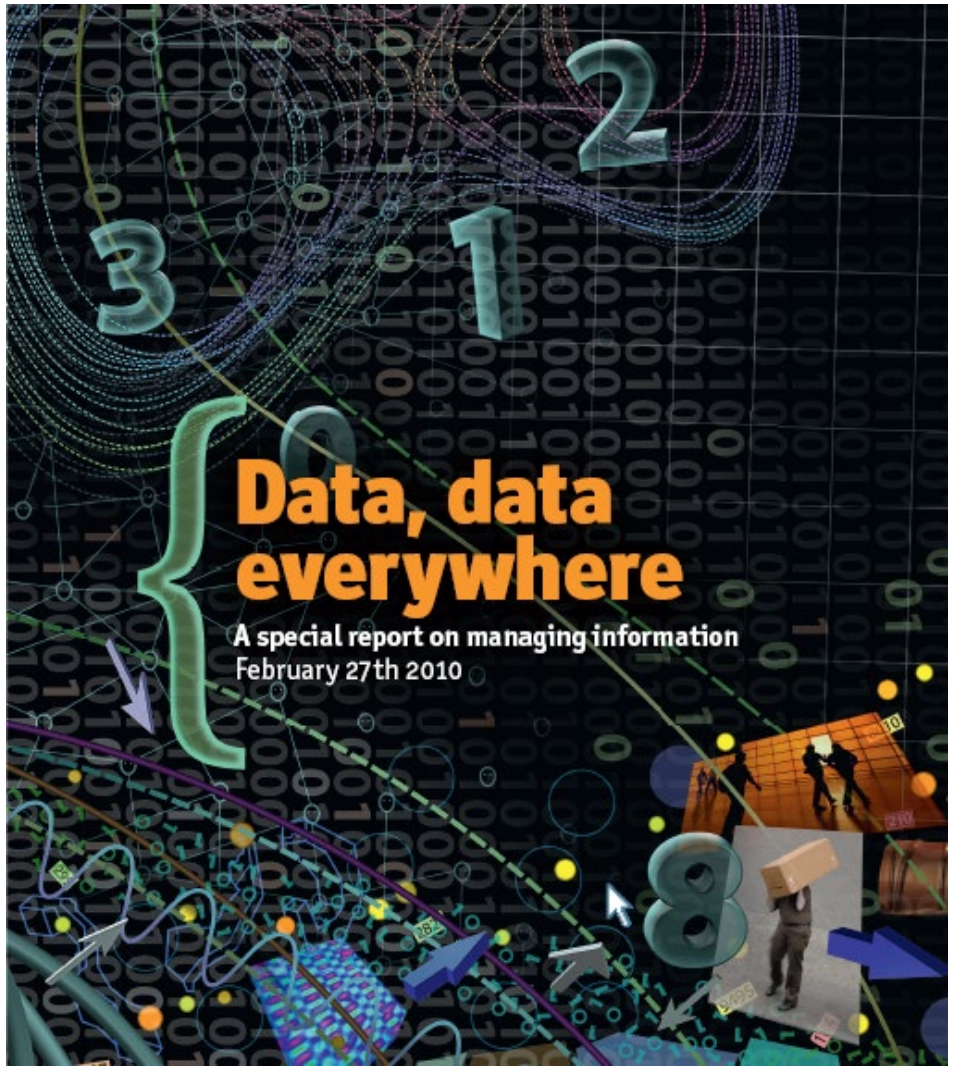


Genomic Cancer Clinical Trials Initiative

GCCTI Research Development Workshop

Making sense of survival curves and analysis: Stats for Smarties!

Martin Stockler
Oncology Director, NHMRC Clinical Trials Centre
Professor of Oncology and Clinical Epidemiology, University of Sydney
Medical Oncologist, Concord Cancer Centre and Chris O'Brien Lifehouse at RPA

NHMRC Clinical Trials Centre
The University of Sydney
Concord Cancer Centre
Chris O'Brien Lifehouse

acord *turning good ideas into successful studies*

Guide for connoisseurs, not stats for dummies

Connoisseur	(one who) understands and is competent to judge
Evaluate	form an idea of amount, number, or value
Appreciate	recognize full worth, understand fully, grasp implications
Recognise	identify from having encountered previously
Hyperbolic	exaggerated, overstating the truth
Claim	assertion that something is true

Survival curves and analysis for connoisseurs

0. Events, risks, odds, hazards, hazard ratios, multivariable
1. Survival curves and comparisons
2. Where to draw the line
3. Truth in reporting

Survival time

Interval from time 0, e.g. randomisation, to some event, e.g.

- death from any cause (overall survival).
- specified event (time-to-event)
- specified event or death (event-free survival, composite)

- Event: occurrence of a specified outcome
- End point: measured outcome of interest in an individual

Event (end point)

Time to death (OS)
progression (TTP)
progression or death (PFS)*
relapse or death (RFS)*
local failure or death* (LFFS)*

*composite (earliest of several)

How soon (quickly), rather than just if...

Survival distribution

- How survival times are distributed in a group of individuals
- The probabilities of the observed survival times
- Best depicted as a Kaplan-Meier Survival Curve (KMSC)
- Applicable to events other than death
- Typically, not everyone has died (had the event)

The problem to be solved

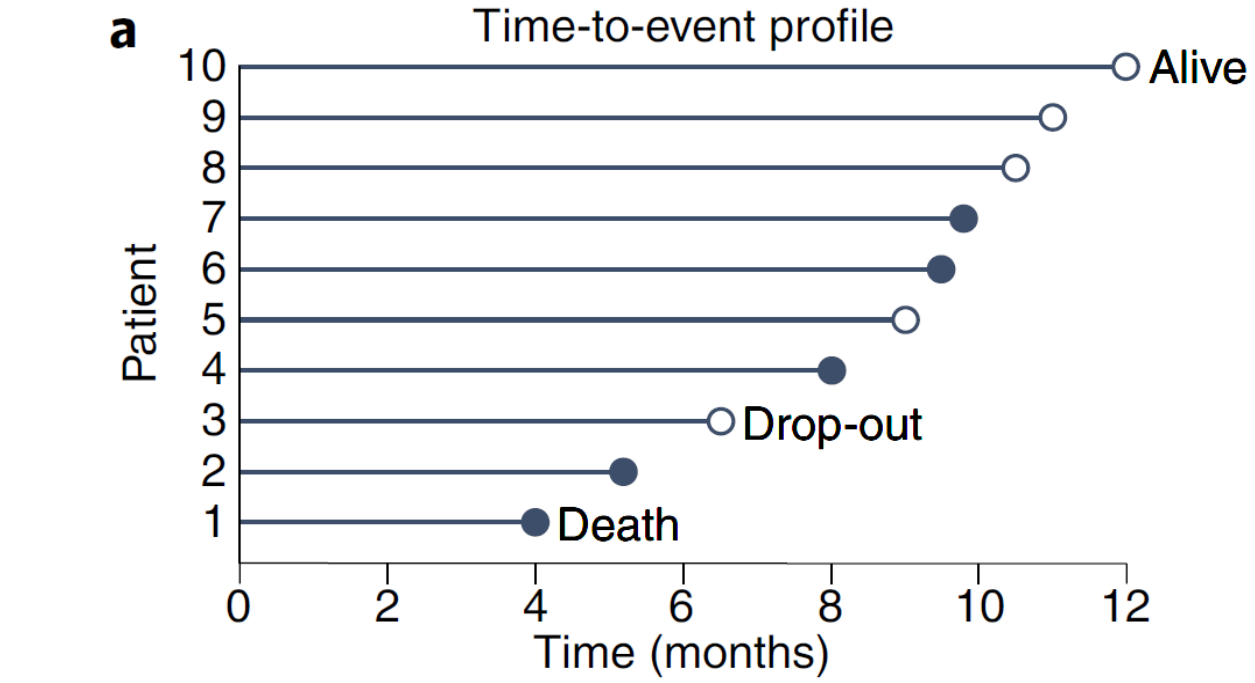
- Describe survival before everyone has died (had the event)
- Individuals followed different lengths of time

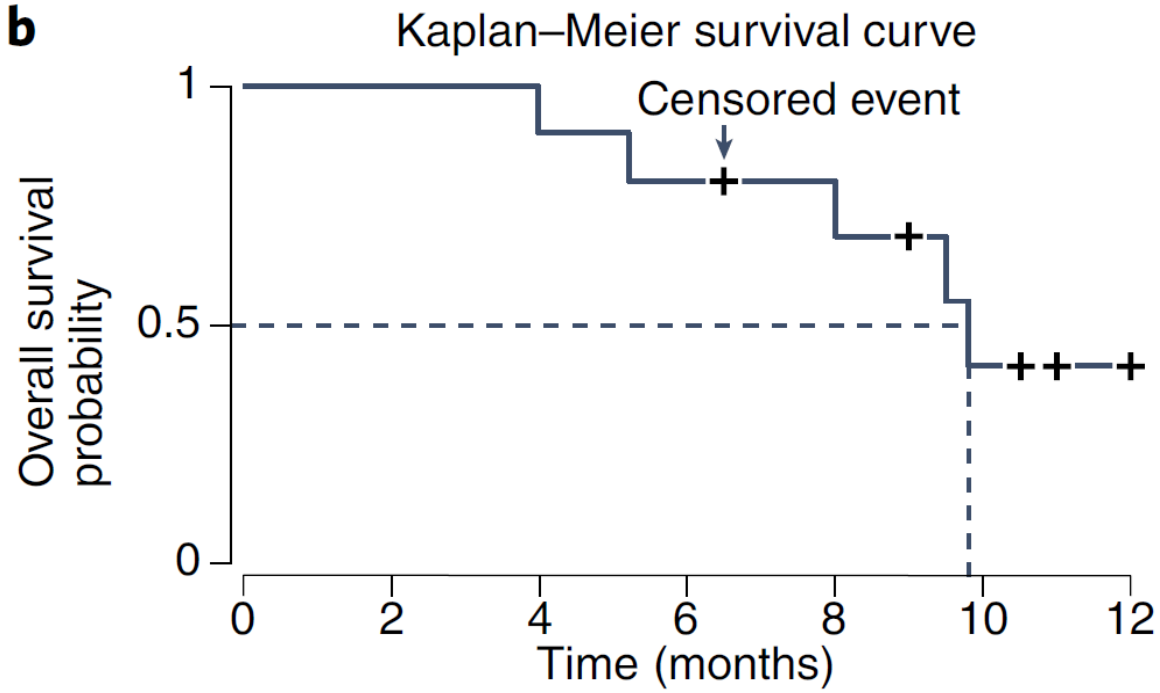
- Some died during follow-up:
  their survival time is known exactly (complete observation)

- Others alive at last follow-up:
  their survival time is known to be at least
  as long as their follow-up time (censored observation)

Kaplan-Meier survival curve

- Depicts survival times (time to death)
- Y is estimated probability of living ≥X
- If censoring is non-informative,
  provides an unbiased estimate of
  final results (when all have died) based on
  preliminary results (when some have died)



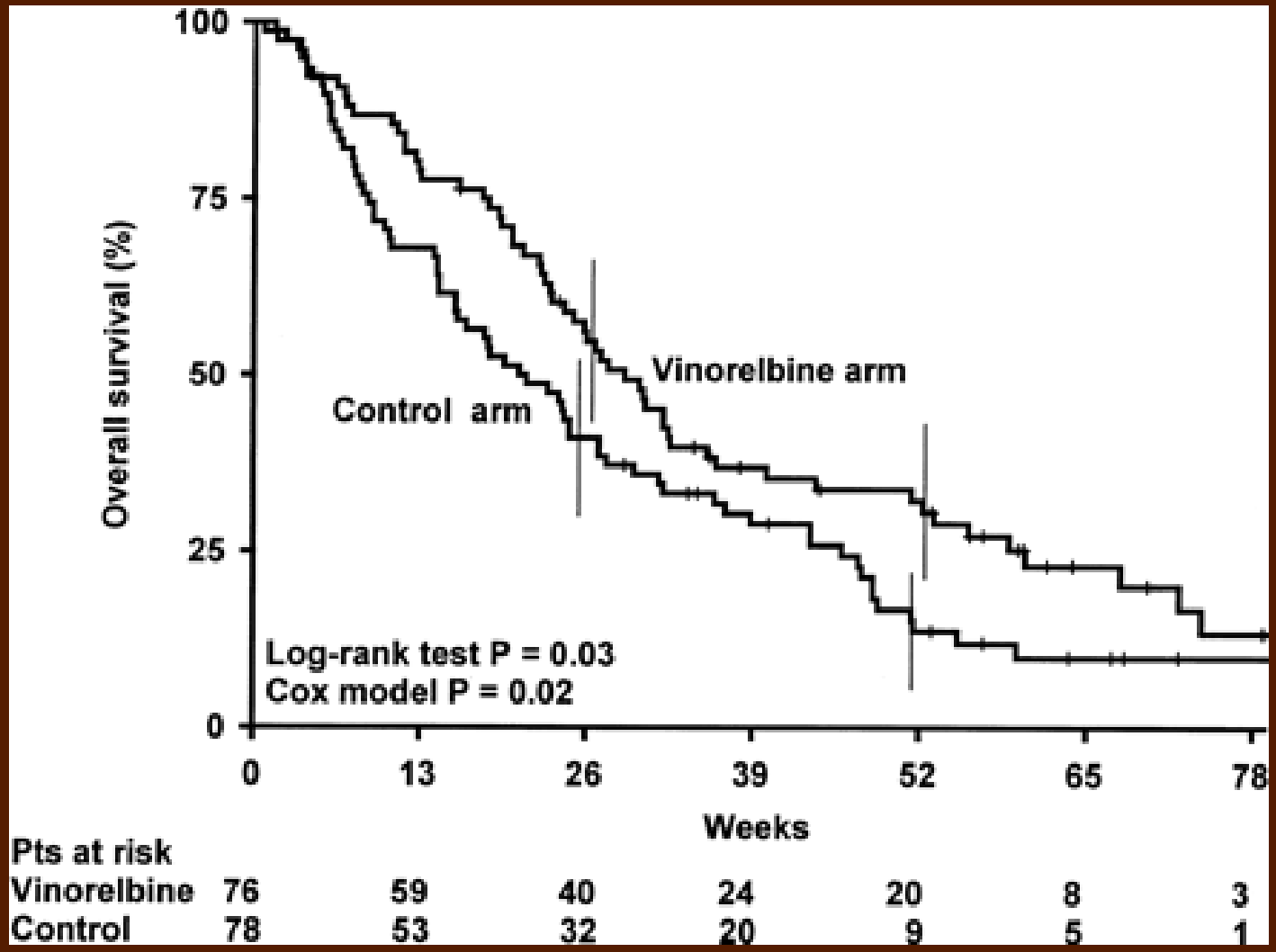


Dey T. Survival analysis. Nature Methods 2022

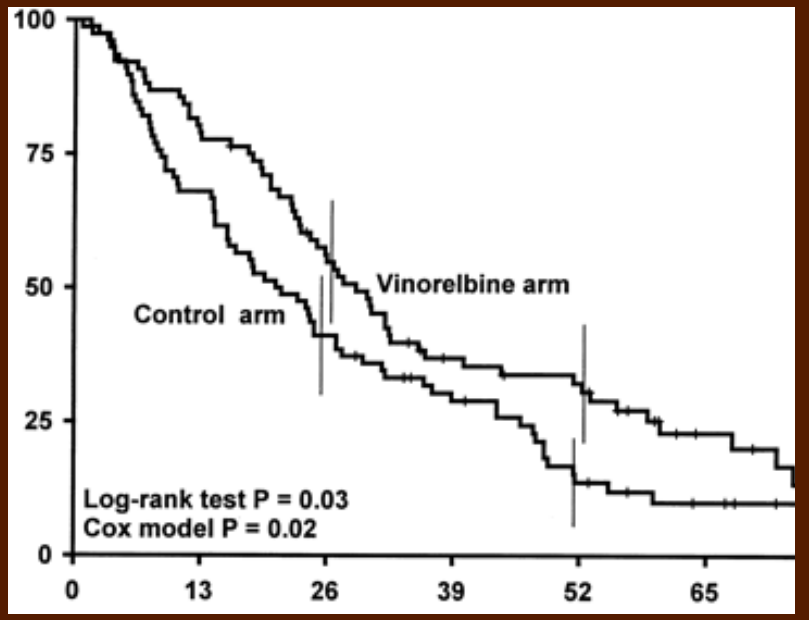
Kaplan-Meier survival curves

- Non-parametric: shape of distribution (curve) doesn't matter
- Key assumption: censoring is non-informative,
  i.e. the reason/mechanism/timing of censoring
  is not associated with subsequent outcome
- Applicable to events other than death
- Facilitate comparisons

Do these curves (distributions) differ?

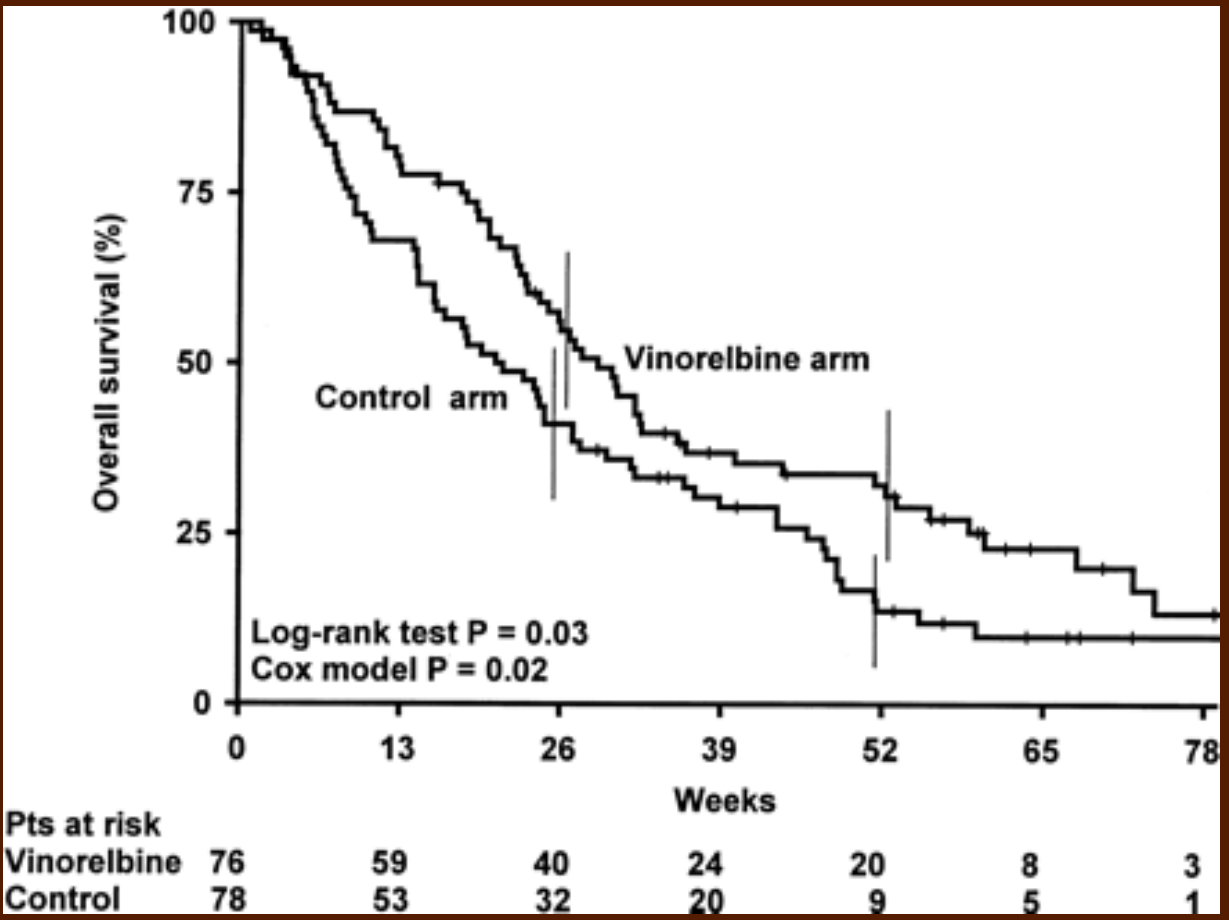


Comparing survival curves with non-parametric tests



- More different than expected by chance?
- Non-parametric tests – shape not assumed
- Key assumptions for non-parametric tests (& KMSC)
  - Censoring unrelated to prognosis
  - Survival probabilities similar for subjects recruited early and late
  - Events happened at times specified

Do these curves differ more than expected by the play of chance?

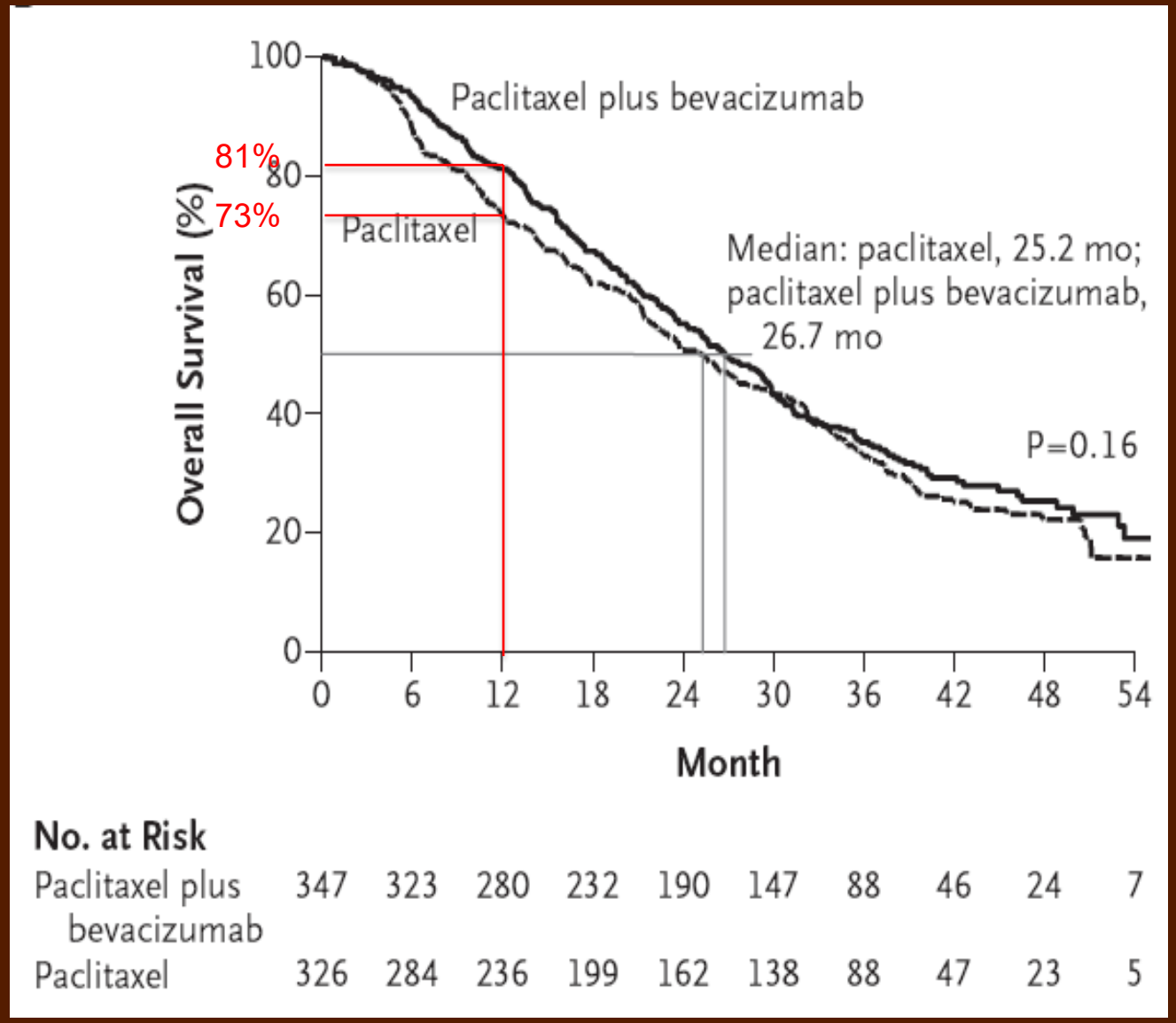


Log-rank test
(Peto-Mantel-Haenszel test)
Observed vs expected numbers of deaths
Equal weight to all time points

Gehan-Breslow-Wilcoxon rank-sum test
(Mann-Whitney test modified for censoring)
Survival times longer in 1 group than other
More weight to early time points

But…
Summary measure of effect?
Multivariable analysis?
Continuous variables?

Where and when to draw the (finish) line?
Paclitaxel ± bevacizumab in MBC. Miller K, NEJM 2007



No. at Risk										
Paclitaxel plus bevacizumab	347	323	280	232	190	147	88	46	24	7
Paclitaxel	326	284	236	199	162	138	88	47	23	5

Reporting overall survival benefits

- N = 1,300
- Hazard ratio 0.68, 95% CI 0.57 to 0.80
- 4 Year survival rates 63% vs 50%
- How would you report this effect?

The NEW ENGLAND JOURNAL of MEDICINE

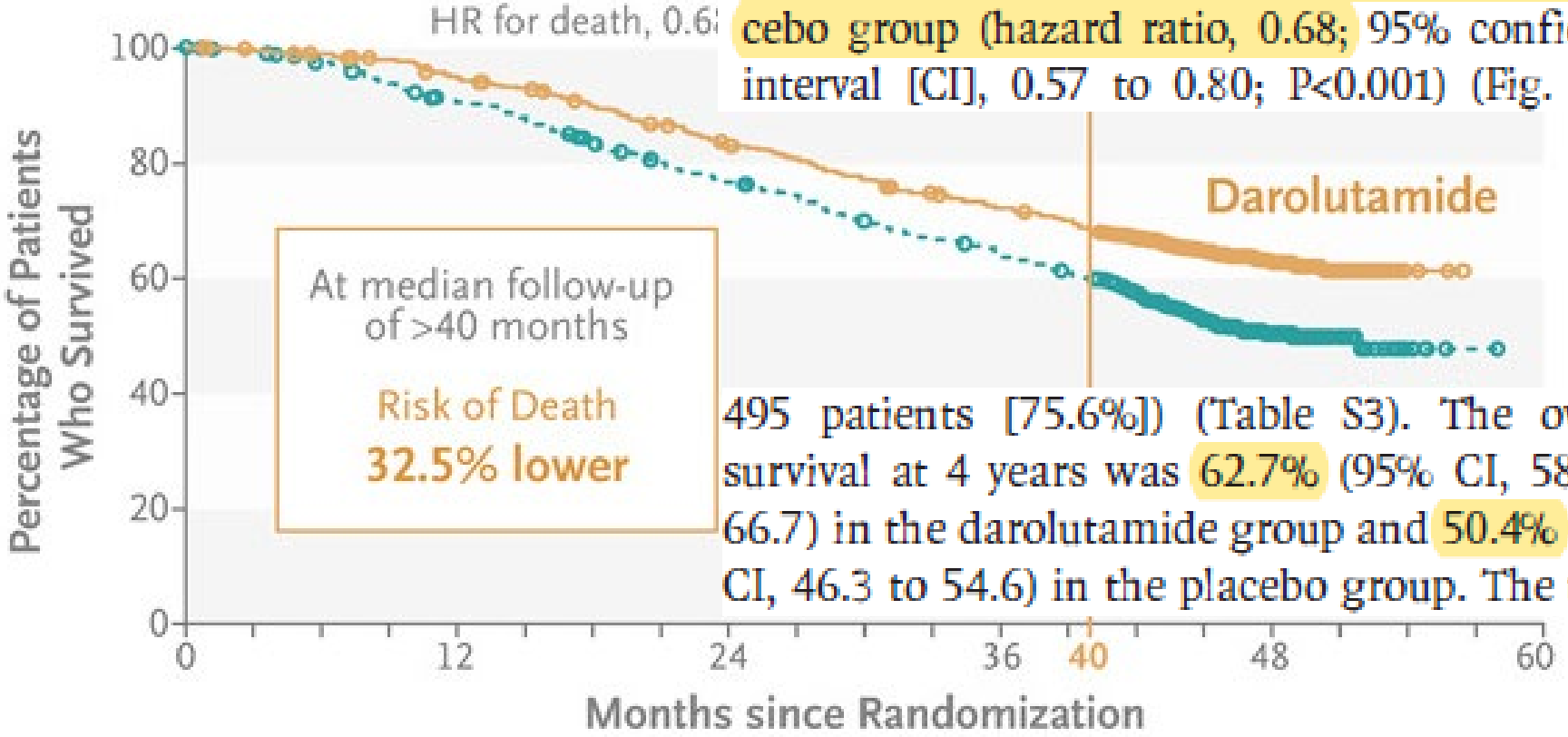
RESEARCH SUMMARY

Darolutamide and Survival in Metastatic, Hormone-Sensitive Prostate Cancer

Smith MR et al. DOI: 10.1056/NEJMoa2119115

PRIMARY END POINT

The primary analysis of overall survival was performed after 533 patients had died (229 patients in the darolutamide group and 304 patients in the placebo group). The risk of death was 32.5% lower in the darolutamide group than in the placebo group (hazard ratio, 0.68; 95% confidence interval [CI], 0.57 to 0.80; P<0.001) (Fig. 1). A



495 patients [75.6%]) (Table S3). The overall survival at 4 years was 62.7% (95% CI, 58.7 to 66.7) in the darolutamide group and 50.4% (95% CI, 46.3 to 54.6) in the placebo group. The treat-

Hazard ratio (2 curves)

- Ratio of hazards from 2 curves, eg
- $\frac{\text{Hazard in the experimental group}}{\text{Hazard in the control group}}$
- Relative measure of effect (X:C)
- Accounts for whole distribution (curve)

Darolutamide in mHSPC. ARASENS Smith NEJM 2022

PRIMARY END POINT

The primary analysis of overall survival was performed after 533 patients had died (229 patients in the darolutamide group and 304 patients in the placebo group). The risk of death was 32.5% lower in the darolutamide group than in the placebo group (hazard ratio, 0.68; 95% confidence interval [CI], 0.57 to 0.80; P<0.001) (Fig. 1). A

	Dead	Alive	Total	Death Risk	Alive Risk	Survival Rate 4Y
eXp	229	425	654	.35	.65	.63
Con	304	347	651	.47	.53	.50
Total	533	772	1305			
Absolute difference, AR = |C-X|				.12	.12	.13
Relative Ratio, RR = X/C				.74	1.23	1.26
Relative Reduction, RRR = 1 - X/C				26%		
Relative Increase, RI = X/C – 1					23%	26%
Hazard ratio (X/C)				.68		
Hazard reduction (1 - X/C)				32%		
NNT to prevent 1 (1/ARR)				8		

Reporting overall survival benefits

- N = 1,300
- Hazard ratio 0.68, 95% CI 0.57 to 0.80
- 4 Year survival rates 63% vs 50%
- How would you report this effect?

a) Absolute improvement in 4YSR 13%
b) Relative reduction in the hazard 32%
c) Risk of death reduced 32%
d) To prevent 1 death in 4y, you need to treat 8

Survival curves and analysis for connoisseurs

0. Events, risks, odds, hazards, hazard ratios, multivariable
1. Survival curves and comparisons
2. Where to draw the line
3. Truth in reporting

ACORD 2024 Protocol Development Workshop

Asia-Pacific Clinical Oncology Research Development Initiative

Intensive, 6-day, residential, protocol-writing workshop

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acord *turning good ideas into successful studies*

Survival curves and analysis for connoisseurs

0. Events, risks, odds, hazards, hazard ratios, multivariable
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3. Truth in reporting

Risks, odds, hazards (typically of death)

Risk (r) number with event / total number

Odds (o) number with event / number without event

$$o = r \;/\; (1 - r)$$

$$r = o \;/\; (1 + o)$$

(when r & o are small, $r \cong o$)

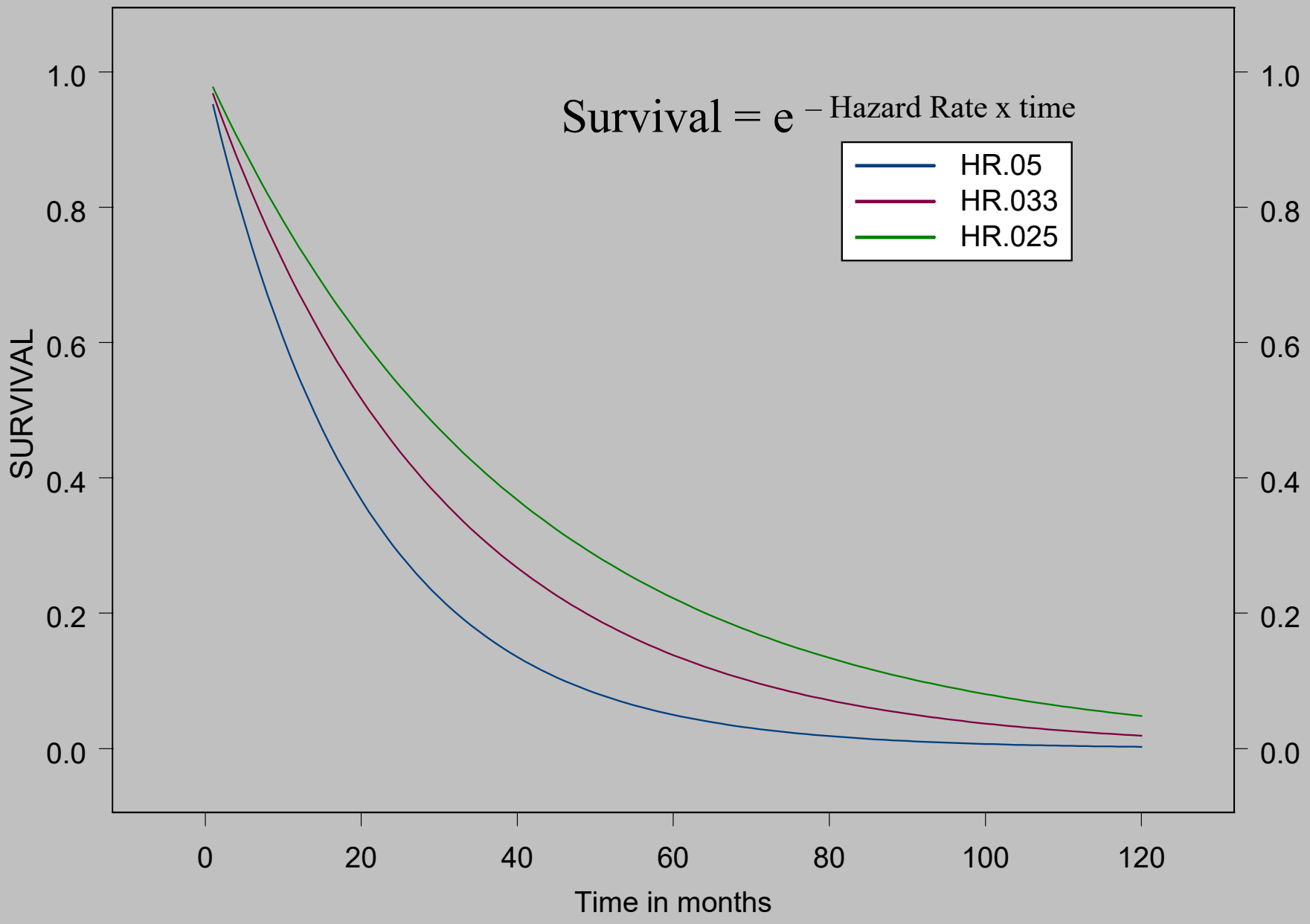
Hazard rate risk per unit time (during an interval)

Hazard (h) risk at time t (instantaneous)

Hazard

- Doesn’t have to be constant over time, but if it is…
- Constant hazard =
  exponential decay
  fraction surviving is constant

Exponential Survival Curves & Proportional Hazards



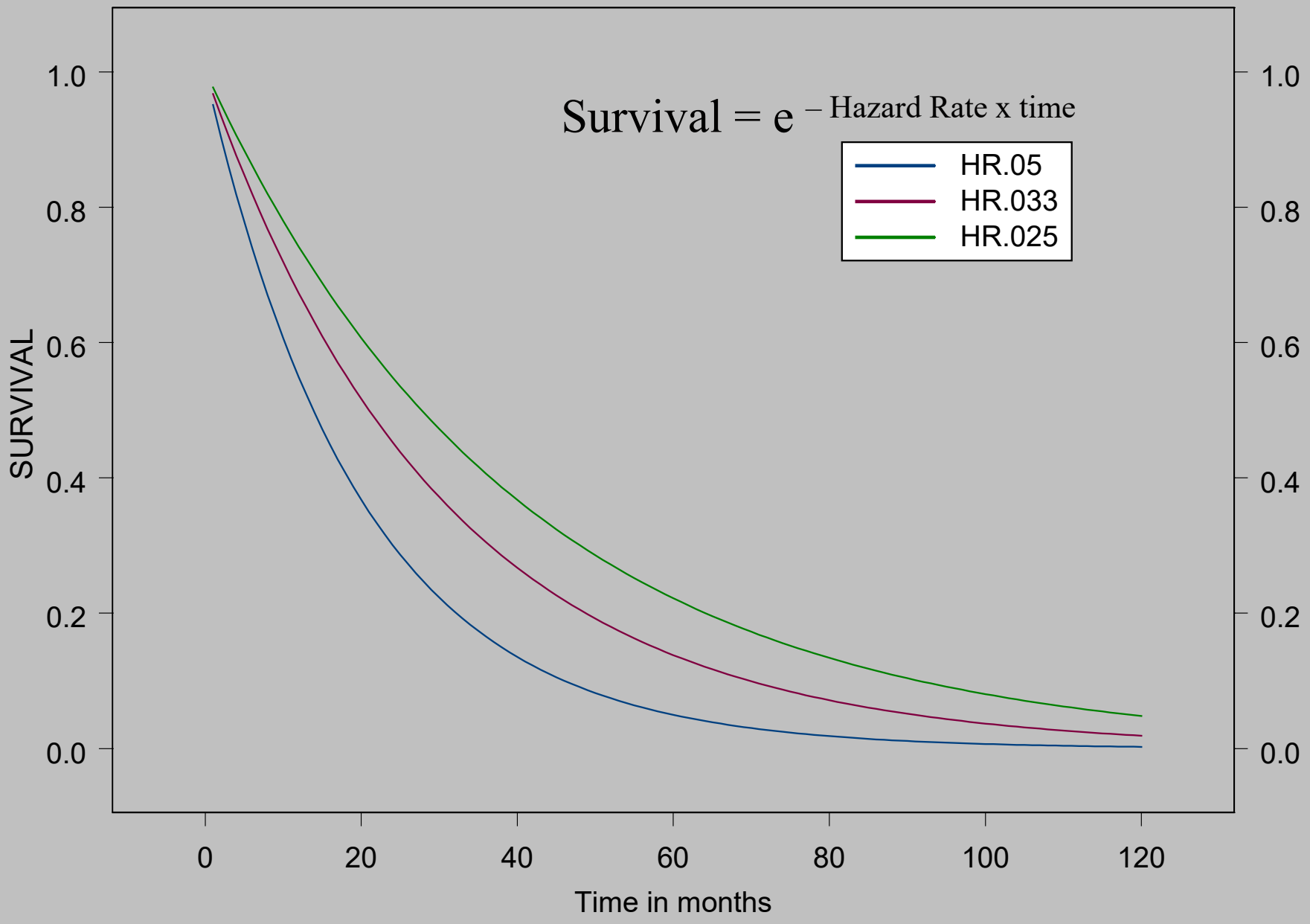
Hazard ratio (2 curves)

- Ratio of hazards from 2 curves, eg
- $\frac{\text{Hazard in the experimental group}}{\text{Hazard in the control group}}$
- Relative measure of effect (X:C)
- Accounts for whole distribution (curve)

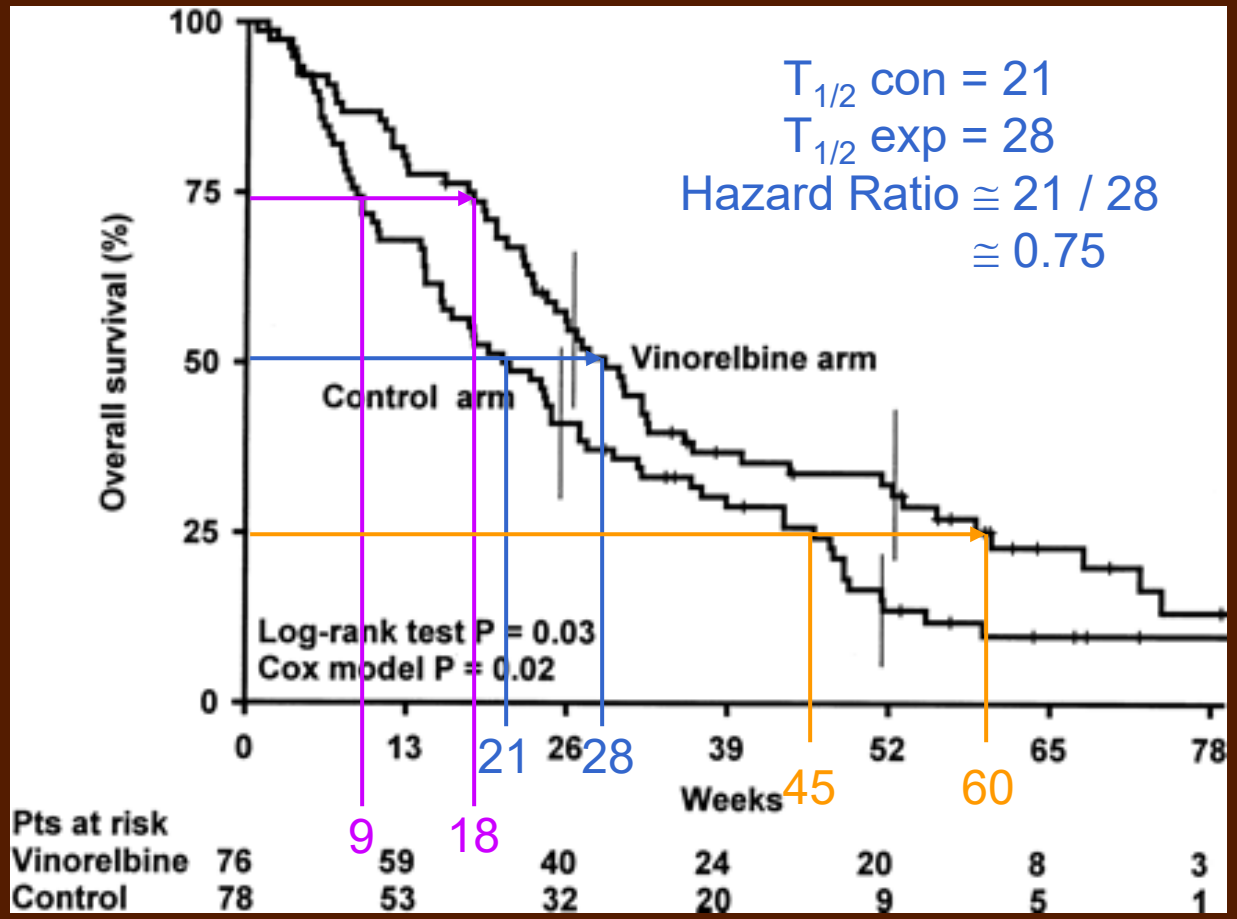
Hazard ratio (2 curves)

- Doesn't have to be constant over time, but if it is…
- Constant hazard ratio (2 curves) = proportional hazards (Cox Model)
- Variable hazard ratio = proportional hazards violation

Exponential Survival Curves & Proportional Hazards



Hazard Ratio ≅ Ratio of survival times at given percentiles



	†	T_{50}	T_{75}	T_{25}	Cox Model HR
Exp	59	28	18	60	
Con	76	21	9	45	
Ratio	.76	.75	.50	.75	0.65 (0.45, 0.93)
P	.001		.03		.02

Test of proportional hazards assumption:
do ratios of survival time differ more than expected by chance?
If not, then Cox Proportional Hazards Regression OK

Survival curves and analysis for connoisseurs

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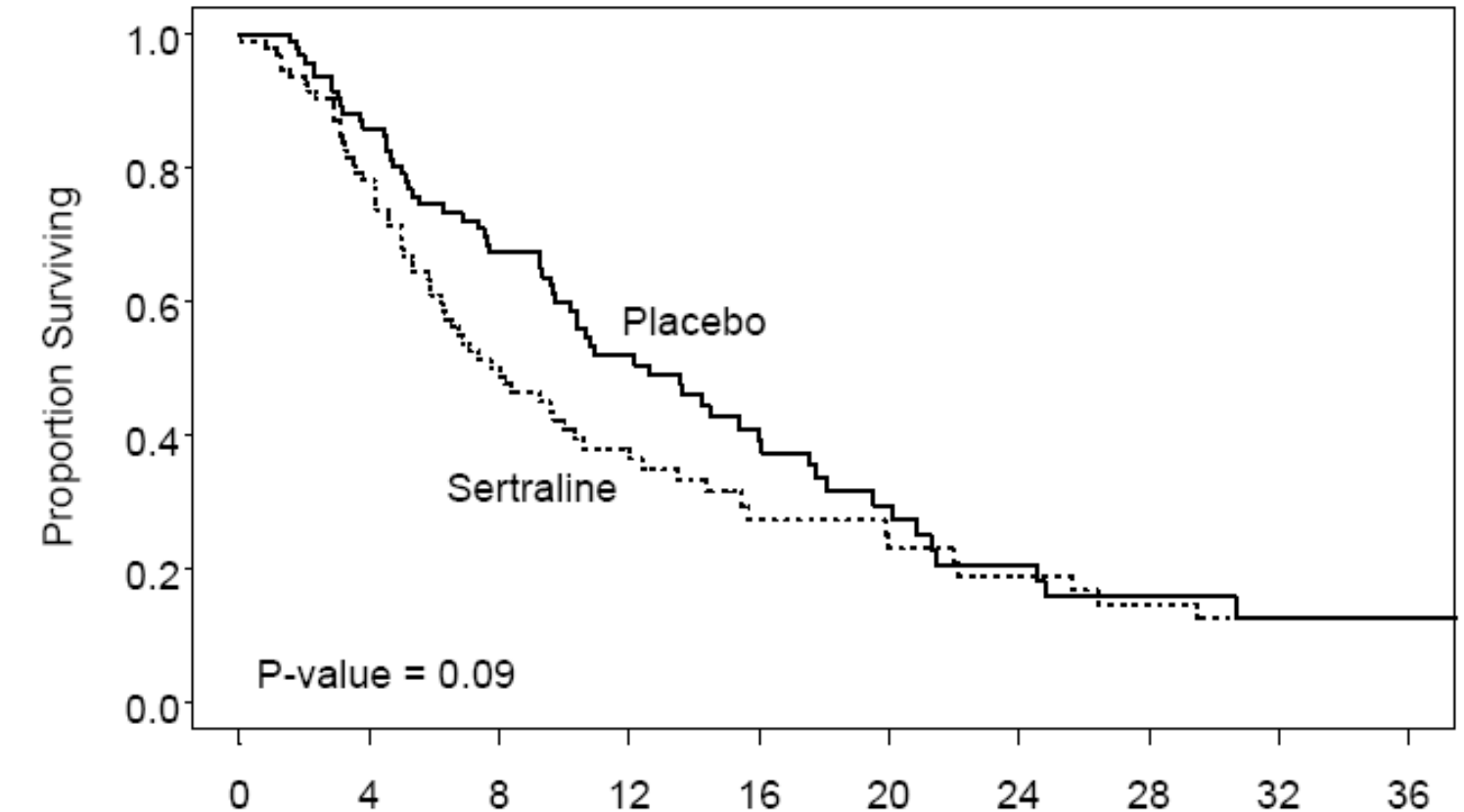
1. Survival curves and comparisons
2. Where to draw the line
3. Proportional hazards regression
4. Flat tails, plateaus, numbers at risk
5. Non-proportional hazards: don’t cross me!
6. Restricted mean survival times

Cox Proportional Hazards Regression

- A method for investigating the effect of variables on the time it takes a specified event to happen.
- No assumption about the shape of the survival curves
- Does assume that the effects of the variables on survival (hazard ratios) are constant over time.
- “You should not use Cox regression without the guidance of a Statistician” StatsDirect Guide

Sertraline vs Placebo in advanced cancer

Stockler et al. Lancet Oncol 2007; 603-12



Number at Risk

Placebo	94	76	56	37	22	13	9	6	4	3
Sertraline	95	70	41	25	13	11	9	7	5	4

Possible Causes?

Sertraline? Chance?

Baseline imbalances?
- known factors
- unknown factors

Factors (x variables)
- Univariable: 1
- Multivariable: >1

Outcomes (y variables)
- Univariate: 1
- (Multivariate: >1)

Univariable analysis evaluates prognostic factors 1 at a time

	% yes	Univariable models	
		HR	P
Treatment group = sertraline (vs placebo)	**50**	**1.3**	**0.10**

Univariable analysis evaluates prognostic factors 1 at a time

	% yes	Univariable models HR	P
Treatment group = sertraline (vs placebo)	**50**	**1.3**	**0.10**
Primary Site (each versus the rest)			
Lung	**15**	**2.2**	**0.001**
Colorectal	**15**	**1.5**	**0.1**
Prostate	**14**	**1.0**	**0.9**
Breast	**17**	**0.8**	**0.4**
Past treatment included			
Opioids at baseline	**26**	**2.1**	**<0.001**
Chemotherapy in the past	**83**	**1.8**	**0.02**
Steroids at baseline	**11**	**1.5**	**0.2**
Liver or brain metastases at baseline	**34**	**1.6**	**0.01**
Performance status at baseline			
Karnofsky 70 or worse	**24**	**1.6**	**0.02**
ECOG 2 or worse	**22**	**1.3**	**0.3**
Blood tests at baseline			
ALP >101	**50**	**2.1**	**<0.001**
CRP >10	**50**	**2.0**	**<0.001**
Haemoglobin <12.3	**50**	**1.6**	**0.01**
Albumin <38	**49**	**1.5**	**0.03**

Multivariable analysis evaluates prognostic factors simultaneously

	% yes	Univariable models		Multivariable model	
		HR	P	HR	P
Treatment group = sertraline (vs placebo)	**50**	**1.3**	**0.10**	**1.27**	**0.2**
Primary Site (each versus the rest)					
Lung	**15**	**2.2**	**0.001**	**2.26**	**<0.001**
Colorectal	**15**	**1.5**	**0.1**		
Prostate	**14**	**1.0**	**0.9**		
Breast	**17**	**0.8**	**0.4**		
Past treatment included					
Opioids at baseline	**26**	**2.1**	**<0.001**	**1.99**	**0.001**
Chemotherapy in the past	**83**	**1.8**	**0.02**	**2.34**	**0.002**
Steroids at baseline	**11**	**1.5**	**0.2**		
Liver or brain metastases at baseline	**34**	**1.6**	**0.01**	**1.65**	**0.01**
Performance status at baseline					
Karnofsky 70 or worse	**24**	**1.6**	**0.02**	**1.75**	**0.01**
ECOG 2 or worse	**22**	**1.3**	**0.3**		
Blood tests at baseline					
ALP >101	**50**	**2.1**	**<0.001**	**2.17**	**<0.001**
CRP >10	**50**	**2.0**	**<0.001**		
Haemoglobin <12.3	**50**	**1.6**	**0.01**		
Albumin <38	**49**	**1.5**	**0.03**		

Survival curves and analysis for connoisseurs

0. Events, risks, odds, hazards, hazard ratios, multivariable
1. Survival curves and comparisons (univariable)
2. Where to draw the line (pre-specify)
3. Proportional hazards regression (multivariable)
4. Flat tails, plateaus, numbers at risk
5. Non-proportional hazards: don’t cross me!
6. Restricted mean survival times

Follow-up is generally insufficient to estimate long term outcomes in trials of immunotherapy and targeted drugs

- Accrual, analysis, presentation, market ASAP
- Results to median follow-up time are reliable
- Results up to median follow-up are reliable
- Furry, horizontal tails are unstable (wag)
- Check numbers at risk
- Ignore estimates based on fewer at risk than the percentile estimated, e.g.

at least 50 at risk to estimate median (50^{th})

25 at risk to estimate 25^{th} (lower typical)

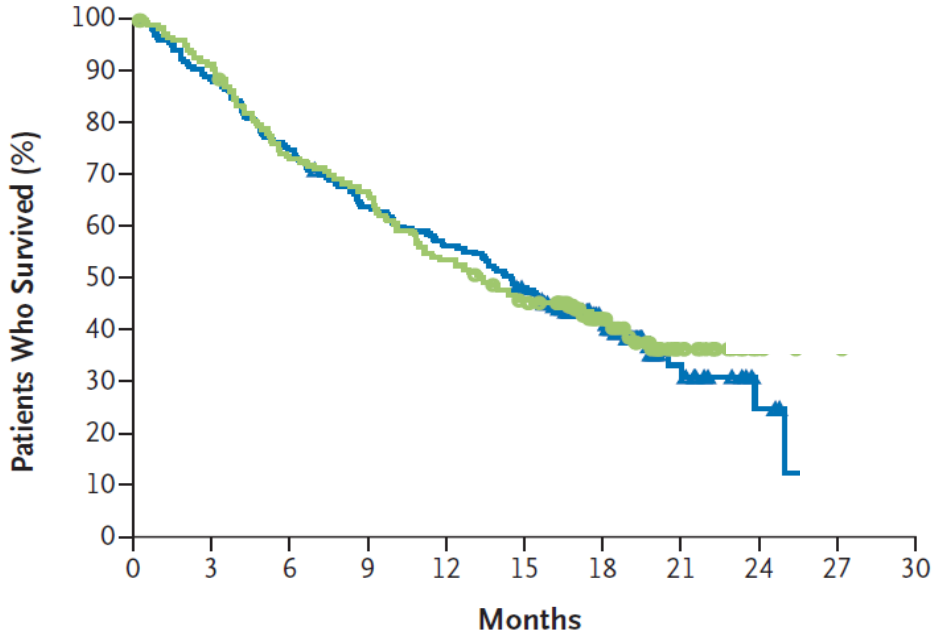
10 at risk to estimate 10^{th} (best case)

Plateau = cure?

B Overall Survival

	Median Overall Survival (95% CI) *mo*	1-Yr Overall Survival Rate %
Nivolumab (N=211)	14.4 (11.7–17.4)	56
Chemotherapy (N=212)	13.2 (10.7–17.1)	54

Hazard ratio for death, 1.02 (95% CI, 0.80–1.30)

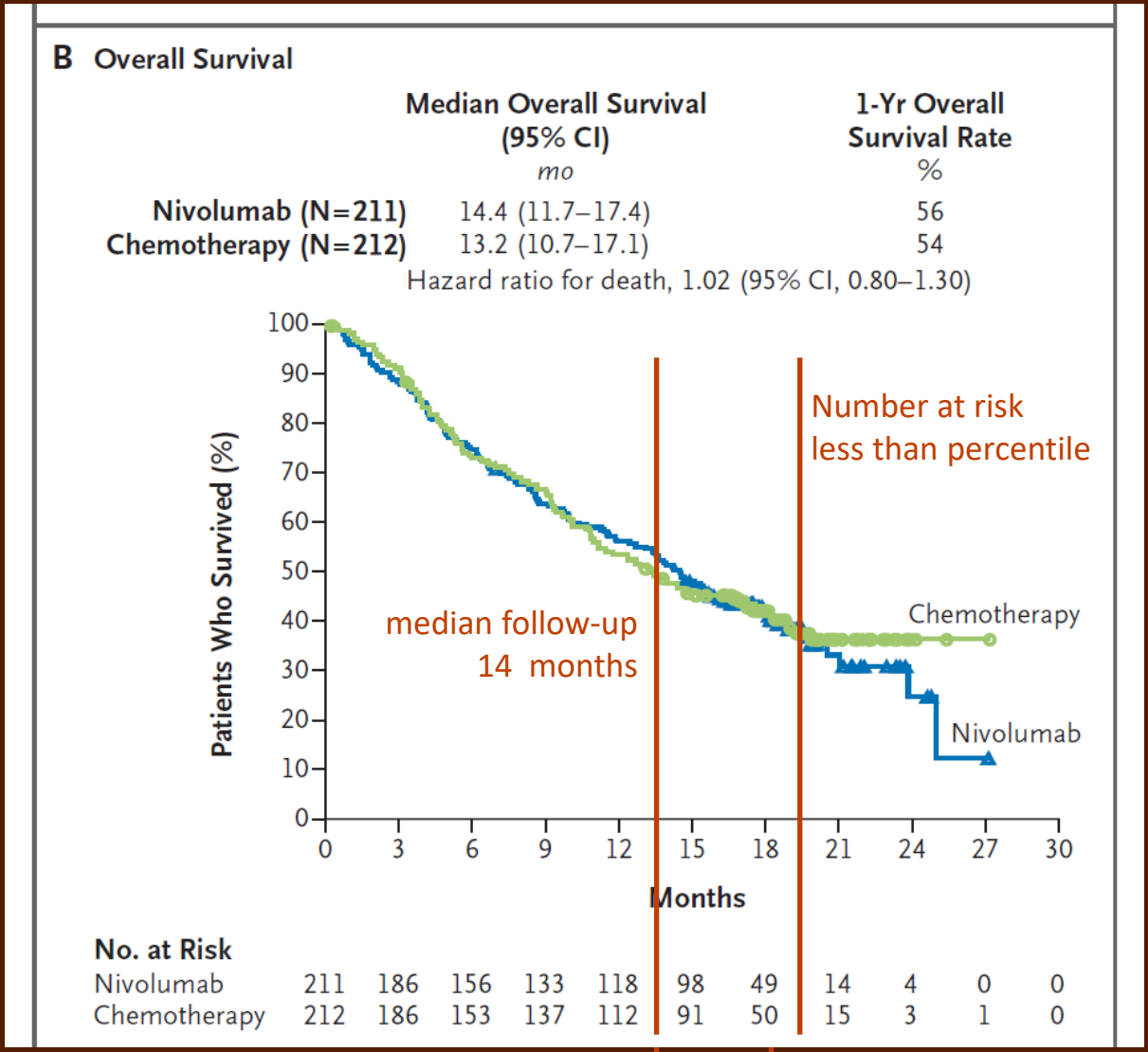


No. at Risk

Nivolumab	211	186	156	133	118	98	49	14	4	0	0
Chemotherapy	212	186	153	137	112	91	50	15	3	1	0

Nivolumab vs PBD chemo 1st line in advanced NSCLC. Carbone NEJM 2017

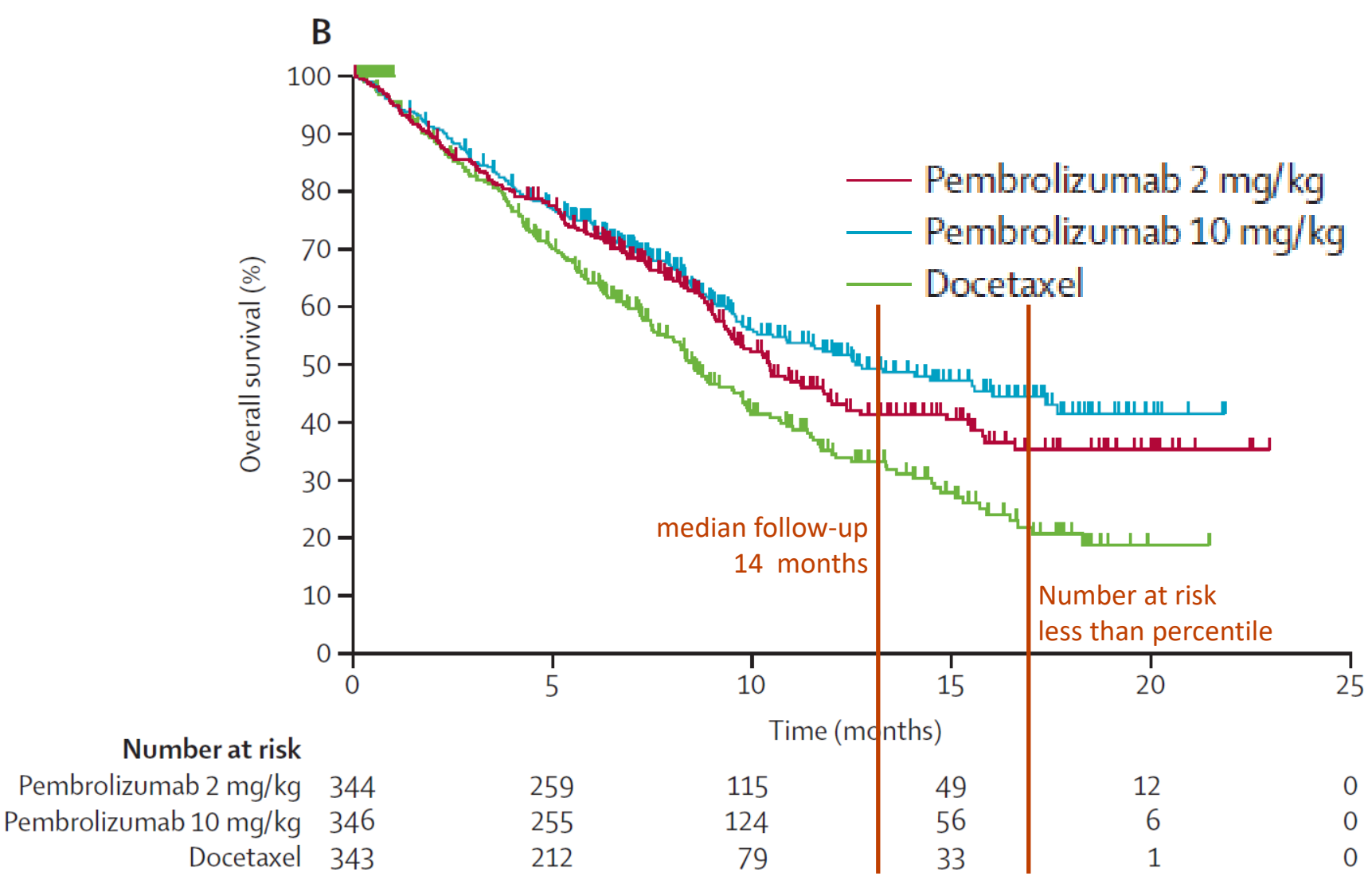
Plateau = inadequate follow-up



Nivolumab vs PBD chemo 1st line in advanced NSCLC. Carbone NEJM 2017

Median follow-up? Numbers at risk < percentile?

Pembro vs docet 2L NSCLC PDL1>1%
Herbst, Lancet 2016. KEYNOTE-10



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The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2014.56.2736

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Pooled Analysis of Long-Term Survival Data From Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma

Dirk Schadendorf, F. Stephen Hodi, Caroline Robert, Jeffrey S. Weber, Kim Margolin, Omid Hamid, Debra Patt, Tai-Tsang Chen, David M. Berman, and Jedd D. Wolchok

See accompanying editorial doi: 10.1200/JCO.2014.59.5041

Dirk Schadendorf, University Hospital Essen, Essen, Germany; F. Stephen Hodi, Dana-Farber Cancer Institute, Boston, MA; Caroline Robert, Institute Gustave Roussy, Villejuif, France; Jeffrey S. Weber, Moffitt Cancer Center, Tampa, FL; Kim Margolin, University of Washington, Seattle, WA; Omid Hamid, The Angeles Clinic and Research Institute, Los Angeles, CA; Debra Patt, The US Oncology Network, McKesson Specialty Health, Houston, TX; Tai-Tsang Chen, Bristol-Myers Squibb, Wallingford, CT; David M.

ABSTRACT

Purpose

To provide a more precise estimate of long-term survival observed for ipilimumab-treated patients with advanced melanoma, we performed a pooled analysis of overall survival (OS) data from multiple studies.

Methods

The primary analysis pooled OS data for 1,861 patients from 10 prospective and two retrospective studies of ipilimumab, including two phase III trials. Patients were previously treated (n = 1,257) or treatment naive (n = 604), and the majority of patients received ipilimumab 3 mg/kg (n = 965) or 10 mg/kg (n = 706). We also conducted a secondary analysis of OS data (n = 4,846) with an additional 2,985 patients from an expanded access program. OS rates were estimated using the

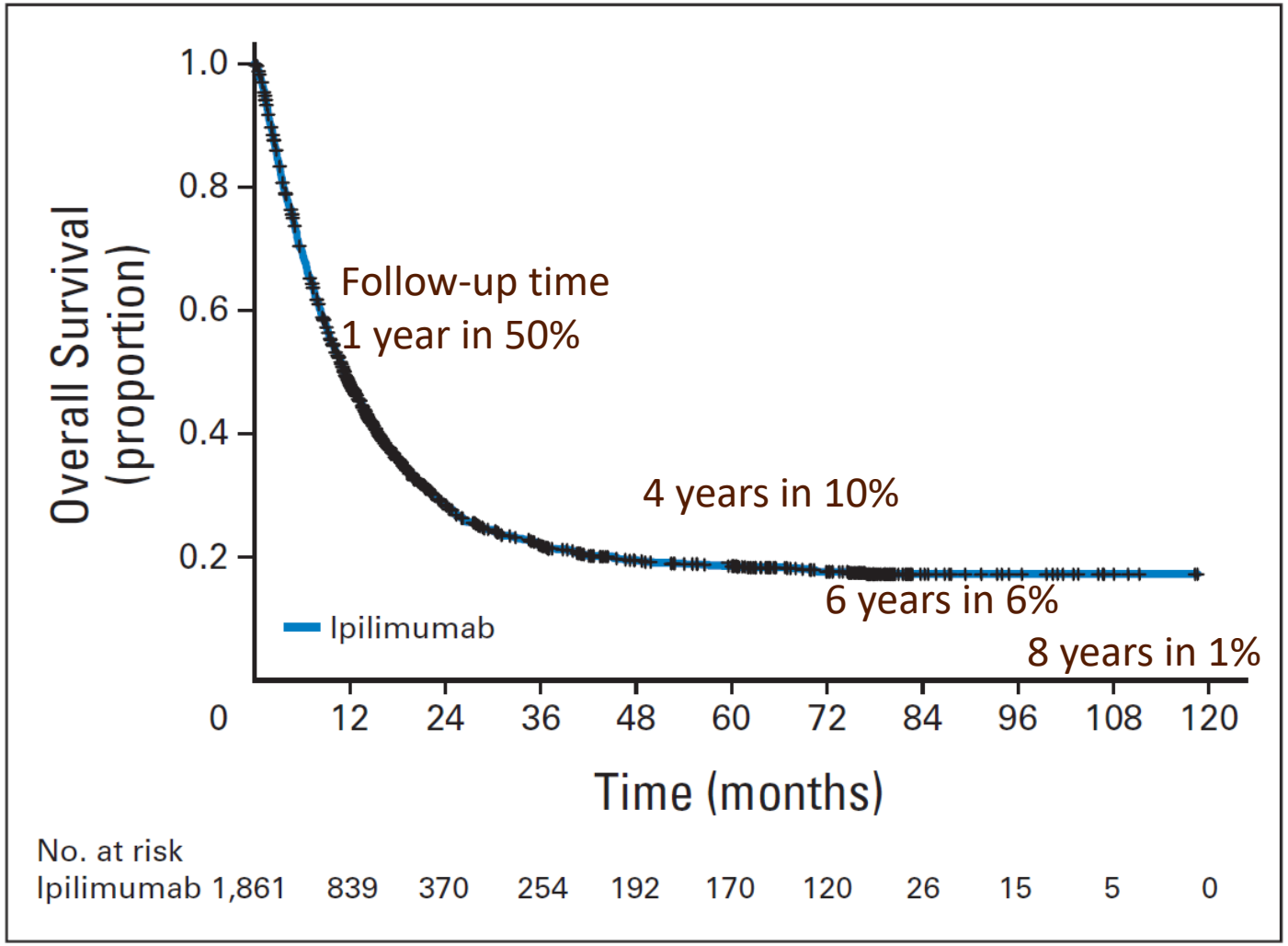
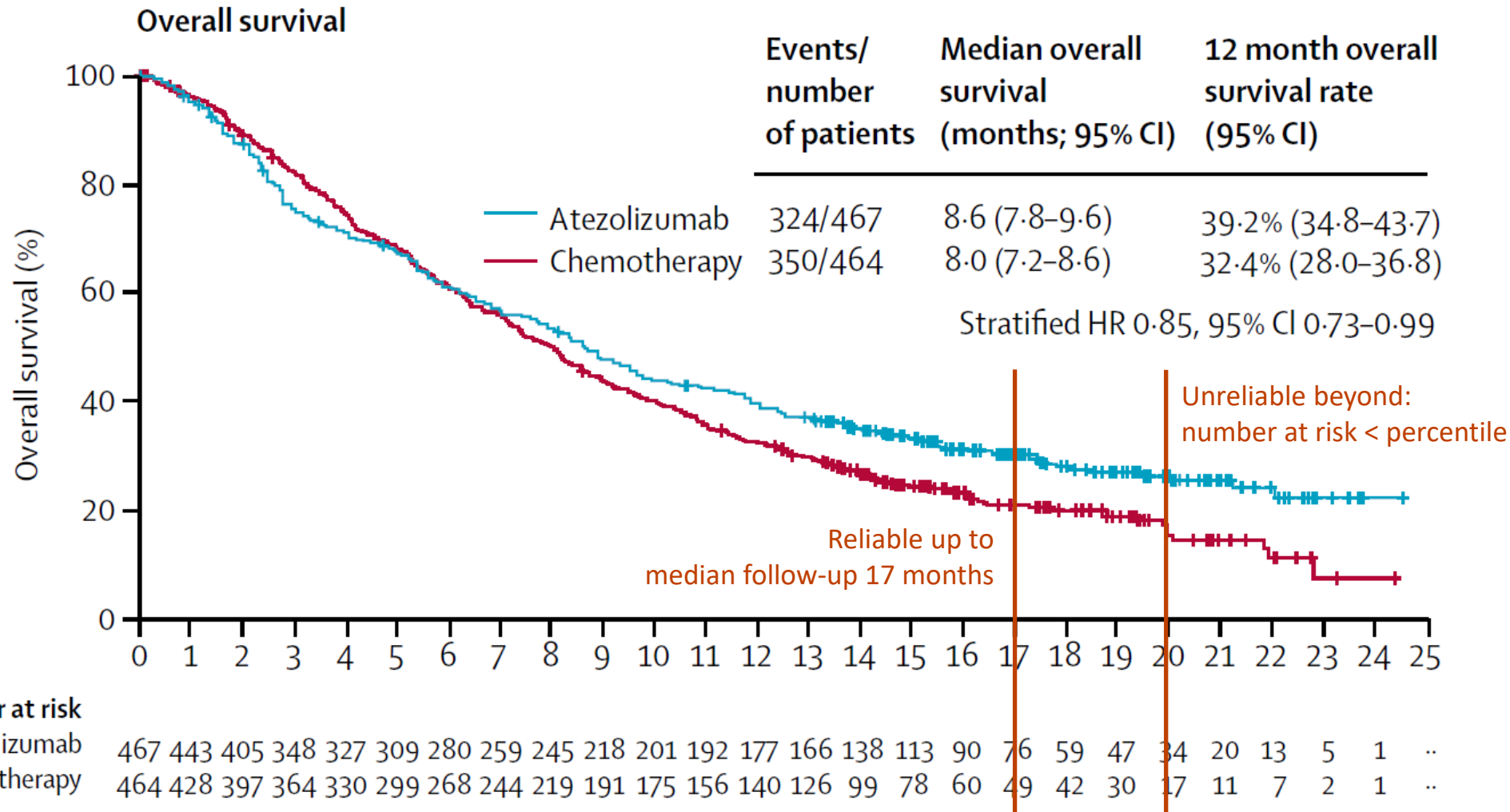


Fig 1. Primary analysis of pooled overall survival (OS) data. Individual patient data were pooled from 10 prospective trials and two retrospective, observational studies of ipilimumab in metastatic melanoma (n = 1,861). Median OS was 11.4 months (95% CI, 10.7 to 12.1 months) with a 3-year survival rate of 22% (95% CI, 20% to 24%). Crosses indicate censored patients.

Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial

Thomas Powles, Ignacio Durán, Michiel S van der Heijden, Yohann Loriot, Nicholas J Vogelzang, Ugo De Giorgi, Stéphane Oudard, Margitta M Retz, Daniel Castellano, Aristotelis Bamias, Aude Fléchon, Gwenaëlle Gravis, Syed Hussain, Toshimi Takano, Ning Leng, Edward E Kadel III, Romain Banchereau, Priti S Hegde, Sanjeev Mariathasan, Na Cui, Xiaodong Shen, Christina L Derleth, Marjorie C Green, Alain Ravaud



Survival curves and analysis for connoisseurs

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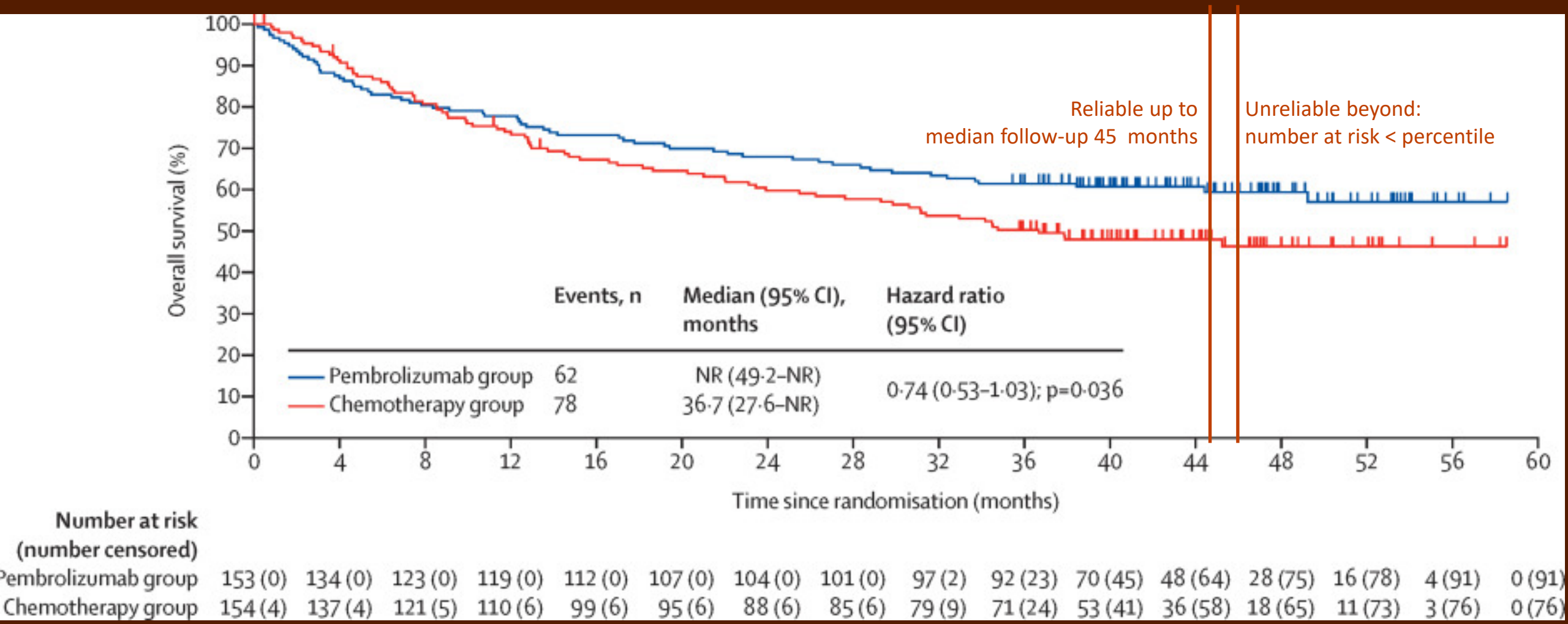
6. Restricted mean survival times

Crossing survival curves.

Diaz LA. Pembro vs Chemo MSI-high/MMR-d mCRC KN-177. Lancet Oncol 2022



When survival curves cross

- Effect of interest differs over time
- Favours different curve (group) at different times
- Proportional hazards assumption is violated
- Hazard ratio is an unsuitable measure of effect(s)
- Proportional hazard assumption tested?
- Alternatives?

Crossing survival curves: alternatives

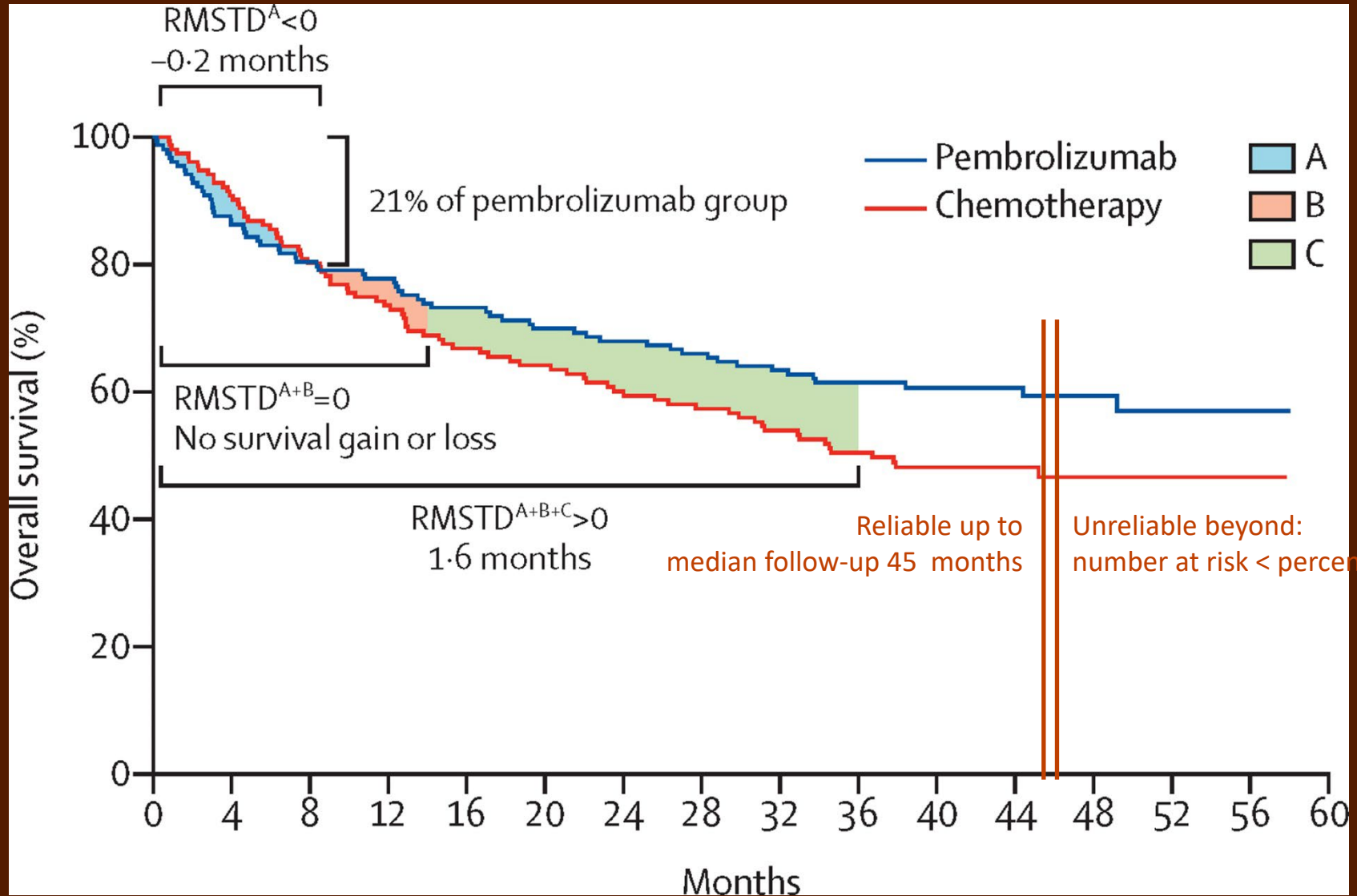
- Survival rates at a pre-specified time (Trinquart)

- Restricted mean survival time (RMST, Parmar)
- Area under the curve to a specified time point
- A valid summary measure for each curve
- Ratios or differences in RMSTs
  are valid measures of the treatment effect

- But, a single-number summary belies
  different effects at different times

Crossing survival curves: Restricted Mean Survival Time Difference (RMSTD)

Bomze D, Lancet Oncol 2022, on Diaz L, Pembro v Chemo MSI-high/MMR-d mCRC KN-177. Diaz LA Lancet Oncol 2022



Reliable up to median follow-up 45 months

Unreliable beyond: number at risk < percentile

Survival curves and analysis for connoisseurs

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5. Non-proportional hazards: don’t cross me!
6. Restricted mean survival times

Connoisseurs' guide for evaluating survival curves

1. Numbers of events
2. Median duration of follow-up
3. Numbers at risk over time
4. Censoring over time and by treatment group
5. Size and constancy of treatment effect
6. Use and interpret hazard ratios properly
7. Survival rates at pre-specified time(s)
   Restricted Mean Survival Times
8. Main result (finish line) determined a priori?

Overcoming the hazards of survival analysis in oncology

1.	Time-to-event analysis	M Stockler
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5.	RMST as a potential solution	M Parmar
6.	Common Sense Oncology	B Gyawali
7.	Panel discussion	

Template

	Dead	Alive	Total	Death Risk	Death Odds	Survival Risk (p)	Survival Odds
eXp							
Con							
Total							
Absolute Difference							
Relative Ratio							
Relative Risk Reduction							

Example ENZAMET 476
MFU 68 mo

	Dead	Alive	Total	Death Risk	Death Odds	Survival Risk (p)
eXp	208	355	563	.37	.59	.67
Con	268	294	562	.48	.91	.57
Total	576	649	1125			
Absolute Difference	60	61		.10		.10
Relative Ratio				.77	1.54	1.17

Example ENZAMET 476 MFU 68 mo

	Dead	Alive	Total	Death Risk	Death Odds	Survival Risk (p)	Survival Odds
eXp	208	355	563	.37	.59	.67	1.7
Con	268	294	562	.48	.91	.57	1.1
Total	576	649	1125				
Absolute Difference	60	61		.10		.10	
Relative Ratio				.77	1.54	1.17	1.55
Relative Risk Reduction				.23			

Risks, odds, ratios, and reductions

	Dead	Alive	ALL	**Risk** of Death	
Observation	23	57	80	23 / 80	.29
Treatment	10	71	81	10 / 81	.12
Ratios					
Relative Red'n					
Absolute Red'n				.29 - .12	.17

Risks, odds, ratios, and reductions

	Dead	Alive	ALL	Risk of Death	
Observation	23	57	80	23 / 80	.29
Treatment	10	71	81	10 / 81	.12
Ratios				.12 / .29	.41
Relative Red'n				1 - .41	.59
				p = .01	
Absolute Red'n				.29 - .12	.17

Risks, odds, ratios, and reductions

	Dead	Alive	ALL	**Risk** of Death		**Odds** of Death	
Observation	23	57	80	23 / 80	.29	23 / 57	.40
Treatment	10	71	81	10 / 81	.12	10 / 71	.14
Ratios				.12 / .29	.41	.40 / .14	.35
Relative Red'n				1 - .41	.59	1 - .35	.65
				p = .01			
Absolute Red'n				.29 - .12	.17	.40- .14	.26

Template

	Dead	Alive	Total	Death Risk	Death Odds	Survival Risk (p)	Survival Odds
eXp							
Con							
Total							
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Relative Red'n				1 - .41	.59	1 - .35	.65
				p = .01			
Absolute Red'n				.29 - .12	.17	.40- .14	.26

What is the end point? What are the results?

Originally, the end point was
the event, often bad, that ended follow-up,
e.g. death, myocardial infarction, progression, etc…

Results most simply summarised by the
number (proportion) who had the event (group summary)

Currently, how failure (success) is defined in each subject

- Event occurred (yes or no: 'dichotomous')
- Time-to-event (continuous, and perhaps censored)
- Death before the event: success or failure?
- Event-free survival (time alive and event-free)_

Key points

- Event timing rather than occurence
- Incomplete observations
- Maximise use of available information
- Key assumptions
  - KM estimates: censoring is uninformative
  - Hazard ratios (Cox models): hazards are proportional
  - Sample size calculations: hazards are constant
- Valid claims supported by data

48% REDUCTION in relative risk of death with ERLYAND® (apalutamide) in mHSPC[1*]

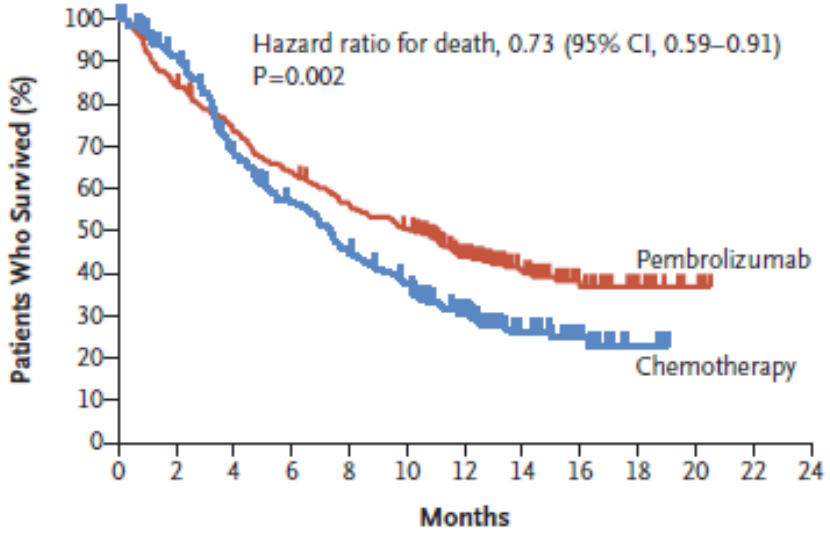
*In combination with ADT vs placebo after adjustment for crossover; median OS: NR vs 39.8 months; HR=0.52; 95% CI: 0.42-0.64; p<0.0001; IPCW sensitivity analysis

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 16, 2017 VOL. 376 NO. 11

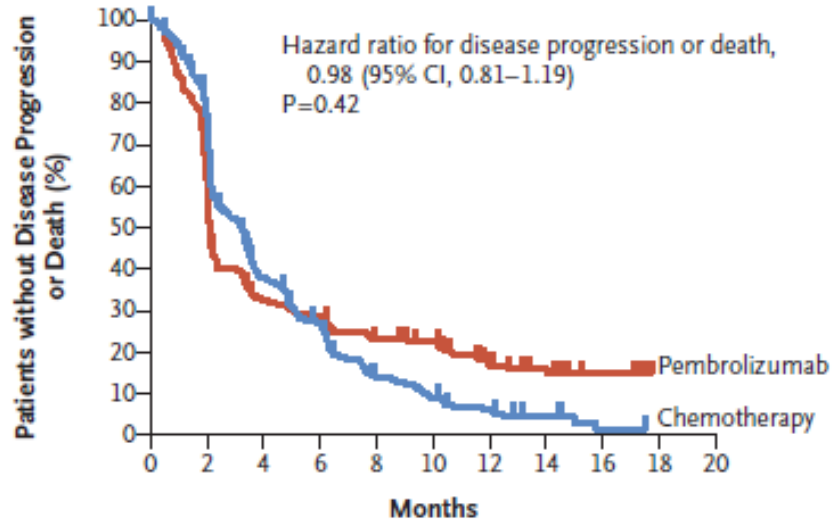
Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma

A Overall Survival



No. at Risk													
Pembrolizumab	270	226	194	169	147	131	87	54	27	13	4	0	0
Chemotherapy	272	232	171	138	109	89	55	27	14	3	0	0	0

B Progression-free Survival



No. at Risk											
Pembrolizumab	270	165	85	73	56	51	23	16	7	0	0
Chemotherapy	272	188	85	56	27	17	10	5	1	0	0

Where to draw the line?

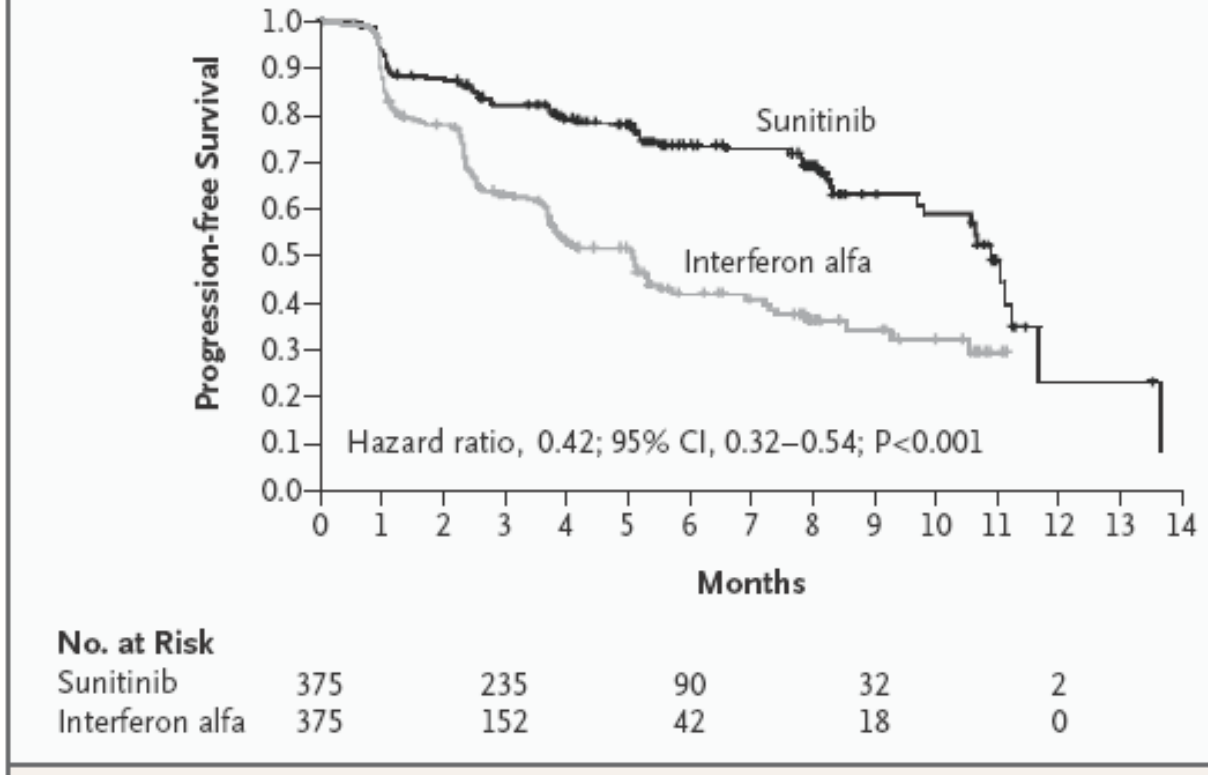


Figure 2. Kaplan–Meier Estimates of Progression-free Survival (Independent Central Review).

Overcoming the hazards of survival analysis in oncology

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3. RFS in adjuvant therapy trials
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5. RMST as a potential solution
6. Common Sense Oncology
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EUROPEAN UROLOGY 80 (2021) 7–11

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

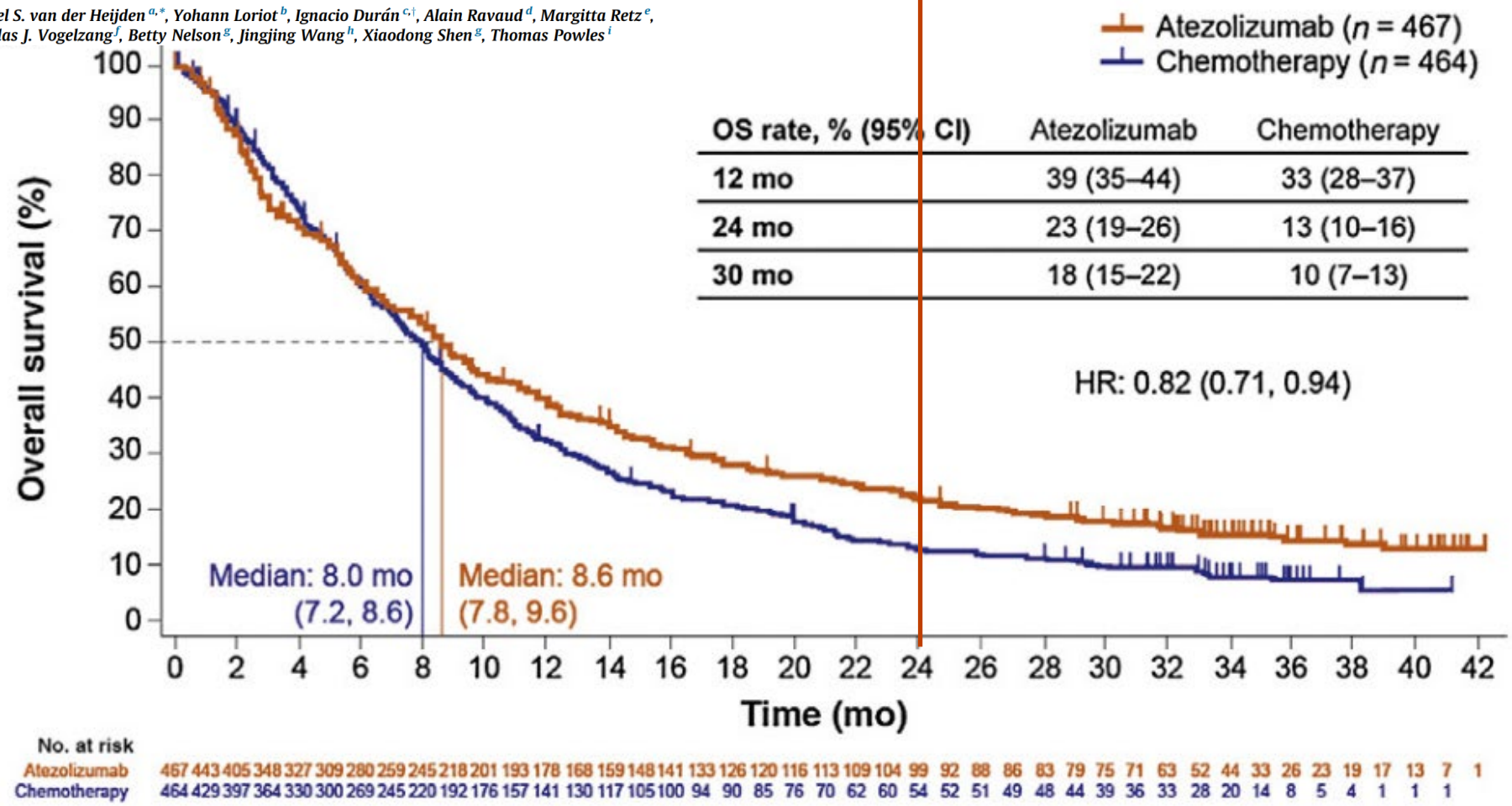
European Association of Urology

Brief Correspondence

Atezolizumab Versus Chemotherapy in Patients with Platinum-treated Locally Advanced or Metastatic Urothelial Carcinoma: A Long-term Overall Survival and Safety Update from the Phase 3 IMvigor211 Clinical Trial

Michiel S. van der Heijden [a,], Yohann Loriot [b], Ignacio Durán [c,†], Alain Ravaud [d], Margitta Retz [e], Nicholas J. Vogelzang [f], Betty Nelson [g], Jingjing Wang [h], Xiaodong Shen [g], Thomas Powles [i]*

apy, updated OS showed long-term durable remission. With a median of 33 mo of follow-up, the 24-mo OS rate was 23% with atezolizumab and 13% with chemotherapy.



OS rate, % (95% CI)	Atezolizumab	Chemotherapy
12 mo	39 (35–44)	33 (28–37)
24 mo	23 (19–26)	13 (10–16)
30 mo	18 (15–22)	10 (7–13)

Survival curves for onconnoisseurs

0. Thinking and talking about survival time
1. Comparing survival curves
2. Proportional hazards
3. Where to draw the line
4. Flat tails, plateaus, numbers at risk
5. Non-proportional hazards: don't cross me!
6. Restricted mean survival time

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ELSEVIER

Journal of Clinical Epidemiology 67 (2014) 622–628

Journal of Clinical Epidemiology

The statistical significance of randomized controlled trial results is frequently fragile: a case for a Fragility Index

Michael Walsh[a,b,c,*], Sadeesh K. Srinathan[d], Daniel F. McAuley[e,f], Marko Mrkobrada[g], Oren Levine[b], Christine Ribic[a,b], Amber O. Molnar[h], Neil D. Dattani[i], Andrew Burke[g], Gordon Guyatt[a,b], Lehana Thabane[a], Stephen D. Walter[a,b], Janice Pogue[a,c], P.J. Devereaux[a,b,c]

[a]*Department of Clinical Epidemiology and Biostatistics, McMaster University, 1280 Main Street West, Hamilton, Ontario, Canada, L8S4L8*

P-value is the probability of the observed results on the basis of chance alone (i.e. null hypothesis true)

The fragility index is the number of events needed change the p-value from <0.05 to >0.05

Results with a low fragility index are questionable

Fragility index. Walsh J Clin Epi 2014

399 trials in leading journals
- median sample size 682
- median number of events 112
- p-value from 0.01 to 0.05 in 47%

Fragility index
- median 8
- interquartile range 3 to 18
- i.e. ≤3 in 25% of trials

Fragility Index

Surely results from oncology trials are more robust…

RESULTS

Fragility Index

2

A fragility index of 2 indicates that if 2 patients in the experimental group were "converted" from NOT having the primary endpoint to HAVING the primary endpoint, the study would lose statistical significance ($p > 0.05$). The higher the fragility index, the more robust the results of a study are. Learn more about an "acceptable" fragility index.

	Original Study	Fragility Index	"Fragile" Study
Control group with outcome (N)	350		350
Control group without outcome (N)	114		114
Experimental group with outcome (N)	324	+ 2	326
Experimental group without outcome (N)	143	- 2	141
P value	0.04		0.056

The fragility of phase 3 trials supporting FDA-approved anticancer medicines: a retrospective analysis

Joseph C Del Paggio, Ian F Tannock

Summary

Background The fragility index of trial results—ie, the minimum number of changes from non-events to events resulting in loss of statistical significance—can provide a measure of confidence that a positive effect reported in a randomised controlled trial is real. We aimed to calculate the fragility index of randomised controlled trials supporting US Food and Drug Administration (FDA)-approved anticancer drugs.

Lancet Oncol 2019

Published Online
July 8, 2019
http://dx.doi.org/10.1016/S1470-2045(19)30338-9

The fragility of phase 3 trials supporting FDA-approved anticancer medicines: a retrospective analysis

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Lancet Oncol 2019

Published Online
July 8, 2019
http://dx.doi.org/10.1016/S1470-2045(19)30338-9

36 RP3 of oncology drugs approved by FDA 2014-2018

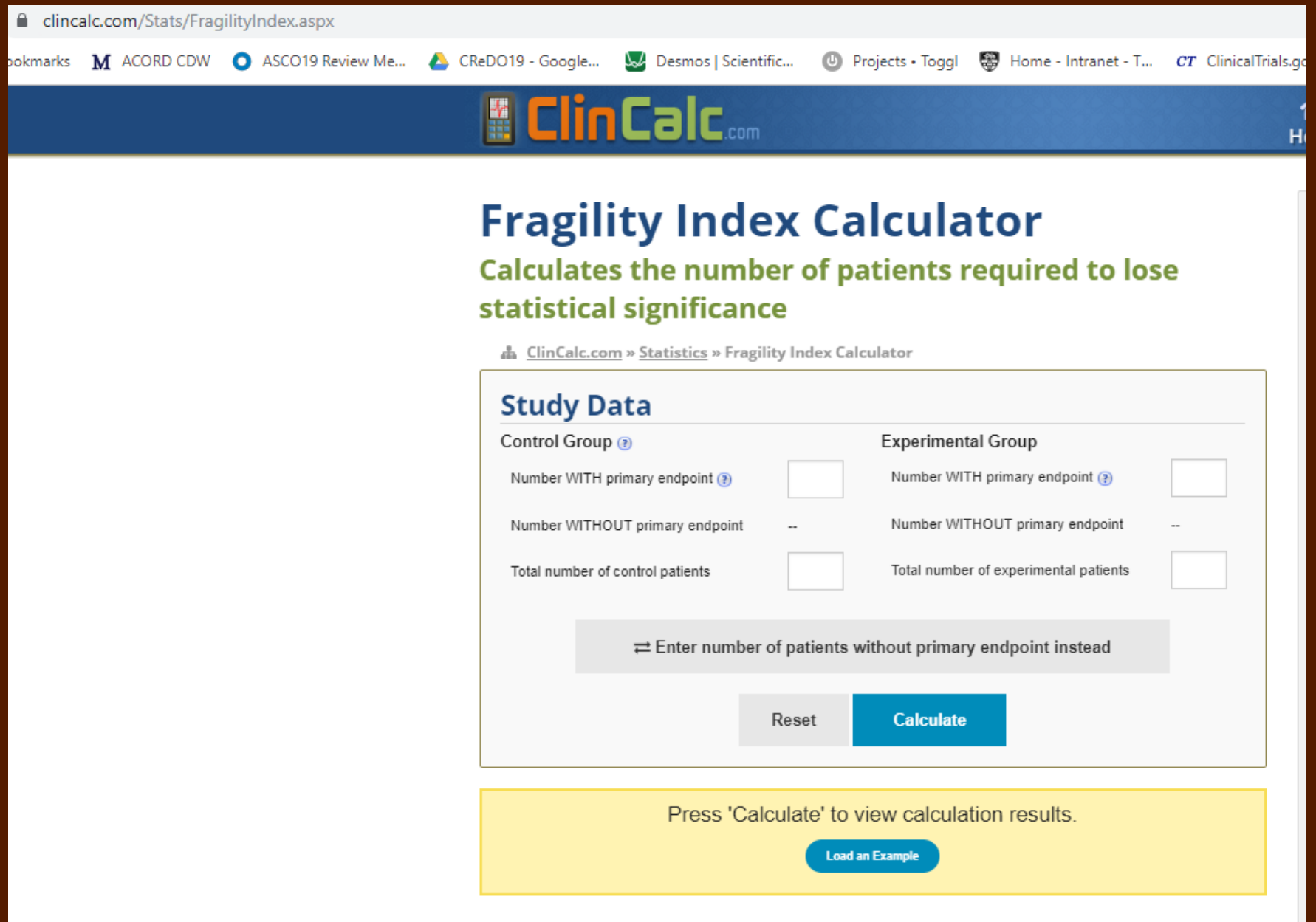
Fragility Index

calculable in 17/36

median 2, IQR 0–27

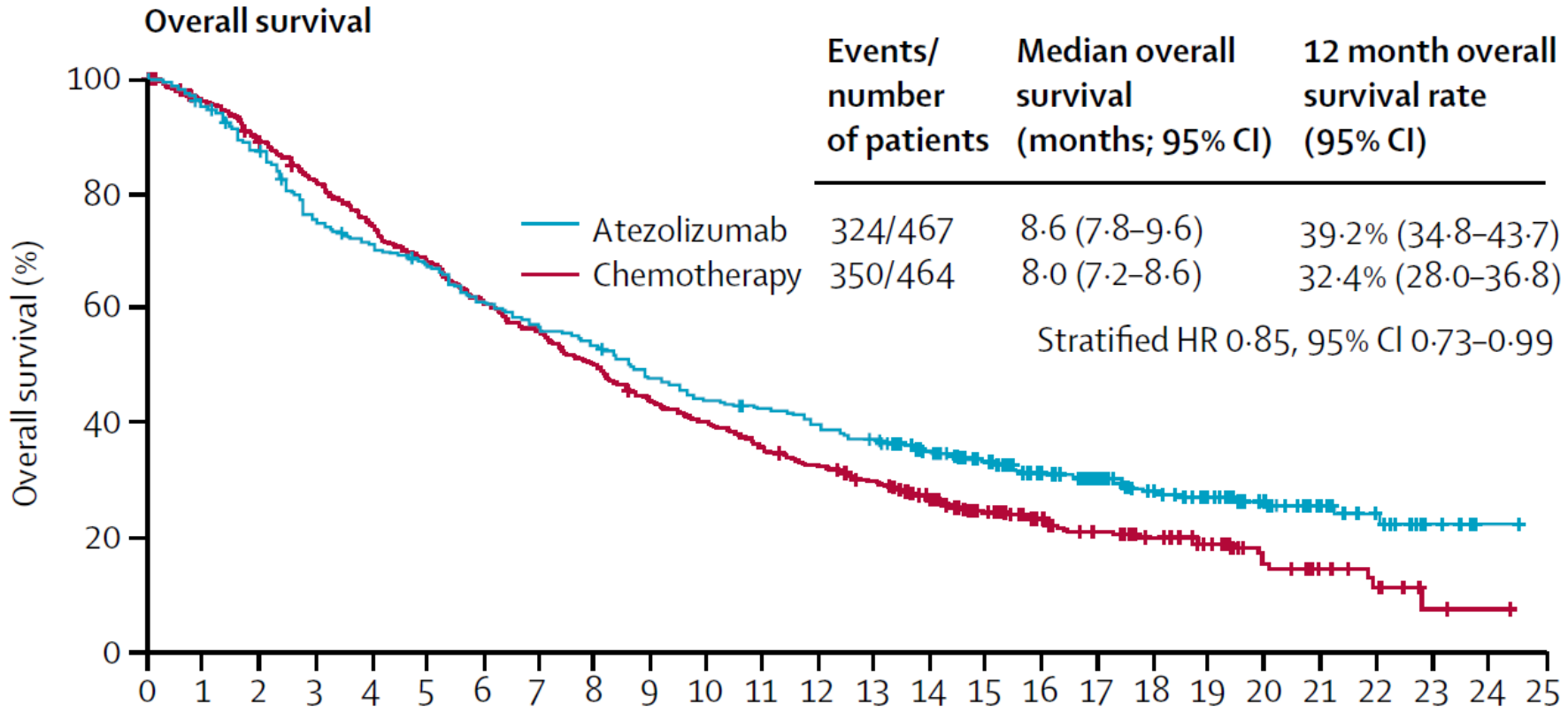
≤2 in 9 of 17 (53%), and ≤1% of sample size.

< number lost to follow-up in 5/17 (29%)


clincalc.com/Stats/FragilityIndex.aspx
ookmarks
ACORD CDW
ASCO19 Review Me...
CReDO19 - Google...
Desmos | Scientific...
Projects • Toggl
Home - Intranet - T...
ClinicalTrials.gc
ClinCalc.com
Fragility Index Calculator
Calculates the number of patients required to lose statistical significance
ClinCalc.com » Statistics » Fragility Index Calculator
Study Data
Control Group
Number WITH primary endpoint
Number WITHOUT primary endpoint
--
Total number of control patients
Experimental Group
Number WITH primary endpoint
Number WITHOUT primary endpoint
--
Total number of experimental patients
⇄ Enter number of patients without primary endpoint instead
Reset
Calculate
Press 'Calculate' to view calculation results.
Load an Example

Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial

Thomas Powles, Ignacio Durán, Michiel S van der Heijden, Yohann Loriot, Nicholas J Vogelzang, Ugo De Giorgi, Stéphane Oudard, Margitta M Retz, Daniel Castellano, Aristotelis Bamias, Aude Fléchon, Gwenaëlle Gravis, Syed Hussain, Toshimi Takano, Ning Leng, Edward E Kadel III,



Number at risk

Atezolizumab	467	443	405	348	327	309	280	259	245	218	201	192	177	166	138	113	90	76	59	47	34	20	13	5	1	..
Chemotherapy	464	428	397	364	330	299	268	244	219	191	175	156	140	126	99	78	60	49	42	30	17	11	7	2	1	..

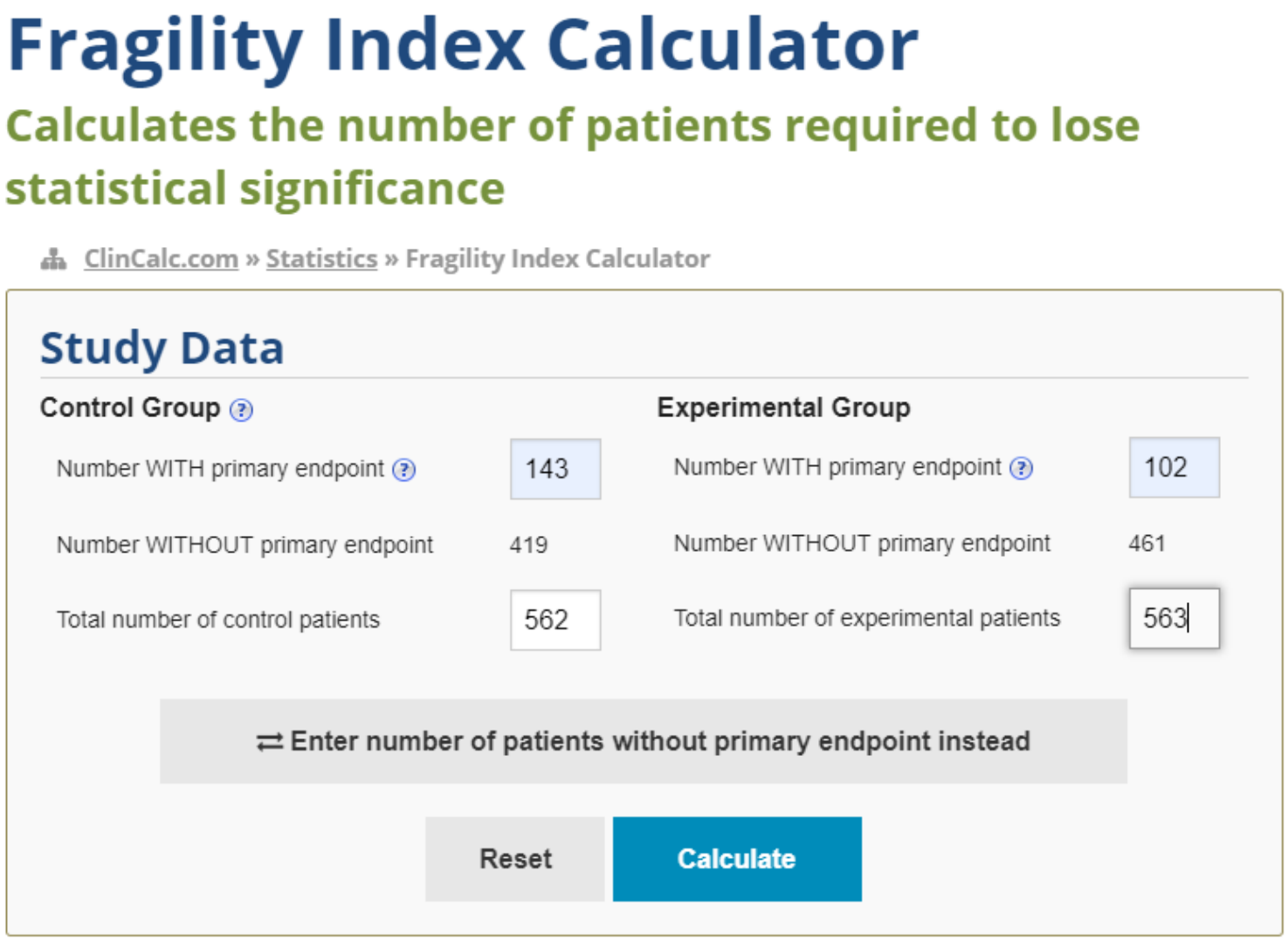
Study Data

Control Group		Experimental Group	
Number WITH primary endpoint	350	Number WITH primary endpoint	324
Number WITHOUT primary endpoint	114	Number WITHOUT primary endpoint	143
Total number of control patients	464	Total number of experimental patients	467

⇄ Enter number of patients without primary endpoint instead

Reset | Calculate

Enzalutmide with standard first-line therapy in metastatic prostate cancer Davis NEJM 2019



Enzalutmide with standard first-line therapy in metastatic prostate cancer Davis NEJM 2019

Fragility Index

14

A fragility index of 14 indicates that if 14 patients in the experimental group were "converted" from NOT having the primary endpoint to HAVING the primary endpoint, the study would lose statistical significance ($p > 0.05$). The higher the fragility index, the more robust the results of a study are. **Learn more about an "acceptable" fragility index**.

	Original Study	Fragility Index	"Fragile" Study
Control group with outcome (N)	143		143
Control group without outcome (N)	419		419
Experimental group with outcome (N)	102	+ 14	116
Experimental group without outcome (N)	461	- 14	447
P value	0.003		0.056

Survival curves for onconnoisseurs

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4. Flat tails, plateaus, numbers at risk
5. Non-proportional hazards: don’t cross me!
6. Restricted mean survival time
7. The fragility index

Asia-Pacific Clinical Oncology Research Development Initiative (ACORD)

1-Day Concept Development Workshop
- come with a 1-sentence title
- leave with a 1-page concept outline

1-Week Protocol Development Workshop (Sep 2021)
- come with a 1-page concept outline
- leave with a 20-page study protocol

The ACORD Concept Development Workshop
Come with an idea, leave with a concept outline

Our goal is to train clinicians in
excellent clinical research methods and
propel oncology research in our region.

The aim of this workshop aim is to
help each participant
turn their good idea into
a successful concept outline.

A successful concept outline is one that
persuades important people
to support a study.

Today's Program

9:00	Introductory information and ideas	45m
9:45	Writing your concept outline part 1	70m
	Tea break	
11:30	Small group discussions of your concepts	90m
	Lunch	
2:00	Writing your concept outline part 2	60m
3:00	Small group discussions of your concepts	90m
	Tea break	
4:45	Resources, next steps, evaluation	45m
5:30	Depart	

ACORD 1-Week Protocol Development Workshop
August 29 to 3 September 2021

Turning good ideas into successful clinical studies

The ACORD Protocol Development Workshop
Come with a page, leave with a protocol

Our goals are to train clinicians in
excellent clinical research methods and
propel oncology research in the region.

Workshop aim is to help each participant
turn their good idea into
a successful clinical research protocol.

A successful protocol is one that results in
a reported study answering a good question.