Statistical Challenges in Immunotherapy: Non Proportional Hazard Model

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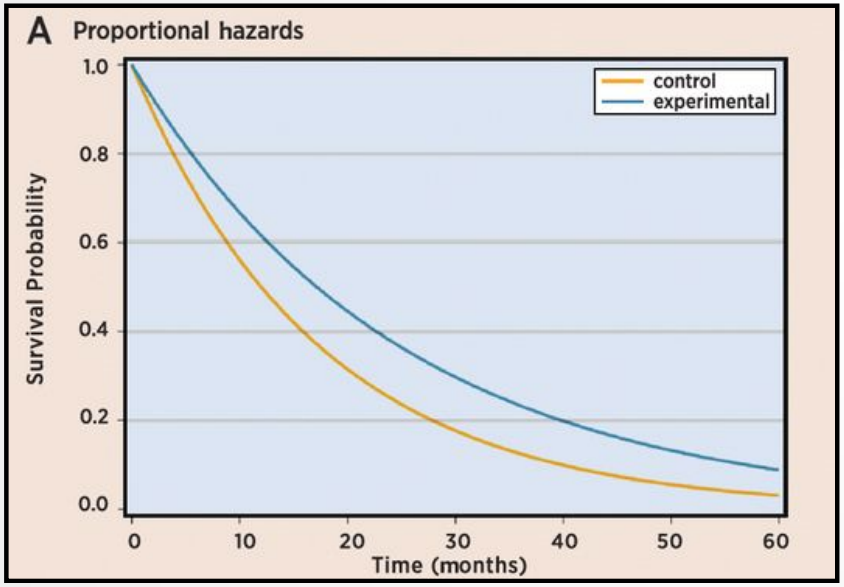
Statistical Challenges

- Biomarker
- Efficacy Endpoint
- Study Design & Analysis

Survival Kinetic

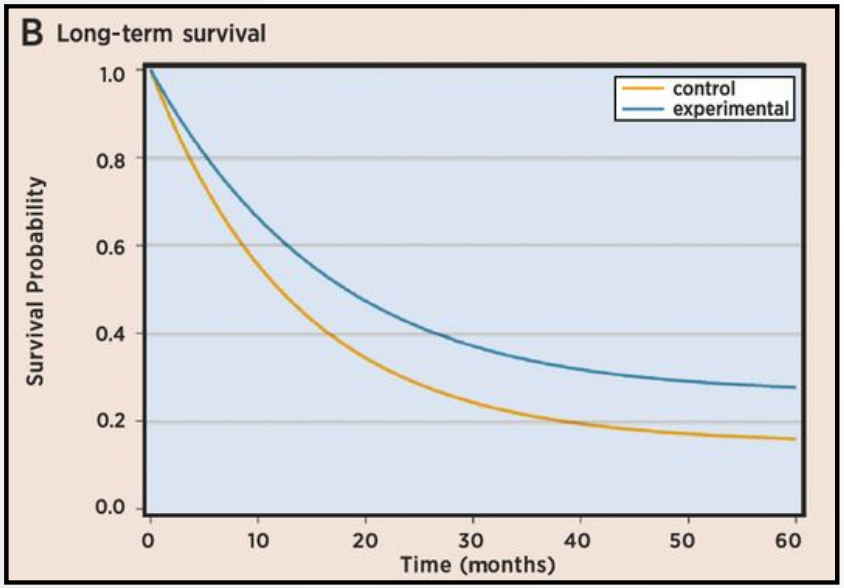
A - Proportional Hazards Model (PHM)



1. We assume anything that affects the hazards does so by the same ratio during the observation period (i.e., proportional hazards).
2. The relative clinical effect of the experimental group over the control group is observed from the beginning.
3. All patients enrolled in the study are subject to the event of interest; therefore, the survival curves will eventually drop down to zero survival probability.

Survival Kinetic

B - Proportional Hazards Cure Rate Model (PHCRM)

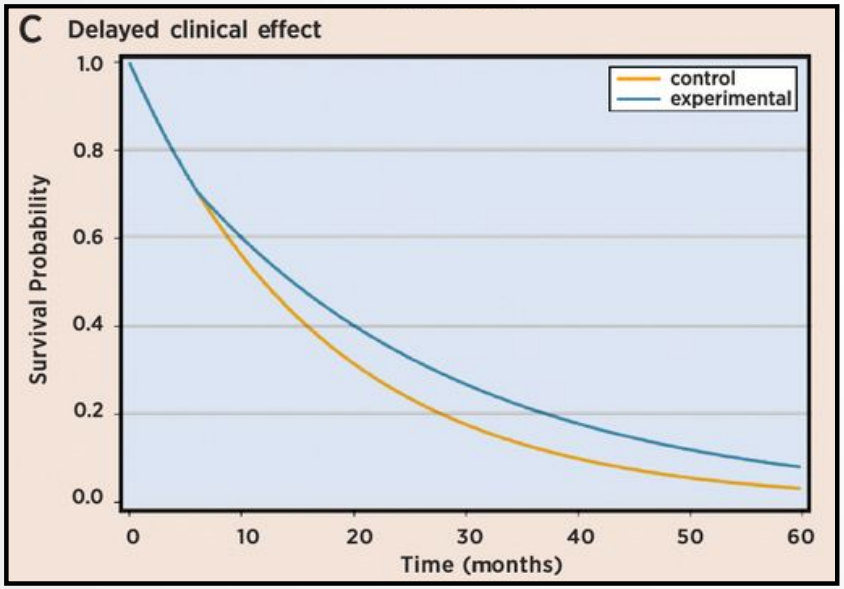


1. The population is assumed to consist of patients who are either susceptible or non susceptible to the event of interest (i.e., a proportion of patients are expected to remain alive or free of disease even after long follow-ups).

2. PHCRM assumes proportional hazards between two treatment groups among susceptible patients, while the long-term survival rates are also assumed proportional between two groups among non susceptible patients, such that the risk ratio of the entire population is consistent within each of these two subpopulations.

Survival Kinetic

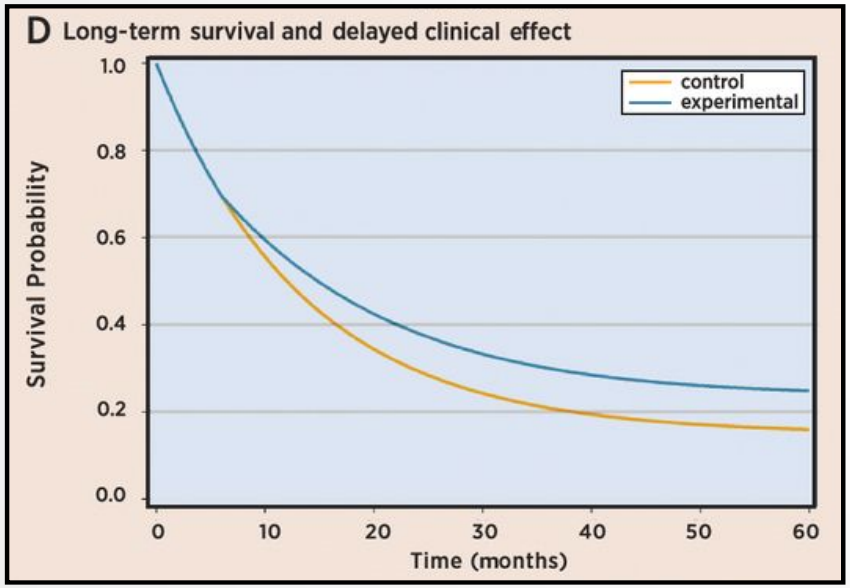
C – Non Proportional Hazards Model (NPHM)



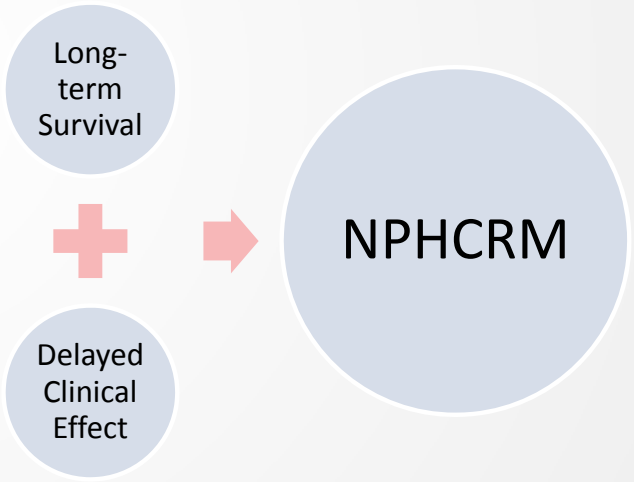
1. Non proportional hazards imply the hazard ratio (HR) changes over time during the observation period.
2. The simplest NPHM is under the piecewise exponential distribution assumption with two intervals, in which the HR within each interval remains constant.
3. A special case of NPHM is the PHM when hazards in both groups remain constant and the HRs are identical in both intervals .

Survival Kinetic

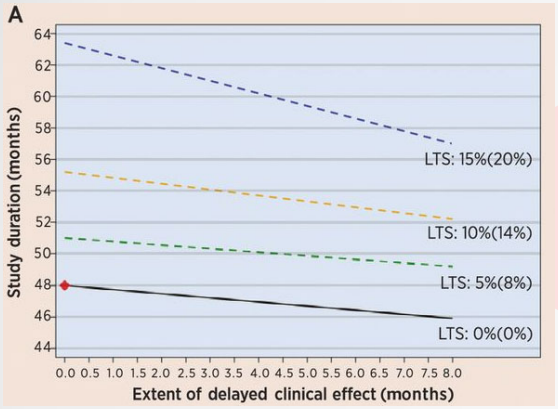
D – Non Proportional Hazards Cure Rate Model (NPHCRM)

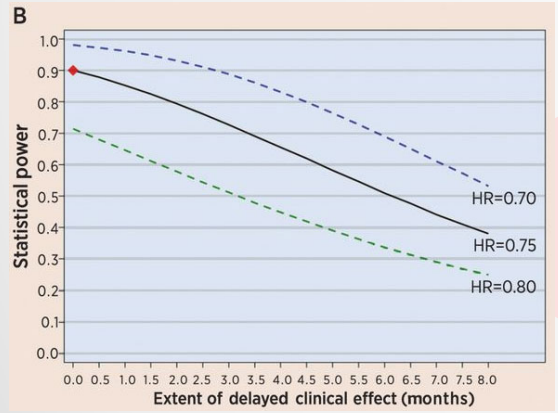


Both long-term survival and delayed clinical effect are incorporated in the NPHCRM



Impact of Cross-Over & Delayed Clinical Effect on Power & Study Duration





The prolongation of the trial duration ranged from 3 months to 16 months when the proportion of long-term survivors (LTS) in the control group increased from 5% to 15%, with the numbers in the parentheses representing the proportions of LTS for the entire study. The slight decrease in trial duration was caused by the increasing number of events in the experimental group during the delay.

♦The red diamonds in both panels represent the study design with no delayed clinical effect and 90% power when HR = 0.75 and median OS for the control arm = 12 months. The trial duration was estimated to be 48 months.

When HR after separation remained at 0.75, the statistical power decreased from 90% to 38% with corresponding increase in duration of delayed clinical effect from 0 to 8 months. An observed relative treatment difference of HR = 0.7 would lead to an absolute increase in statistical power of 8% to 15% (blue dashed curve) for various durations of delayed clinical effect. A worse observed treatment effect of HR = 0.8 is shown as a green dashed curve with statistical power ranging from 25% to 71%.

The presence of delayed clinical effect and long-term survival would lead to a loss of statistical power and prolongation of trial duration.

Delayed Clinical Effect in Immunotherapy

It is now well understood that chemotherapy and immunotherapy do not share the same survival kinetics:

Chemotherapy Survival Kinetic

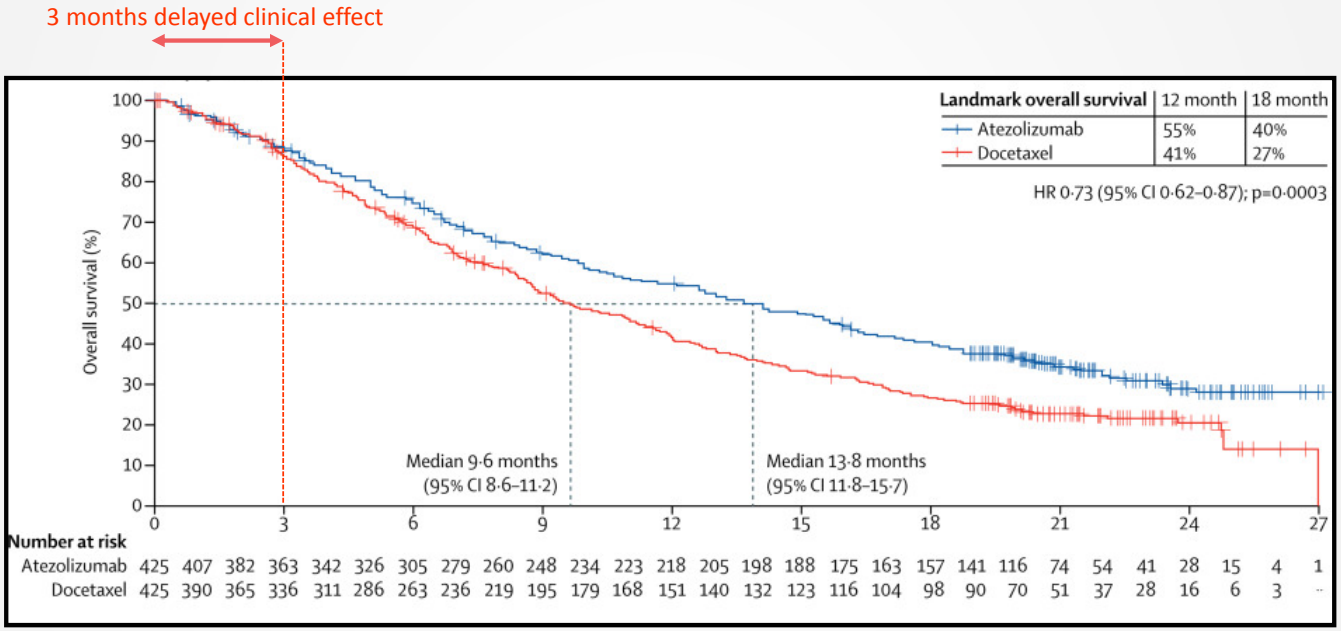
- Patients treated with chemotherapy show early antitumor effects. When compared with a control arm, improved OS or PFS for the experimental arm is demonstrated by an early separation between the survival curves.

Immunotherapy Survival Kinetic

- In contrast with chemotherapy's immediate and direct cytotoxic effect on a tumor, immunotherapy stimulates the patient's immune system to mount an antitumor response. The time needed to mount this response inserts the delay in clinical effect observed consistently across many trials.
- Due to emergence of supporting data and increase in number of trials involving checkpoint inhibitors, cross-over of patients is expected.

Delayed Clinical Effect in Immunotherapy

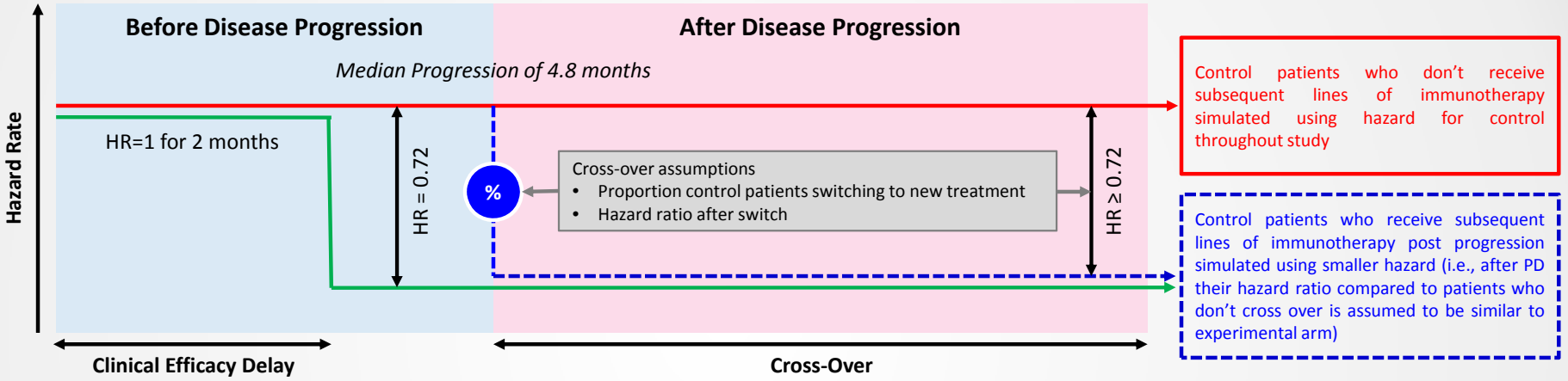
A PHASE III, OPEN-LABEL, MULTICENTER, RANDOMIZED STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF ATEZOLIZUMAB COMPARED WITH DOCETAXEL IN PATIENTS WITH NON SMALL CELL LUNG CANCER AFTER FAILURE WITH PLATINUM CONTAINING CHEMOTHERAPY [OAK]



Source: Achim Rittmeyer 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. The Lancet, Volume 389, Issue 10066, 21–27 January 2017, Pages 255–265.

Impact of Cross-Over & Delayed Clinical Effect on Power

Simulation Assumptions



Results

N	Events	Power for PHM	Delayed Treatment Effect	% Cross-over in Control Arm	Post-cross-over Hazard Ratio	Power	Δ Power	Observed Hazard Ratio
720	540	97%	-	15%	0.76	93%	-4%	0.75
720	540	97%	X	0%	0.76	90%	-7%	0.76
720	540	97%	X	15%	0.76	81%	-16%	0.78

Combined impact on power is not simply addition of individual effects.

Assumptions: log-rank test; 2-sided α=0.05; median rPFS 4.8 months; median OS control 12 months; TPP HR=0.72; HR=1 for first 2 months; drop-out 5% / 2 years; event ratio 75%.

Interim Analysis & Group Sequential Procedure

- In an immuno-oncologic randomized clinical trial with long term survival and delayed clinical effect, one needs to reconsider the implementation of conventional interim analyses when the intention is to stop the study early for either positive or futile outcome.

- If the treatments exhibit delayed clinical benefit, implementation of superiority interim analysis may have smaller stopping probability for a positive outcome whereas futility interim analysis could increase the chance of terminating the study early and erroneously discarding an active agent.

- The study design example from Chen (2013) indicates that a 4-fold decrease in true-positive rate and an 8-fold increase in false-negative rate would be seen at the interim analysis with 50% information fraction if the delayed clinical effect was not considered in the study design [Chen TT. Statistical issues and challenges in immuno-oncology. J Immunother Cancer 2013;**1**:1–9.].