Quantifying the (long-term) treatment benefit with cancer immunotherapies

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Joint work with Dr. Lu Tian (Stanford) and Dr. LJ Wei (Harvard)

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  - Mace Rothenberg
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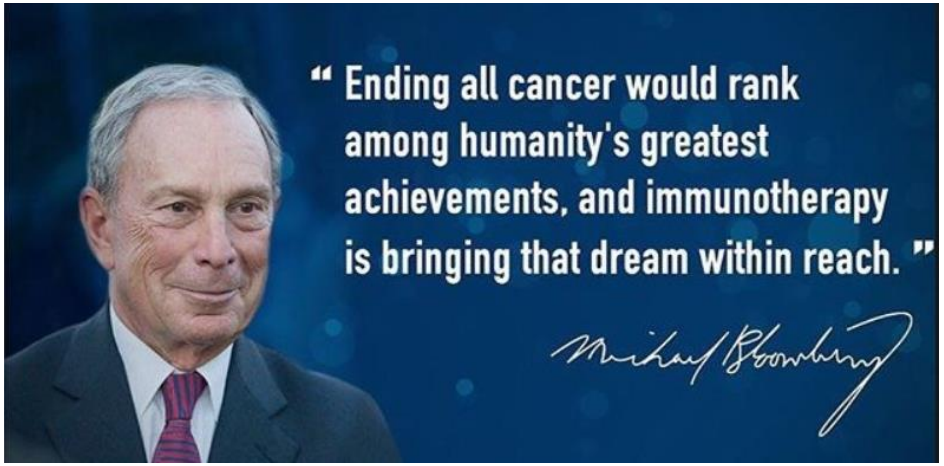
  - BESPONSA® (inotuzumab ozogamicin) team: Jane Liang White, Tao Wang

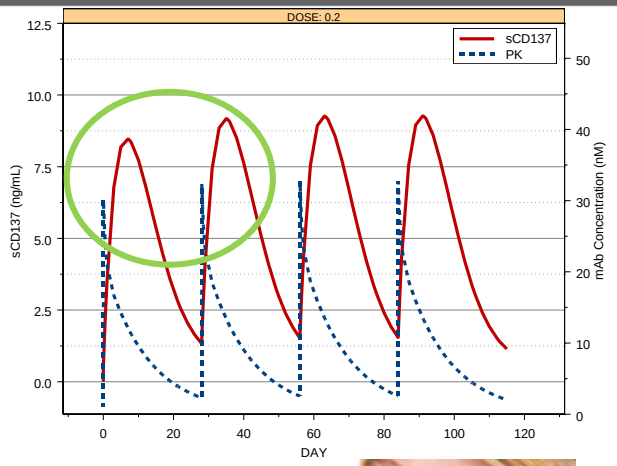
Immunotherapy: frontier of (cancer) drug development

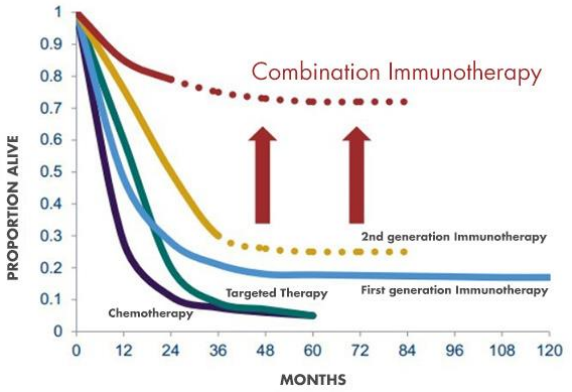


Challenges in IO dose finding: Manage toxicity, dose optimization

Due to the life-threatening nature of cancer, a high degree of dose limiting toxicity (DLT) is generally considered acceptable.

- Late/cumulative effect of IO: Late-onset toxicity not observed in traditional 1-cycle DLT window
- Select the optimal dose & schedule
  - Higher dose -> higher toxicity, but no necessarily higher activity → More is not necessarily better
  - How about dosing schedule?
- How about dose finding for combination agents?
  - Complexity increases on 2-dimensional space
  - Partial ordering





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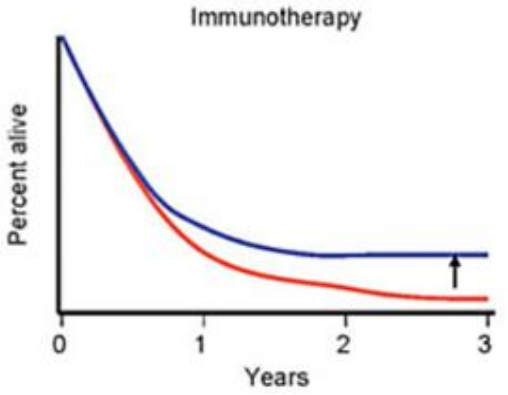
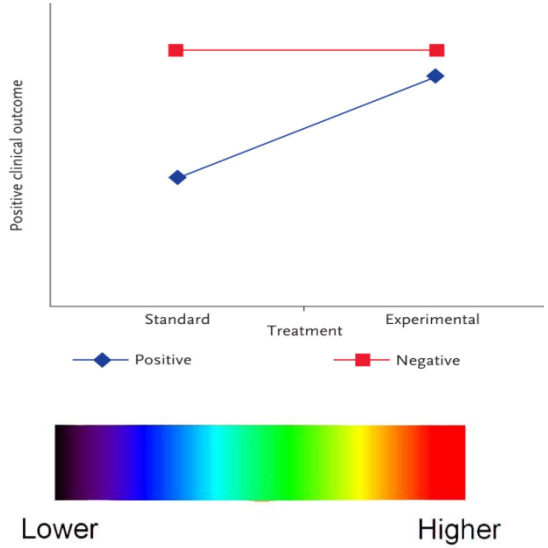
Challenges in IO efficacy evaluation

- Non-proportional hazards and late separation in curves due to delayed (late) anti-tumor effect; Durable responses lead to long-term benefit (cured effect)
  - LR test and HR still optimal?
  - Timing of IA?
- Weak/negative correlation between PFS and OS
  - Careful with futility IA based on PFS
- Predictive biomarker
  - Ignoring may lead to trial failure
  - PD-L1 expression continuous (no perfect dichotomization), TMB (how many mut/mb?), gene signatures etc.





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Ref: Huang B. Some statistical considerations in the clinical development of cancer immunotherapies. Pharmaceutical statistics. 2018 Feb;17(1):49-60.

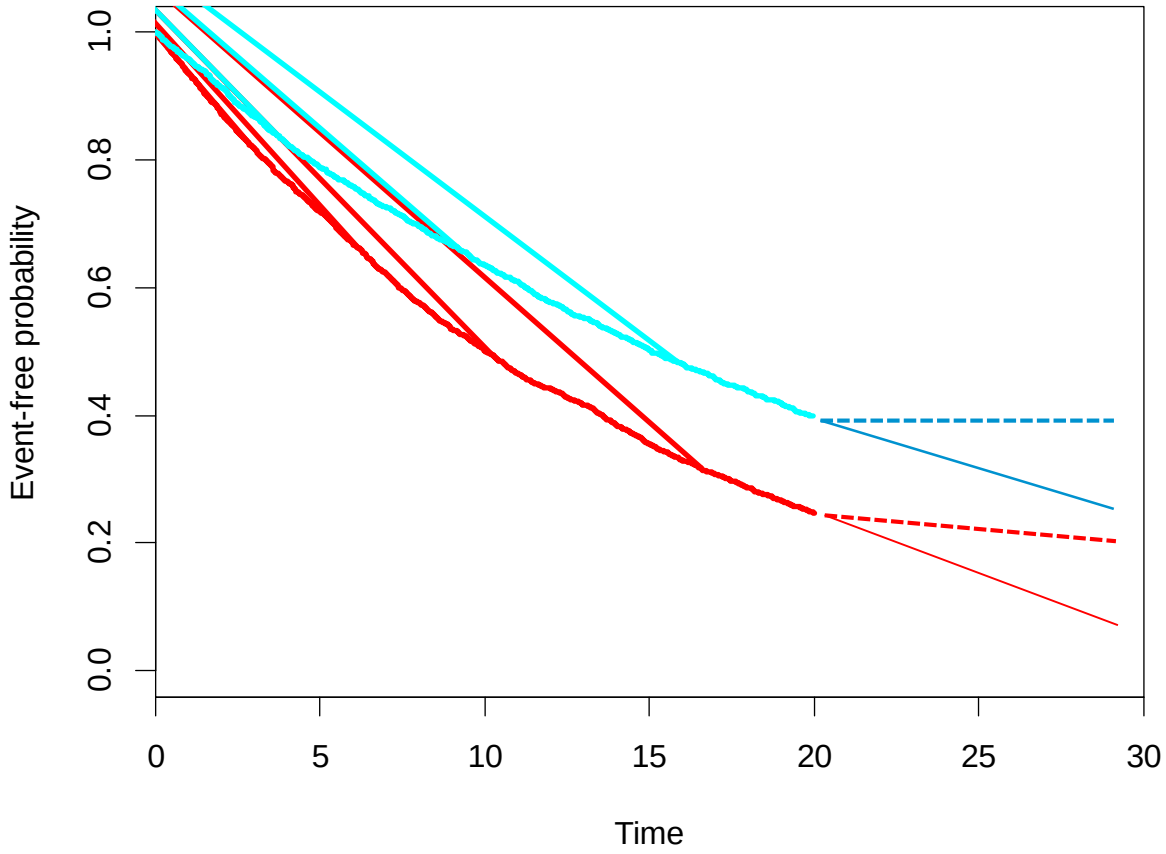
Limitation of Log-rank test, HR (from Cox model) and the medians

- The log-rank test is optimal under the proportional hazard (PH) assumption, but may lose power under NPH
  - Equivalent to the score test in the Cox-PH model
- The power of log-rank test is event driven
  - Low power with small events; not sensitive to separated flat tails

- Interpretation of HR from Cox model is a problem under NPH
- Only a relative measure of effect

- The median is an arbitrary percentile (despite good clinical interpretation)
  - Not a global summary measure – does not capture what's before and after

Graphical examples



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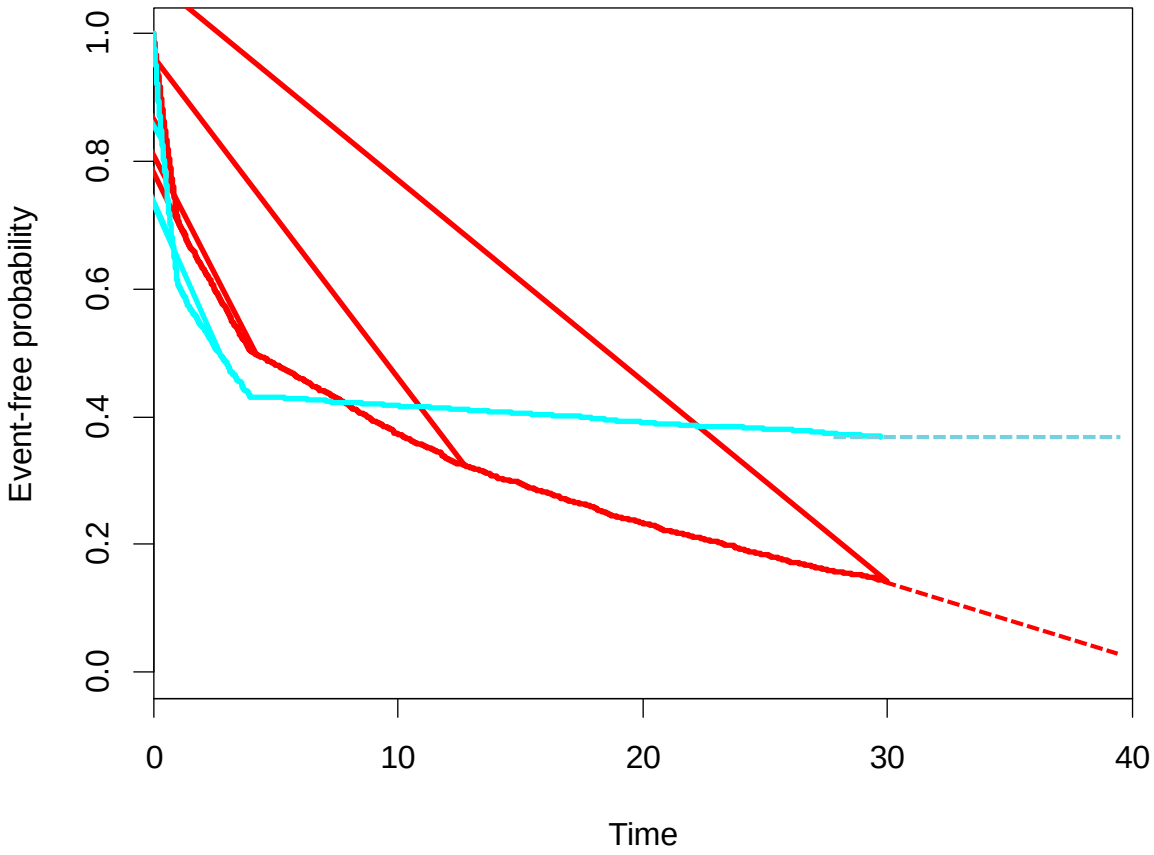
Graphical examples



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Alternative methods to the rank-based methods

- t-time event-free probability
- Win-ratio (in particular for prioritized multiple endpoints)
- Net-benefit
- Generalized pairwise comparison
- Kaplan-Meier based method
  - RMST
  - Weighted KM based test

Restricted mean survival time (RMST)

- Mean survival time (life expectancy) truncated by time τ: area under the survival curve $S(t)$ from 0 to τ

$$\mathrm{RMST}(\tau) = \int_0^{\tau} S(t)dt$$

- $S(t)$ can be estimated by the KM estimator $\hat{S}(t)$. The variance of the observed RMST estimator is (Klein and Moeschberger, 2005)

$$\sum_{i=1}^{D} \left[\int_{t_i}^{\tau} \hat{S}(t)\, dt \right]^2 \frac{d_i}{Y_i(Y_i - d_i)}$$

# of events at t_i

# of pts at risk at t_i

- Measure treatment effect by difference and ratio in the RMSTs of different drugs

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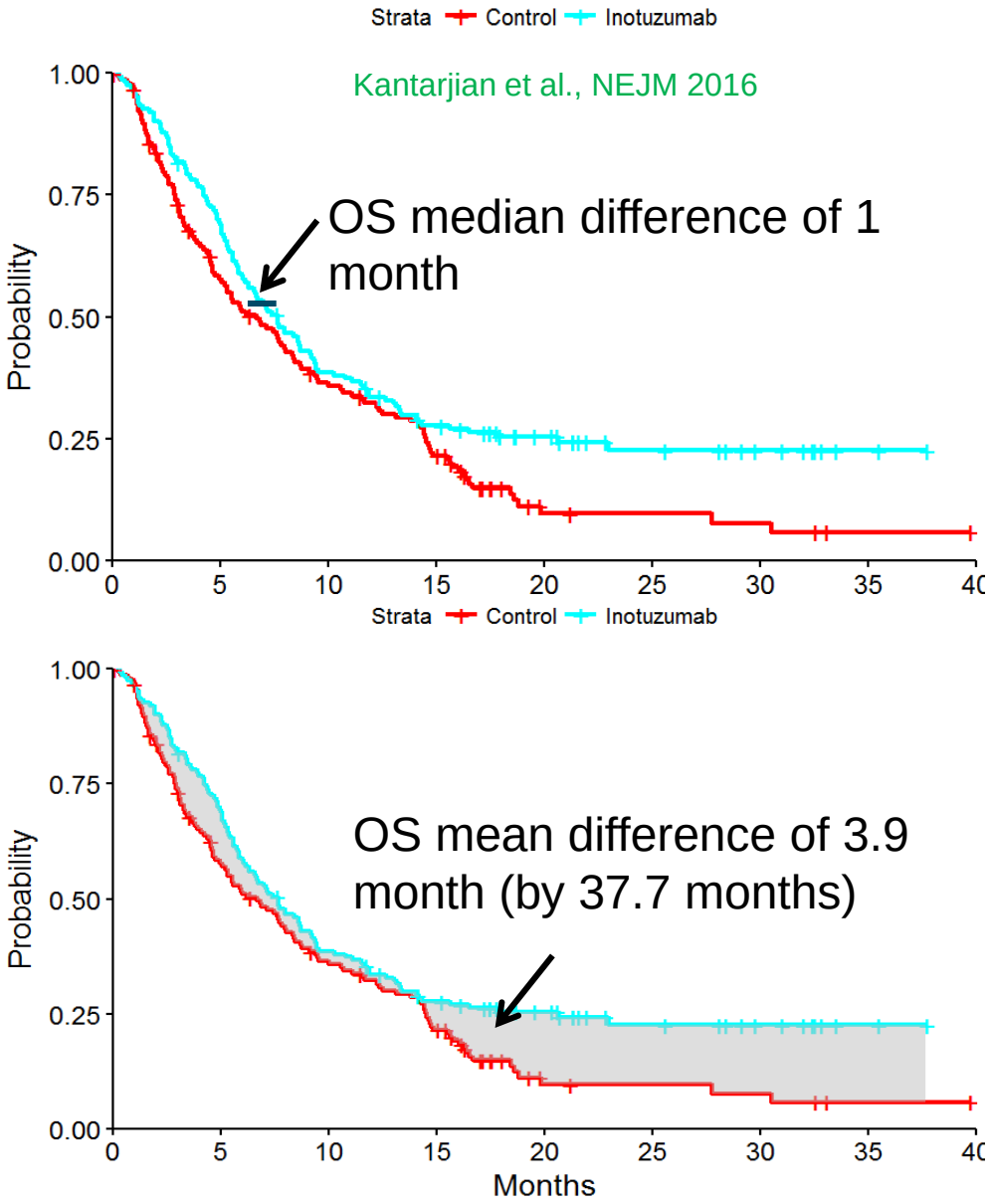
Versus the HR, the median, t-time event-free probability

- **Versus the HR**
  - Clinical interpretation (whether or not PH holds)
  - Non-parametric
  - Dual presentation of relative and absolute effect
- **Versus the median/t-time event-free probability**
  - Informative global summary, no arbitrary percentile/cutoff
  - RMST curve: temporal profile by different truncation points



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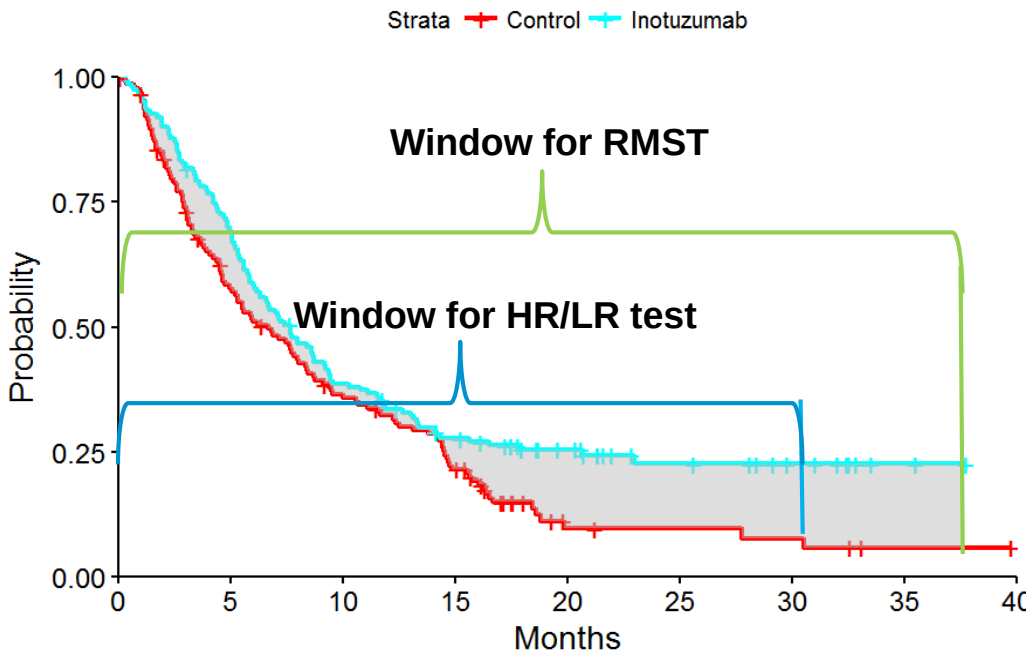
Time-window of RMST vs Time-window of HR/LR test

Under mild conditions on the censoring distribution:

- One can make inference on RMST up to **the last follow-up time (either event or censored) for the arm with shorter follow-up**

In contrast,

- For HR/LR test, one can only use data up to **the minimum of (last event time for any arm, the last follow-up time of the arm with the shorter follow-up)**



Reference:

- Tian L, Jin H, Uno H, Lu Y, Huang B, Anderson K, Wei LJ. On the Empirical Choice of the Time Window for Restricted Mean Survival Time, submitted (under review).
- Huang B, Kuan P. (2018). Comparison of the Restricted Mean Survival Time with the Hazard Ratio in Superiority Trials with a Time-to-Event Endpoint, *Pharmaceutical Statistics* 17(3):202-13

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A composite endpoint to measure the effect of cancer treatment including immunotherapy

What's a desirable future cancer treatment?

- (future) cancer treatment may not be a "cure", but can effectively control the disease, and patients can live a "normal" life with the disease for a long period of time
- What are the characteristics of a desirable cancer treatment for patients and doctors?
  - ✓ **Life extending (OS benefit)**
  - ✓ **High likelihood of tumor response (reduction in size)**
  - ✓ **Fast time to response**
  - ✓ **Long duration of being in response (durable response)**
  - ✓ **Manageable side effect**
  - ✓ **Improved/not-worsening HRQOL**

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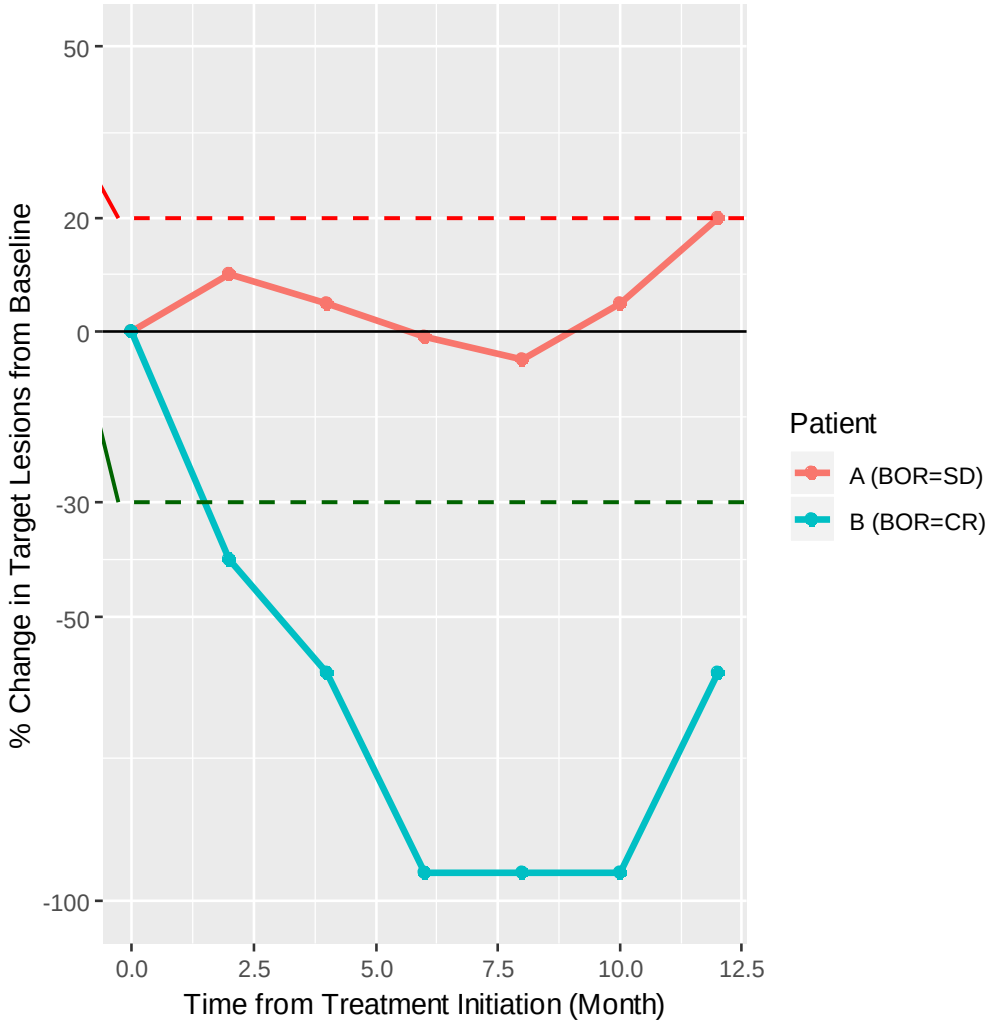
Limitation of PFS

- “Disease stabilization” may not translate to long-term survival benefit
- Cannot distinguish tumor reduction from no change/slight increase
- With cancer becoming a chronic disease, we will lose the capability to design faster and smaller trials with PFS endpoint



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A composite endpoint of duration of response in the ITT population

Research Letter

June 2018

Evaluating Treatment Effect Based on Duration of Response for a Comparative Oncology Study

Bo Huang, PhD[1]; Lu Tian, ScD[2]; Enayet Talukder, PhD[1]; Mace Rothenberg, MD[3]; Dae Hyun Kim, MD, ScD[4]; Lee-Jen Wei, PhD[5]

Method

To evaluate treatment effect of a drug, there are three states:

- 0: Time zero (randomization or first dose)
- 1: Time zero to response, progression or death (whichever is earlier)
- 2: Time from response(R) (or state 1) to progression (P) or death (D)

Parameter of interest:

The mean duration a patient expected to spend at state 2 (from response to progression or death) before time τ, for responders, this is equivalent to the duration of response (DOR) by traditional definition (but conditional on responders only).

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Method

The mean duration of response (by time τ) then is:

$$E\,[\min(T[P/D], \tau) - \min(T[R], T[P/D], \tau)\,]$$

$$= E\,[\min(T[P/D], \tau)] - E[\min(T[R], T[P/D], \tau)\,]$$

$$= (\text{AUC of PFS curve from } 0 \text{ to } \tau) - (\text{AUC of P/D/R-free curve from } 0 \text{ to } \tau)$$

$$= \text{area between the PFS curve and P/D/R-free curve from } 0 \text{ to } \tau$$

which can be interpreted as the expected duration of response up to time τ for a patient receiving treatment.

Variance term can be derived analytically, or by bootstrapping

- Programming code available at https://web.stanford.edu/~lutian/Software.HTML

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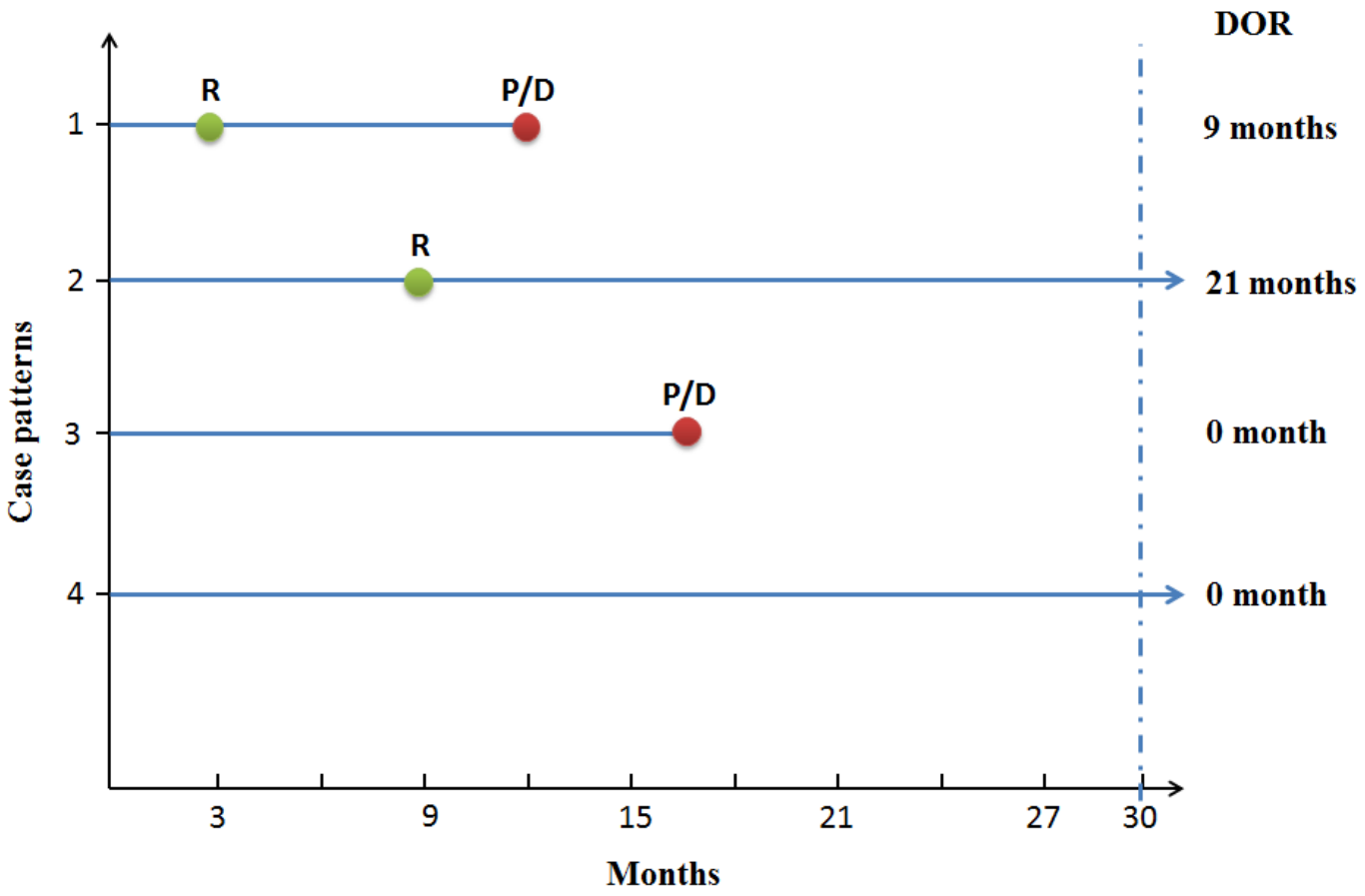
Possible patterns of times to response (R) and progression/death (P/D) up to Month-30



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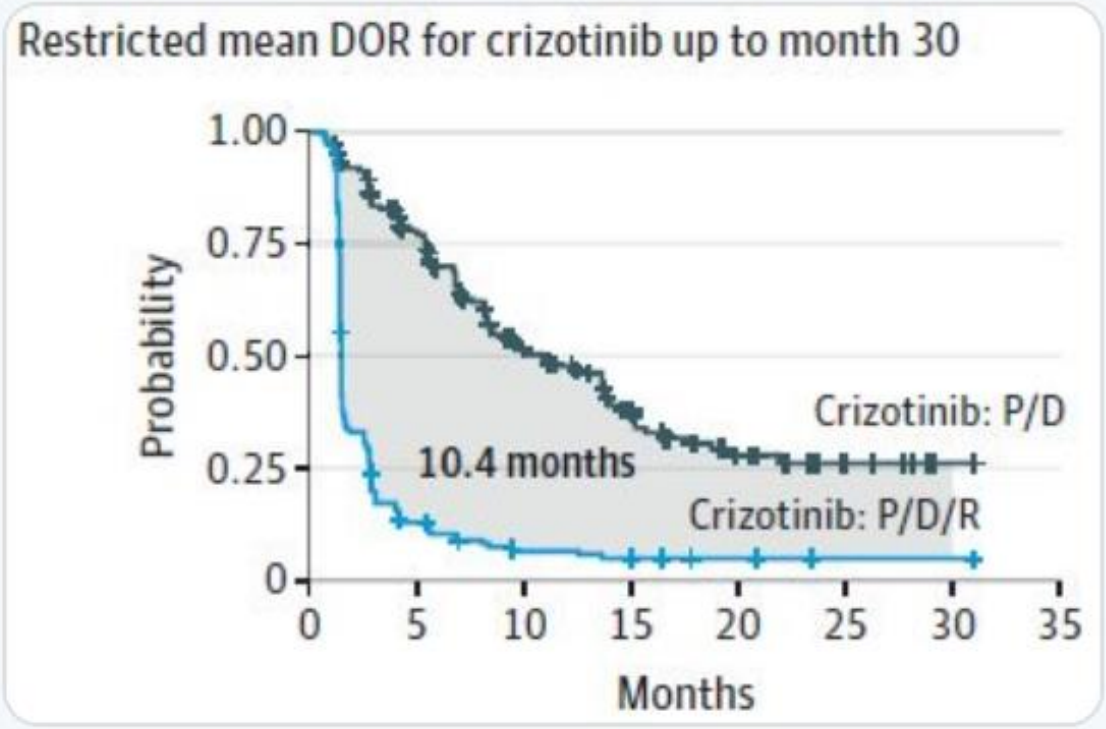
Restricted mean DOR for Crizotinib up to Month-30

JAMA Oncology @JAMAOnc · Apr 21

Read this specific proposal and explanation for how to define duration of response in #clinicaltrials **of** #cancer treatments ja.ma/2HzKV6j



33 45

shaded area between

- P/D event-free curve
- P/D/R event-free curve

A simulated study to compare endpoints and analysis methods

Scenario 1 (no "cured" effect)

- N=400 pts (1:1)
- ORR 50% in Arm A (new drug) and 25% in Arm B (SOC)
- Exponential distribution assumed for TTR & DOR for responders, PFS
  - Arm A: mPFS 10 months for non-responders, for responders, mTTR 2 months, mDOR 12 months
  - Arm B: mPFS 10 months for non-responders, for responders, mTTR 4 months, mDOR 8 months
- Uniform accrual in 12 months
- Data cut = 25, 50, 75 months from start of accural
- tau=minimax follow-up time

Scenario 2 (with "cured" effect)

- N=400 pts (1:1)
- ORR 50% in Arm A and 25% in Arm B
- Exponential distribution assumed for TTR & DOR for responders, PFS
  - Arm A: mPFS 10 months for non-responders, for 80% of responders, mTTR 2 months, mDOR 12 months, for 20% of responders, mTTR 2 months, mDOR 60 months
  - Arm B: mPFS 10 months for non-responders, for 80% of responders, mTTR 4 months, mDOR 8 months, for 20% of responders, mTTR 4 months, mDOR 60 months
- Others specifications same as Scenario 1

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Result (Scenario 1 – no “cured” effect)

	PFS					DOR (ITT)	
	HR	Median Diff	Power (LR)	RMST Diff	Power (RMST)	Mean Diff	Power (RMST)
25 mos	0.88	1.37m	19.2%	1.00m	20.0%	3.92m	99.8%
50 mos	0.87	1.38m	26.6%	1.74m	26.2%	5.21m	99.9%
75 mos	0.87	1.38m	27.8%	2.00m	28.0%	5.57m	99.9%

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Result (Scenario 2 – with “cured” effect)

	PFS					DOR (ITT)	
	HR	Median Diff	Power (LR)	RMST Diff	Power (RMST)	Mean Diff	Power (RMST)
25 mos	0.84	2.06m	30.2%	1.31m	30.8%	4.32m	99.8%
50 mos	0.83	2.07m	43.2%	2.57m	43.8%	6.12m	99.9%
75 mos	0.83	2.07m	45.0%	3.35m	45.2%	7.01m	99.9%

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Summary and Discussion

- Conventional methods for TTE endpoints such as HR/median/LR tests have limitations
- OS endpoint will be harder to meet with the advance of cancer treatment
- PFS endpoint has limitations as a surrogate endpoint
- With the advances in cancer treatment (including immunotherapies), it is expected that a higher proportion of patients will respond to treatment (higher ORR, higher CR rate)
- Mean is the gold standard in many therapeutic areas
- A composite endpoint (DOR) and measure (mean) was proposed as an alternative method for statistical inference to assess TTR, ORR, DOR simultaneously
  - Mean duration of complete response in the ITT population could be potentially useful and efficient for next generation cancer therapies

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thank you
danke
謝謝
ngiyabonga
teşekkür ederim
gracias
obrigado
merci
dziękuję
bedankt
terima kasih
sukriya
kop khun krap
go raibh maith agat
dakujem
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grazie
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спасибо
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