 1.2)
	P value	<0.001	0.052
End of study (60 months)	Treatment (TX)	38.5 (36.6, 40.4)	26.0 (24.6, 27.5)
	Placebo (PL)	29.4 (27.3, 31.8)	22.2 (20.4, 23.9)
	Difference (TX - PL)	9.0 (6.3, 12.0)	3.8 (1.6, 6.2)
	P value	<0.001	<0.001

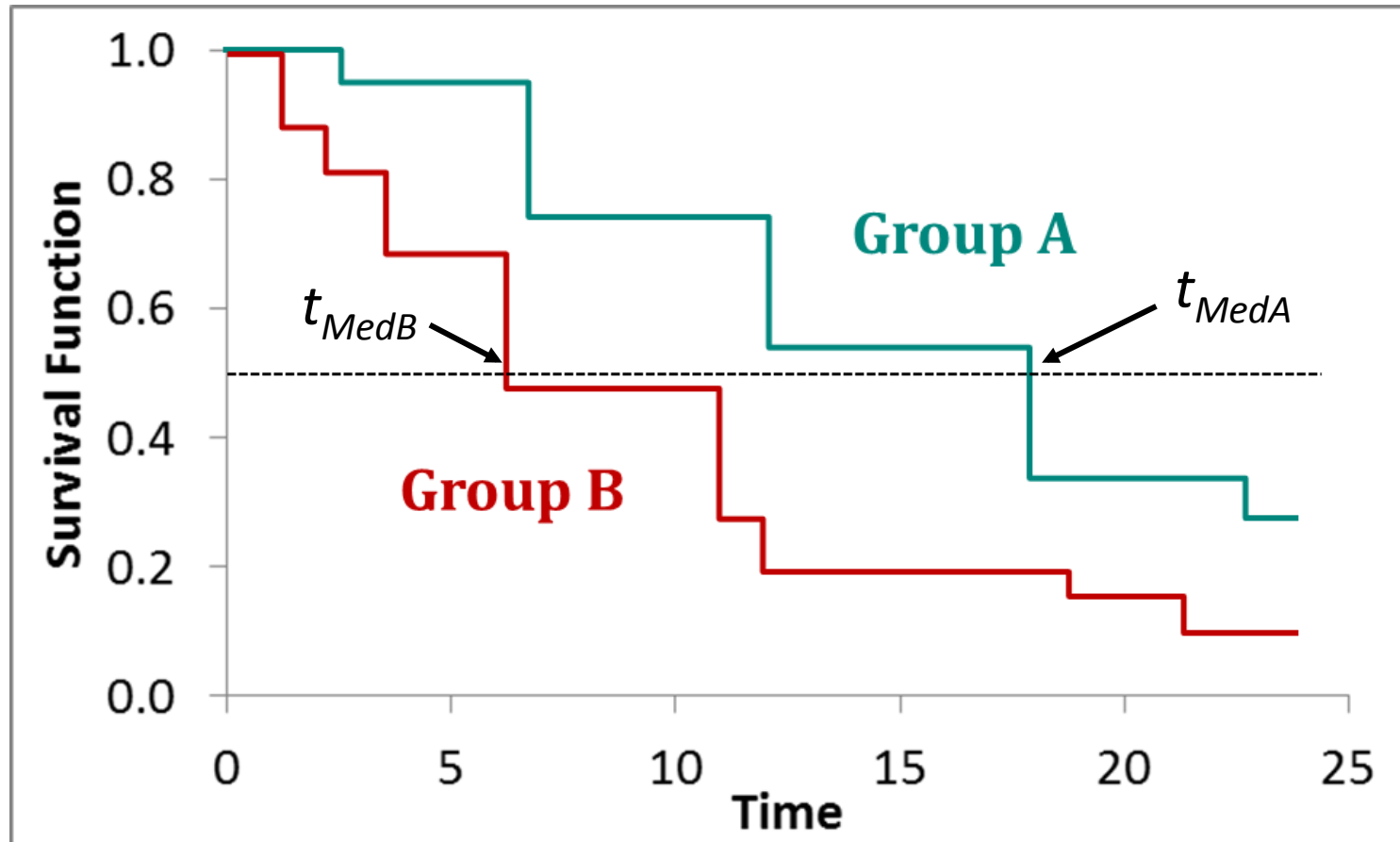
Confidence intervals and p-values obtained through 1000 bootstrap samples

Client:

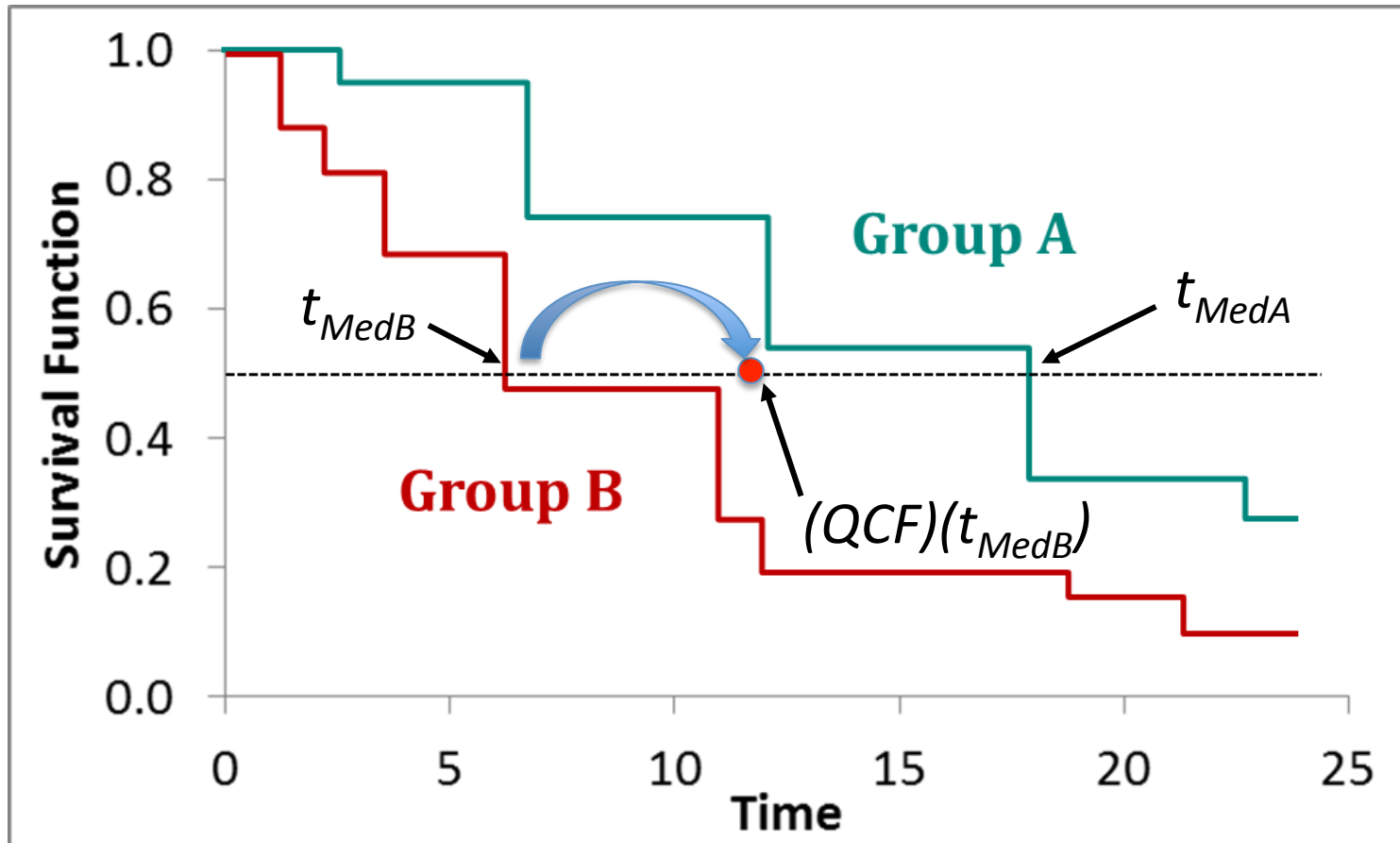
“Why are the results so different from the clinical trial?”

- In clinical trials, median survival times are reported; mean survival times are generally not calculated
- QALYs are analogous to restricted mean survival times
- QASA results not directly comparable to clinical trial results
- No standard method currently exists for comparing median survival times after accounting for quality of life
- We propose an exploratory method to make QASA results more comparable to primary outcomes in clinical trials

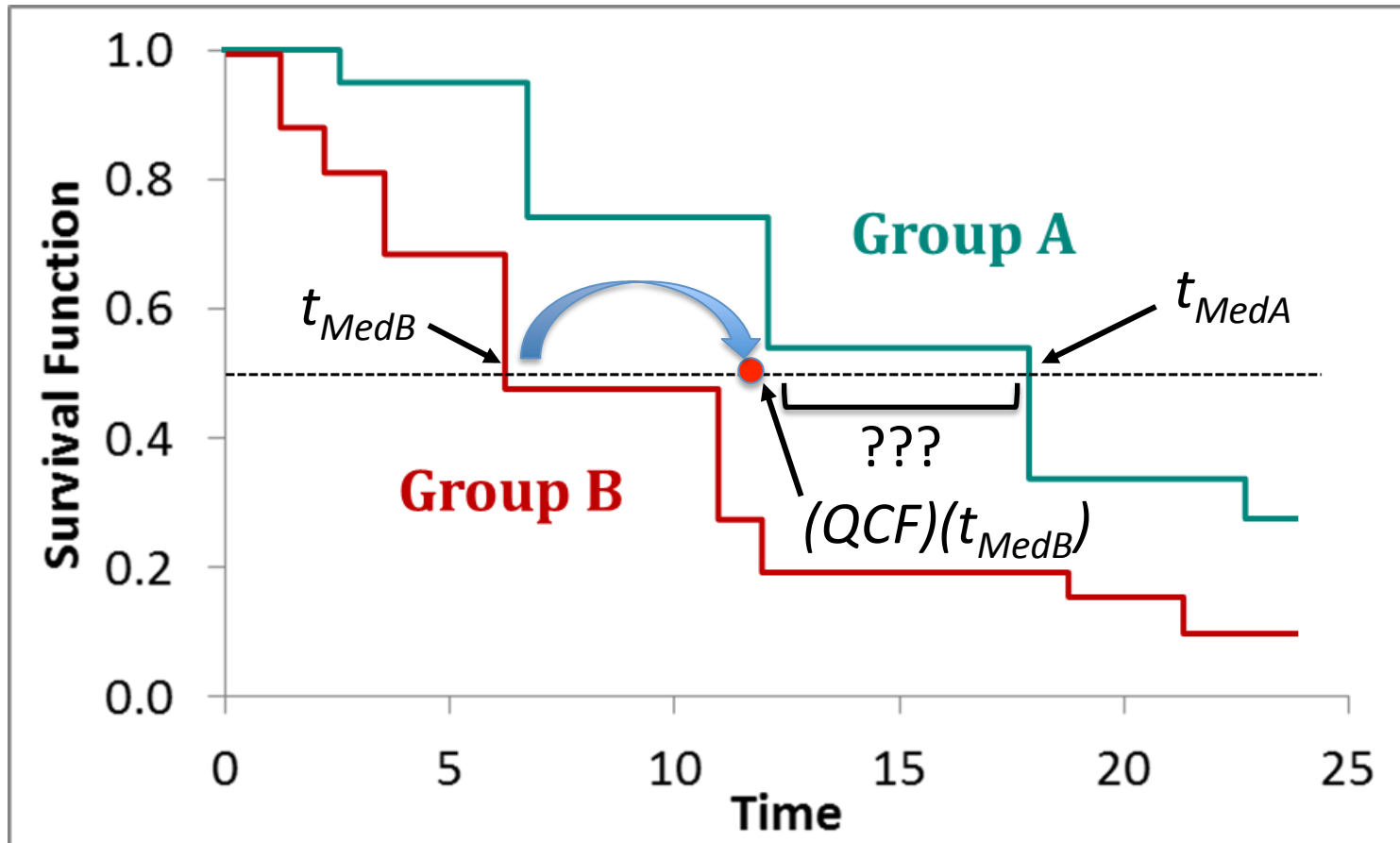
Exploratory Method of Quality-Corrected Median Survival



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Exploratory Method of Quality-Corrected Median Survival



- Quality Correction Factor (QCF)
 - Ratio of HR-QoL for Group B to Group A
 - Should account for variation and be weighted by survival
 - [Area under Quality-Adjusted Plot] / [Area under Unadjusted Plot]
- Build the equation:

$$QCF = \frac{\int_0^{\text{Med}B} S_B(t) Q_B(t) dt}{\int_0^{\text{Med}B} S_A(t) Q_A(t) dt} \bigg/ \frac{\int_0^{\text{Med}B} S_B(t) dt}{\int_0^{\text{Med}B} S_A(t) dt}$$

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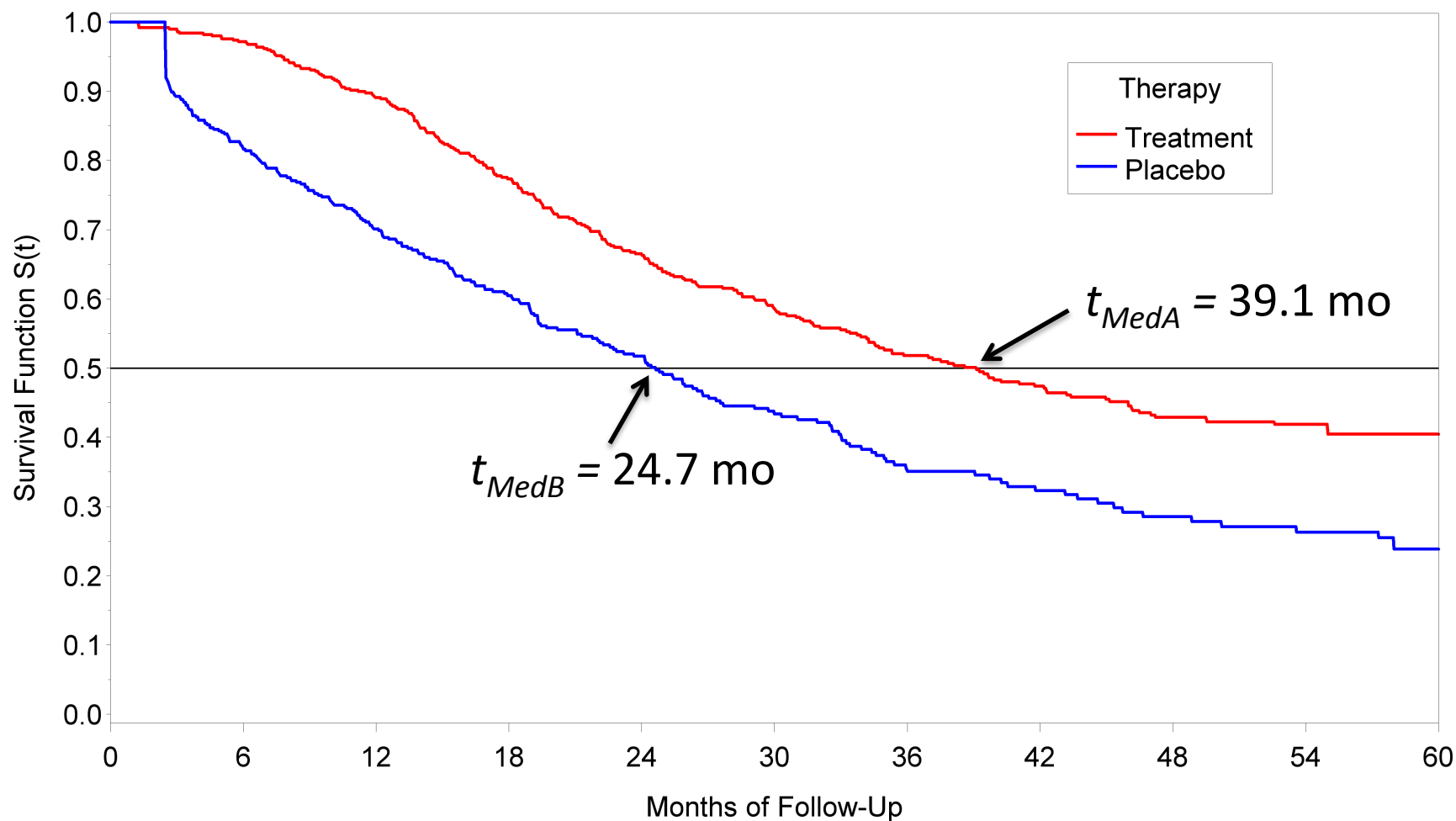
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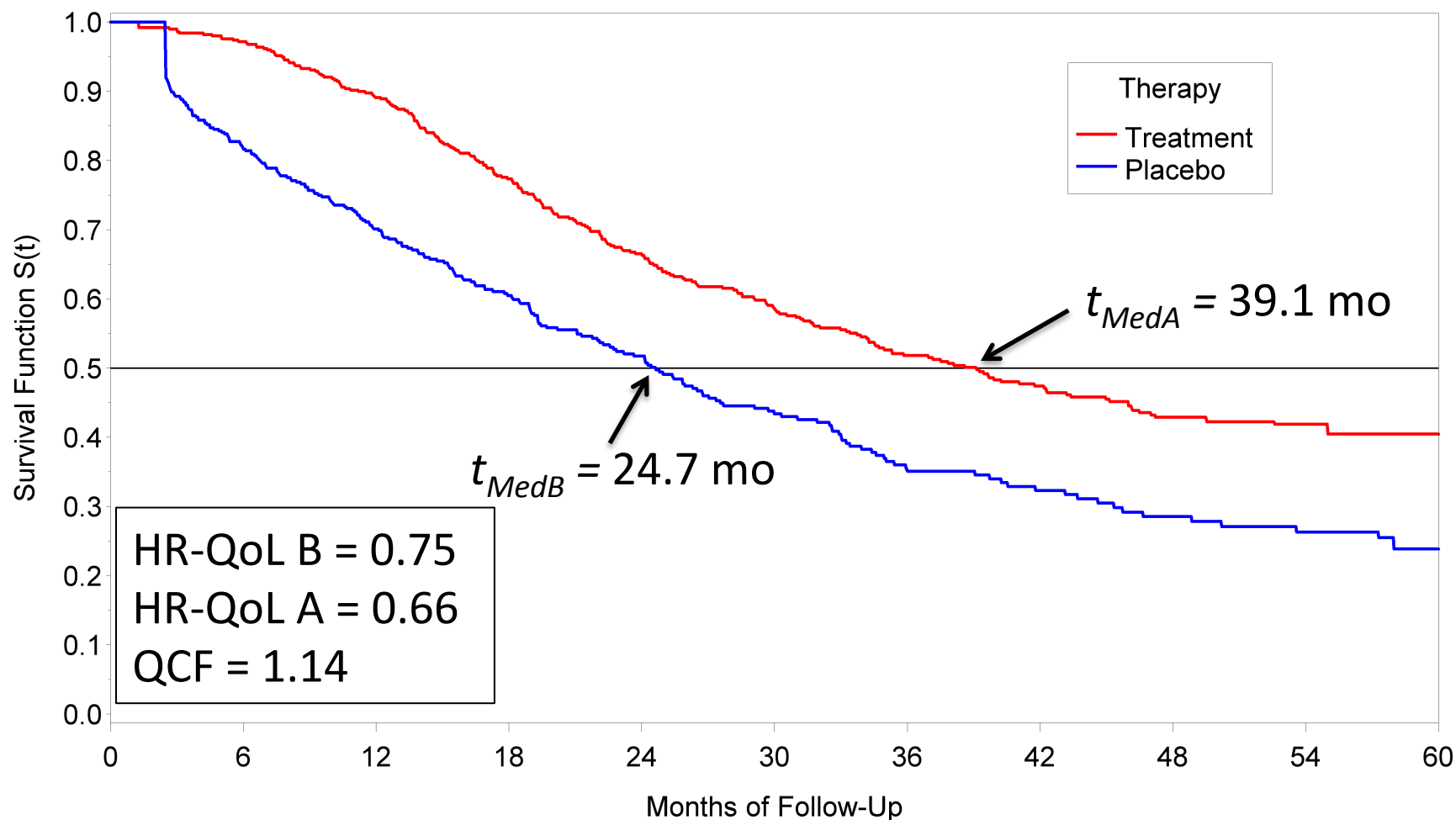
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- Then we ask: $t \downarrow MedA - [(QCF)(t \downarrow MedB)] = 0$???

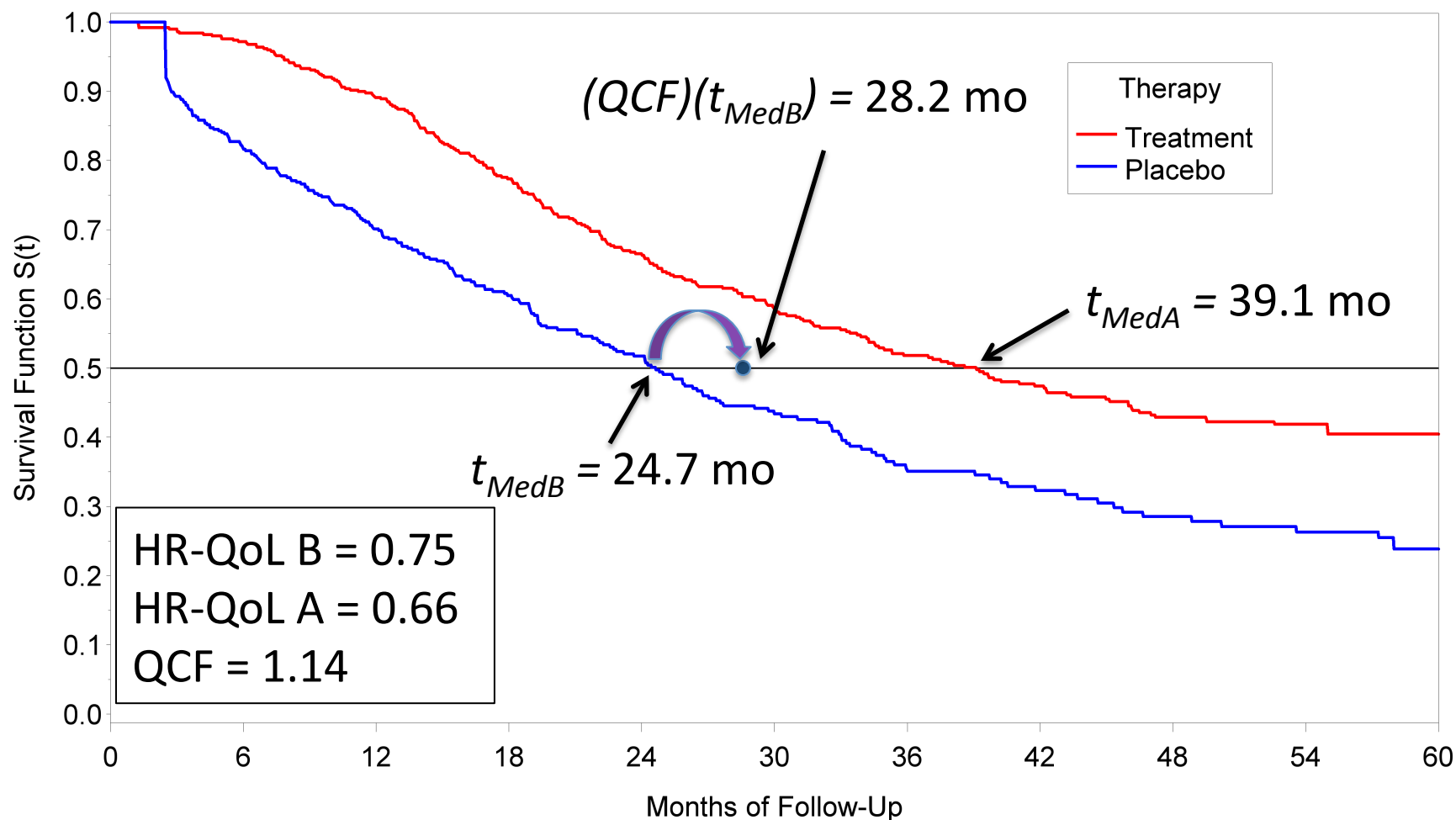
Exploratory Method of Quality-Corrected Median Survival



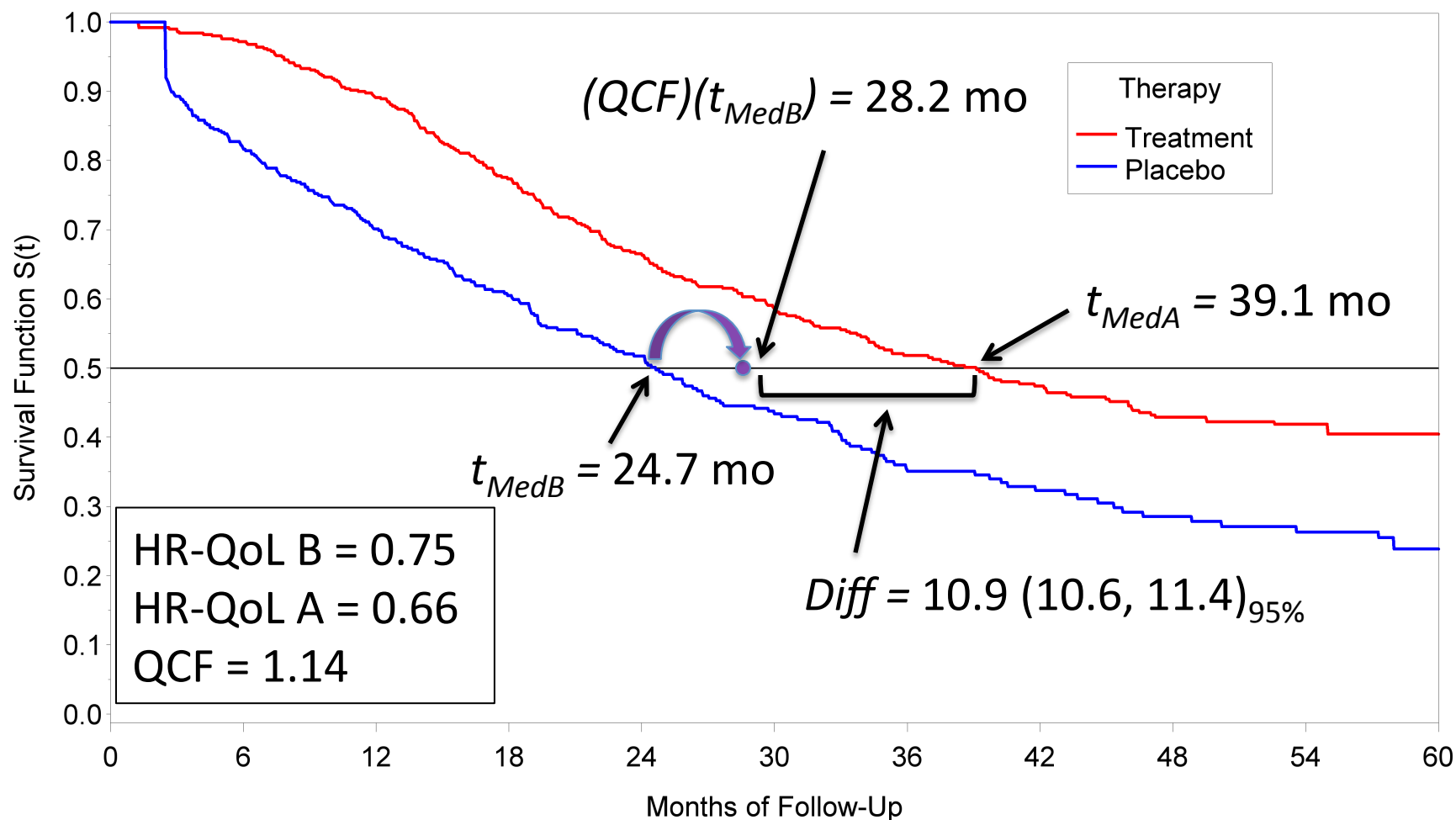
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Exploratory Method of Quality-Corrected Median Survival



- Patients on Treatment (“red pill”) had better survival outcomes but poorer quality of life profiles compared to patients on Placebo (“blue pill”).
- Through QASA techniques, the trade-off between quantity and quality of life still favored patients on Treatment (“red pill”).
- No standard method exists for adjusting median survival for quality of life
- Exploratory method can be of benefit when it is desired to compare quality-adjusted results with the primary outcomes of clinical trials.

Conclusions

TAKE THE RED PILL!



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