Estimation of treatment effect under non-proportional hazards

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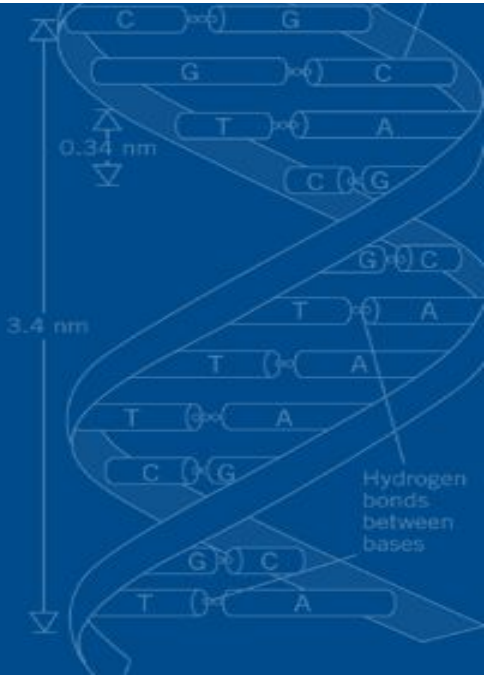
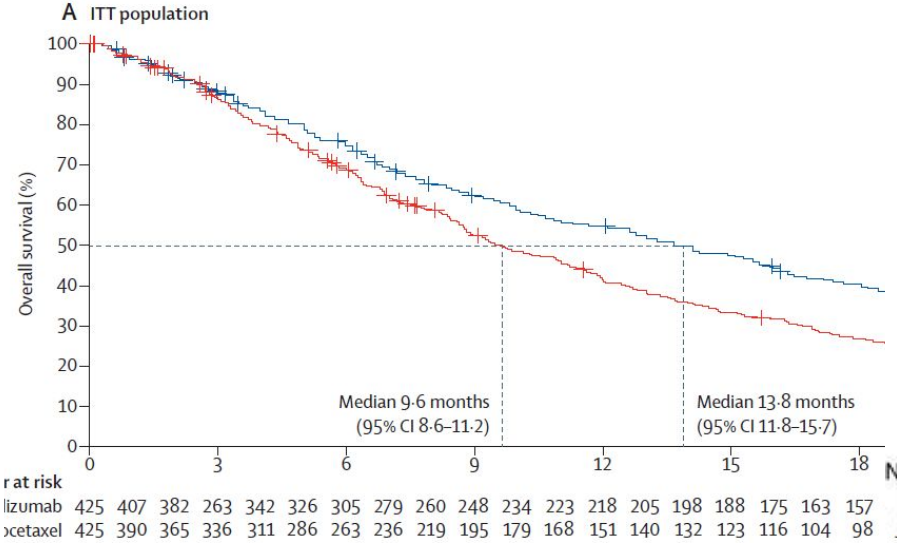


Non-Proportional Hazards (NPH)

NPH = hazard ratio (treatment effect) changes over time

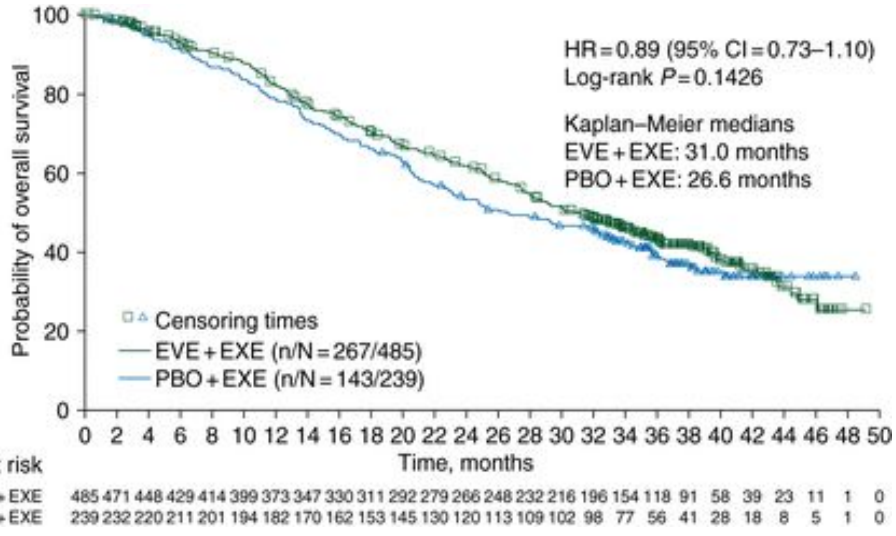
- Delayed treatment effect (late separation of curves)
  - Cancer immunotherapies (due to its MOA)
- Diminishing effect (merging curves)
  - Overall survival confounded by subsequent therapies

Delayed Effect (OAK)



Rittmeyer, A., et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial (2017) The Lancet, 389 (10066), pp. 255-265.

Diminishing Effect (BOLERO II)



Piccart M., et al. Everolimus plus exemestane for hormone-receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: overall survival results from BOLERO-2. Ann Oncol. 2014 Dec;25(12):2357-6

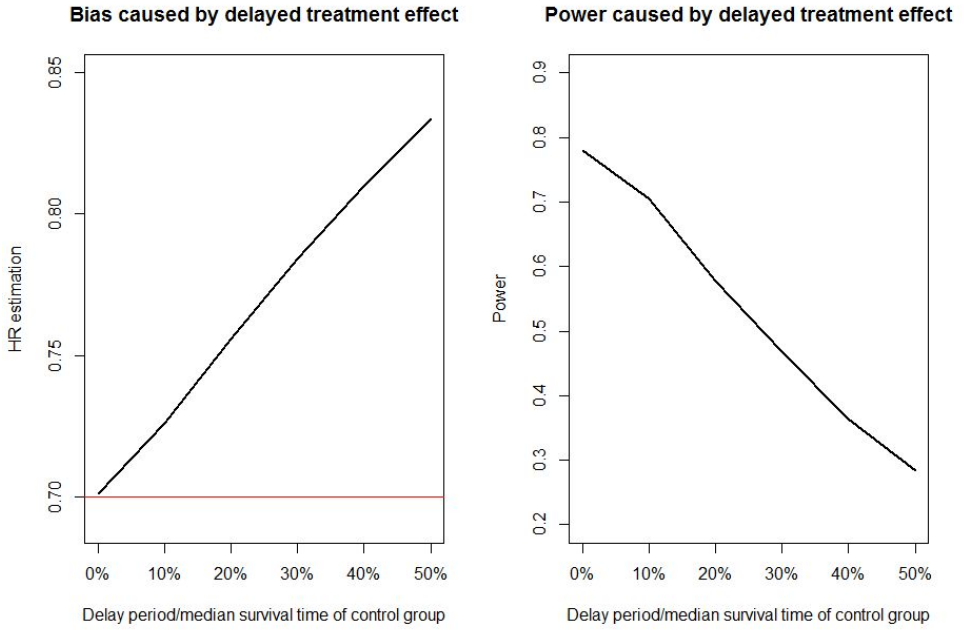
Impact on Analysis

1. Log-rank test power is reduced by 30% for a 3-month delay (with 12-month median control)

2. Hazard ratio estimate is biased (Cox model)
   - Proportional hazards (constant hazard ratio) assumption is violated
   - Treatment effect is diluted
     - Cox model averages out the treatment effect across all time points

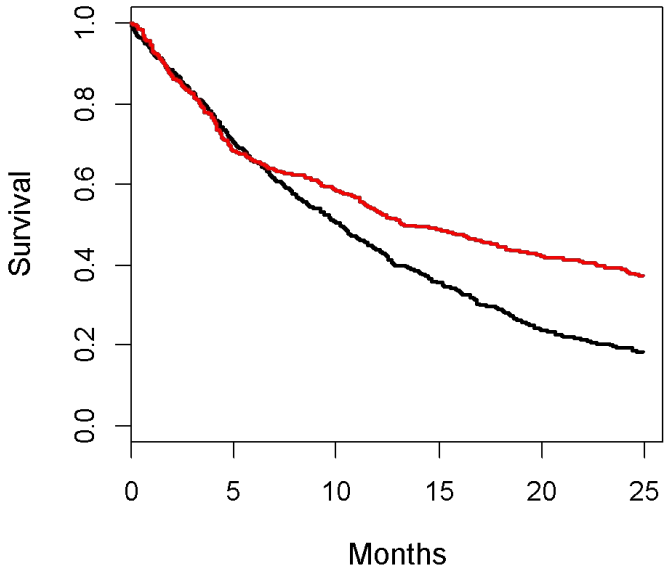
Delayed treatment effect

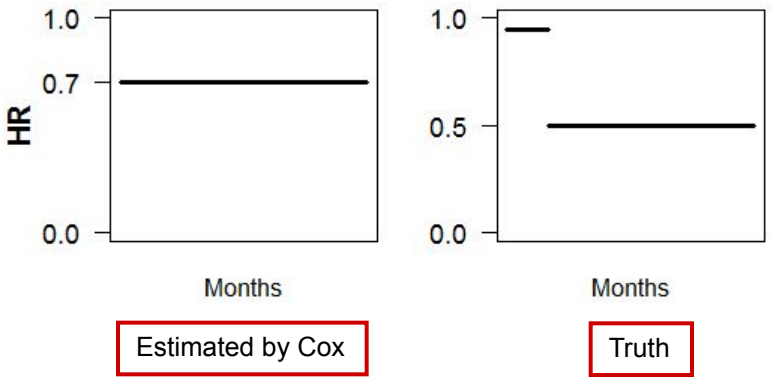
$$\text{HR}=\begin{cases}1 & for\ t \le t^0\\ 0.7 & for\ t > t^0\end{cases}$$



Impact on Clinical Interpretation

1. Clinical interpretation and decision making
   - Hazard ratio = risk reduction
   - Potentially misleading if only reporting a constant effect over time based on the standard Cox model
     - E.g, a patient who can not stay on treatment for a sufficient time may be unlikely to get benefits
2. Evaluation for health economics



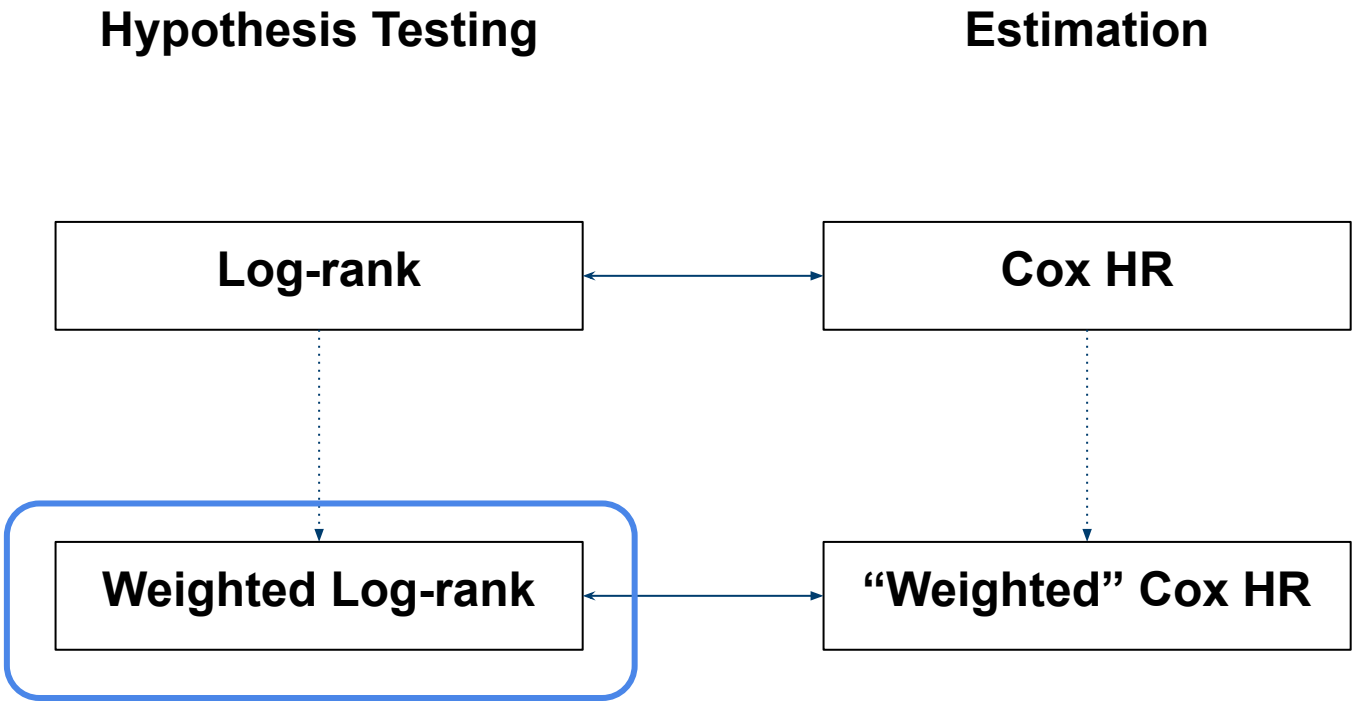


Efforts on NPH

Cross-Pharma Working Group on NPH

- Objectives:
  - To address the issue of NPH for design, analysis and interpretation
    - Across Oncology, ImmunoOncology
    - Focus on Phase III / regulatory trial setting
- Milestones:
  - Duke Margolis workshop Feb. 5, 2018 with FDA and EMA participants
  - Two manuscripts under review
    - Alternative analysis methods for time to event endpoints under non-proportional hazards: a comparative analysis
    - Robust design and analysis of clinical with trial non-proportional hazards: a straw man guidance
- Members
  - AZ, BMS, Merck, B&I, Novartis, Eli Lilly, Abbvie, Roche/Genentech, Bayer, Janssen, Takeda, Amgen, Pfizer, GSK, Celgene, Sanofi

Overview of Analysis Methods

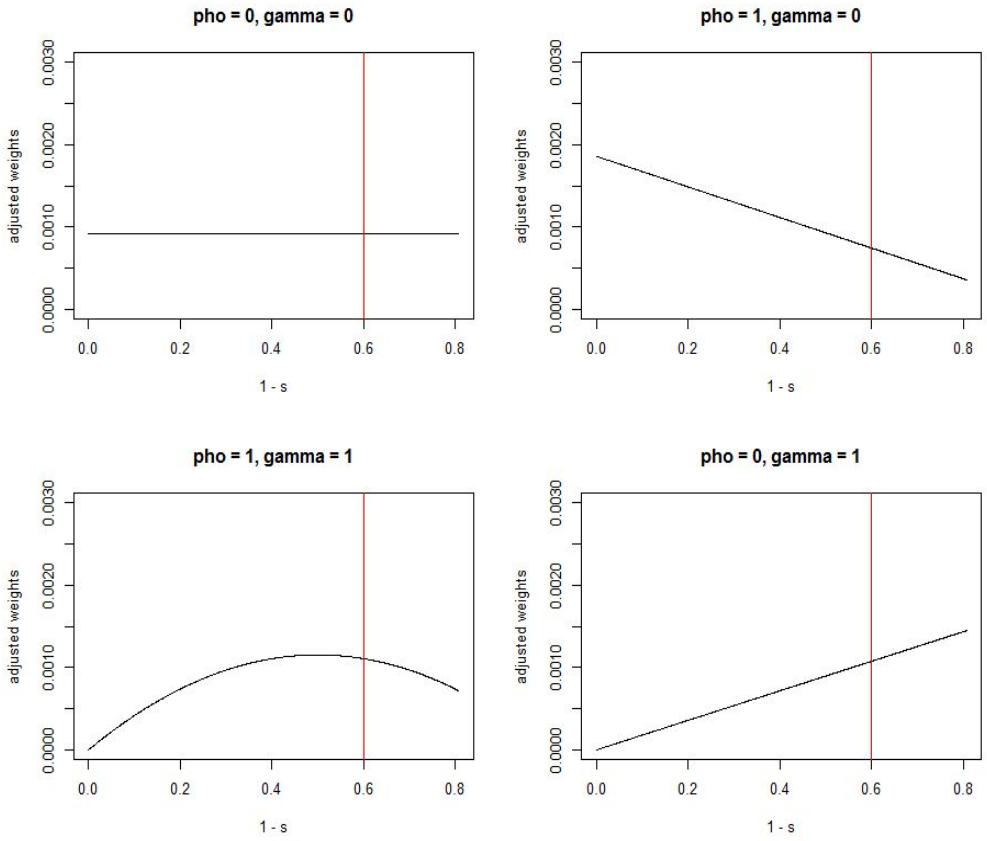


Weighted Log-Rank Tests

- Log-rank test
  - $Z = \frac{\sum_{j=1}^{J}(O_{1j} - \frac{O_j}{N_j}N_{1j})}{\sqrt{\sum_{j=1}^{J} V_j}}$
- Weighted Log−rank test
  - $Z = \frac{\sum_{j=1}^{J} W_j(O_{1j} - \frac{O_j}{N_j}N_{1j})}{\sqrt{\sum_{j=1}^{J} W_j^2 V_j}}$
- Weight functions
  - Fleming-Harrington weight:

    $W(t) = S(t)^{\rho}(1 - S(t))^{\gamma}$
    - Log-rank test (0,0)
    - Wilcoxon-Prentice (1,0)
  - Piece-wise constant weight

Fleming-Harrington weight family



MaxCombo Test

- Pre-specify a set of K weight functions and select the one with the best Z value
- P-value adjusted to preserve Type-I error
- Examples
  - WG[1]: FH(0,0), FH(1,0), FH(1,1), FH(0,1)
  - Lee[2]: FH(1,0), FH(0,1)

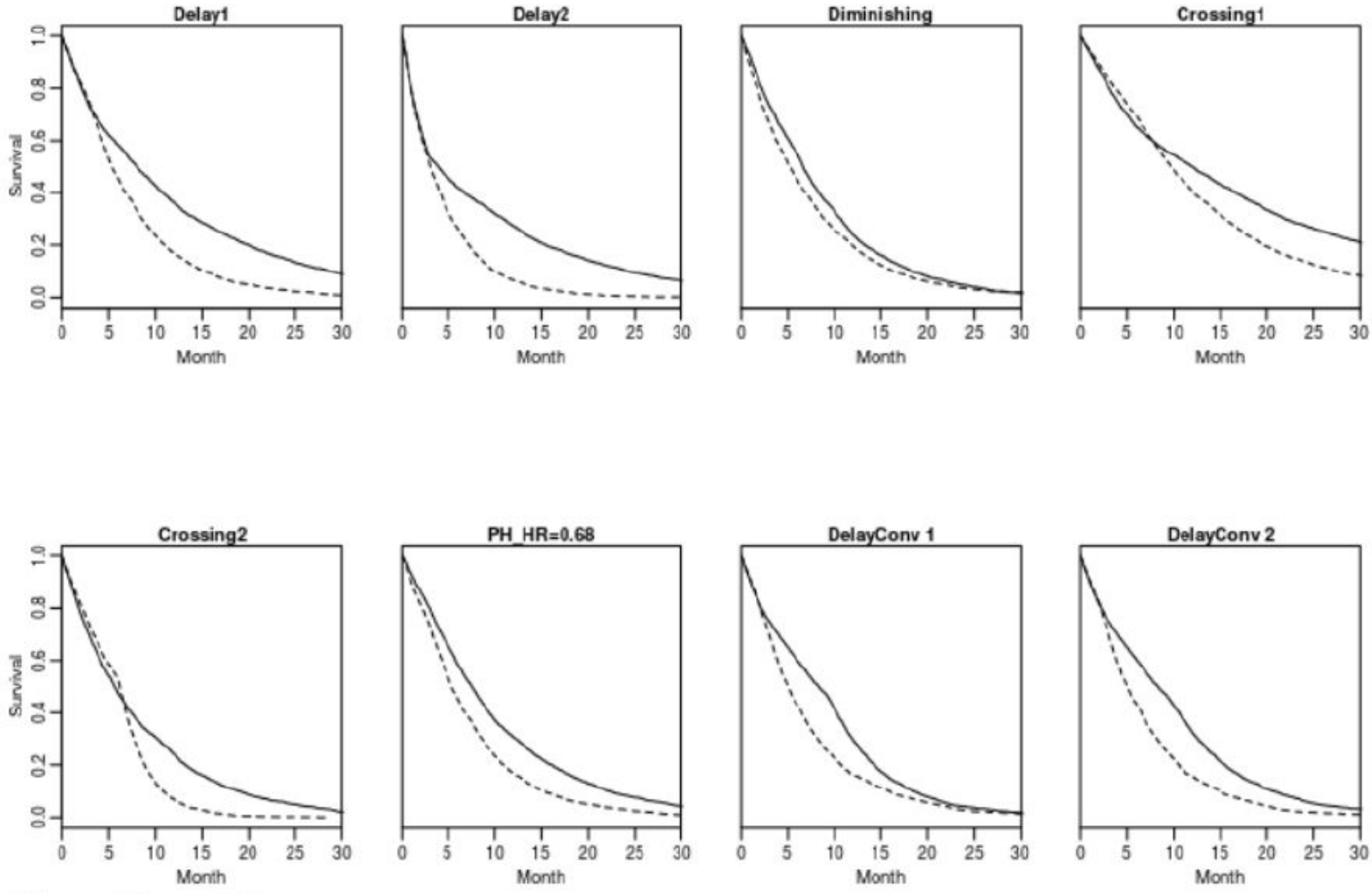
1. Lin, R.S. et.al Alternative analysis methods for time to event endpoints under non-proportional hazards: a comparative analysis. Under review.
2. S Roychoudhury. et al. Robust design and analysis of clinical with trial non-proportional hazards: a straw man guidance. Under review.
3. Lee, S-H. (2007). On the versatility of the combination of the weighted log-rank statistics. Computational Statistics & Data Analysis 51:6557-6564.

Simulation Study #1 (NPH WG)

- Settings
  - 9 patterns (8 NPH/PH, null)
    - delayed effect, diminishing effect, both
  - 3 Categories of tests
    - Rank-based tests
      - Log-rank, weighted log-rank
    - Kaplan-Meier curve-based tests
      - Weighted KM, RMST
    - Combination tests
      - Breslow test, MaxCombo test

Reference: Lin, R.S. et.al Alternative analysis methods for time to event endpoints under non-proportional hazards: a comparative analysis. Under review.

NPH/PH Patterns



Simulation Study #1 Summary

- Testing
  - Type I error is preserved
  - No test achieves the highest power across all scenarios
  - MaxCombo has relatively robust power across patterns

- HR for MaxCombo (Sasieni 1993)
  - Less biased than Cox HR
  - Slightly biased (anti-conservative) under null and PH due to model selection

Reference: Lin, R.S. et.al Alternative analysis methods for time to event endpoints under non-proportional hazards: a comparative analysis. Under review.

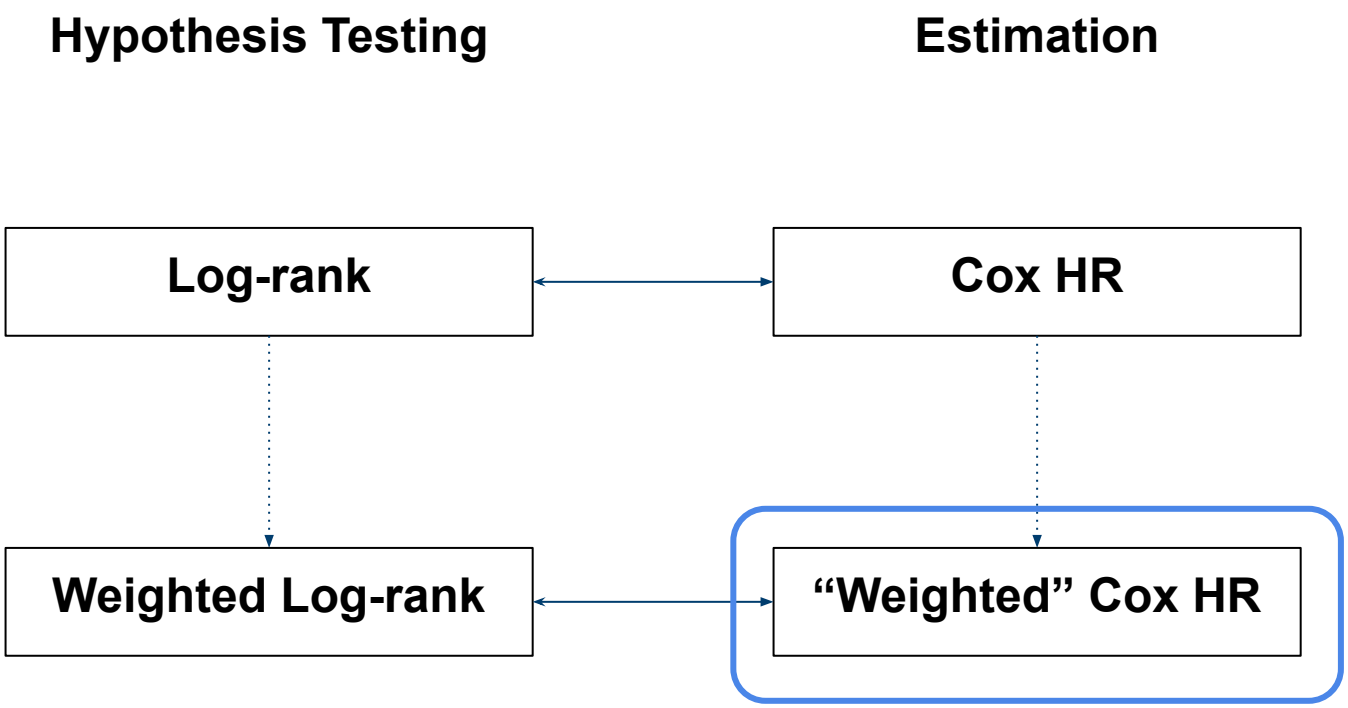
Clinical Interpretation?

- What is the clinical interpretation of the weights?

- Effect size changes over time under NPH
  - “Time-profile”
  - Cannot be summarized by a single measure

We proposed a hazard ratio time-profile estimated via “weighted” Cox

Overview of Analysis Methods



1. Clinical interpretation of the weights
2. HR "time-profile"

"Weighted" Cox Model

- For a weighted log-rank test with normalized W(t), let a Cox model:
  - Hazard: $h(t) = h_0(t)*\exp[\beta*W(t)*X]$
  - Score statistics is equivalent to the weighted log-rank
  - Partial (%) treatment effect
    - Let Y = W(t)*X (a time-varying covariate)
    - Create Y, fit the Cox model and get the coefficient estimate for Y (ie, β)
  - Time-Varying HR (time-profile)
    - $HR(t)=\exp[\beta*W(t)] = [HR_F]^{W(t)}$

Full effect HR_F

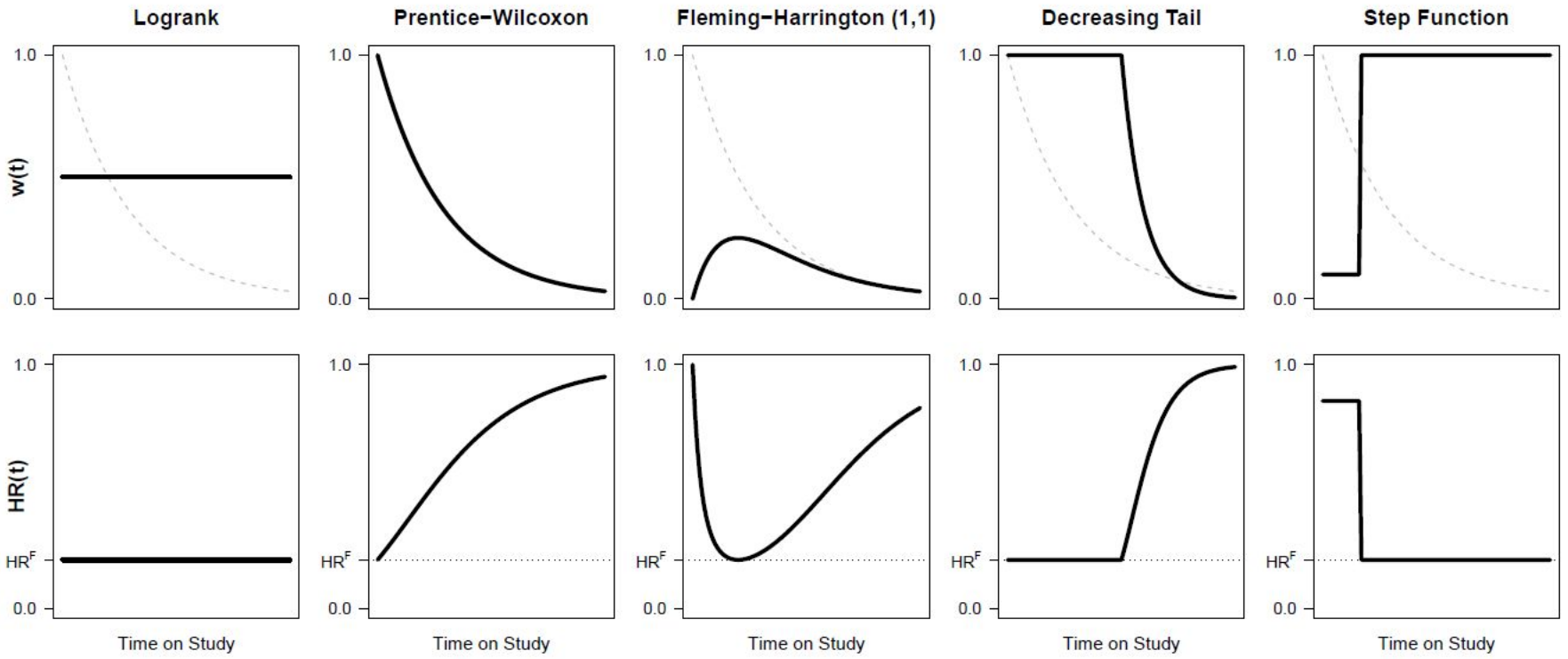
Effect adjusted by W(t)

- Notes:
  - W(t) in [0, 1] with maximum 1. Normalization of W(t) will not change the statistics
  - Sasieni (1993) and Lin (1991) incorporate weight functions into the score function; the score statistics is equivalent to ours.

Reference: Lin, R.S. and Leon L.F., Estimation of treatment effects in weighted log-rank tests. Contemporary Clinical Trials Communications, Volume 8, 2017, Pages 147-155

Examples of Weight Functions & HR Time-Profiles

- The shape of the HR time-profile is determined by the weight function
- The full effect HR_F is estimated from the data

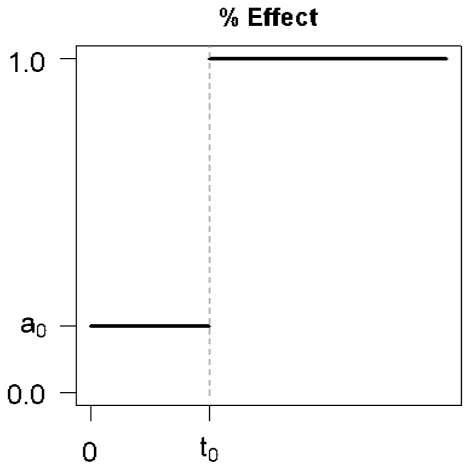


Choice of weight functions

- Predictable
  - Asymptotic properties derived from the martingale framework
- Optimal?
  - $w(t) \propto \log(HR(t))$
  - unknown and hard to estimate
- Meaningful clinical interpretation
  - FH(1,1) or FH(1,0)
    - Full effect takes place at only one time point
      - Not useful for clinical interpretation
      - Over-estimate the actual effect
  - A long period with w(t)=1
    - E.g., piecewise constant weights

Simulation Study #2
Delay Effect

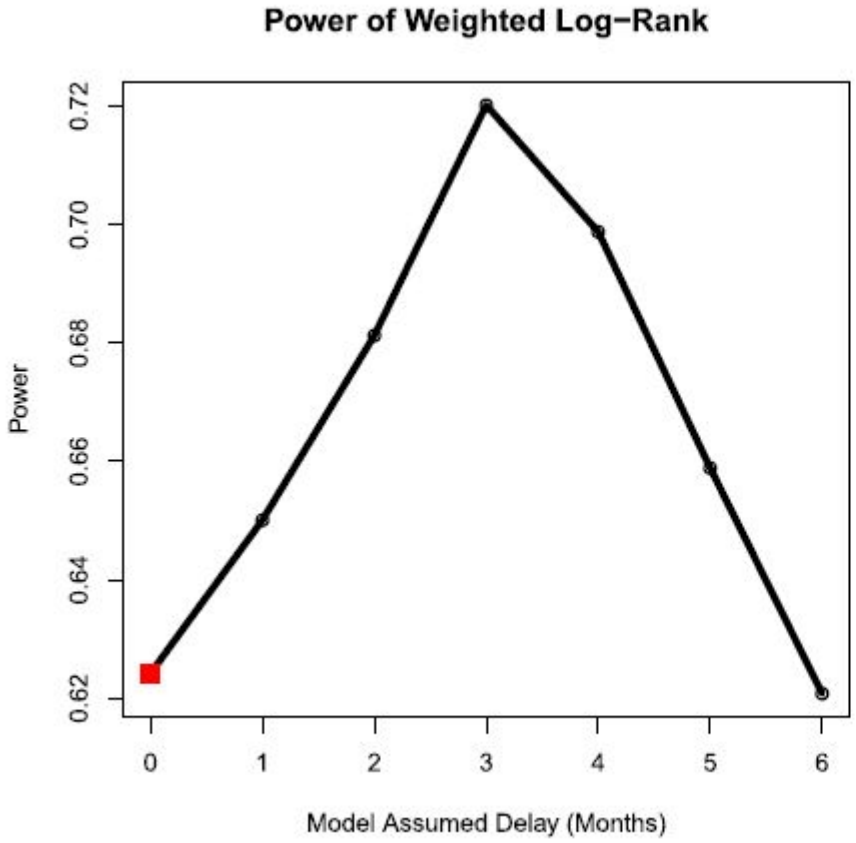
- Settings
  - N = 400 (1:1 randomization)
  - Event-patient ratio 70%
  - Treatment effect
    - HR=0.68 after 3 months
    - HR=0.9 (27%) during 0-3 months
  - Control median survival: 12 mos
  - Varying
    - Delay duration (t_0)
    - Adjustment factor (a_0)
  - Enrollment : 12 mos with ramp-up
  - 10,000 runs

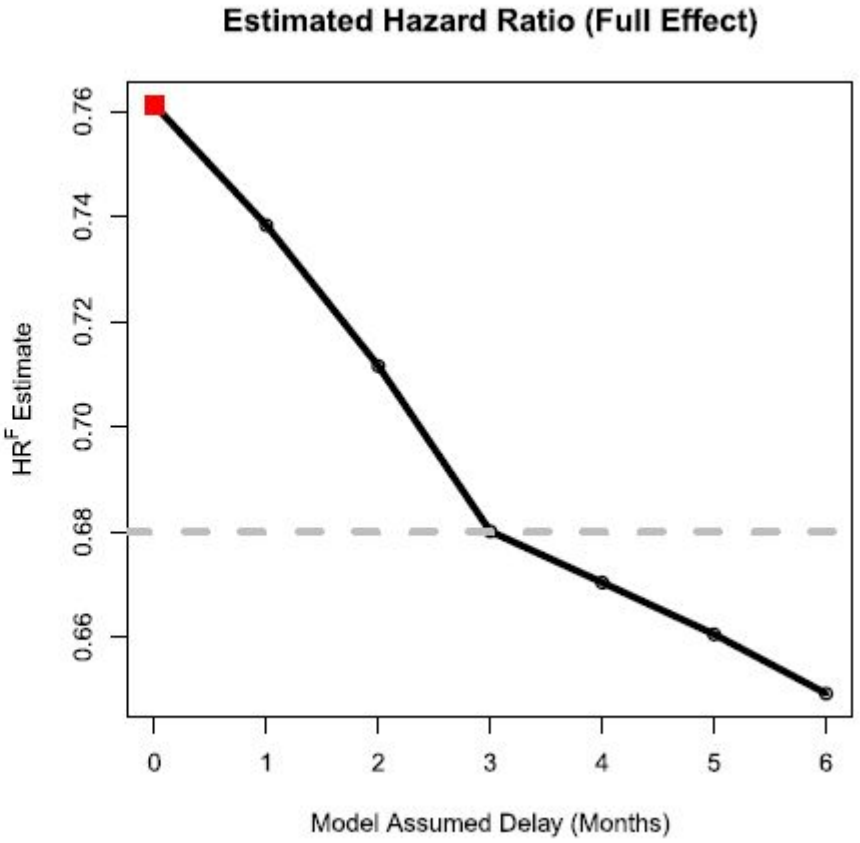


Reference: Lin, R.S. and Leon L.F., Estimation of treatment effects in weighted log-rank tests. Contemporary Clinical Trials Communications, Volume 8, 2017, Pages 147-155

Power and HR Estimates Varying t_0

True t_0 = 3 months; a_0 = 27%





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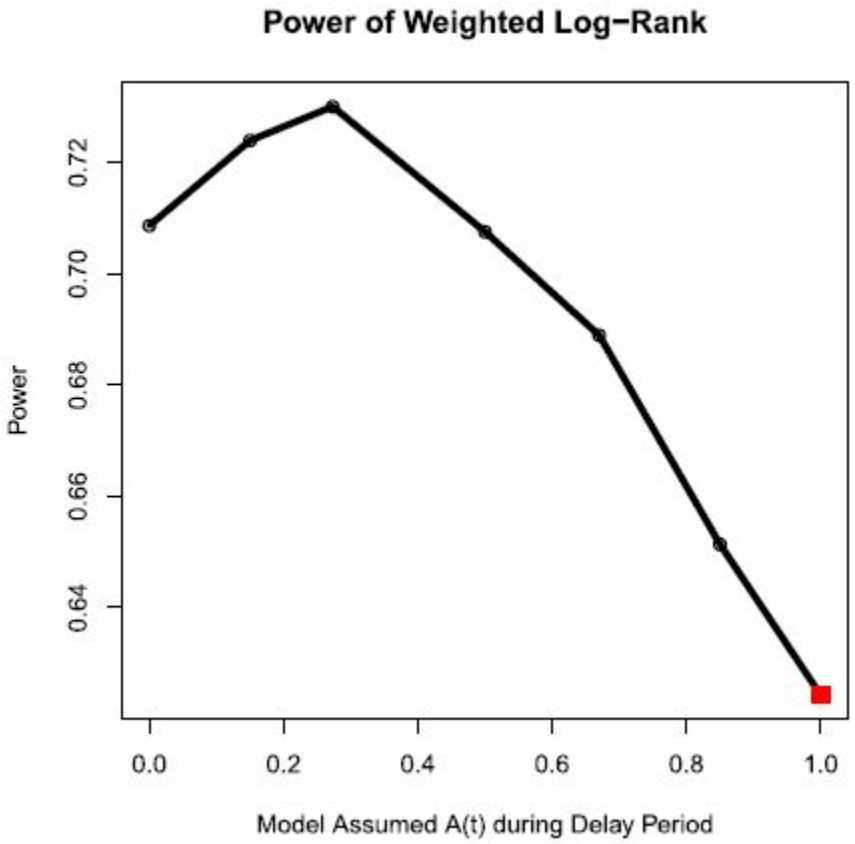
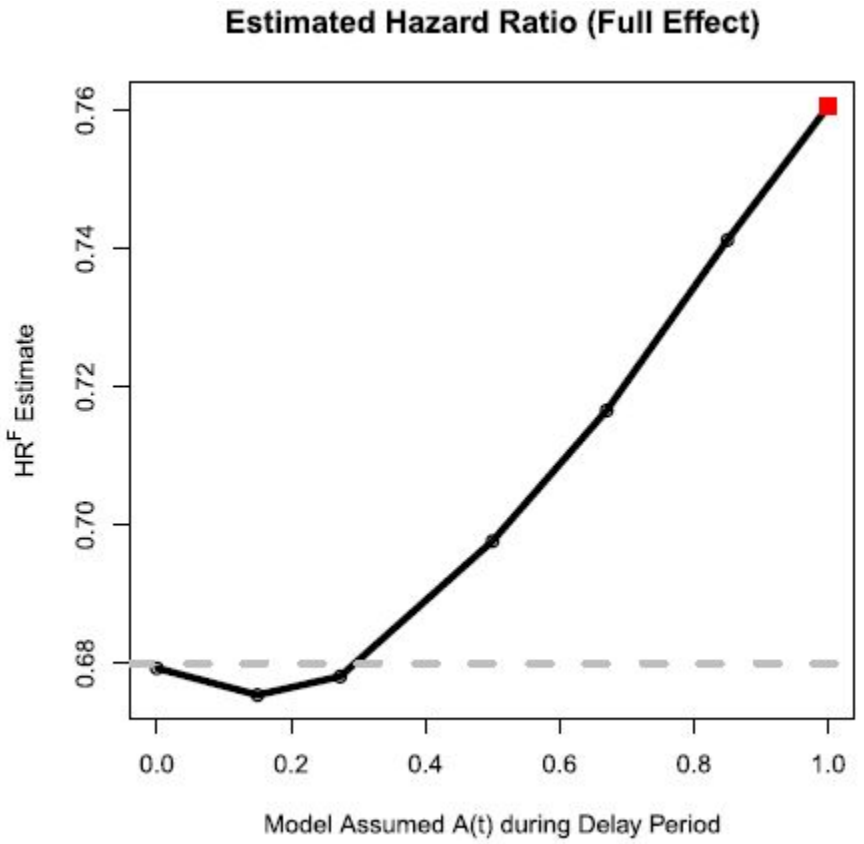


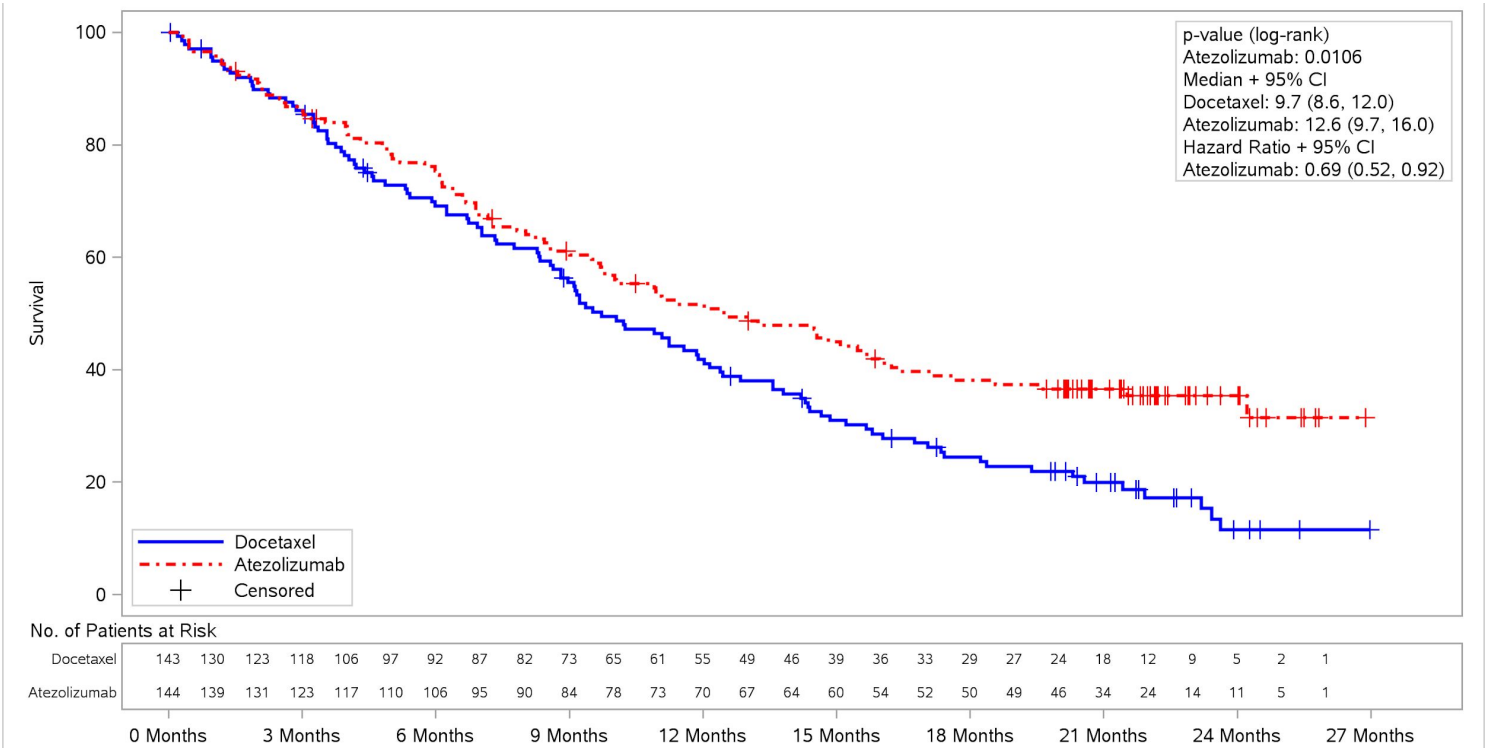


Simulation Study #2 Summary

- Type-I error is preserved
- Power
  - The most powerful test if the weight assumption is correct
  - In general more powerful than standard log-rank tests even if mis-specified
- Hazard ratio estimate
  - Unbiased if the assumption is correct
  - In general less biased than standard Cox models even if mis-specified

Reference: Lin, R.S. and Leon L.F., Estimation of treatment effects in weighted log-rank tests. Contemporary Clinical Trials Communications, Volume 8, 2017, Pages 147-155

Example: Poplar 2L NSCLC



Effect Time-profile	p value*	HR Estimate*
Always full effect (Standard Log-rank)	0.0056	0.68 (0.51, 0.89)
Minimal first 3 mo; full effect after 3 mo	0.0020	0.61 (0.45, 0.84)
Minimal first 8 mo; full effect after 8 mo	0.0006	0.50 (0.34, 0.75)

•*Unstratefied analysis based on data cut Dec 1, 2015

Summary

- Under NPH, “weighted” Cox HRs could be reported in addition to standard Cox HR
  - Connected to the weighted log-rank test
  - Enable reporting of a hazard ratio time-profile
    - Less biased hazard ratio estimate than standard Cox model
    - Potentially more informative description of clinical benefit

Acknowledgements

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Q&A