Statistical Challenges in Immuno-Oncology

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Outline

Cytotoxic vs. cytostatic agents

- Mechanism of action
- Endpoints

Immunotherapies

- Important issues to consider in study design and analysis
- Efficacy
  - Overall Survival

MOA: Cytotoxic vs. Cytostatic Agents

Cytotoxic agents

- Dose-dependent rapid cell kill or tumor shrinkage
- Lack of selectivity leads to undesired toxicity or side effects

Cytostatic agents

- Inhibit or suppress cellular growth or division which leads to delayed progression
- Minimal or less severe toxicity, prolonged duration of treatment at lower dose

Endpoints: Cytotoxic vs. Cytostatic

Cytotoxic

- OS: Clinical benefit
- BOR (WHO or RECIST): Direct cell kill action leads to tumor shrinkage

Cytostatic

- OS: Clinical benefit
- PFS/TTP: Stop or delay tumor growth
- BOR: Some may shrink tumor

Immunotherapies

Stimulate the patient's own immune system to fight cancer

- **Immune cell activation; change in tumor burden**
- **Toxicity or side effects caused by the modulation of immune activity**

Endpoints remain similar

- **OS: clinical benefit**
- **BOR: tumor shrinkage**

Important Issues in Design and Analysis in Immuno-Oncology

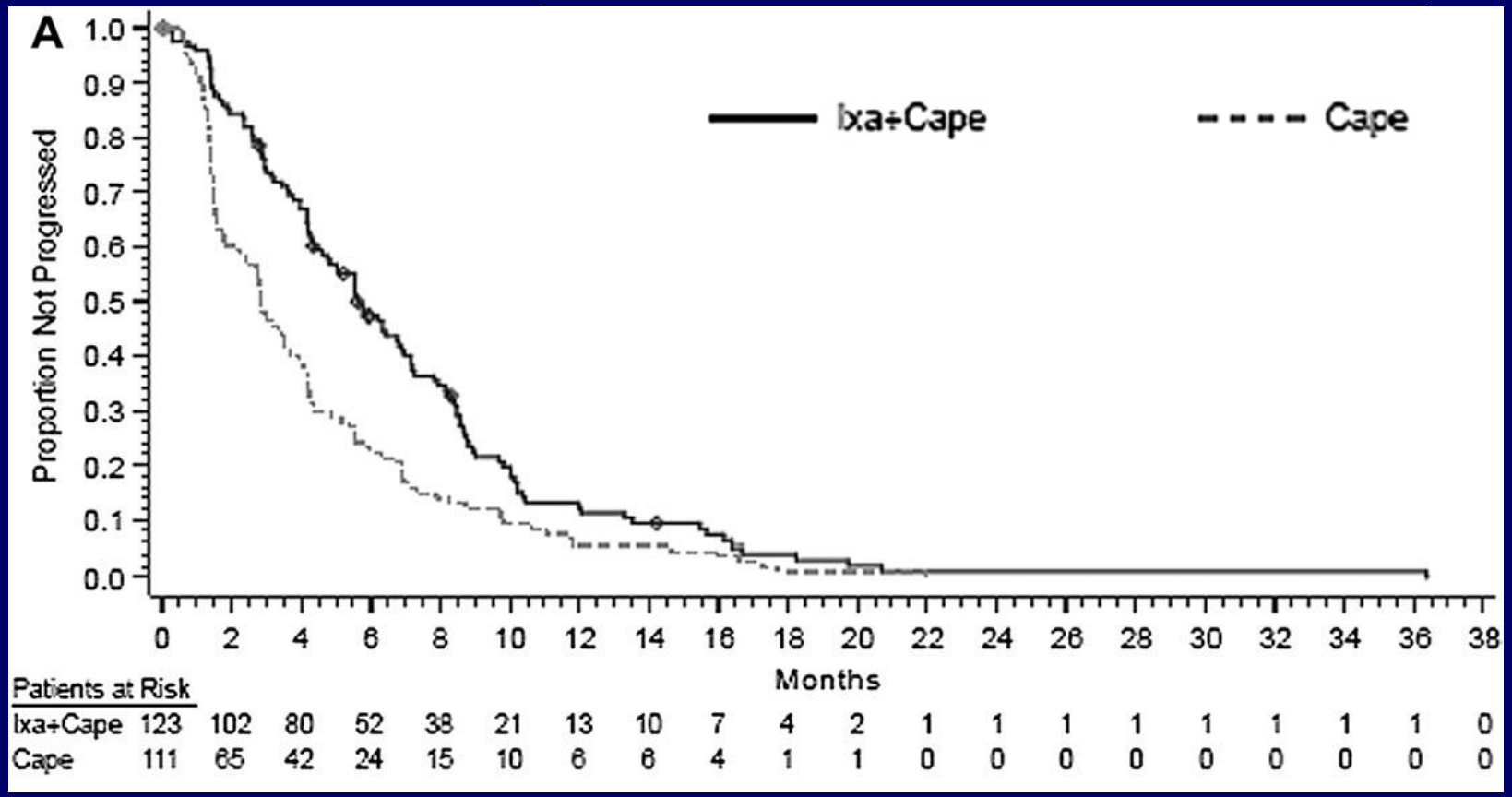
Sample size determination

- Expected number of events
- Timing of analysis

Efficacy analysis

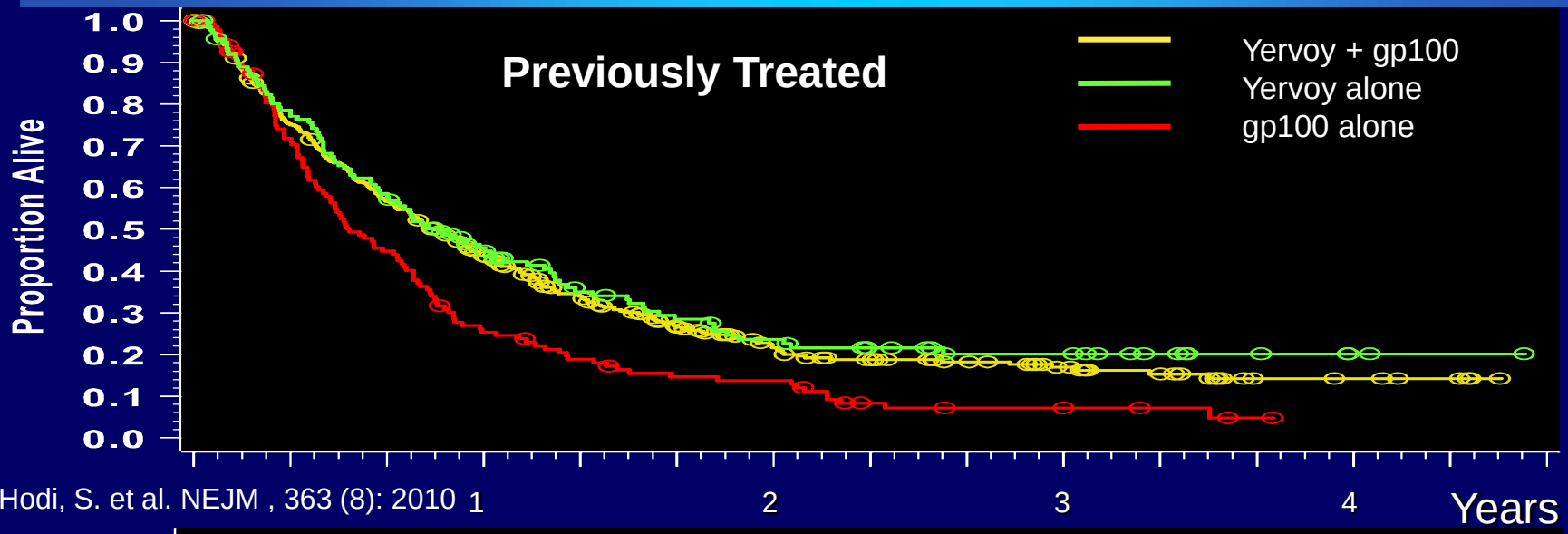
- Interim analysis strategy
- Additional analysis considerations

Typical Survival Curve – Advanced Breast Cancer

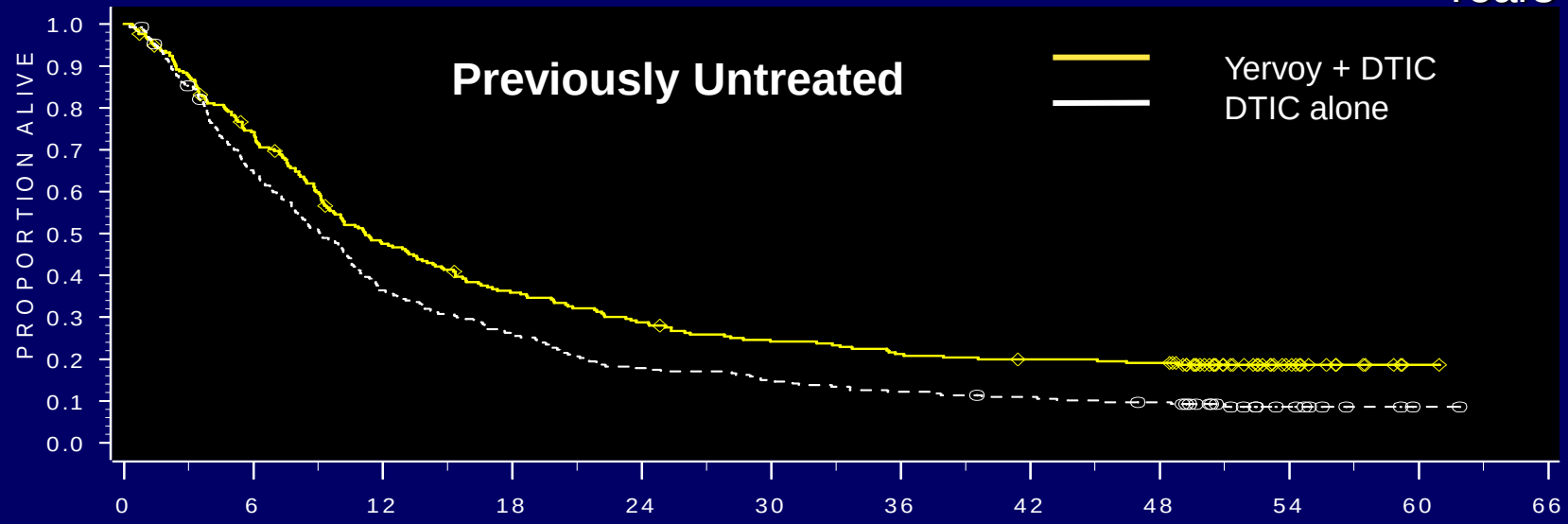


J. Jassem et al. / The Breast 21 (2012) 89–94

Ipilimumab (Yervoy) in Metastatic Melanoma

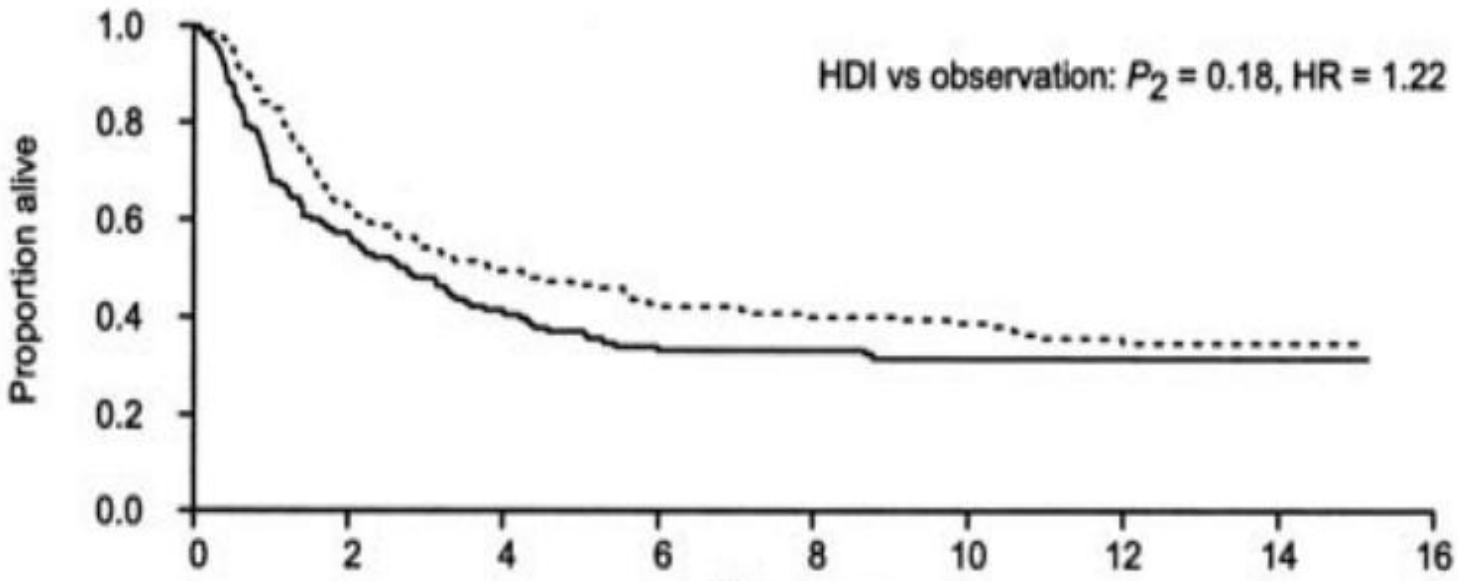


* Hodi, S. et al. NEJM , 363 (8): 2010



* Maio et al. presented at 37th ESMO, 2012

Interferon alfa-2b (Intron-A) – Adjuvant Melanoma

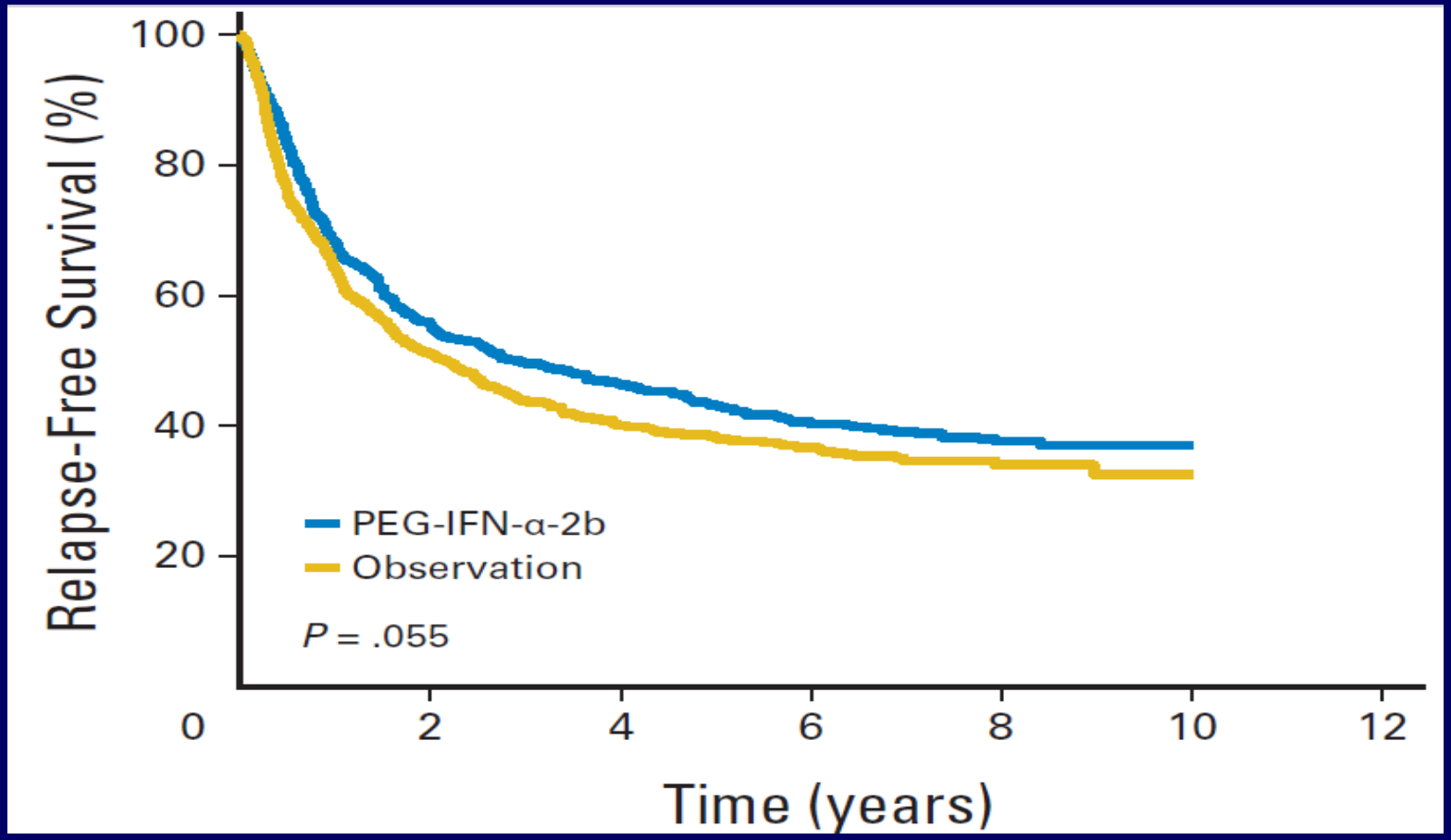


Group	Time interval 0-2	2-4	4-6	6-8	8-10	10-12	12-14	14-16
HDI	54/146	19/90	10/70	3/60	2/56	5/52	0/35	0/10
Observation	60/140	22/80	10/57	1/46	2/43	0/38	0/21	0/6

(events, n/patients at risk, n)

Kirkwood et al., 2004, Clinical Cancer Research

Pegylated Interferon alfa-2b (Sylatron): Relapse-Free Survival – Adjuvant Melanoma



Eggermont, AMM, et al., 2012, Journal of Clinical Oncology

Study Design and Sample Size Determination

Standard study design

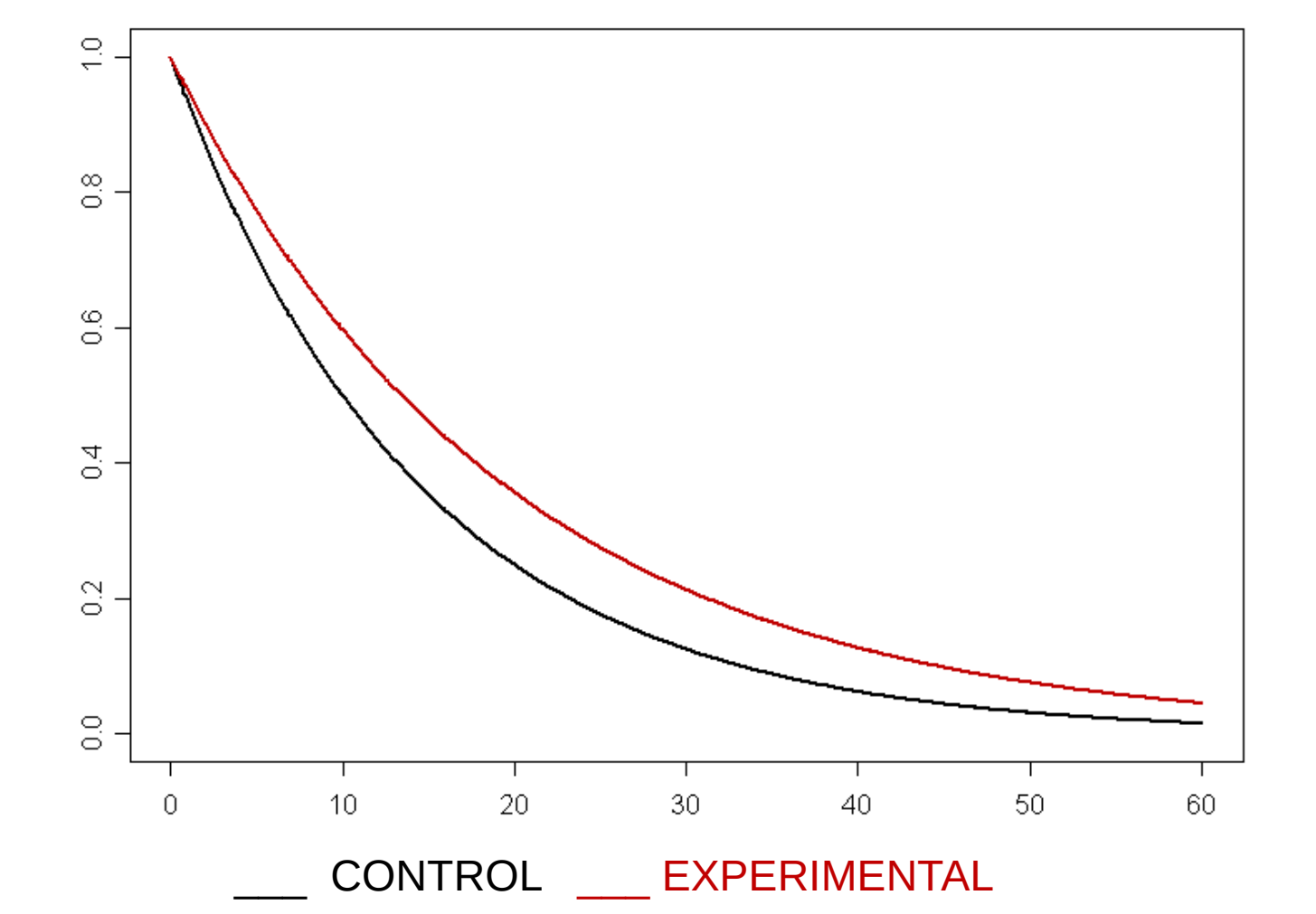
- Assumes exponential distribution

Unconventional study design

- Long-term survival (or “cure rate” or “functional cure”)
- Delayed clinical effect

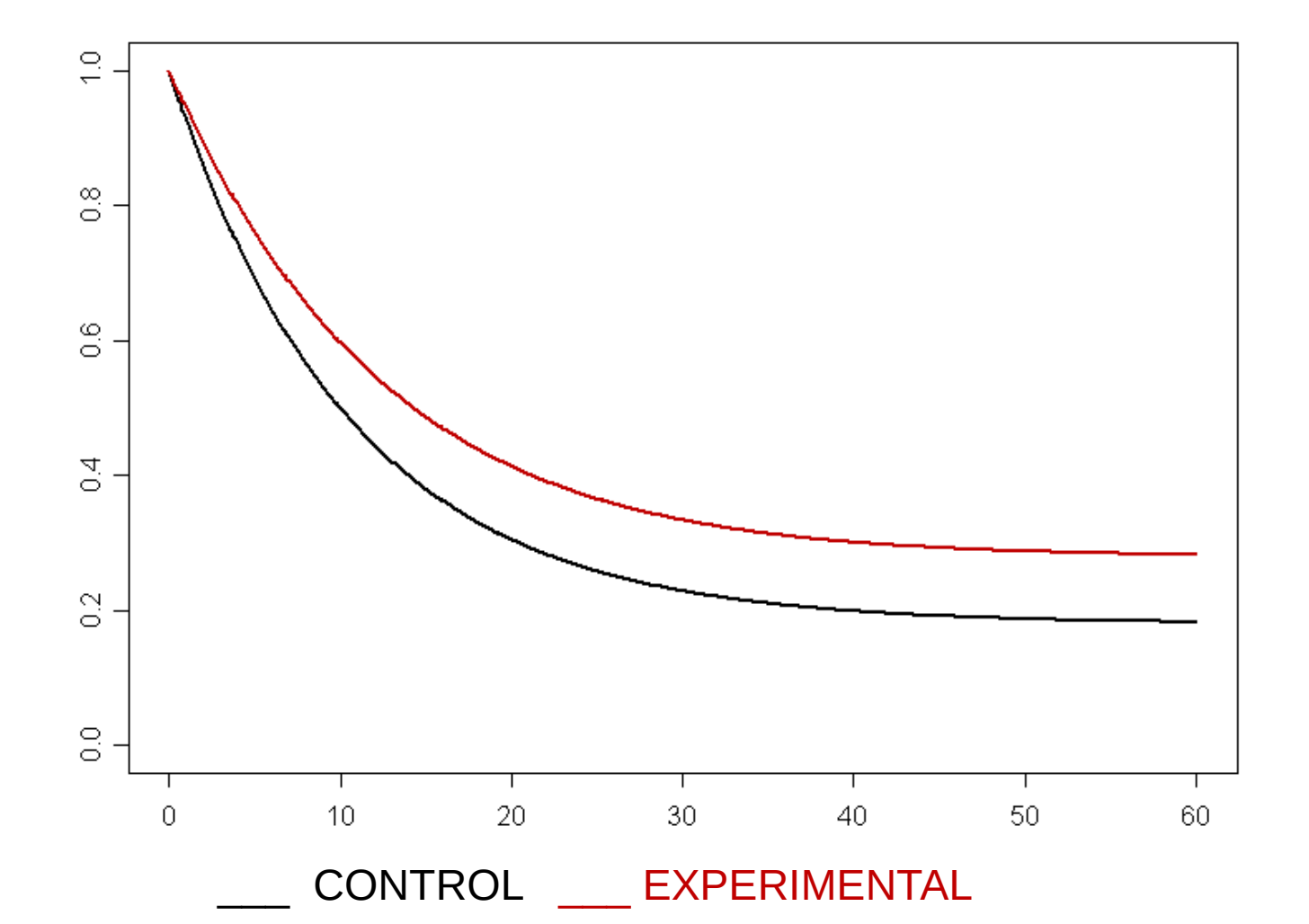
Does unconventional study design impact sample size / power calculation?

Exponential OS Study Design



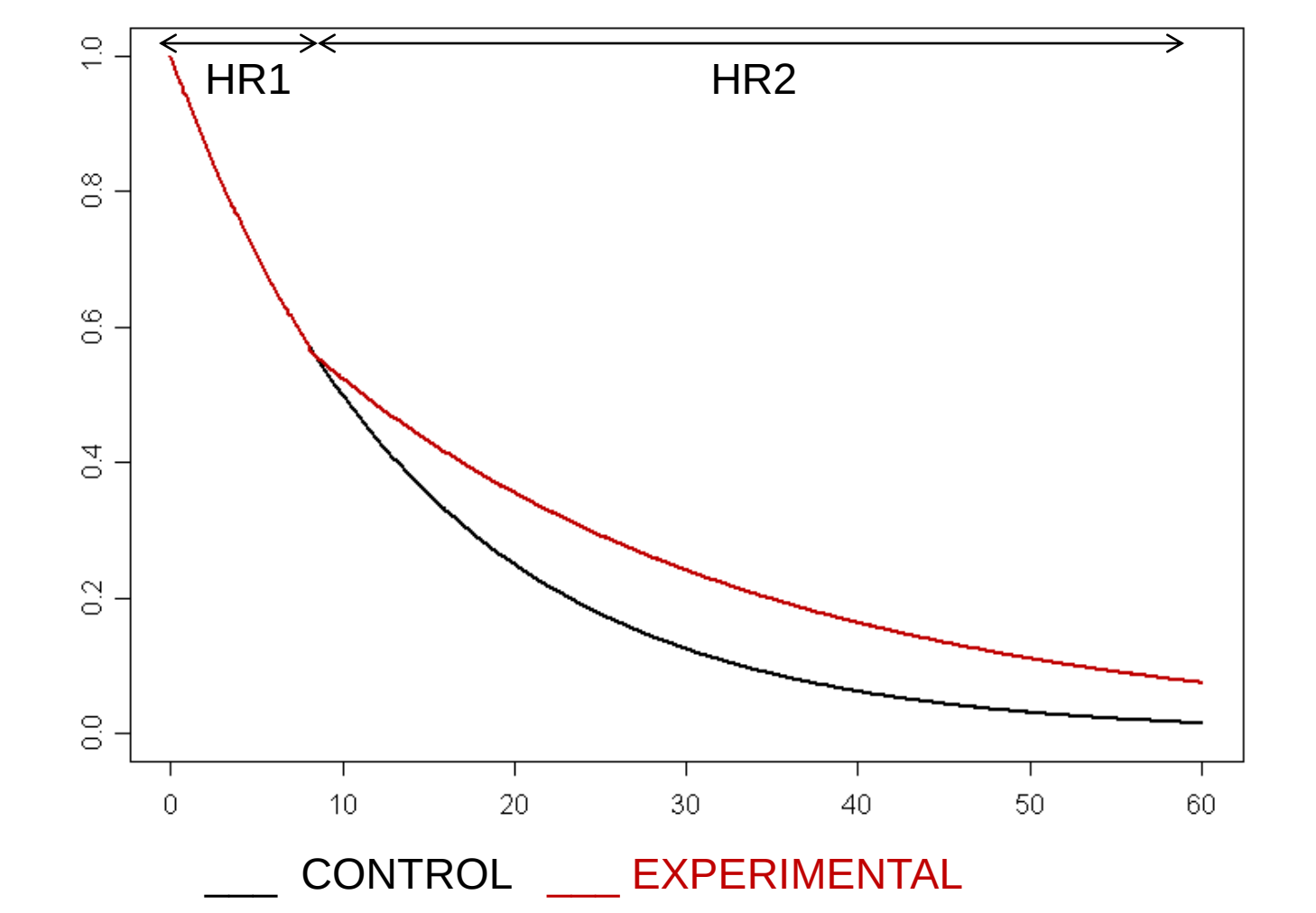
* Proportional hazards model (exponential)

Long-Term (LT) Survival



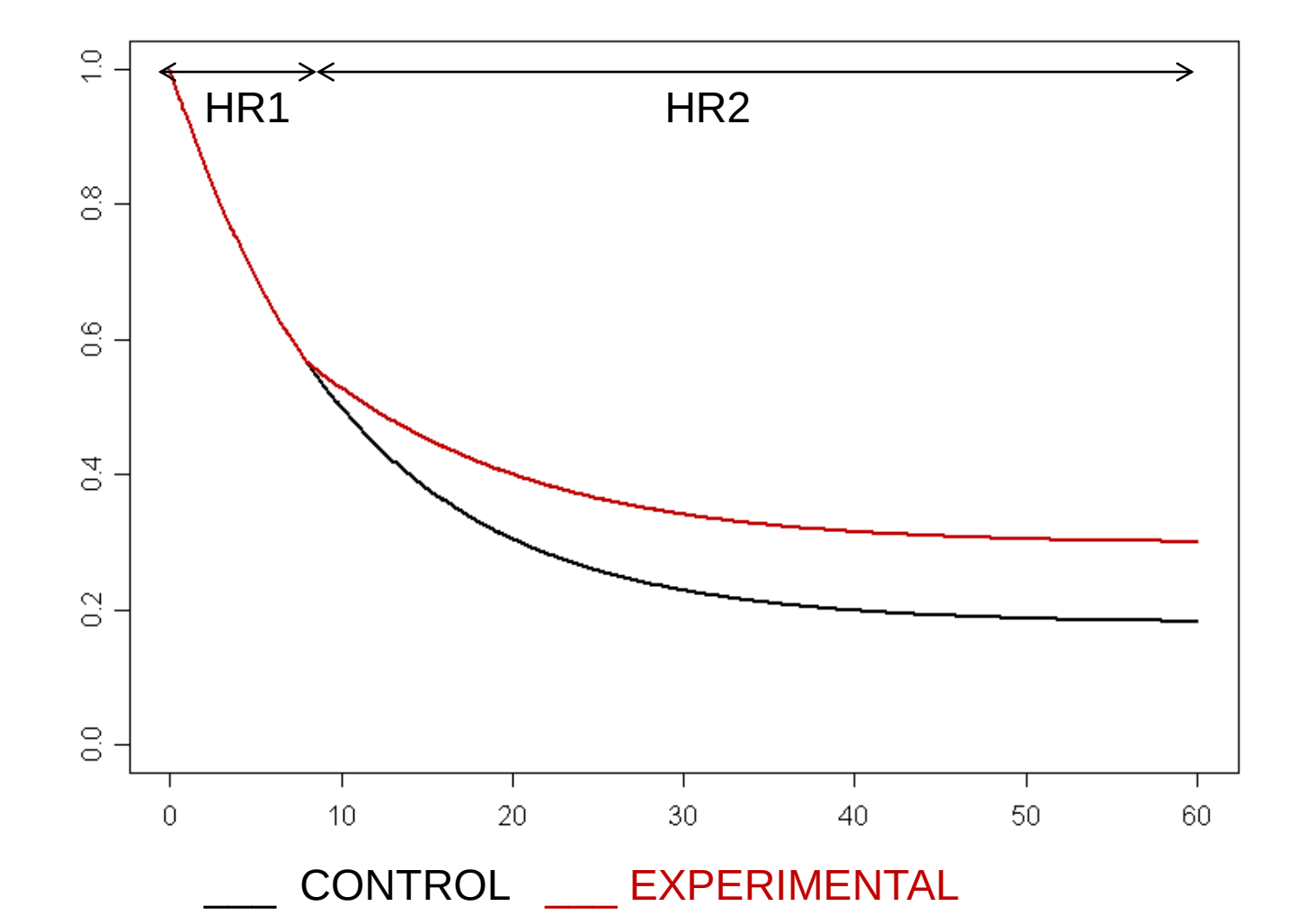
* Proportional hazards cure model

Delayed Clinical Effect



* Non-proportional hazards model

Delayed Clinical Effect with Long-Term Survival



* Non-proportional hazards cure model

Example of a Standard Study Design

Consider the following standard study design

- Exponential distribution
- Median OS: 12 vs. 16 months (HR=0.75)
- Power: 90%
- Two-sided type I error rate: 5%
- Accrual rate: 20 pts/month
- No interim analysis
- Required number of events: 512 events
- Sample size: 680 subjects
- Accrual duration: 34 months
- Study duration: 48 months

Impact of LT Survival and Delayed Clinical Effect on Study Duration and Power

	Standard (exponential)	LT Survival	Delay	LT Survival / Delay
LT survival	--	0.10/0.18	--	0.10/0.17
Delayed effect	--	--	3 m	3 m
Sample size	680	680	680	680
# events	512	512	512	512
Hazard Ratio	0.75	0.75	1/0.75	1/0.75
Power	0.90	0.90	0.70	0.70
Study duration	48	55	47	54

* Based on 10000 simulations

Impact of LT Survival and Delayed Clinical Effect on Study Duration and Power

Long-term survival

- Results in prolonged study duration
- Higher LT survival results in longer study duration

Delayed clinical effect

- Reduces statistical power
- Longer delay results in more power loss

Expected number of events

- Can the number of events be achieved?

Follow-up duration

- Is the study designed to allow sufficient follow-up for all patients?

Interim Analysis Strategy

Necessity of interim analysis

- **Interim analysis vs. final analysis only**

Timing of interim analyses

- **Early vs. late interim analysis**

Type of interim analysis

- **Superiority vs. futility**

Probabilities for Stopping at Interim Analysis

	Standard (exponential)	LT Survival	Delay	LT Survival / Delay
Interim sample size	520	540	480	500
# events	256	256	256	256
PET_a (superiority)	0.25	0.25	0.06	0.06
PET_a (futility)	0.01	0.01	0.08	0.08

PET_a = Probability of Early Termination when agent is active

Using O'Brien-Fleming boundaries

* Based on 10000 simulations

Interim Analysis Strategy - Conclusion

Delayed clinical effect and LT survival

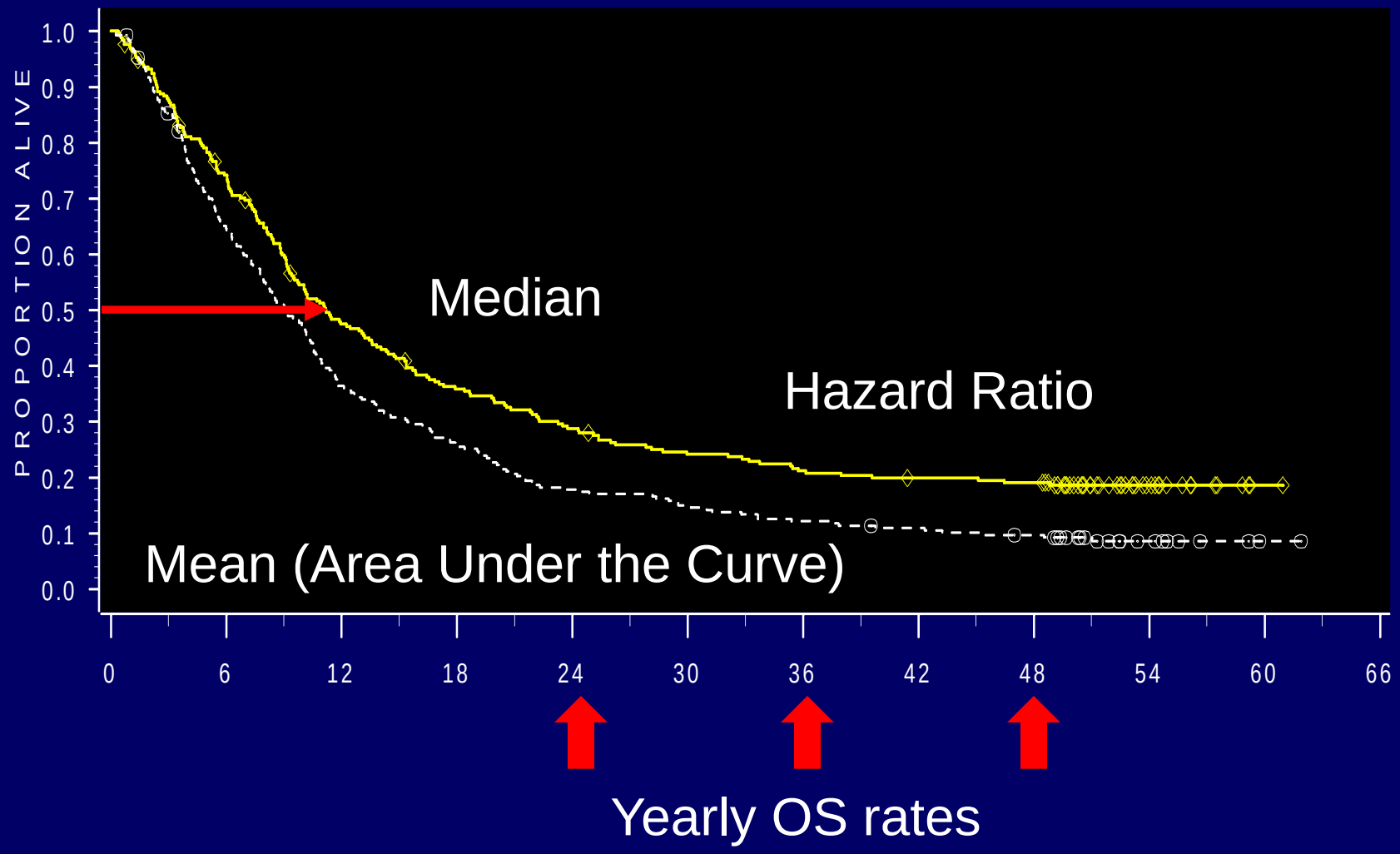
- **Careful consideration warranted:**
  - **Necessity of interim analysis**
  - **Timing of interim analysis**
  - **Type of interim analysis**

Additional Analysis Considerations

Prediction of timing of analyses

- Does the long-term survival alter projected study duration?

Additional Analysis Considerations
Summary Measures



Statistical Analysis Considerations

Primary analysis

- Remains log-rank test and Cox model?

Long-term survival

- Regulatory: Median vs. OS rates
- Market access: Mean
- Cure rate models

Delayed clinical effect

- Fleming-Harrington weighted log-rank test

Summary

- Understand disease characteristics and MOA of therapy
  - Delayed clinical effect
  - Long-term survival
- Implications on study design and analyses

Reference

- **Statistical issues and challenges in immuno-oncology, Tai-Tsang Chen, Journal for ImmunoTherapy of Cancer 2013, 1:18**