Interim Monitoring: Pitfalls and Recommendations

FDA Mini-Symposium on Role of DMCs, Sponsors & Regulators in the Era of Breakthrough Therapy and Accelerated Approval in Oncology Clinical Trials

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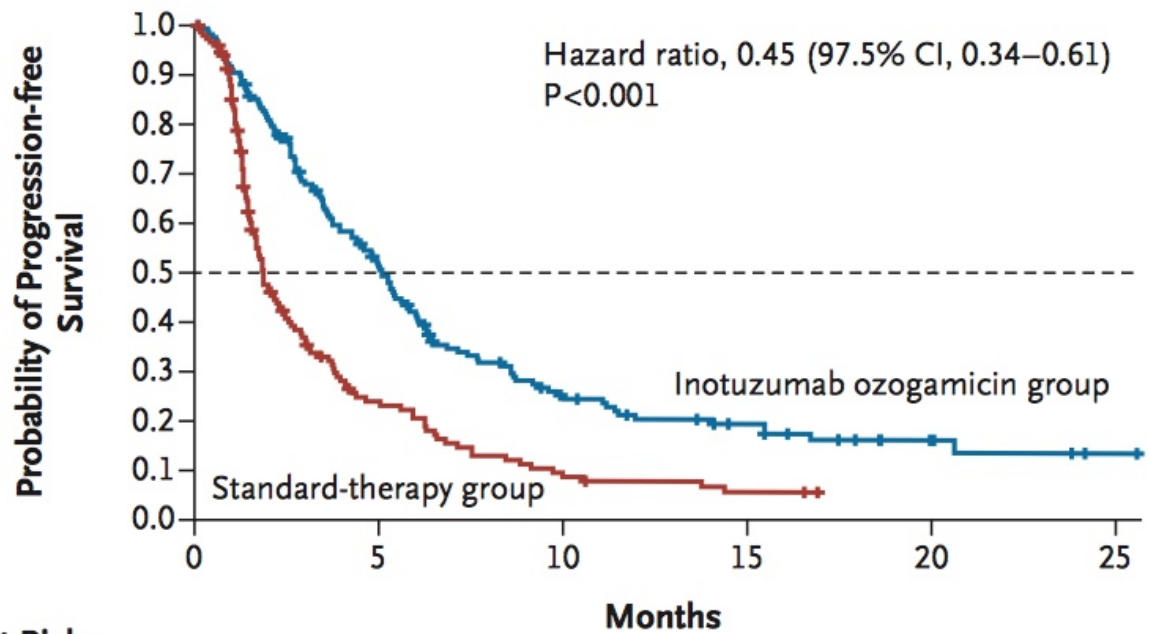
Design Issues

Anticipating Tx effects

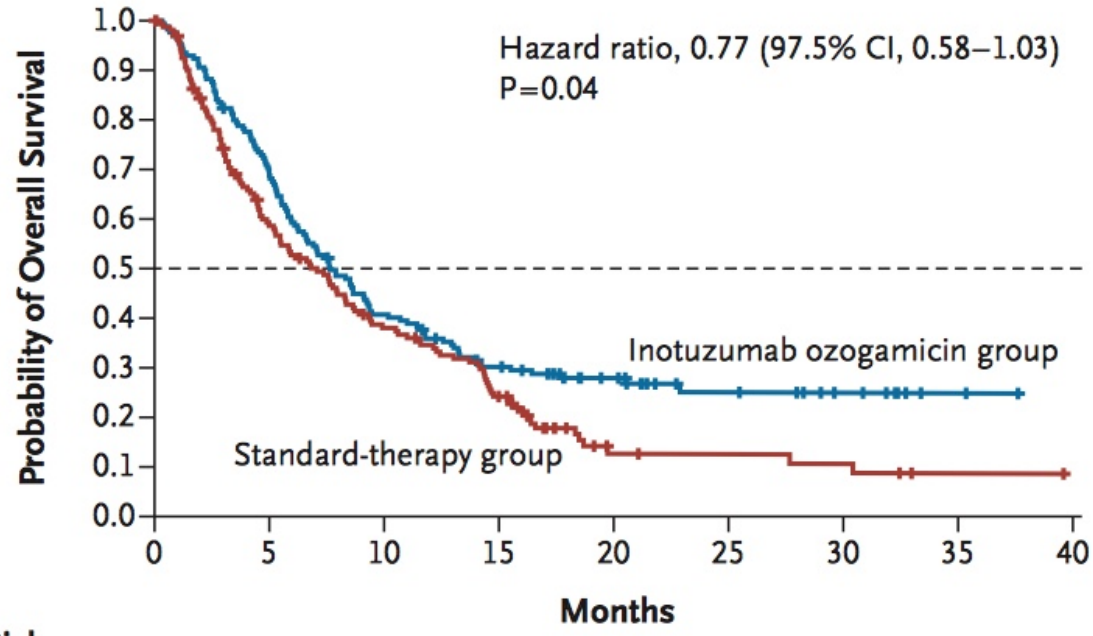
Inotuzumab Ozogamicin versus Standard Therapy for ALL (NEJM 25 Aug 2016)

B Progression-free Survival



No. at Risk						
Inotuzumab ozogamicin group	164	72	28	16	6	1
Standard-therapy group	162	24	6	2	0	0

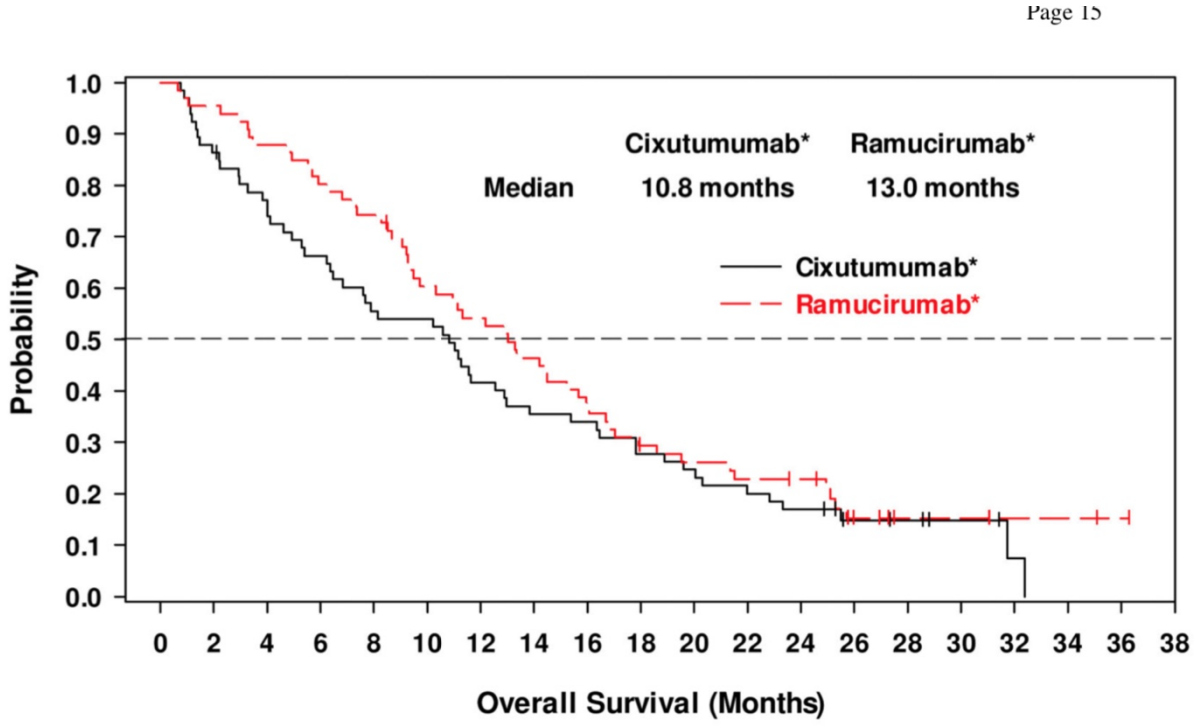
C Overall Survival



No. at Risk

Inotuzumab ozogamicin group	164	112	62	41	24	13	8	2	0
Standard-therapy group	162	85	51	30	6	5	4	1	0

Metastic prostate cancer



Hussain, et al., Eur J Cancer, Sep 2015

Correct assumptions may depend on disease and/or agent

From Alexander, et al., NEJM March 2018

Table 1. Deviations from the Proportional-Hazards Assumption in Recent Immunotherapy Trials.*

Trial	Citation	Progression-free Survival			Overall Survival		
		P Value for Proportional-Hazards Deviation†	Difference in Hazard Ratios‡	Difference in P Values‡	P Value for Proportional-Hazards Deviation†	Difference in Hazard Ratios‡	Difference in P Values‡
CheckMate 017	N Engl J Med 2015;373:123–35	0.03	0.044	0.000	0.44	–0.024	–0.002
CheckMate 025	N Engl J Med 2015;373:1803–13	0.02	0.072	0.046	0.06	–0.067	–0.089
CheckMate 057	N Engl J Med 2015;373:1627–39	<0.001	0.111	0.248	0.003	0.101	0.006
CheckMate 066	N Engl J Med 2015;372:320–30	0.001	0.032	0.000	0.01	0.063	0.000
CheckMate 141	N Engl J Med 2016;375:1856–67	0.007	0.014	0.005	0.03	0.105	0.023
KEYNOTE-045	N Engl J Med 2017;376:1015–26	<0.001	0.122	0.467	0.006	0.138	0.003
KEYNOTE-024	N Engl J Med 2016;375:1823–33	<0.001	0.058	0.000	0.47	0.019	–0.004

* Progression-free and overall survival curves were extracted from the listed publications with the use of DigitizeIt.

† Analysis of the proportional-hazards assumption for each trial was performed by means of standard testing for independence of Schoenfeld residuals and time, with the use of R software, version 3.4.2 (R Project for Statistical Computing), and the "survival" package. P values of less than 0.05 are consistent with deviations from proportional-hazards assumptions.

‡ We considered hazard ratio estimates (treatment vs. control) and P values to evaluate the null hypothesis of no treatment effects. The differences between these key summaries from two distinct analyses — proportional hazards using the entire time-to-event curves versus proportional hazards with the exclusion of the initial 20% of the events — are reported.

Substantial methodology available

Korn and Freidlin, 2018 JCO, Am. J.Bioethics 2011

Freidlin and Korn, Clin Trials, 2009; Cont Clin Trials, 2002

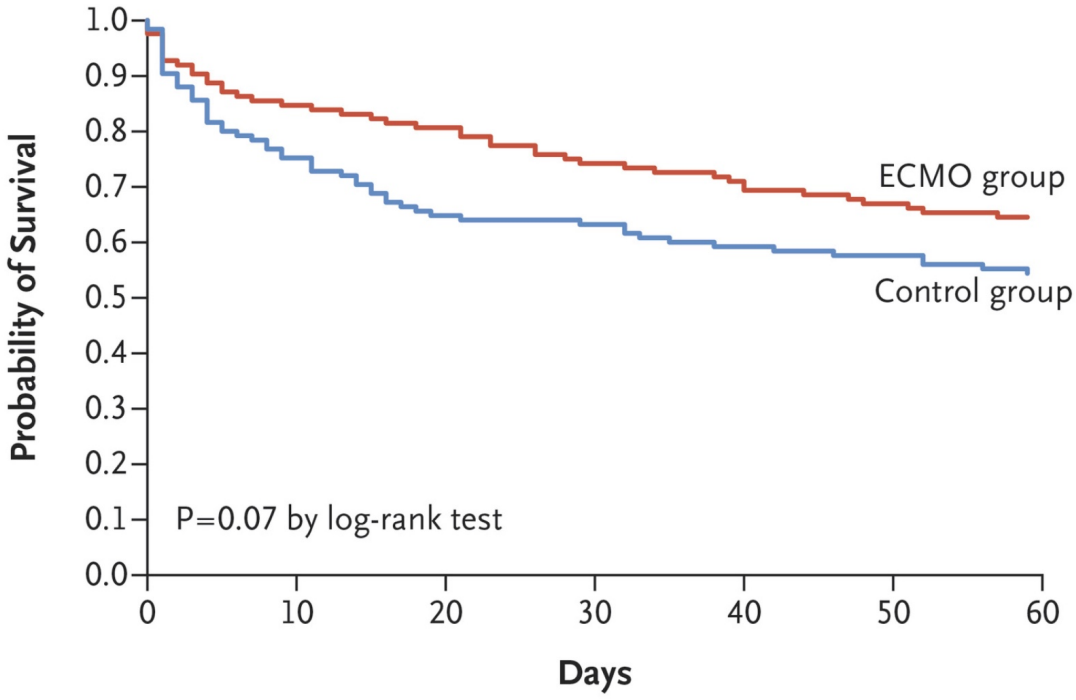
Work presented at Feb 2018 Duke Margolis Workshop

- Oncology Clinical Trials in the Presence of Non-Proportional Hazards

Issues external to the trial

Following the monitoring plan was the wrong thing to do

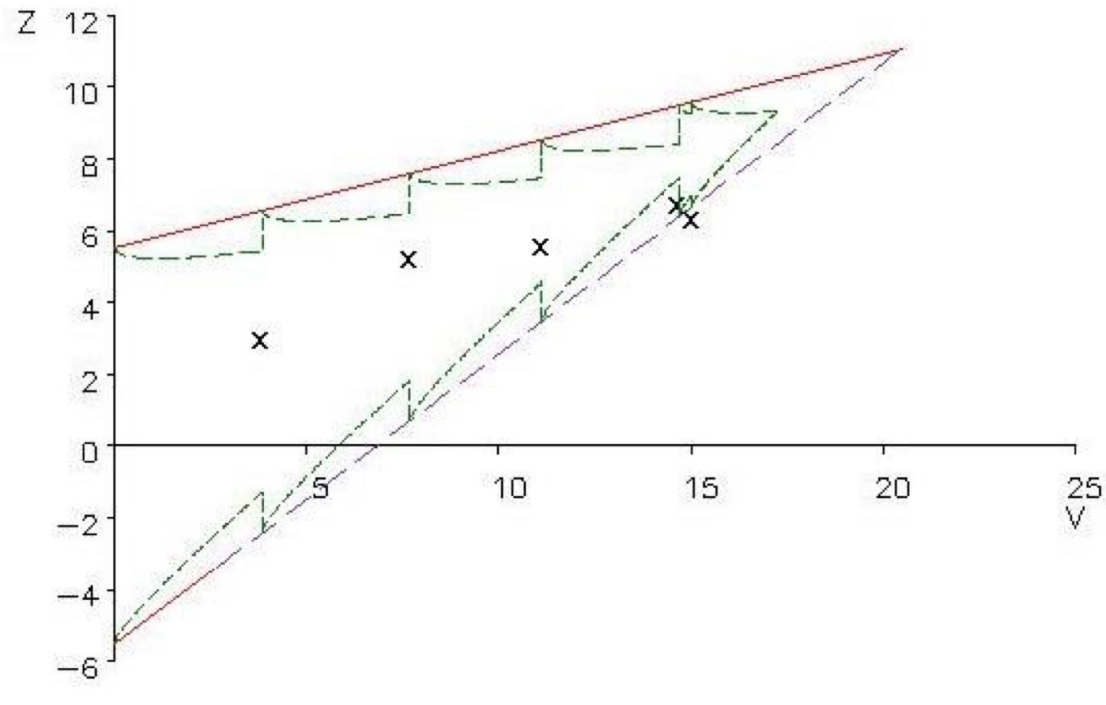
Extracorporeal Membrane Oxygenation ECMO for ARDS (NEJM 24 May 2018)



No. at Risk							
ECMO	124	105	100	92	88	83	80
Control	125	94	81	79	74	72	69

Figure 2

ECMO Stopping Rule: Figure S1



- Trial stopped for futility at 4th interim analysis, with 240/331 patients.
- HR 0.70 favoring ECMO, 95% confidence interval (0.47, 1.04), p = 0.07

Not following the plan was the right thing to do

Heart and Lung Transplants from HCV+ Donors (Woolley, et al.,NEJM 25 April 2019)

- Original Design based on Simon two-stage phase II design.
- Amended to modified SPRT to allow continuous monitoring.
  - Boundaries for superiority and safety

HCV+ Transplanted organs . . .

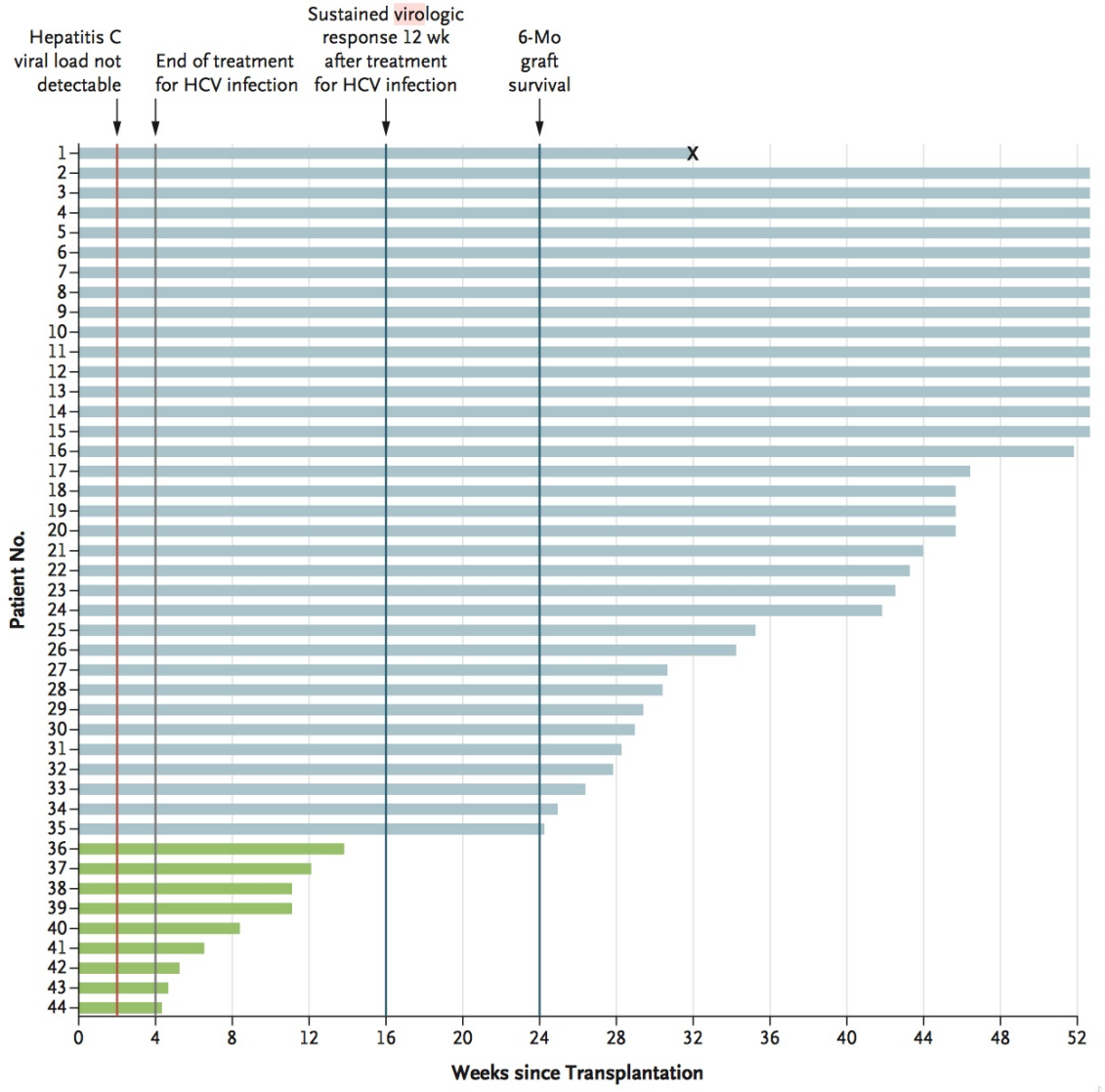


Figure 2: Crossed stopping boundary for efficacy at 13 patients with 6 mo follow-up

Recommendations/Questions

- DMC and FDA should probe whether monitoring plan uses
  - Best available data to anticipate nature of differences.
  - Best available methodology for monitoring
- In the absence of harm, non-significant but positive Tx effects may be important.
  - Be reluctant to stop when HR favors experimental Tx
- Monitoring plans should incorporate interim sensitivity analyses for different types of Tx effects.
- Is a surrogate endpoint risky? (eg, PFS vs OS)

Recommendations . . .

- DMC should be less literal in executing monitoring plans when faced with external information.
- Data sharing between DMCs or between DMC and FDA should be guaranteed confidential, including the use of secure communications.
- Does the FDA perspective on interim futility monitoring coincide with trials not designed for regulatory approval?
- Should we continue to design around proportional hazards?