SURVIVAL ANALYSIS AND COX REGRESSION

LEARNING OBJECTIVES

- Upon the completion of this lecture, you will be able to:
  - Understand when using survival analysis
  - Compute Kaplan-Meier curves
  - Cox Regression Model

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Ensartinib vs Crizotinib for Patients With Anaplastic Lymphoma Kinase–Positive Non-Small Cell Lung Cancer

A Randomized Clinical Trial

Leora Horn, MD, MS; Ziping Wang, MD; Gang Wu, MD; Elena Poddubskaya, MD; Tony Mok, MD; Martin Reck, MD; Heather Wakelee, MD; Alberto A. Chiappori, MD; Dae Ho Lee, MD, PhD; Valeriy Breder, MD, PhD; Sergey Orlov, MD; Irfan Cicin, MD; Ying Cheng, MD; Yunpeng Liu, MD; Yun Fan, MD; Jennifer G. Whisenant, PhD; Yi Zhou, PhD; Vance Oertel, MS; Kim Harrow, MBA; Chris Liang, PhD; Li Mao, MD; Giovanni Selvaggi, MD; Yi-Long Wu, MD

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RCT: Ensartinib vs Crizotinib for Patients With Anaplastic Lymphoma Kinase–Positive Non-Small Cell Lung Cancer

POPULATION

149 Men, 141 Women

Eligible adult patients had advanced, recurrent, or metastatic non-small cell lung cancer that was positive for anaplastic lymphoma kinase

Median age, 54 y (range, 25-90 y)

INTERVENTION

290 Patients randomized

143 Oral ensartinib
225 mg Once daily

147 Oral crizotinib
250 mg Twice daily

SETTINGS / LOCATIONS

120 Centers in 21 countries

PRIMARY OUTCOME

Blinded independent review committee–assessed progression-free survival (PFS) according to Response Evaluation Criteria In Solid Tumours (RECIST), version 1.1

Key Points

Question Is ensartinib superior to crizotinib for patients with advanced anaplastic lymphoma kinase (*ALK*)-positive non-small cell lung cancer (NSCLC) who have not been treated previously with an ALK inhibitor?

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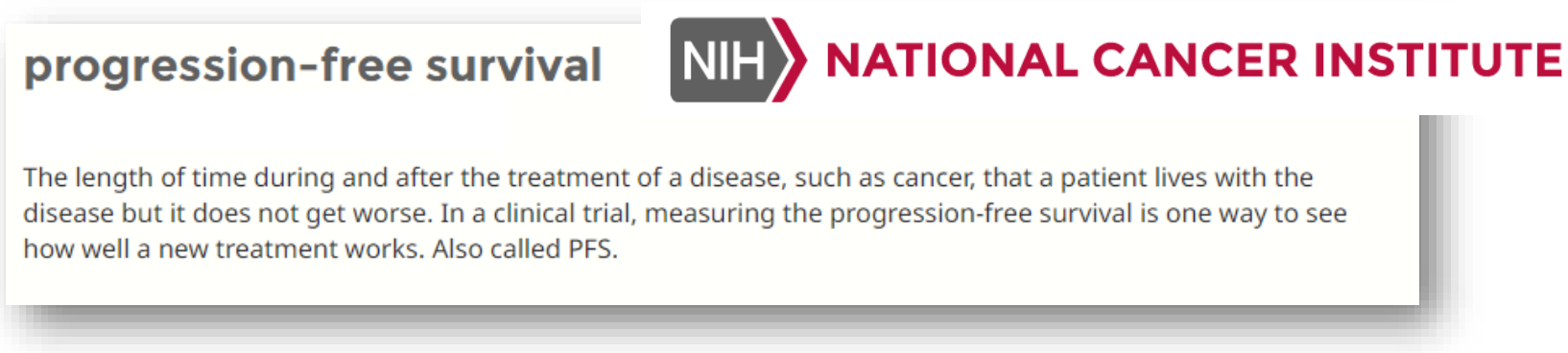
PROGRESSION FREE SURVIVAL

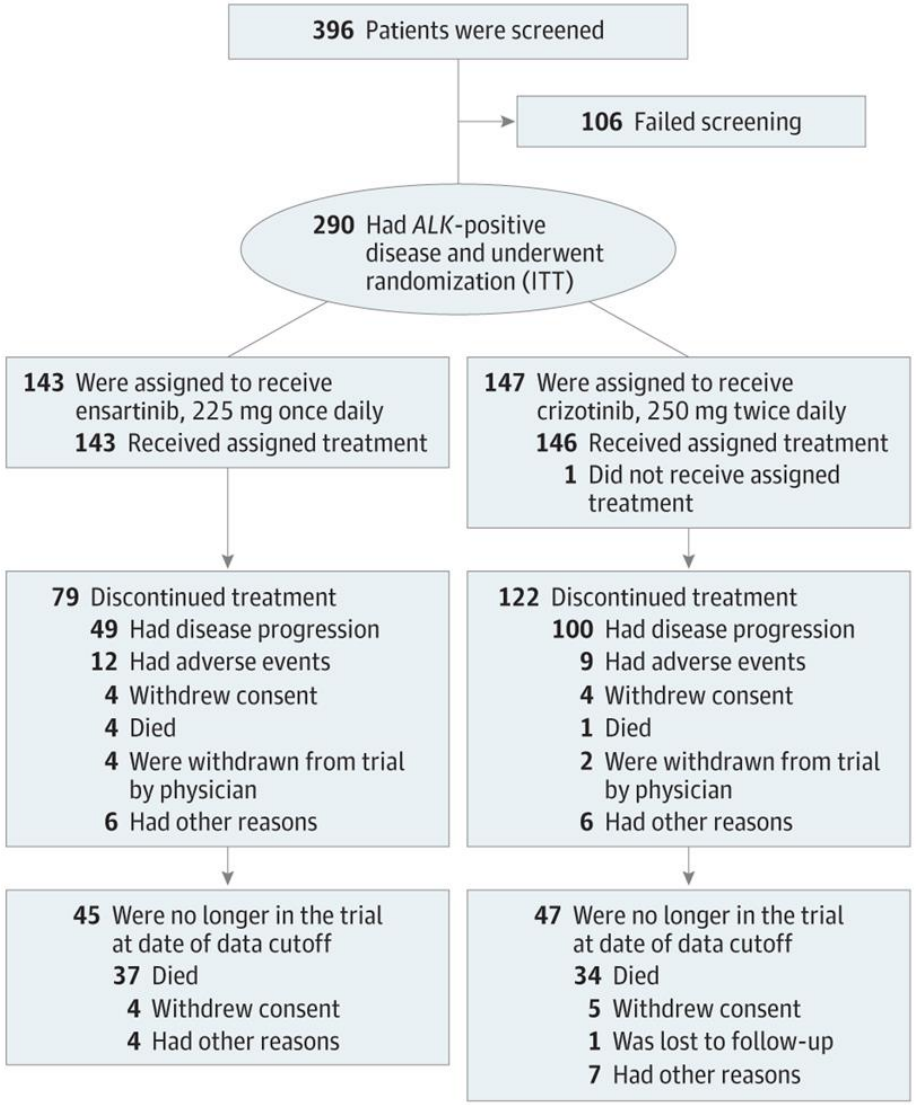
- Progression-free survival refers to the time from randomisation or initiation of treatment to the occurrence of disease progression or death



- Disease progression is defined by the **Response Evaluation Criteria in Solid Tumors (RECIST)** as an increase in the sum of maximum tumour diameters of at least 20%, the development of any new lesions, or an unequivocal increase in non-measurable malignant disease

TIME-TO-EVENT VARIABLE

- **Between July 25, 2016, and November 12, 2018**, 396 patients were screened
- 290 patients (149 men [51.4%]; median age, 54 years [range, 25-90 years]) were randomized
  - ensartinib, 143 patients; crizotinib, 147 patients



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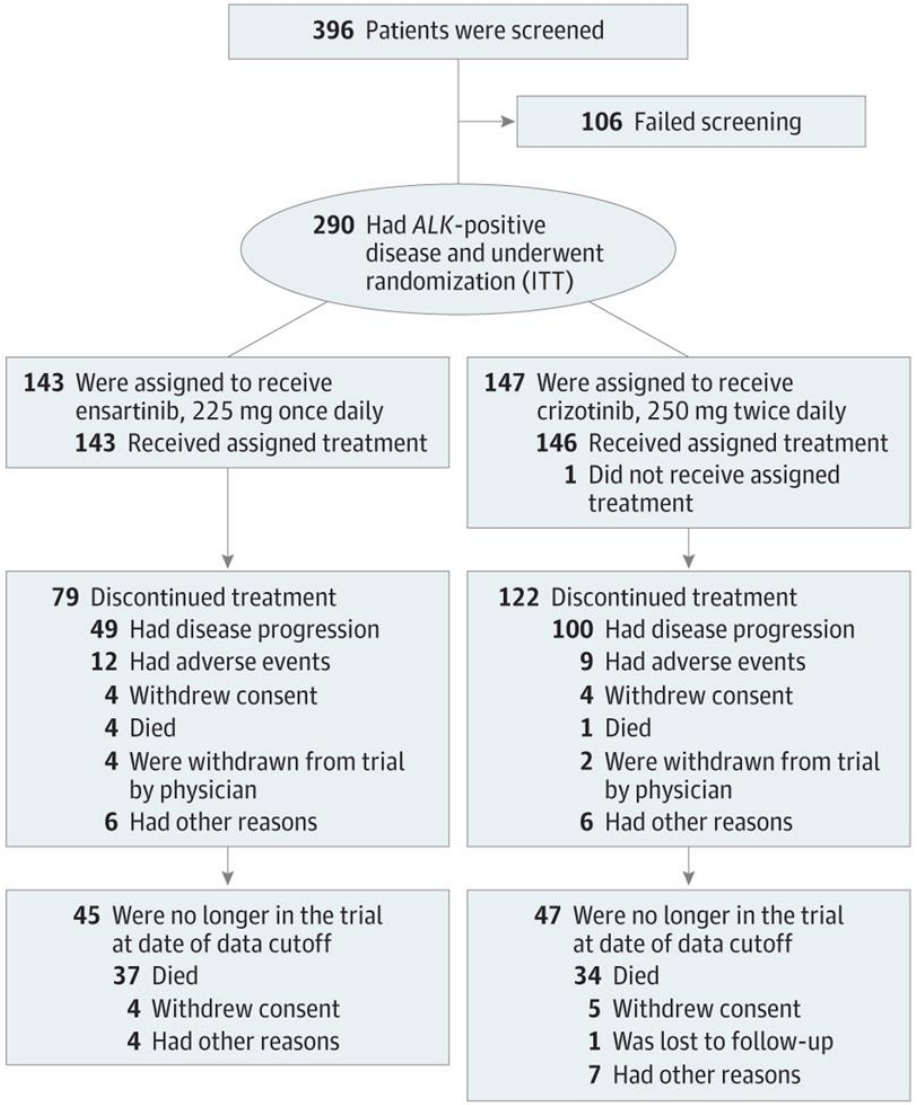

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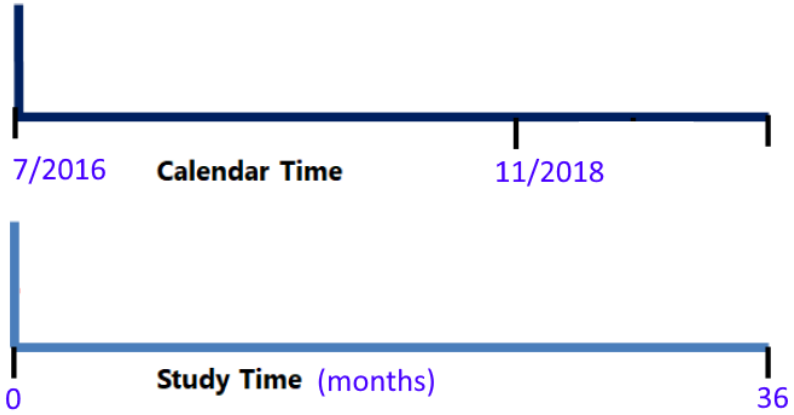

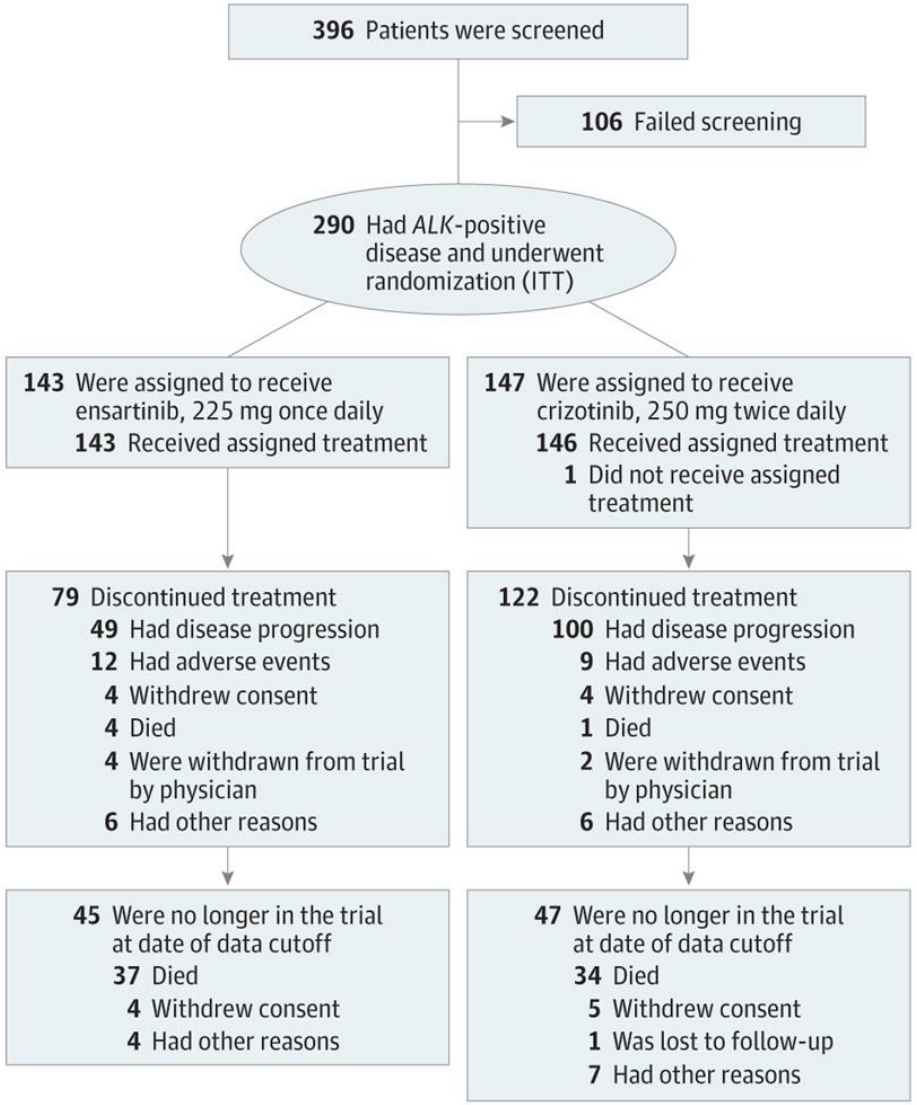

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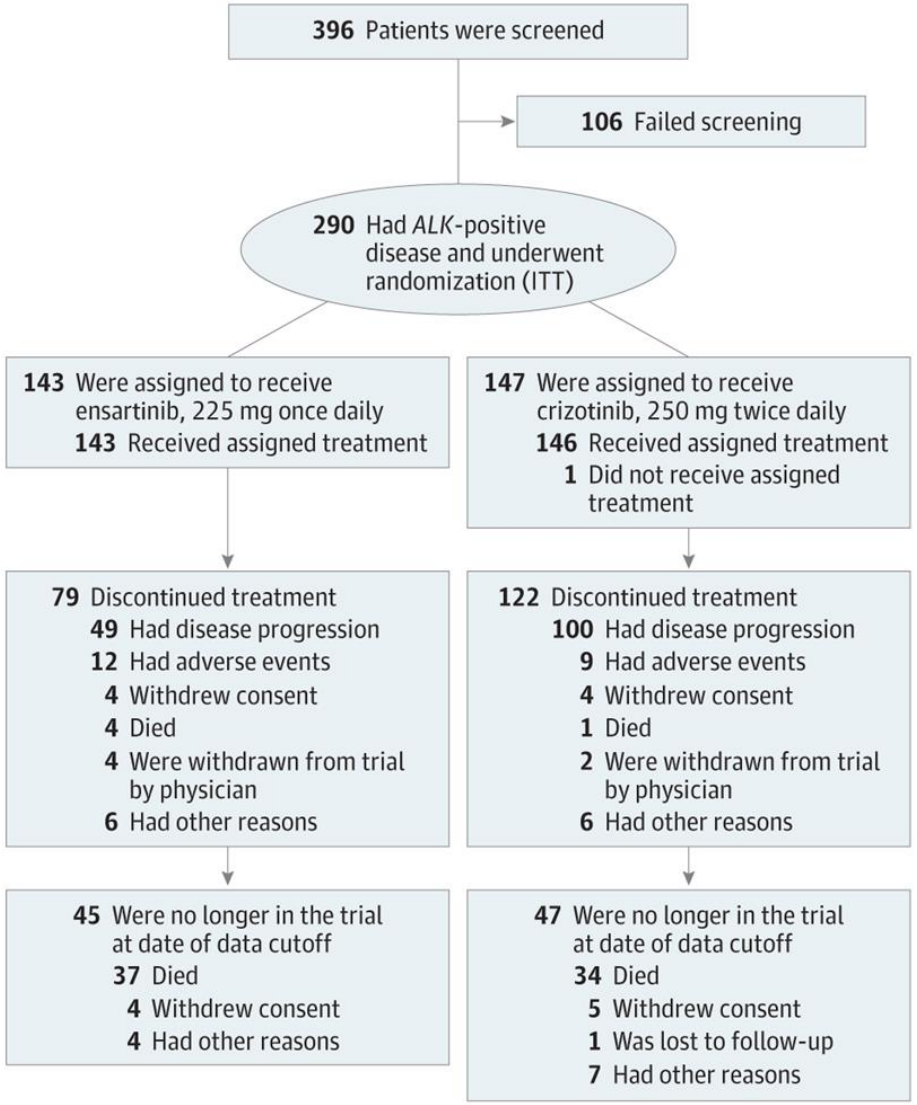

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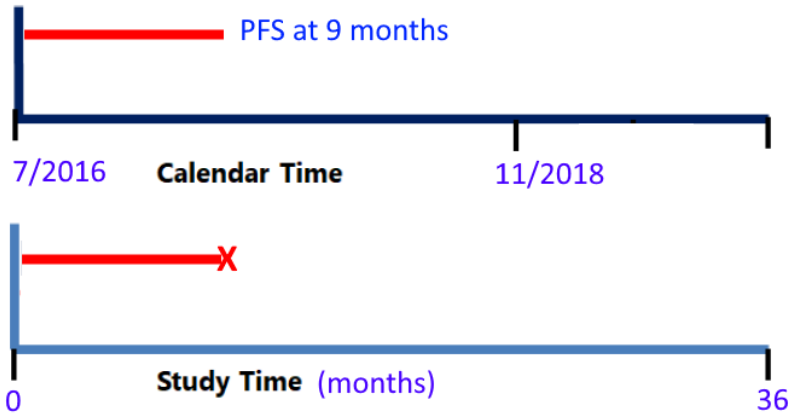

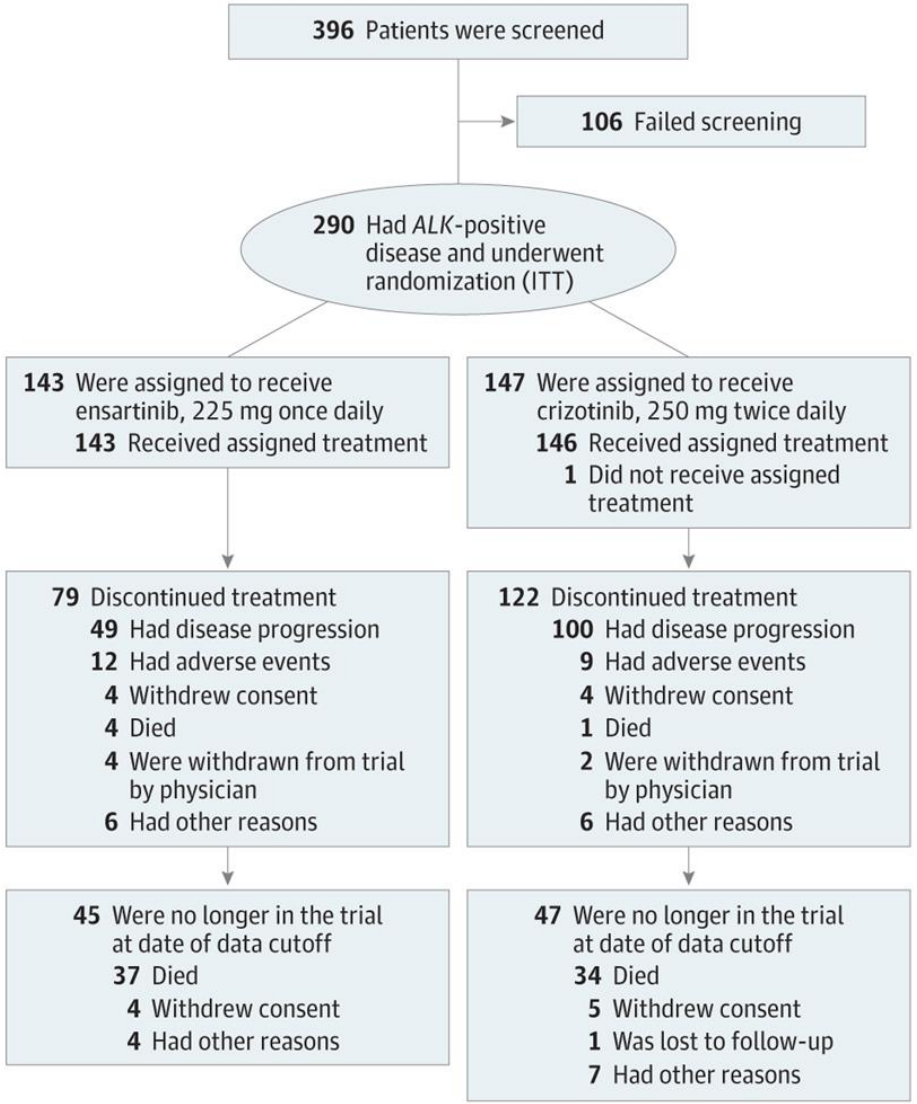

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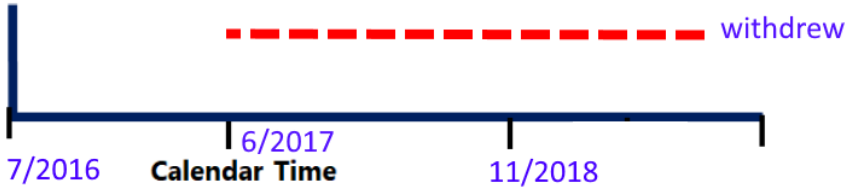

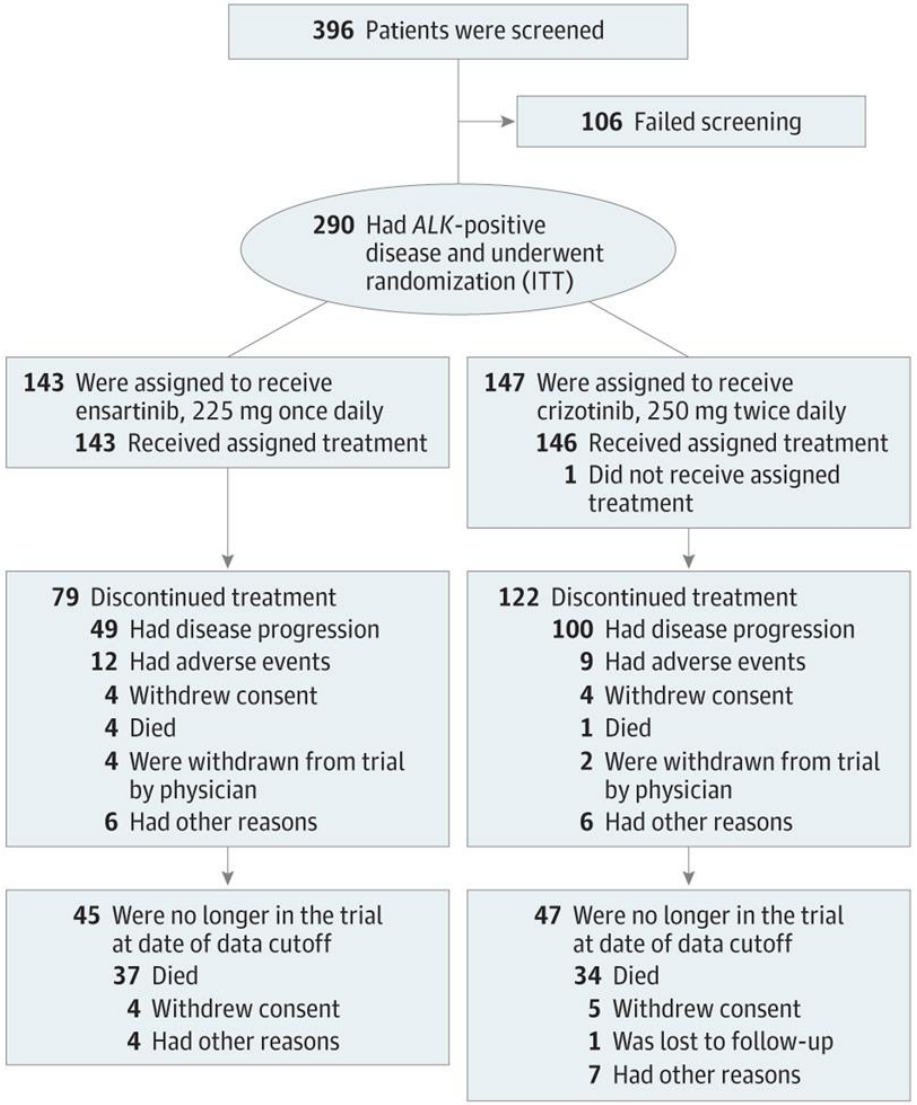

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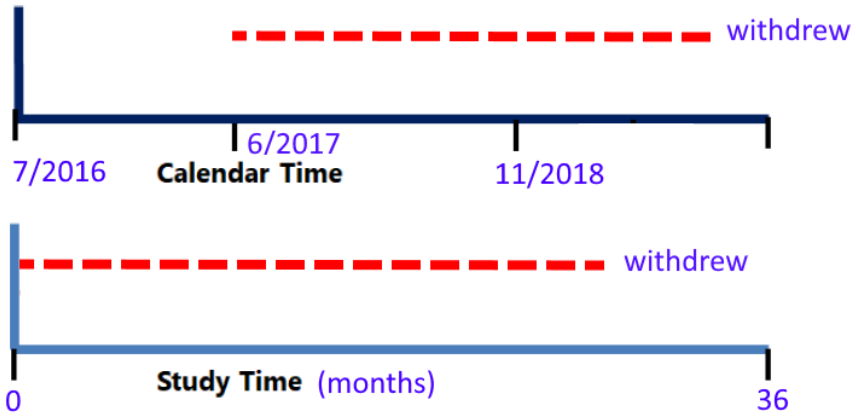

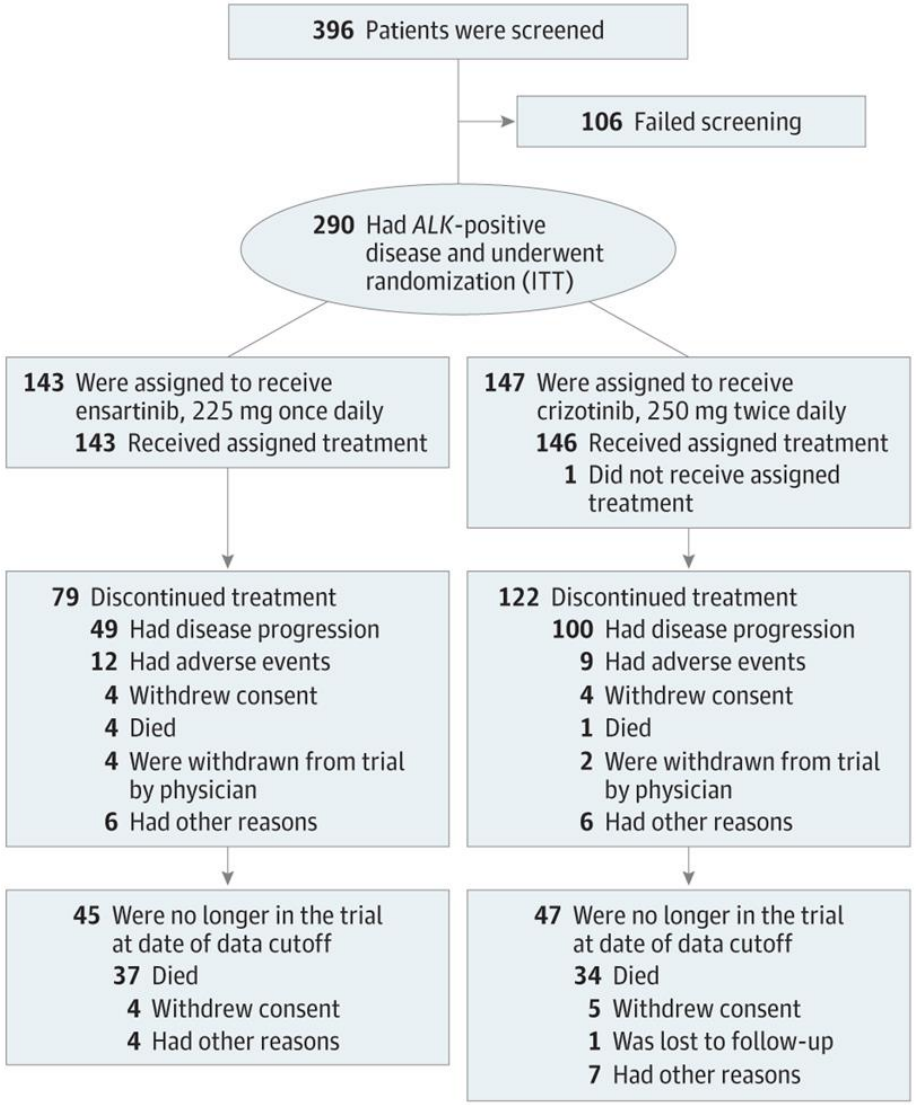

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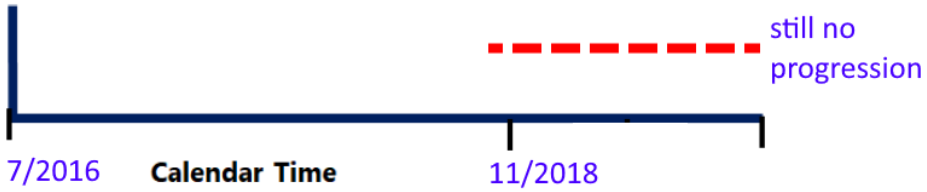

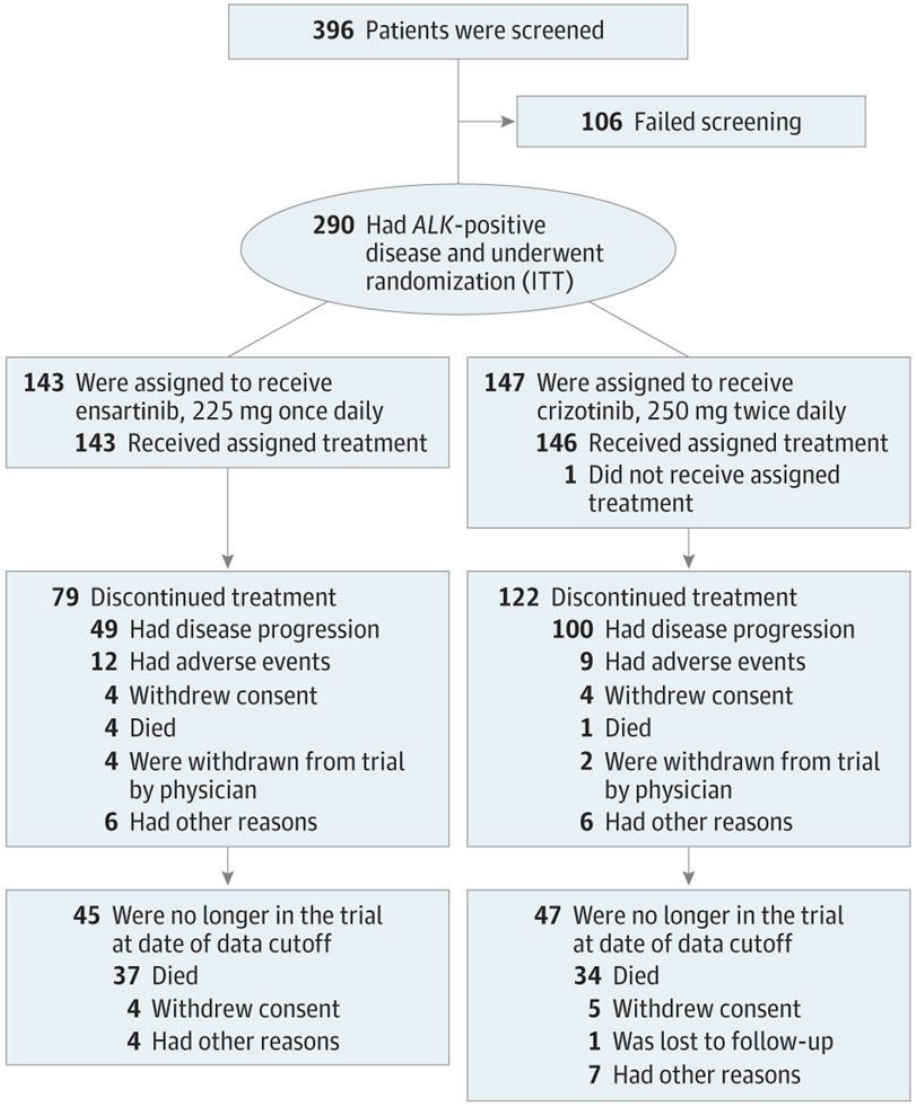

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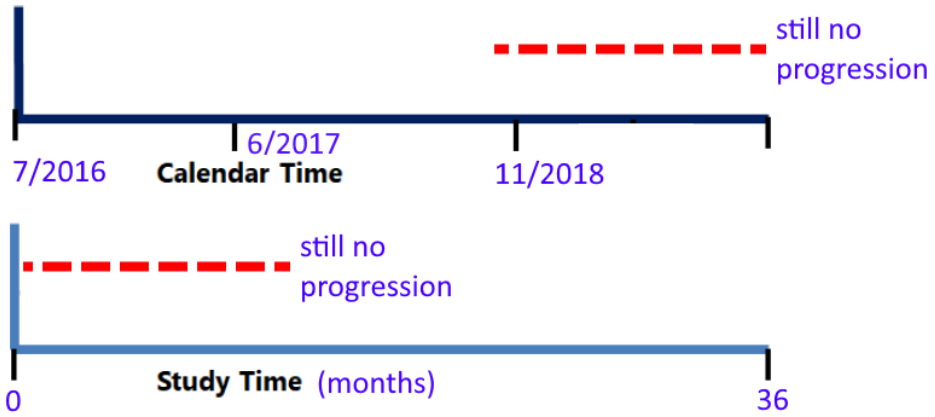

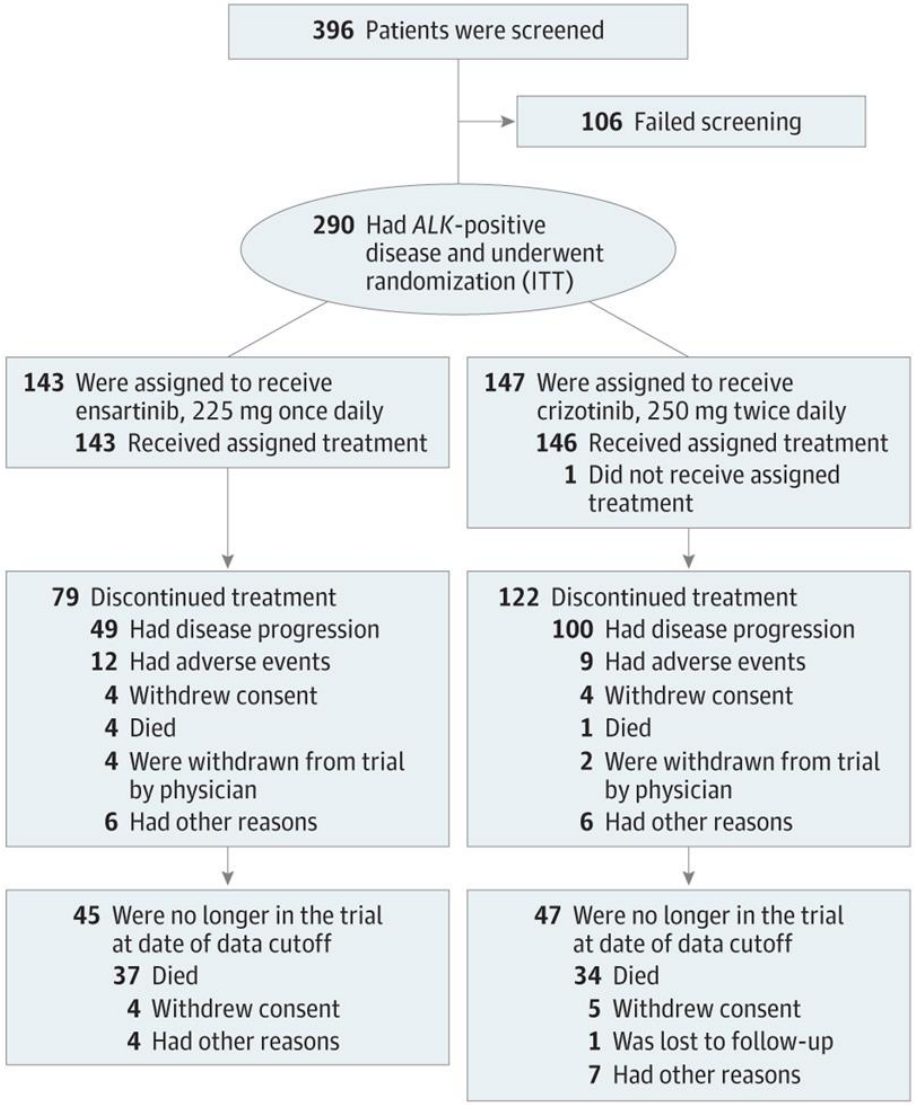

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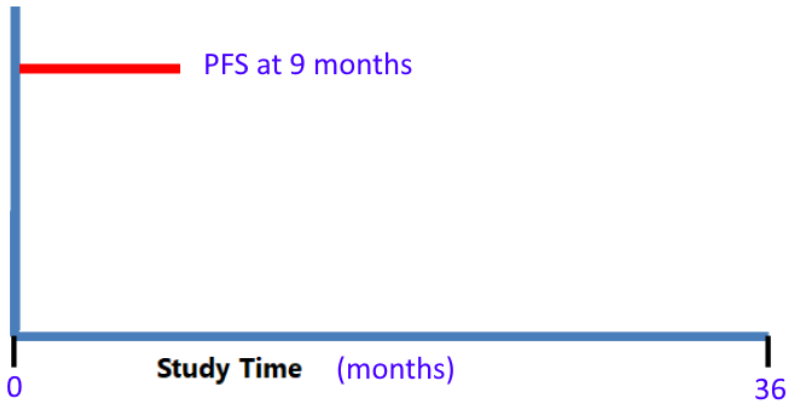

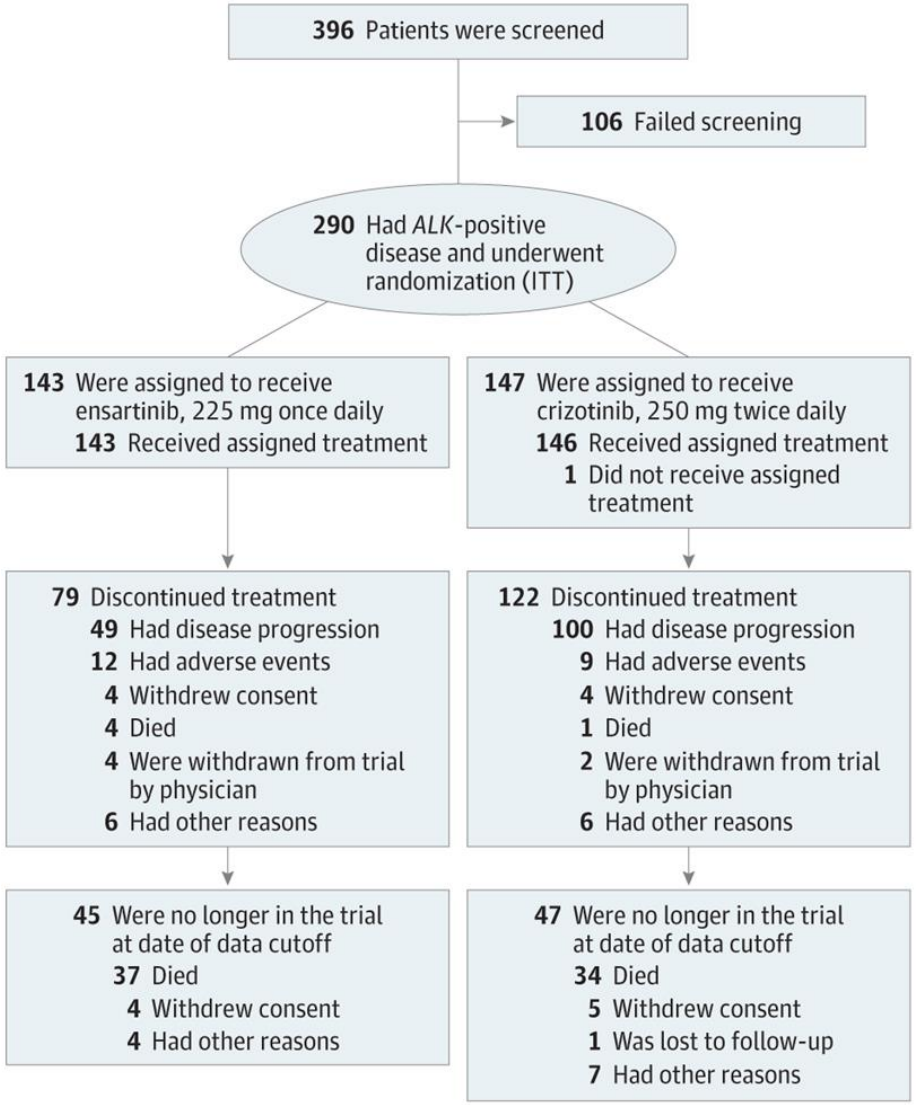

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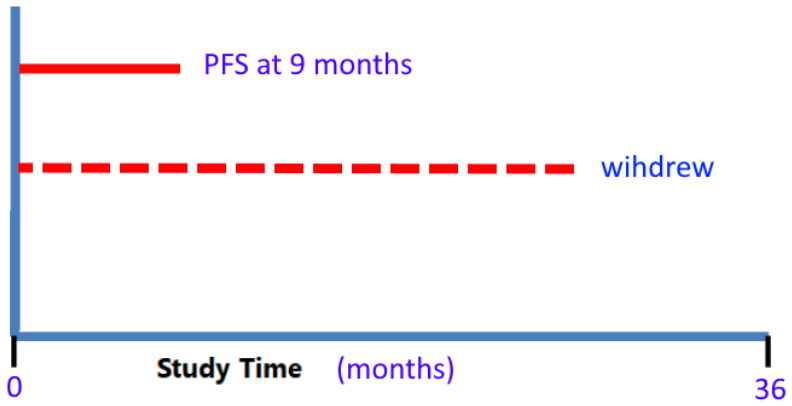

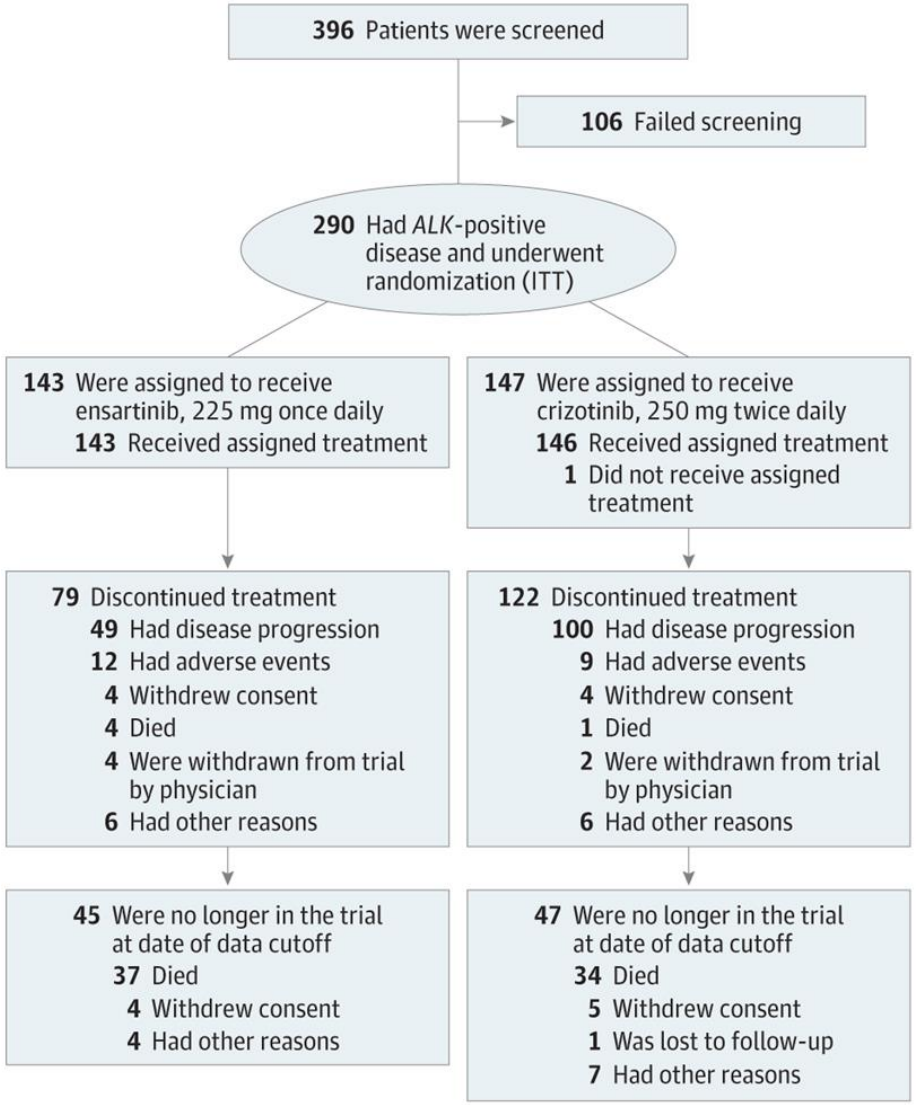

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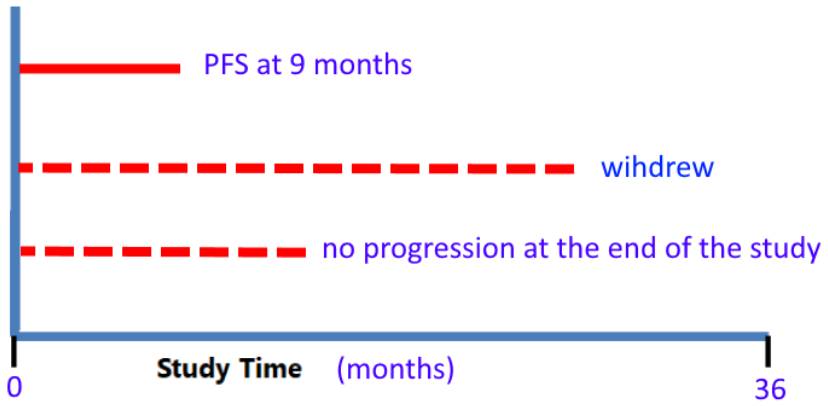

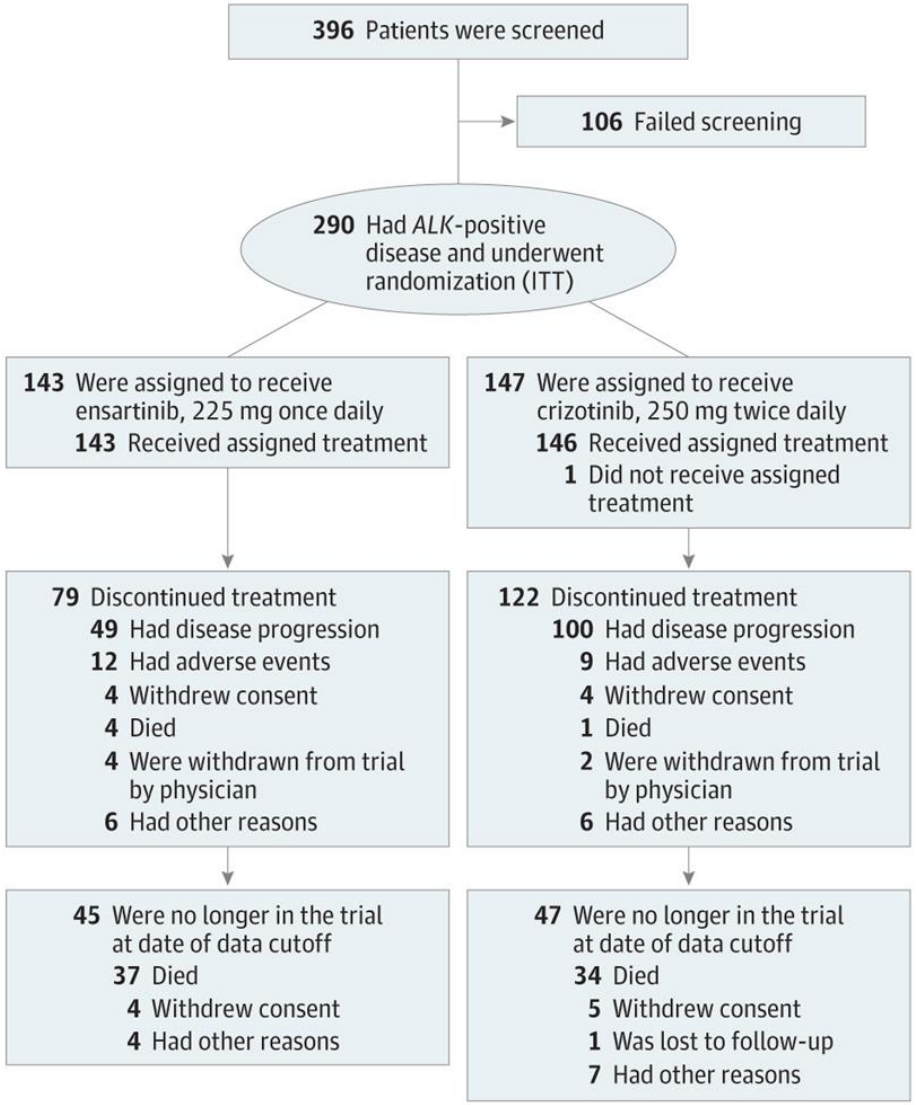

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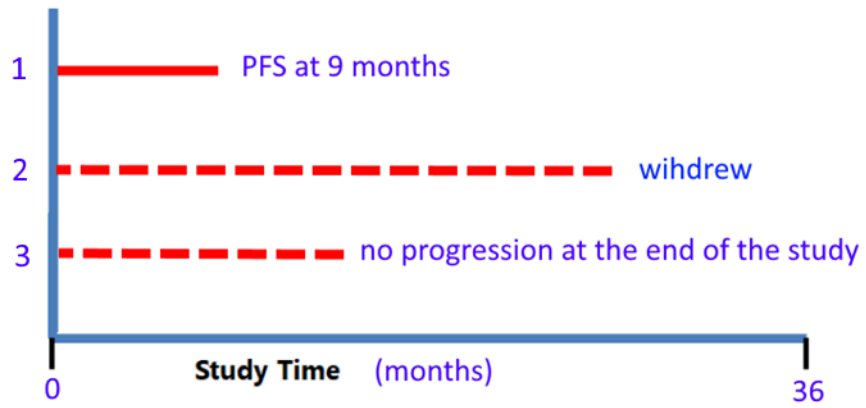
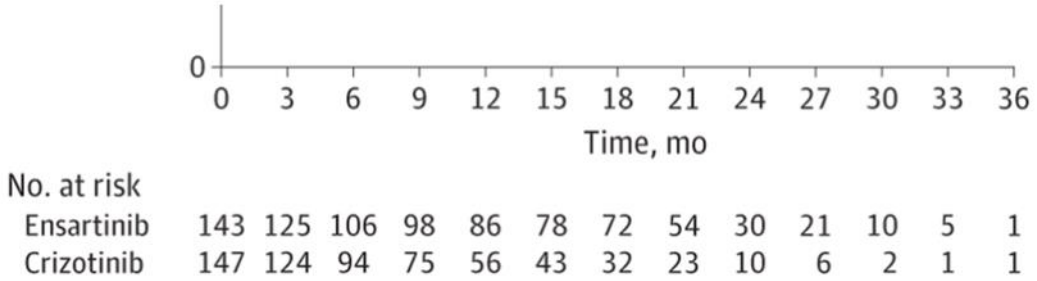
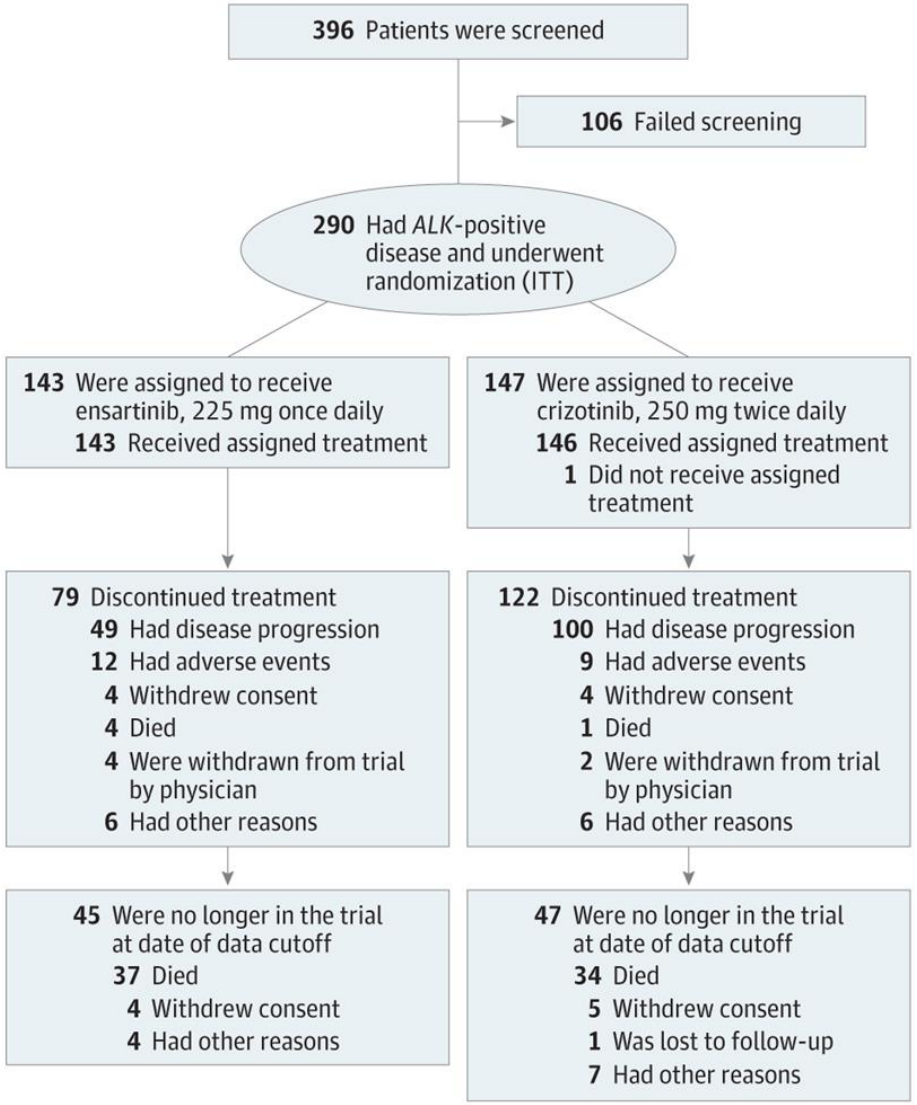


- Patient 1 is a **complete observation**
- Patient 2 and 3 are **censored** observations
  - partial information about the progression free survival time
- Patient 2 had no progression when he/she withdrew (lost follow-up)
  - we know that he/she survived 26 months on the study clock
- Patient 3 survived 1 year on the study clock

TIME-TO-EVENT VARIABLE





ELSEVIER

Clinical Lung Cancer

Volume 14, Issue 1, January 2013, Pages 34-39

Original study

Carboplatin and Paclitaxel Plus ASA404 as First-Line Chemotherapy for Extensive-Stage Small-Cell Lung Cancer: A Multicenter Single Arm Phase II Trial (SAKK 15/08)

PROPORTION OF PATIENTS WITH TUMOR ASSESSMENT AT 24 WEEKS

NOT A TIME-TO-EVENT VARIABLE

Primary Outcome Measures :

1. Progression-free survival rate [Time Frame: at 24 weeks (6 months)]

   The status of progression free survival at 24 weeks (+/- 2 weeks) from trial registration will be assessed. A PFS event is defined as (whichever occurs first):

   - Relapse or progression assessed according to the RECIST 1.1 criteria (Appendix 1)
   - Death of any cause.

RATE OF PROGRESSION

- Suppose we want to compute the rate of the progression
  - PFS is a binary outcome: 1 event out of 3 patients: 1/3 = 33%

- the time *at risk* of progression in study period varies from person to person
- If we compute the rate as 1 event out of 3 patients, we weight equally all 3 patients, as we had observed them for the same time

RATE OF PROGRESSION

- Suppose we want to compute the rate of the progression
  - What about reporting the average time?
    - $\frac{9+22+12}{3} = 14.3$ months

- since only 1 of the 3 patients had progression while in the study, this average is **NOT** capturing average time to progression since enrollment, but only average follow-up time

INCIDENCE RATE OF PROGRESSION

- **Incidence Rate** takes total number of progression that occurred and divide by the total amount of follow-time contributed by the patients:

$$IR = \frac{1}{9 + 22 + 12} = \frac{1\ progression}{43\ months}$$

EXAMPLE 2: INFANT MORTALITY

- **Maternal Vitamin Supplementation and Infant Mortality**
  - *Katz J, West K et al. Maternal low-dose vitamin A or beta-carotene supplementation has no effect on fetal loss and early infant mortality: a randomized cluster trial in Nepal.*
  - *American Journal of Clinical Nutrition (2000) Vol. 71, No. 6,1570-1576*

ABSTRACT

Background: The effect of vitamin A supplementation on the survival of infants aged <6 mo is unclear. Because most infant deaths occur in the first few month of life, maternal supplementation may improve infant survival.

Objectives: The objective was to assess the effect of maternal vitamin A or β-carotene supplementation on fetal loss and survival of infants <6 mo of age.

Design: Married women of reproductive age in 270 wards of Sarlahi district, Nepal, were eligible to participate. Wards were randomly assigned to have women receive weekly doses of 7000 μg retinol equivalents as retinyl palmitate (vitamin A), 42 mg *all-trans*-β-carotene, or placebo. Pregnancies were followed until miscarriage, stillbirth, maternal death, or live birth of one or more infants, who were followed through 24 wk of age.

EXAMPLE 3: INFANT MORTALITY

- **Maternal Vitamin Supplementation and Infant Mortality**
  - A total of 43,559 women were enrolled; 15,892 contributed 17,373 pregnancies and 15,997 live born infants to the trial
- Total follow-up time: 1,627,725 days
- Total deaths in (6 month) follow-up period: 644

EXAMPLE 3: INFANT MORTALITY

- Infant mortality rate in 6-months post birth

$$\hat{IR} = \frac{644 \text{deaths}}{1,627,725} \approx 0.0004 \text{ deaths/day}$$

IR estimate per (1 person) year	• 0.0004 deaths/day × (365days/1year) = 0.146deaths/year
IR estimate per 500 (persons) years	• 0.146deaths/year × 500 = 73 deaths/(500 years)

COMPARING NUMERICALLY TIME TO EVENT DATA BETWEEN TWO (OR MORE) SAMPLES

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EXAMPLE 3: INFANT MORTALITY

- **Vitamin A:** 578,595 person-days follow-up, 236 deaths

$$\hat{IR}_{vitA} = \frac{236 \text{ deaths}}{578,595 \text{ person} - \text{days}} \approx 0.00041 \text{ deaths/person} - \text{days}$$

- **Beta-Carotene:** 516,692 person-days follow-up, 203 deaths

$$\hat{IR}_{BC} = \frac{203 \text{ deaths}}{516,692 \text{ person} - \text{days}} \approx 0.00039 \text{ deaths/person} - \text{days}$$

- **Placebo:** 532,438 person-days follow-up, 205 deaths

$$\hat{IR}_{placebo} = \frac{205 \text{ deaths}}{532,438 \text{ person} - \text{days}} \approx 0.00039 \text{ deaths/person} - \text{days}$$

EXAMPLE 3: INFANT MORTALITY

- **Incidence Rate Ratio:** there are 3 groups
  - make one group the *reference* or comparison group, for example placebo

$$\hat{IRR}_{vitA} = \frac{\hat{IR}_{vitA}}{\hat{IR}_{placebo}} = \frac{0.00041 \text{ deaths/PYs}}{0.00039 \text{ deaths/PYs}} \approx 1.05$$

$$\hat{IRR}_{BC} = \frac{\hat{IR}_{BC}}{\hat{IR}_{placebo}} = \frac{0.00039 \text{ deaths/PYs}}{0.00039 \text{ deaths/PYs}} \approx 1.00$$

EXAMPLE 3: INFANT MORTALITY

- **Incidence Rate Ratio:** there are 3 groups
  - make one group the *reference* or comparison group, for example placebo

$$\hat{IRR} = \frac{\hat{IR}_{BC}}{\hat{IR}_{placebo}} = \frac{0.00039 \text{ deaths/PYs}}{0.00039 \text{ deaths/PYs}} \approx 1.00$$

- The (estimated) child mortality rate in the Beta-Carotene group is the same as the (estimated) child mortality in the placebo group

MORTALITY ON DIALYSIS, RACE AND AGE: EXAMPLE 4

- Mortality on Dialysis, Race and Age:
  - *Kucircka L et al. Association of Race and Age With Survival Among Patients Undergoing Dialysis. Journal of the American Medical Association (2011) Vol. 306, No. 6, 620-626*

Context Many studies have reported that black individuals undergoing dialysis survive longer than those who are white. This observation is paradoxical given racial disparities in access to and quality of care, and is inconsistent with observed lower survival among black patients with chronic kidney disease. We hypothesized that age and the competing risk of transplantation modify survival differences by race.

Objective To estimate death among dialysis patients by race, accounting for age as an effect modifier and kidney transplantation as a competing risk.

Design, Setting, and Participants An observational cohort study of 1 330 007 incident end-stage renal disease patients as captured in the United States Renal Data System between January 1, 1995, and September 28, 2009 (median potential follow-up time, 6.7 years; range, 1 day-14.8 years). Multivariate age-stratified Cox proportional hazards and competing risk models were constructed to examine death in patients who receive dialysis.

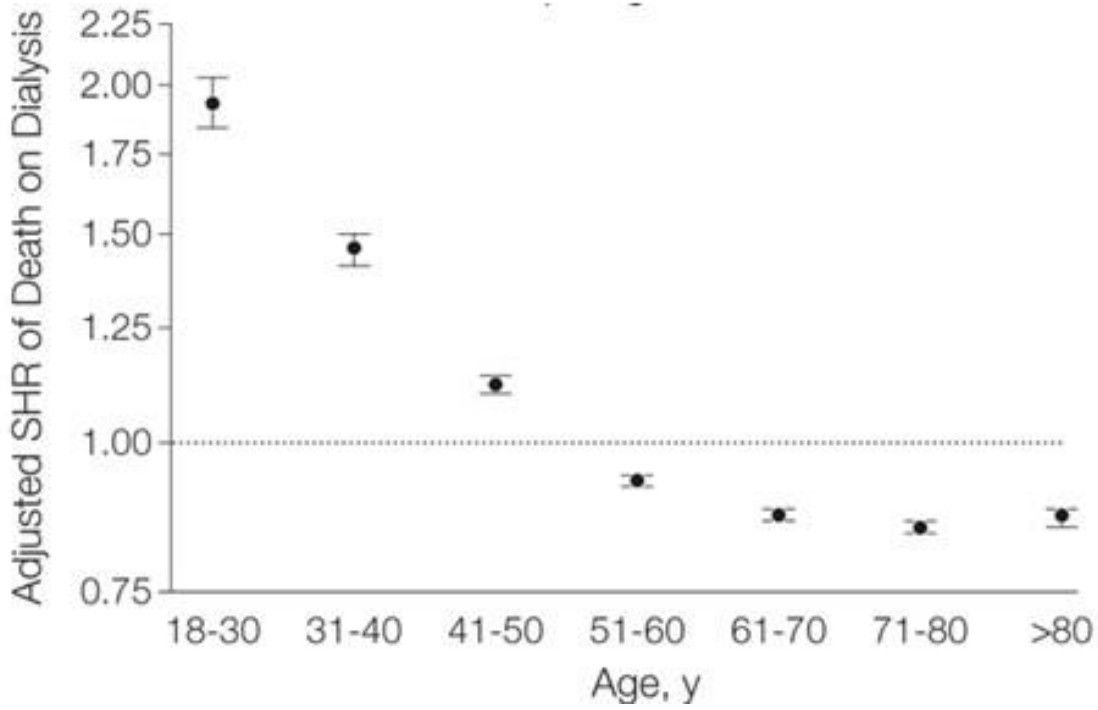
Main Outcome Measures Death in black vs white patients who receive dialysis.

Results Similar to previous studies, black patients undergoing dialysis had a lower

SMORTALITY ON DIALYSIS, RACE AND AGE: EXAMPLE 4

- IRR estimates for mortality in follow-up period (black versus white), presently separately across age groupings (adjusted), presented on log scale

Figure 2. Relative Adjusted Hazard of Death in Black vs White Dialysis Patients, by Age



SUMMARY

- The incidence rate ratio (IRR, estimated by *IRˆR*) can be used to quantify differences in the time to event information from two samples
- The incidence rate ratio can be thought of as a relative risk measure that incorporates differences in subject follow up times into the comparison

CONFIDENCE INTERVAL FOR INCIDENCE RATE RATIOS

OUTLINE

- Estimate and interpret a 95% (or other level) confidence interval for an incidence rate ratio comparing time-to-event outcomes between two populations

PBC TRIAL

- Mayo Clinic: Primary Biliary Cirrhosis (PBC treatment), randomized clinical trial
  - *Dickson E, et al. Trial of Penicillamine in Advanced Primary Biliary Cirrhosis. New England Journal of Medicine. (1985) 312(16): 1011-1015*
- **Primary Research Question:** How does mortality (and hence) survival for PBC patients randomized to receive DPCA (D-Penicillamine) compare to survival for PBC patients randomized to receive a placebo?

PBC TRIAL

- Incidence rates for DPCA and placebo groups
- **DPCA:** 872.5 years of follow-up, 65 deaths

$$\hat{IR}_{DPCA} = \frac{65 \text{ deaths}}{872.5 \text{ PYs}} \approx 0.075 \text{ deaths/PYs}$$

- **Placebo:** 842.5 years of follow-up, 60 deaths

$$\hat{IR}_{placebo} = \frac{60 \text{ deaths}}{842.5 \text{ PYs}} \approx 0.071 \text{ deaths/PYs}$$

PBC TRIAL

- Incidence Rate Ratio

$$\hat{IRR} = \frac{\hat{IR}_{DPCA}}{\hat{IR}_{placebo}} = \frac{0.075 \text{ deaths/PYs}}{0.071 \text{ deaths/PYs}} \approx 1.06$$

- **Interpretation:**
  - The risk of death in the DPCA group (in the study follow-up period) is 1.06 times the risk in the placebo group
  - Subjects in the DPCA groups had 6% higher risk of death in the follow-up period when compared to the subjects in the placebo group

HOW TO GET CONFIDENCE INTERVALS

- Since the IRR is a ratio, the first step is to compute the 95% for the natural log of the IRR

$$\hat{IRR} = 1.06 \implies \ln(\hat{IRR}) = 0.06$$

- 95% CI for $\ln(\hat{IRR})$:

$$\ln(\hat{IRR}) \pm 2 \times \mathrm{SE}(\ln(\hat{IRR}))$$

HOW TO GET CONFIDENCE INTERVALS

- Estimate standard error of $\ln(\hat{IRR})$

$$\mathrm{SE}(\ln(\hat{IRR})) = \sqrt{\frac{1}{E_1} + \frac{1}{E_2}}$$

where E_1 is equal to the events of group 1 and E_2 is equal to the events of group 2

- For PBC trial data
  - $\mathrm{E_{DPCA}} = 65$ deaths
  - $\mathrm{E_{placebo}} = 60$ deaths

$$\mathrm{SE}(\ln(\hat{IRR})) = \sqrt{\frac{1}{65} + \frac{1}{60}} \approx 0.18$$

HOW TO GET 95% CI: PBC TRIAL

$$\hat{IRR} = 1.06 \Longrightarrow \ln(\hat{IRR}) = 0.06$$

- 95% CI for $\ln(\hat{IRR})$

$$0.06 \pm 2 \times 0.18 \Longrightarrow (-0.30; 0.42)$$

- 95% CI for $\hat{IRR}$

$$(e^{-0.30}, e^{0.42}) \Longrightarrow (0.74; 1.52)$$

- In this study, the 158 subjects with primarily biliary cirrhosis (PBC) randomized to receive the drug DPCA had a slightly elevated risk of death when compared to the 154 such subjects randomized to the placebo group (IRR = 1.06).
- After accounting for sampling variability, however, there is no evidence of an association between DPCA and death in the population of patients with PBC. (95% CI for IRR: 0.74 to 1.52)

INTERPRETATION

HOW TO GET 95% CI: ART AND PARTNER TO PARTNER HIV TRANSMISSION

Cohen M, et al. Prevention of HIV-1 Infection with Early Antiretroviral Therapy. New England Journal of Medicine. (2011) 365(6): 493-505

RESULTS

As of February 21, 2011, a total of 39 HIV-1 transmissions were observed (incidence rate, 1.2 per 100 person-years; 95% confidence interval [CI], 0.9 to 1.7); of these, 28 were virologically linked to the infected partner (incidence rate, 0.9 per 100 person-years, 95% CI, 0.6 to 1.3). Of the 28 linked transmissions, only 1 occurred in the early-therapy group (hazard ratio, 0.04; 95% CI, 0.01 to 0.27; P<0.001). Subjects receiving early therapy had fewer treatment end points (hazard ratio, 0.59; 95% CI, 0.40 to 0.88; P=0.01).

HOW TO GET 95% CI: ART AND PARTNER TO PARTNER HIV TRANSMISSION

- ART and Partner to Partner HIV Transmission
  - Of the 28 linked transmissions, only 1 occurred in the early therapy group (hazard ratio 0.04)

$$\hat{IRR} = \frac{\hat{IR}_{early}}{\hat{IR}_{delayed}} = \frac{\frac{1 \text{ linkedtransmission}}{\text{total PYs, early therapy}}}{\frac{27 \text{ linkedtransmissions}}{\text{total PYs, delayed therapy}}} = 0.04$$

HOW TO GET 95% CI: ART AND PARTNER TO PARTNER HIV TRANSMISSION

- HIV discordant (at baseline) couples in which the HIV+ partner was given early ART therapy had 0.04 times the risk of within couple transmission as compared to couples in which the HIV+ partner was given standard therapy
- HIV discordant (at baseline) couples in which the HIV+ partner was given early ART therapy had 96% lower risk of within couple transmission as compared to couples in which the HIV+ partner was given standard therapy

HOW TO GET 95% CI: ART AND PARTNER TO PARTNER HIV TRANSMISSION

$$\hat{IRR} = 0.04 \Longrightarrow \ln(\hat{IRR}) = -3.22$$

$$\mathrm{SE}(\ln(\hat{IRR})) = \sqrt{\frac{1}{1} + \frac{1}{27}} \approx 1.02$$

- 95% CI for $\ln(\hat{IRR})$

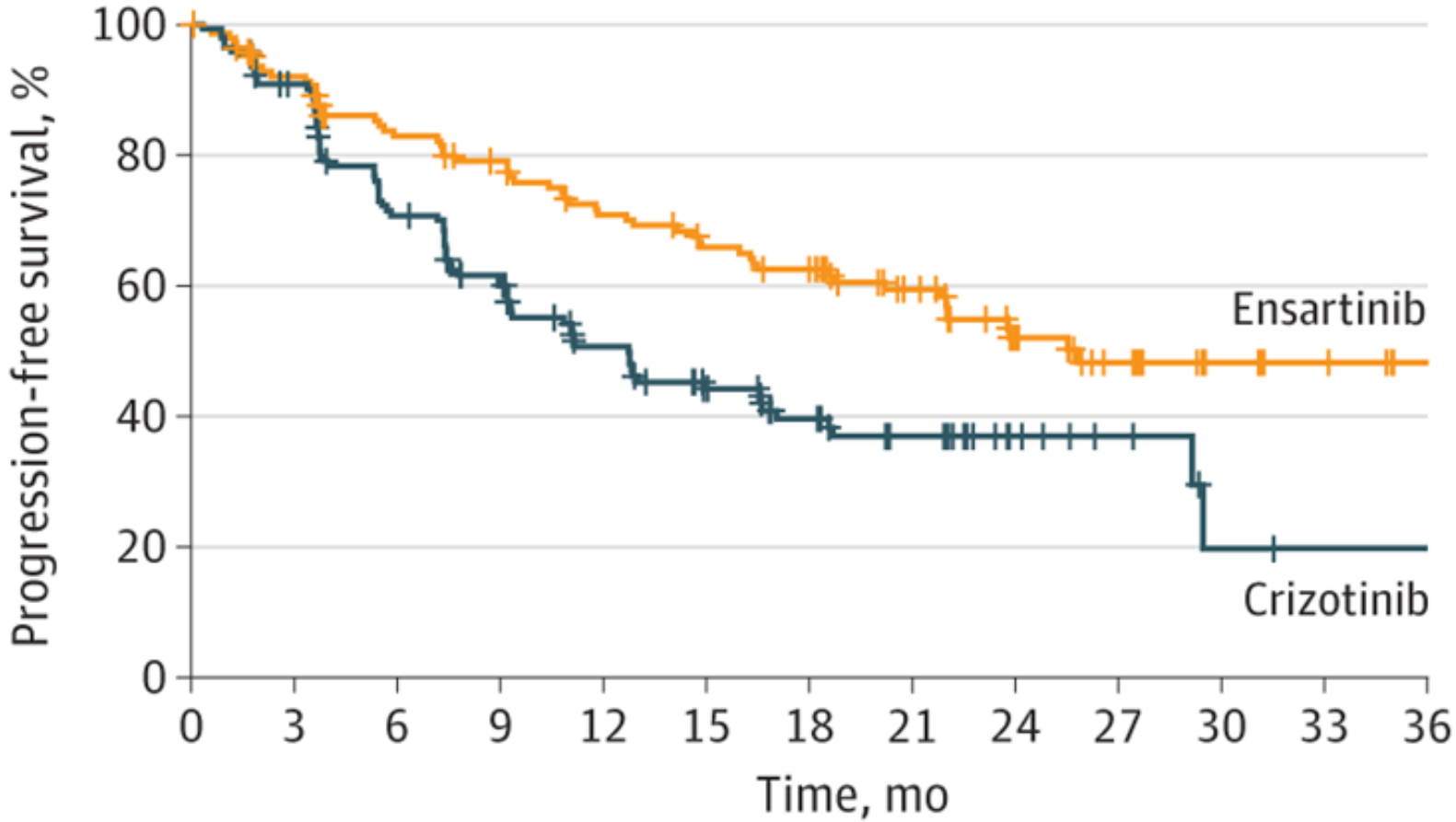
$$-3.22 \pm 2 \times 1.02 \Longrightarrow (-5.26; -1.18)$$

- 95% CI for $\hat{IRR}$

$$(e^{-5.26}, e^{-1.18}) \Longrightarrow (0.01; 0.31)$$

INTERPRETATION

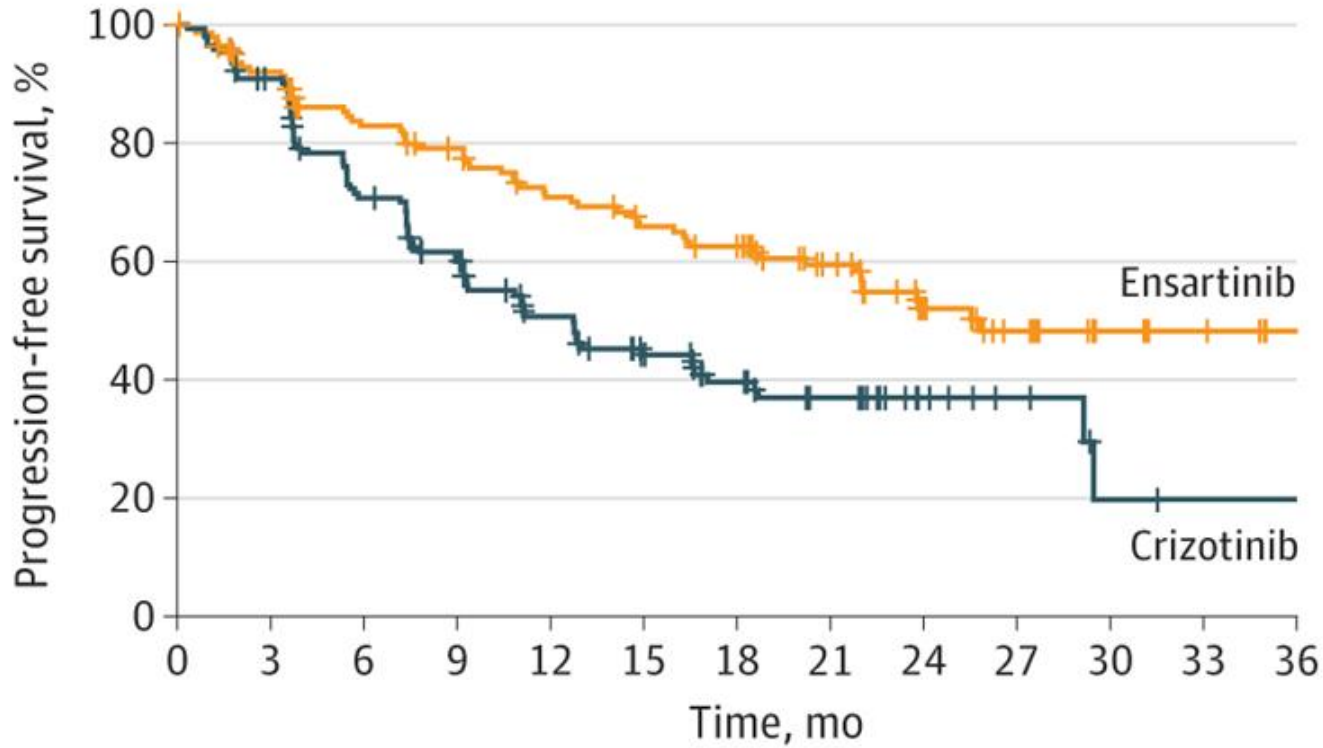
- In a study of 1,763 HIV sero-discordant couples, the risk of partner-to-partner transmission among the 866 randomized to receive early ART therapy was 96% lower than among the 877 randomized to receive standard ART therapy.
- After accounting for sampling variability, the early ART therapy could reduce risk of partner transmission from 69% to 99% at the population level



No. at risk

Ensartinib	143	125	106	98	86	78	72	54	30	21	10	5	1
Crizotinib	147	124	94	75	56	43	32	23	10	6	2	1	1

	Ensartinib (n = 143)	Crizotinib (n = 147)
mPFS (95% CI), mo	25.8 (21.8-NR)	12.7 (9.2-16.6)



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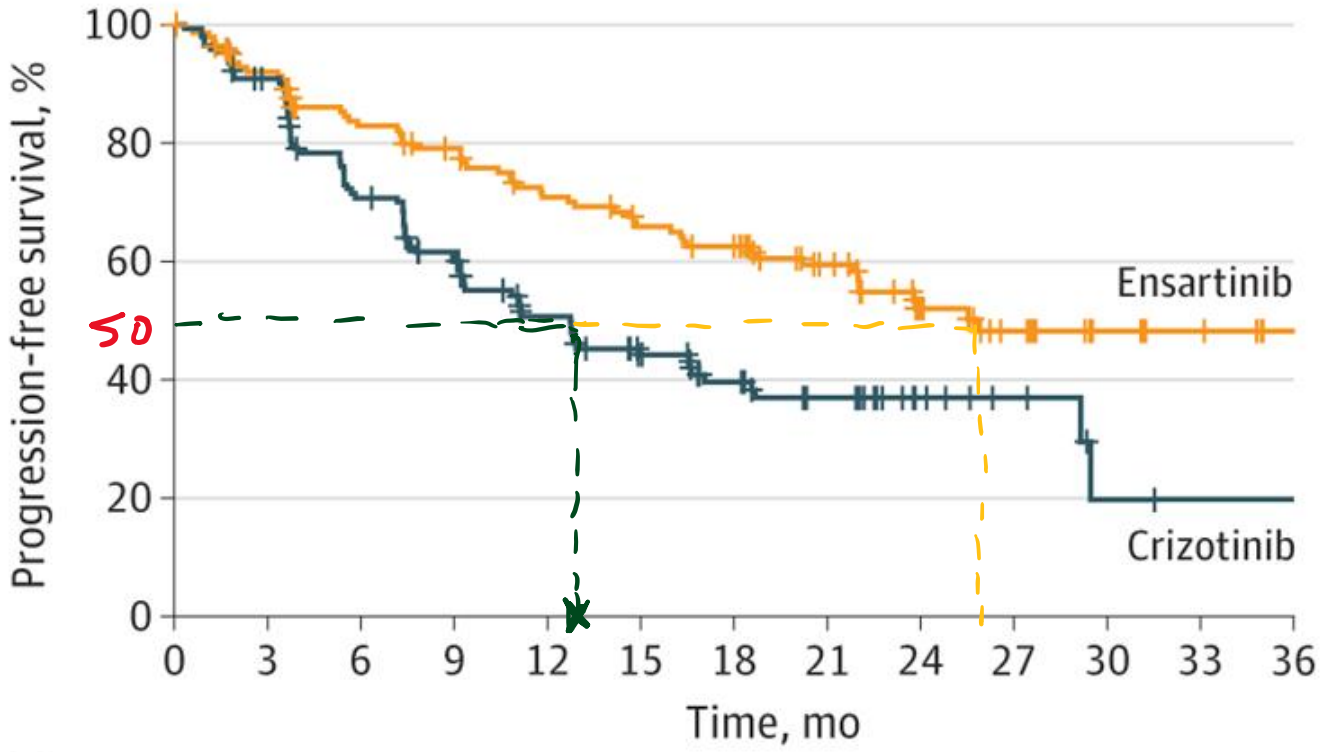

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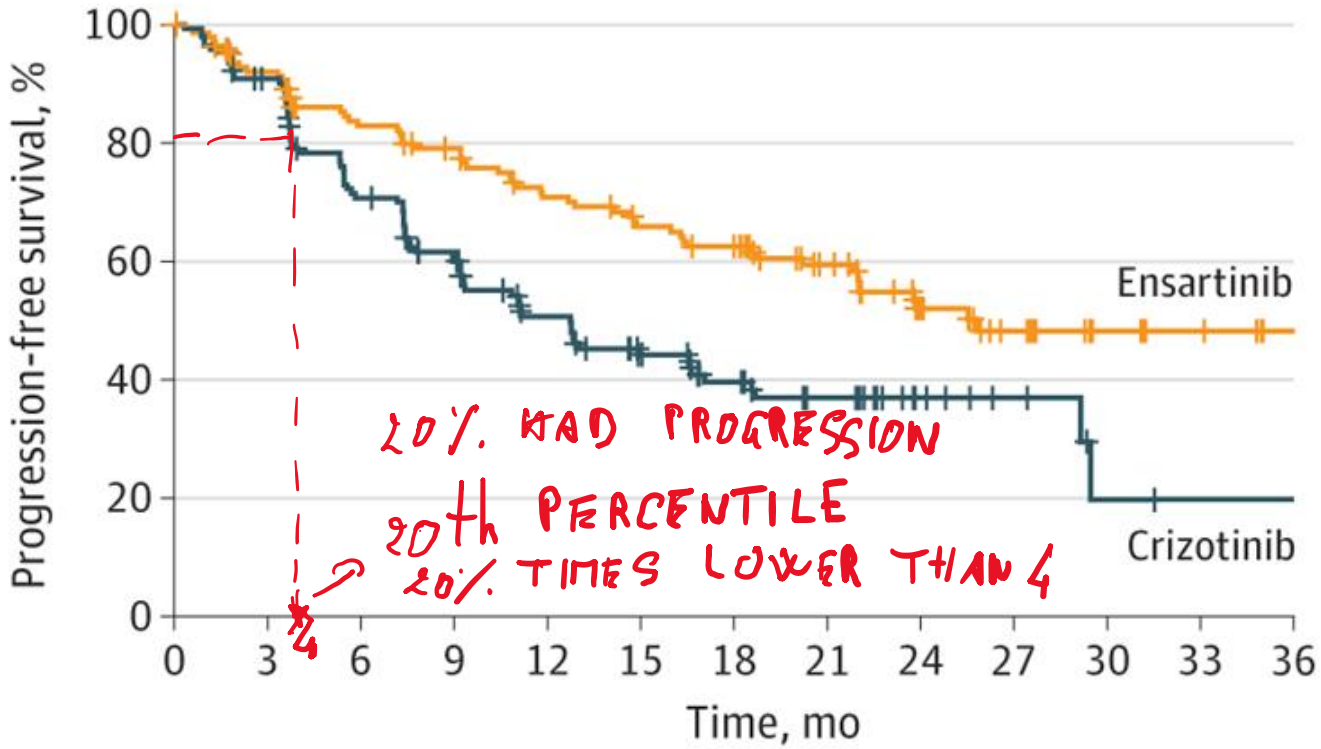

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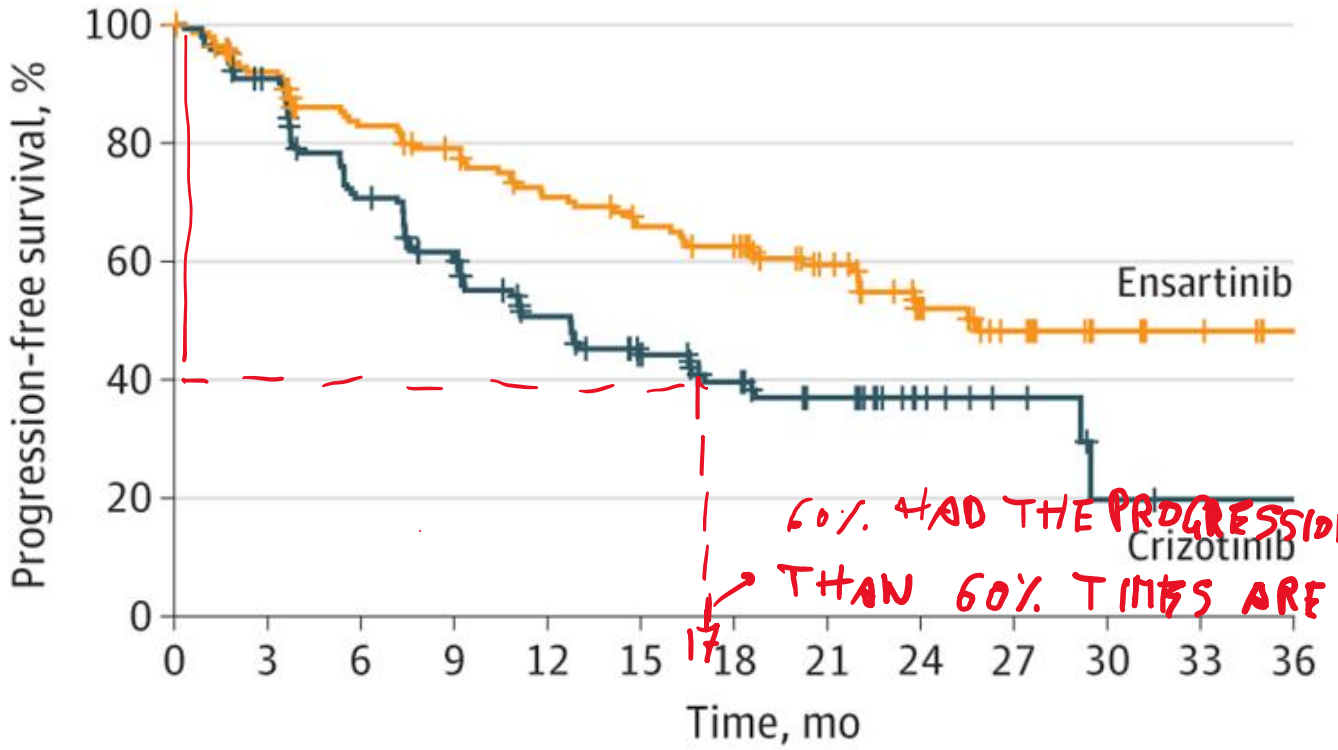

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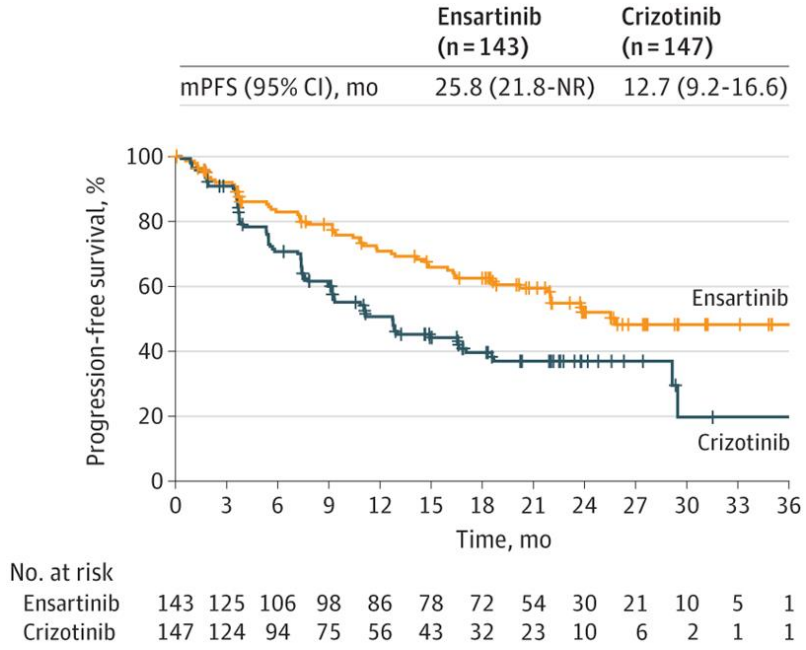
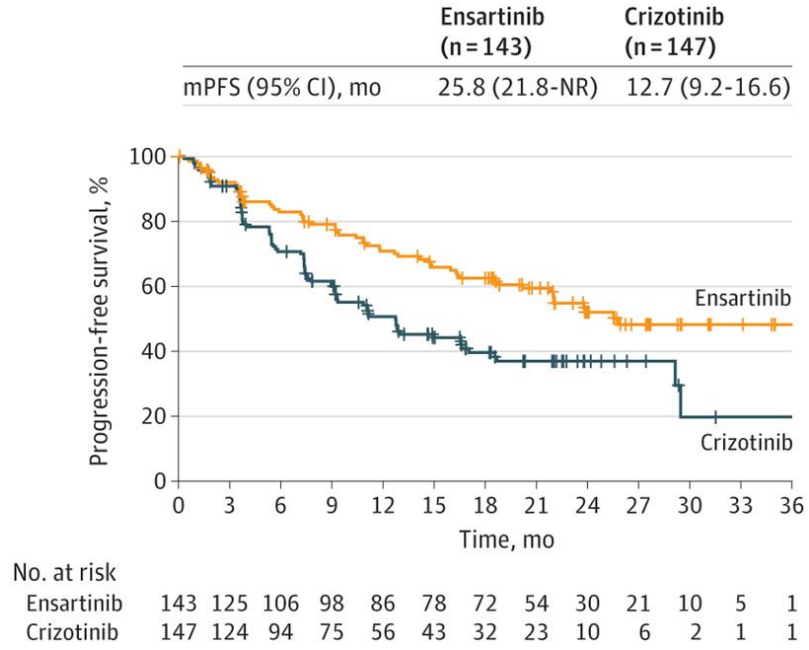
KAPLAN-MEIER CURVES



- Suppose we have data on 12 patients (hypothetical data):
  - 2 3+ 6 6 7+ 10 15+ 15 16 27 30 30+
  - times are in months, censoring is indicated by a +

- The curve will start at 1 at time 0, and will not change until the first event time
- The curve will only change at event times
- At each event time, the total number of persons at risk for progression are those who haven't neither had the progression nor the censoring

KAPLAN-MEIER CURVES



- At each time t, the PFS probability is estimated by:
  - $S(t) = \frac{N(t)-E(t)}{N(t)} \times S(t-1)$
  - PFS probability is given by the product of
  - probability to survived until time t-1: $S(t-1)$
    - The probability to survived time t: $\frac{N(t)-E(t)}{N(t)}$

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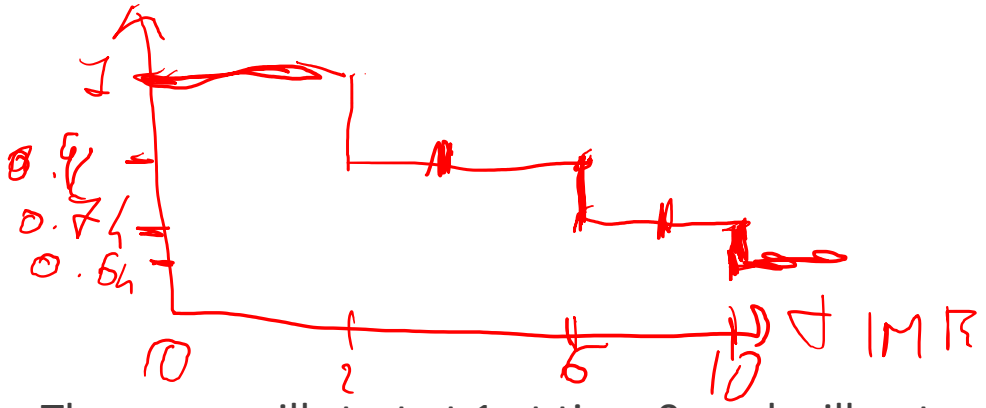
  - The first step is at month 2 (first event)
  - $S(2) = \frac{12-1}{12} = \frac{11}{12} \approx 0.92$
- What month is the next step?

KAPLAN-MEIER CURVES



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  - $S(6) = \frac{10-2}{10} \times 0.92 = 0.8 \times 0.92 \approx 0.74$

KAPLAN-MEIER CURVES

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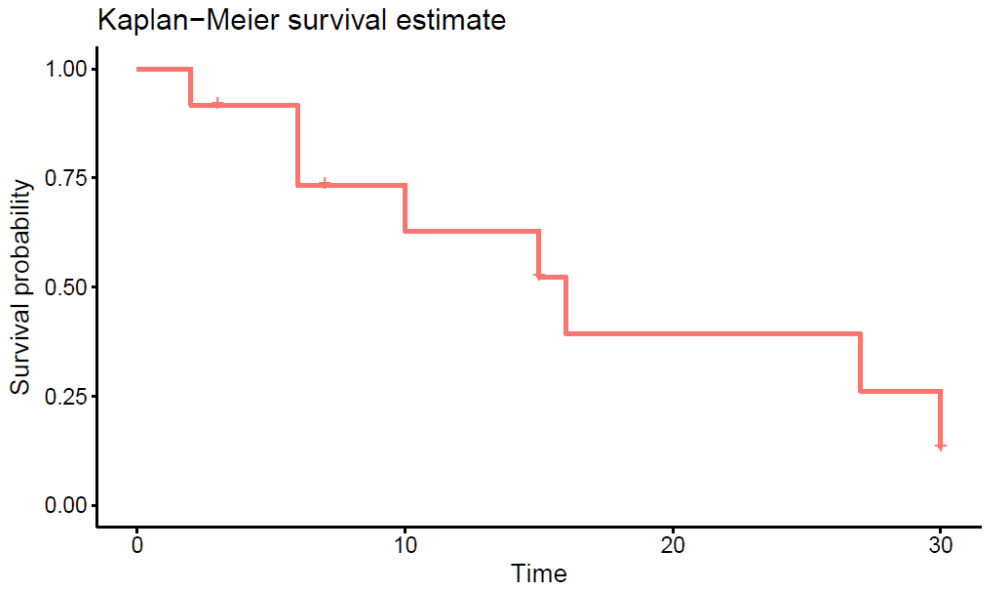
- What month is the next step?
  - $S(6) = \frac{10-2}{10} \times 0.92 = 0.8 \times 0.92 \approx 0.73$
- What month is the next step?
  - $S(10) = \frac{7-1}{7} \times 0.73 = 0.86 \times 0.73 \approx 0.63$

KAPLAN-MEIER CURVES

- Suppose we have data on 12 patients (hypothetical data):
  - 2 3+ 6 6 7+ **10 15+ 15 16 27 30 30+**
  - times are in months, censoring is indicated by a +

Times	No at risk	No of events	
2	12	1	0.92
6	10	2	0.73
10	7	1	0.63
15	6	1	0.52
16	4	1	0.39
27	3	1	0.26
30	2	1	0.13

KAPLAN-MEIER CURVES



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27	3	1	0.26
30	2	1	0.13

COMPUTE KM ESTIMATE OF SURVIVAL FOR THE FOLLOWING DATA

Patient	Time-to-event (months)	Survival (1=died; 0=censored)
1	10	0
2	2	1
3	4	0
4	8	1
5	12	0
6	14	0
7	10	1
8	1	0
9	3	0

COMPUTE KM ESTIMATE OF SURVIVAL FOR THE FOLLOWING DATA

Patient	Time-to-event (months)	Survival (1=died; 0=censored)
1	10	0
2	2	1
3	4	0
4	8	1
5	12	0
6	14	0
7	10	1
8	1	0
9	3	0

T(months)	N	Event	Censored	S(t)
0	9	0	0	
1	9	0	1	
2	8	1	0	
3	7	0	1	
4	6	0	1	
8	5	1	0	
10	4	1	1	
12	2	0	1	
14	1	0	1	

PRODUCT-LIMIT ESTIMATE

T(months)	N	Event	Censored	S(t)
0	9	0	0	1
1	9	0	1	1
2	8	1	0	
3	7	0	1	
4	6	0	1	
8	5	1	0	
10	4	1	1	
12	2	0	1	
14	1	0	1	

PRODUCT-LIMIT ESTIMATE

T(months)	N	Event	Censored	S(t)
0	9	0	0	1
1	9	0	1	1
2	8	1	0	(7/8)*1=0.875
3	7	0	1	
4	6	0	1	
8	5	1	0	
10	4	1	1	
12	2	0	1	
14	1	0	1	

PRODUCT-LIMIT ESTIMATE

T(months)	N	Event	Censored	S(t)
0	9	0	0	1
1	9	0	1	1
2	8	1	0	(7/8)*1=0.875
3	7	0	1	0.875
4	6	0	1	0.875
8	5	1	0	
10	4	1	1	
12	2	0	1	
14	1	0	1	

PRODUCT-LIMIT ESTIMATE

T(months)	N	Event	Censored	S(t)
0	9	0	0	1
1	9	0	1	1
2	8	1	0	(7/8)*1=0.875
3	7	0	1	0.875
4	6	0	1	0.875
8	5	1	0	(4/5)*0.875=0.70
10	4	1	1	
12	2	0	1	
14	1	0	1	

PRODUCT-LIMIT ESTIMATE

T(months)	N	Event	Censored	S(t)
0	9	0	0	1
1	9	0	1	1
2	8	1	0	(7/8)*1=0.875
3	7	0	1	0.875
4	6	0	1	0.875
8	5	1	0	(4/5)*0.875=0.70
10	4	1	1	(3/4)*0.70=0.525
12	2	0	1	
14	1	0	1	

PRODUCT-LIMIT ESTIMATE

T(months)	N	Event	Censored	S(t)
0	9	0	0	1
1	9	0	1	1
2	8	1	0	(7/8)*1=0.875
3	7	0	1	0.875
4	6	0	1	0.875
8	5	1	0	(4/5)*0.875=0.70
10	4	1	1	(3/4)*0.70=0.525
12	2	0	1	0.525
14	1	0	1	

PRODUCT-LIMIT ESTIMATE

T(months)	N	Event	Censored	S(t)
0	9	0	0	1
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3	7	0	1	0.875
4	6	0	1	0.875
8	5	1	0	(4/5)*0.875=0.70
10	4	1	1	(3/4)*0.70=0.525
12	2	0	1	0.525
14	1	0	1	0.525

- Is there any statistically significant difference between the trial arms?

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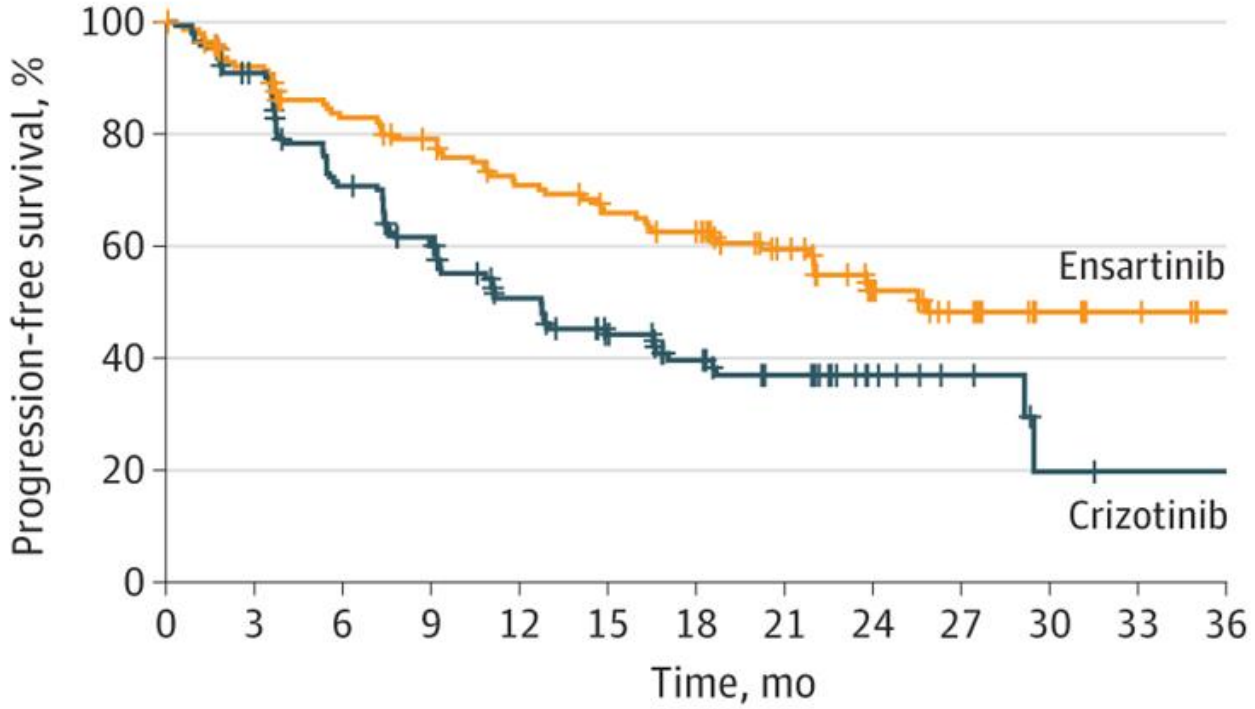
mPFS (95% CI), mo	25.8 (21.8-NR)	12.7 (9.2-16.6)



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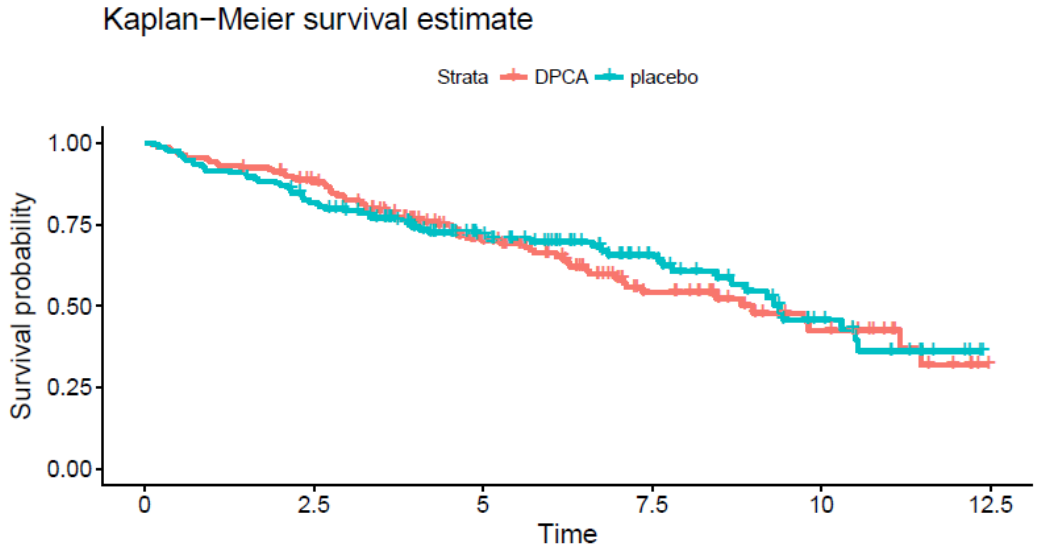
- In this study, the 158 subjects with primarily biliary cirrhosis (PBC) randomized to receive the drug DPCA had a slightly elevated risk of death when compared to the 154 such subjects randomized to the placebo group (IRR = 1.06).
- After accounting for sampling variability, however, there is no evidence of an association between DPCA and death in the population of patients with PBC. (95% CI for IRR: 0.74 to 1.52)



INTERPRETATION

- Is DPCA better than pacebo? Is there a stastically significant difference?

OBJECTIVE

- Describe the approach to getting a p-value for comparing incidence rates between two populations:
- The log-rank test compares the Kaplan-Meier curves for the two groups (and can be extended to compare more than two populations)

Describe the approach to getting a p-value for comparing incidence rates between two populations:

The log-rank test compares the Kaplan-Meier curves for the two groups (and can be extended to compare more than two populations)

PBC TRIAL

- 95% CI for $\hat{IRR}$: $(0.74, 1.52)$
  - 95% CI contains the null value 1
    - What does this mean about the p-value for comparing the incidence rates?
- There are two approaches to getting a p-value, which yield very similar results:
  - A two sample z-test
  - The log rank test

LOG RANK TEST

- Log Rank Test: this test compares the distance between the Kaplan Meier Curves in two samples to get a p-value

$$H_0 : IR_{DPCA} = IR_{placebo} \qquad H_0 : S(t)_{DPCA} = S(t)_{placebo}$$
$$H_A : IR_{DPCA} \neq IR_{placebo} \qquad H_0 : S(t)_{DPCA} \neq S(t)_{placebo}$$

- Idea: the log rank test compares the number of events observed at each event time in the two groups, to the number of expected events in each group
  - The discrepancies between the observed and expected event counts are aggregated across all event times and standardized by the uncertainty from sampling variability (standard error)

LOG RANK TEST TECHNICAL

- To compare survival curves, a log-rank test creates 2×2 tables at each event time and combines across the tables
  - Similar to MH-test
- Provides a χ^2 statistic with 1 degree of freedom (for a two sample comparison) and a p-value
- Same procedure for hypothesis testing

LOG RANK TEST PBC TRIAL

- The total, aggregated discrepancy, or distance between what is observed in the samples is compared to the distribution of such discrepancies across samples of the same size, when the null is true
  - This gets translated into a p-value
- For the DPCA/placebo comparison, the p-value from the log rank test is 0.75 (almost identical to the p-value from the two sample z approach)

- Is there any statistically significant difference between the trial arms?
- We want to make hypothesis about PFS (true values) in the two treated populations
- $H_0: S_T(t) = S_C(T)$

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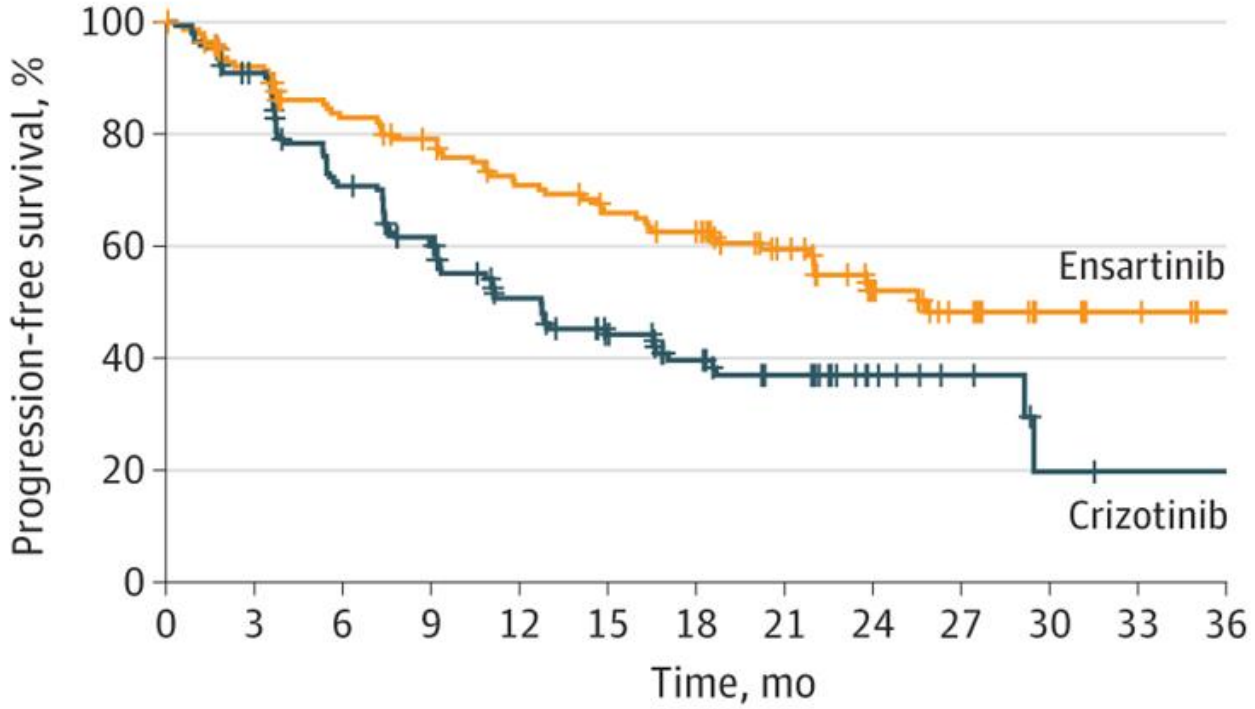

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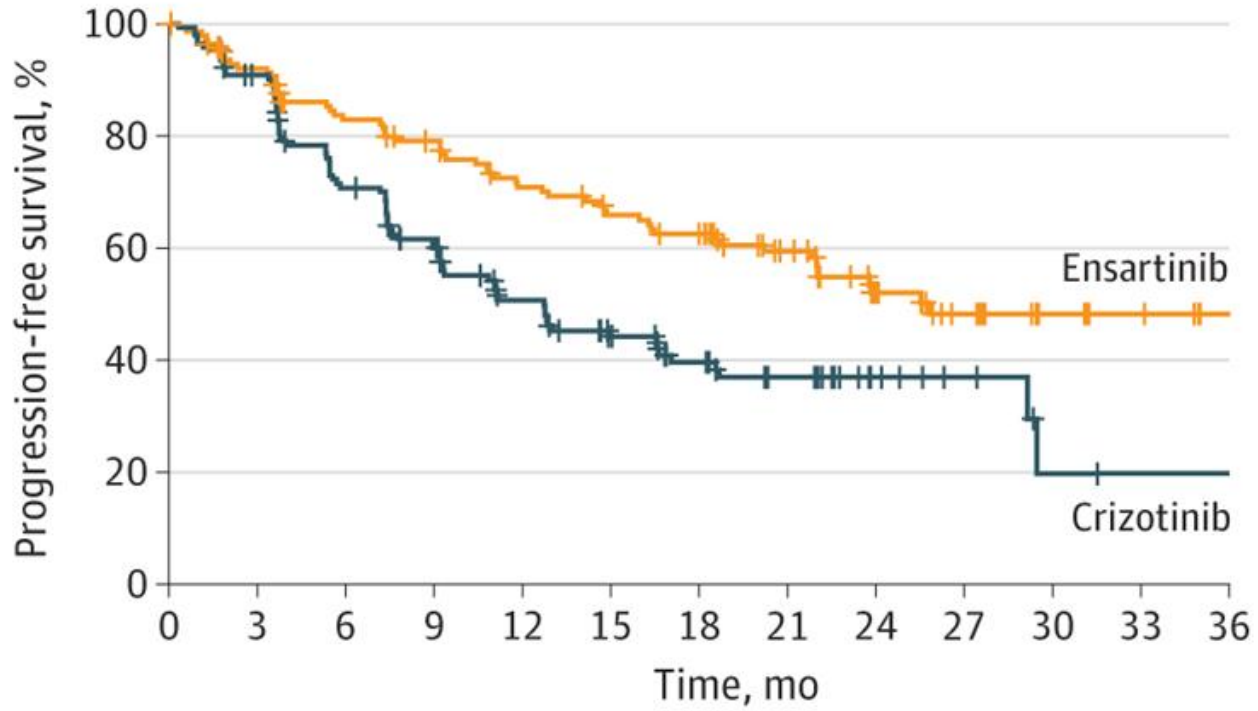

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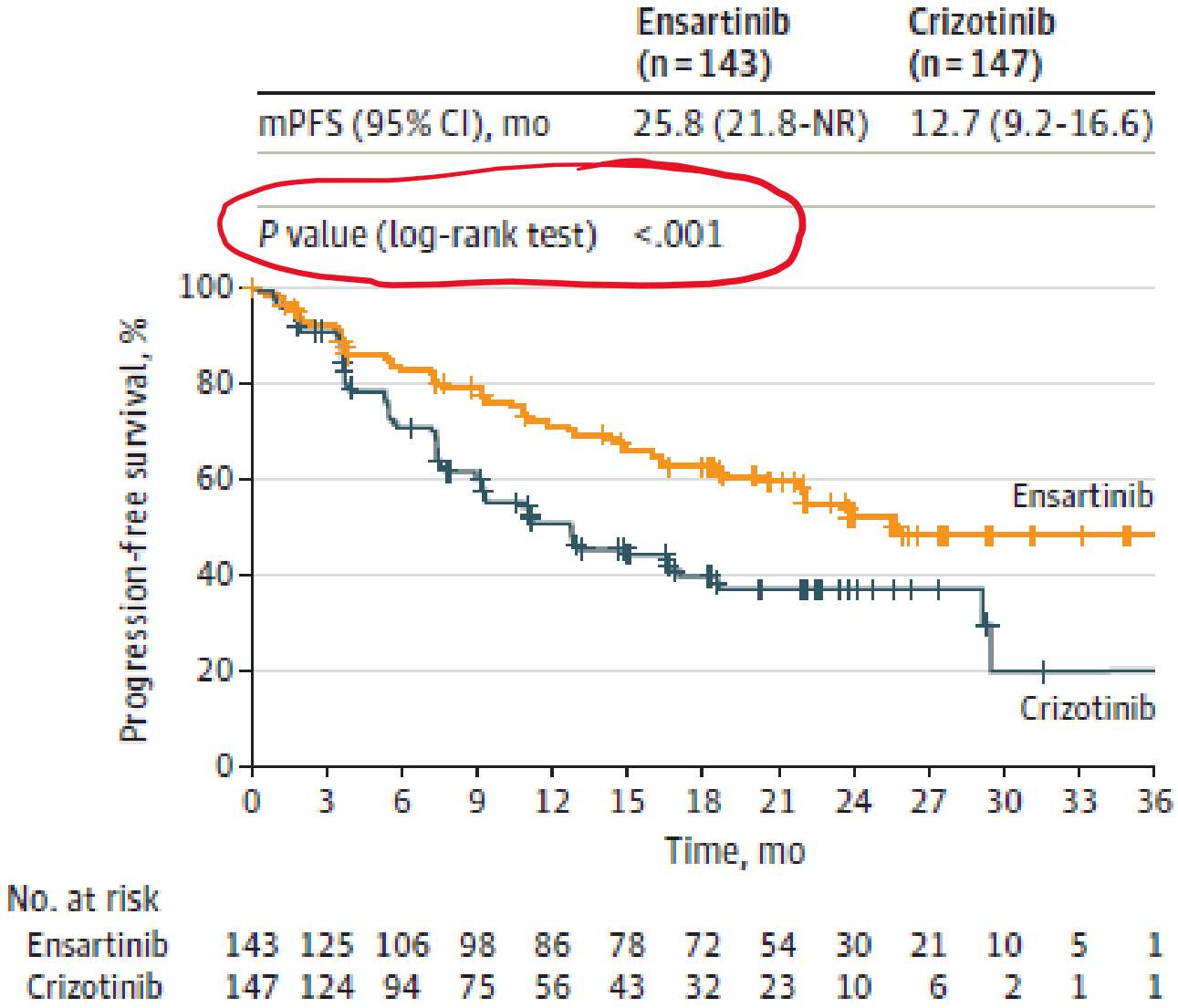

- The mPFS in the ensartinib group was statistically superior to that in the crizotinib group.
- 25.8 months [range, 0.03-44.0 months] vs 12.7 months [range, 0.03-38.6 months]
- log-rank *P* < .001

	Ensartinib (n = 143)	Crizotinib (n = 147)
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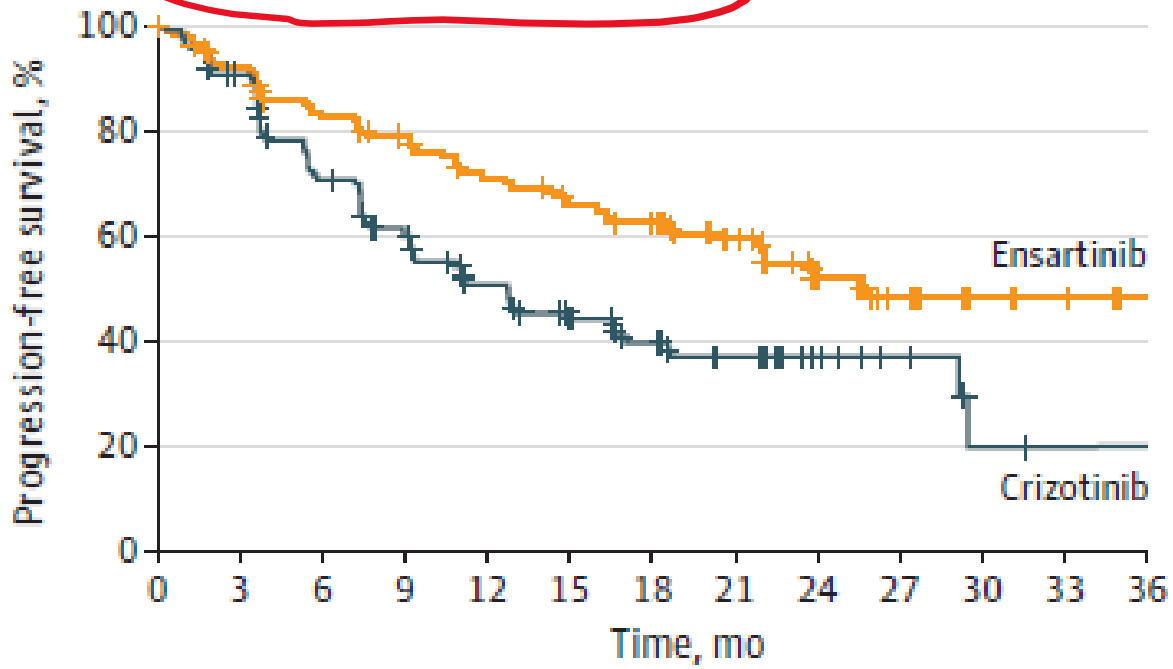
P value (log-rank test)	<.001	



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OTHER STATISTICAL TESTS

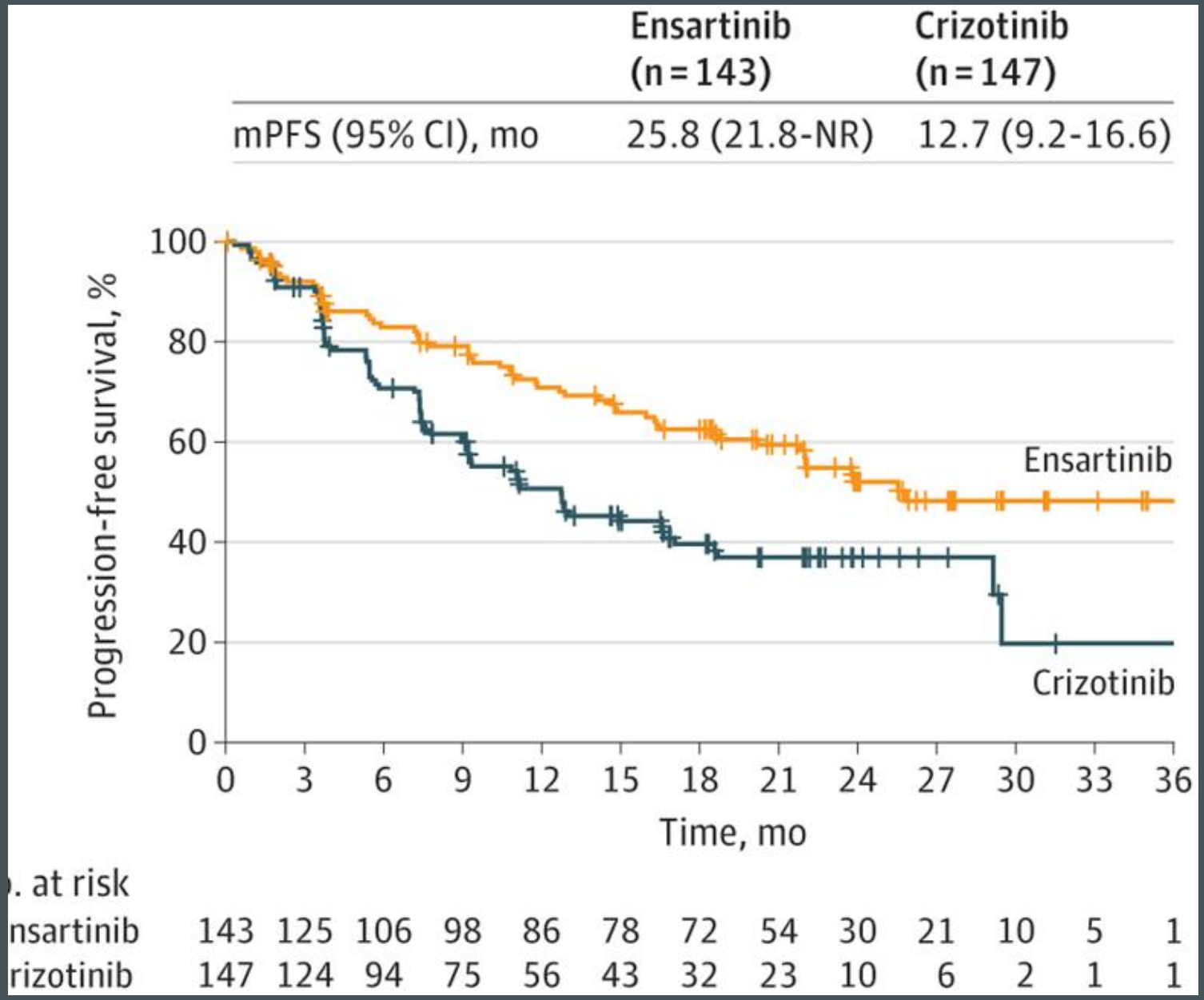
- Other tests are possible
  - Gehan's generalized Wilcoxon test
  - Tarone-Ware test
  - Peto-Peto-Prentice test
- Generally they give similar results, but emphasize different parts of survival curve

LIMITATIONS OF KAPLAN-MEIER CURVES

- Mainly descriptive
- Doesn't control for covariates
- Requires categorical predictors
- Cannot deal with time-dependent variables

COX REGRESSION MODEL

ESTIMATE THE RELATIONSHIP BETWEEN A RISK FACTOR AND THE RISK OVER TIME TO THE EVENT



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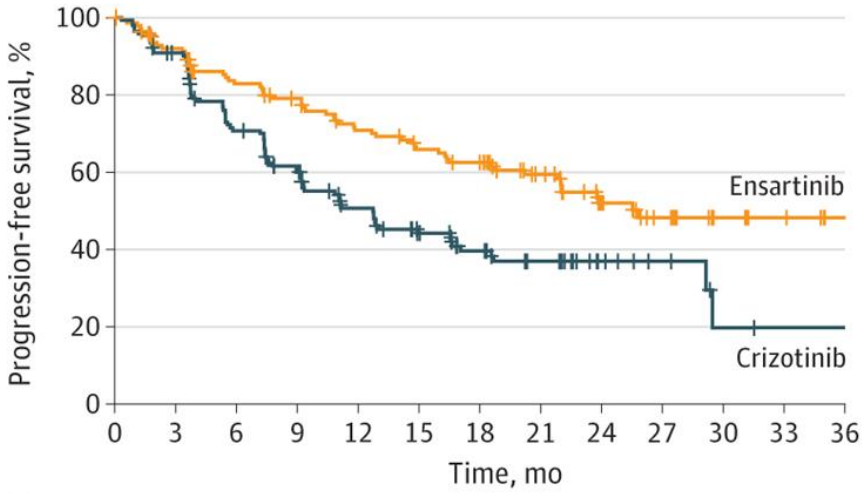

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- Risk/protective factor X_1
  - Experimental treatment vs Standard treatment
- Aim: to quantify the risk increase/reduction associated to X_1

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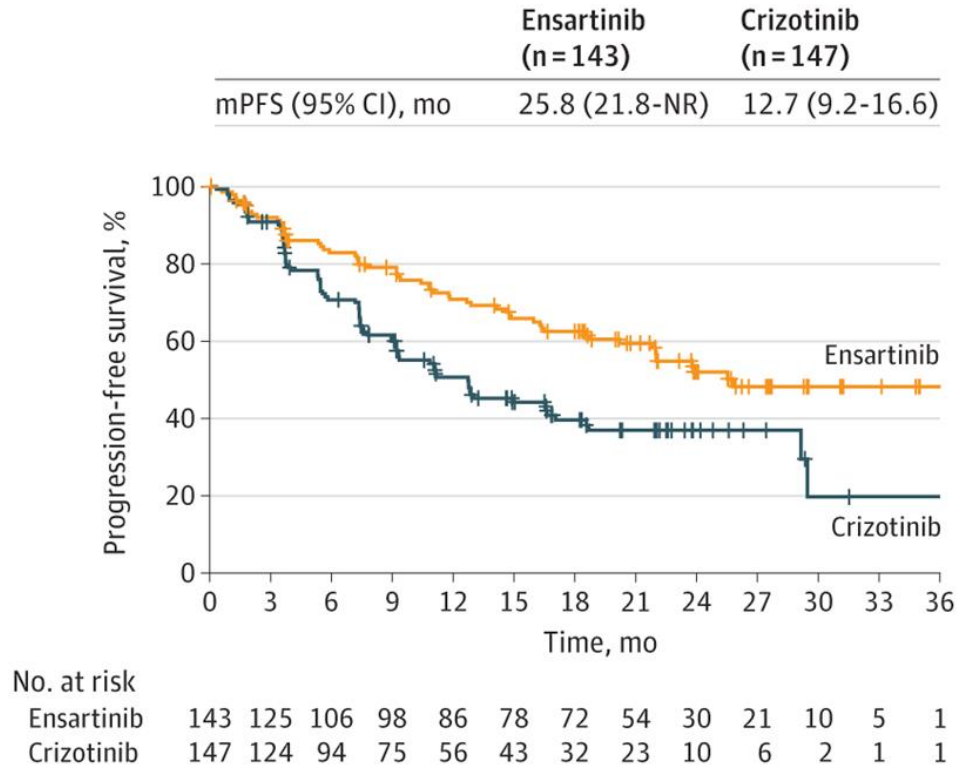

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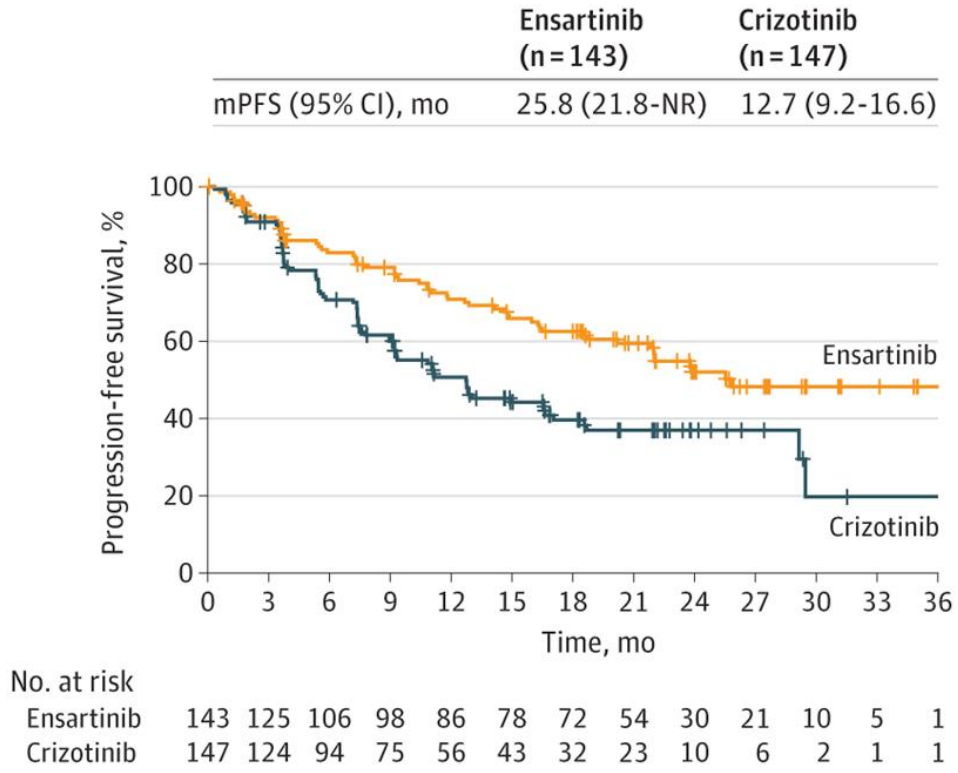
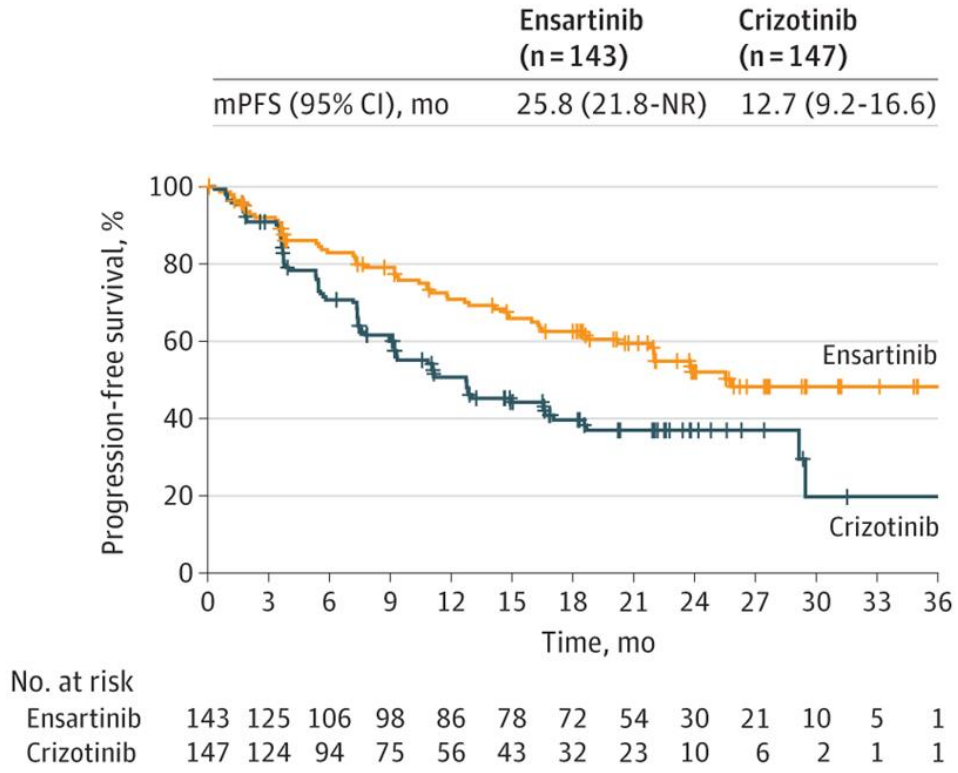
- $h(t)$

COX REGRESSION MODEL



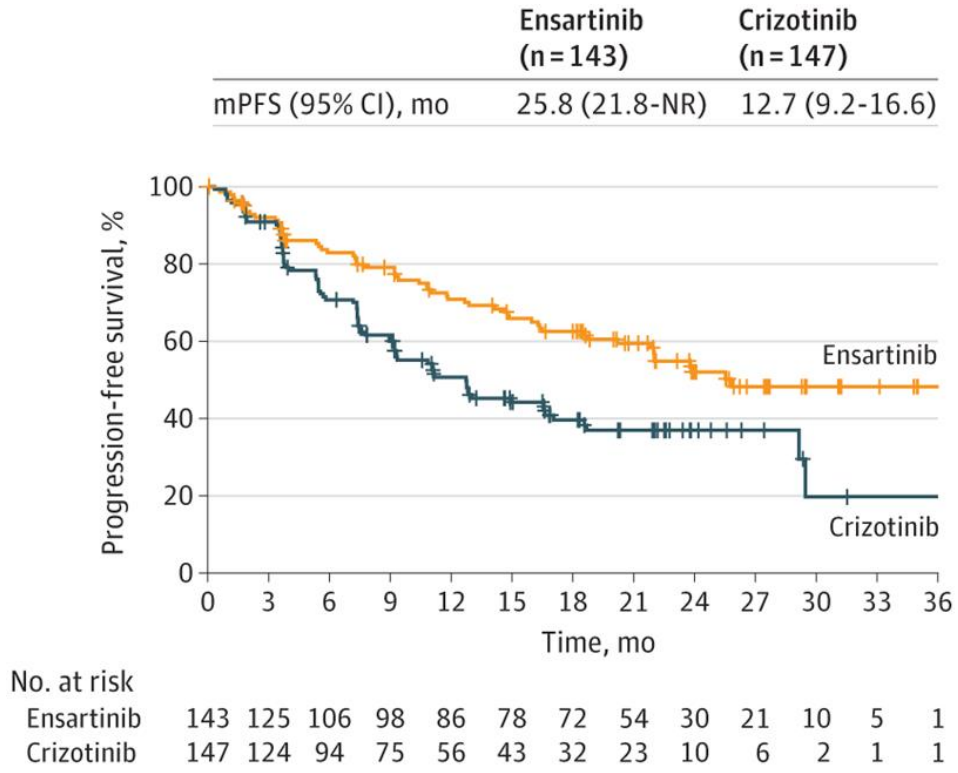
- Hazard: risk at time t
  - $h(t)$
- Risk/protective factor X_1
  - Experimental treatment vs Standard treatment
- Aim: to quantify the risk increase/reduction associated to X_1
- $h(t)$ X_1

COX REGRESSION MODEL



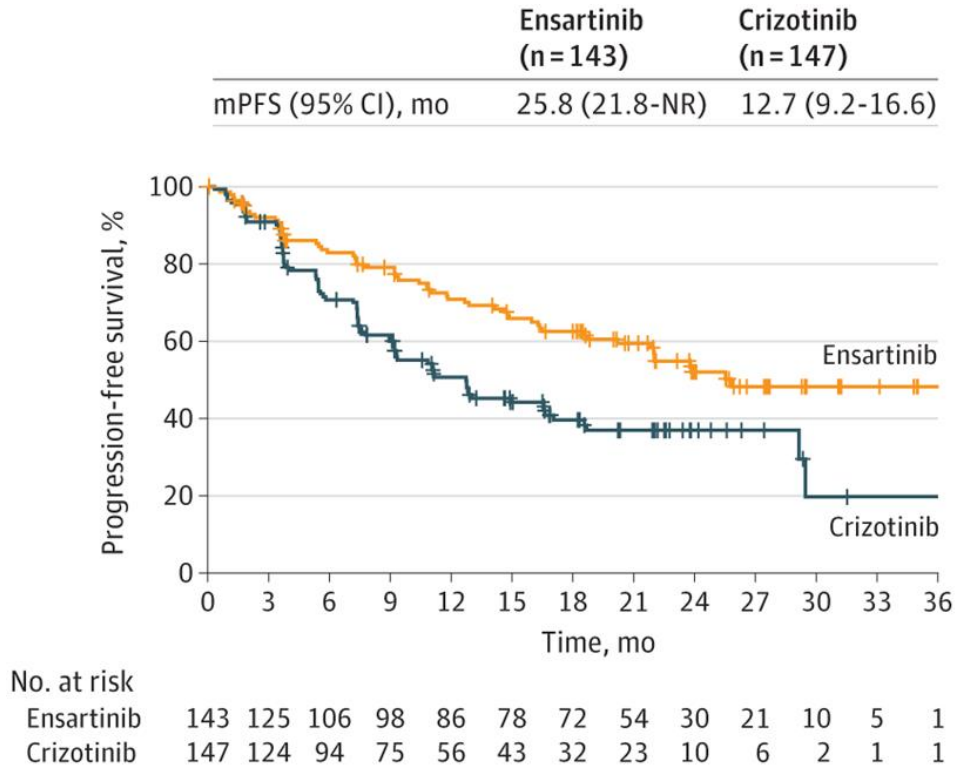
- Hazard: risk at time t
  - $h(t)$
- Risk/protective factor X_1
  - Experimental treatment vs Standard treatment
- Aim: to quantify the risk increase/reduction associated to X_1
- $h(t) = \quad \beta X_1$

COX REGRESSION MODEL



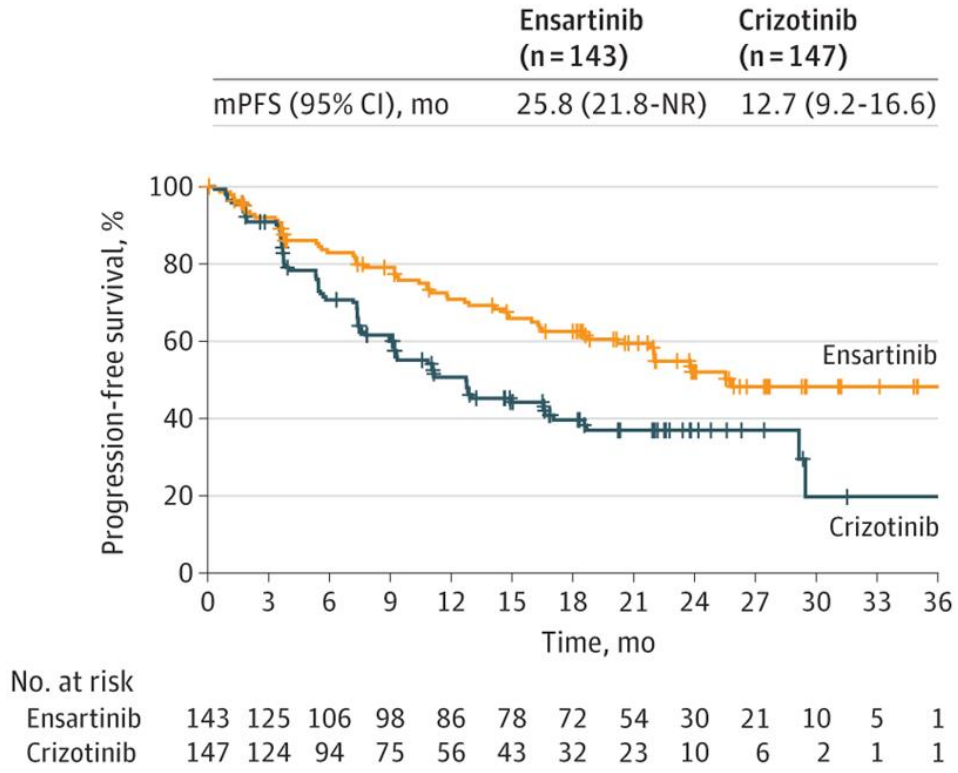
- Hazard: risk at time t
  - $h(t)$
- Risk/protective factor X_1
  - Experimental treatment vs Standard treatment
- Aim: to quantify the risk increase/reduction associated to X_1
- $h(t) = \lambda(t) + \beta X_1$

COX REGRESSION MODEL



- Hazard: risk at time t
  - $h(t)$
- Risk/protective factor X_1
  - Experimental treatment vs Standard treatment
- Aim: to quantify the risk increase/reduction associated to X_1
- $\log(h(t)) = \lambda(t) + \beta X_1$

COX REGRESSION MODEL

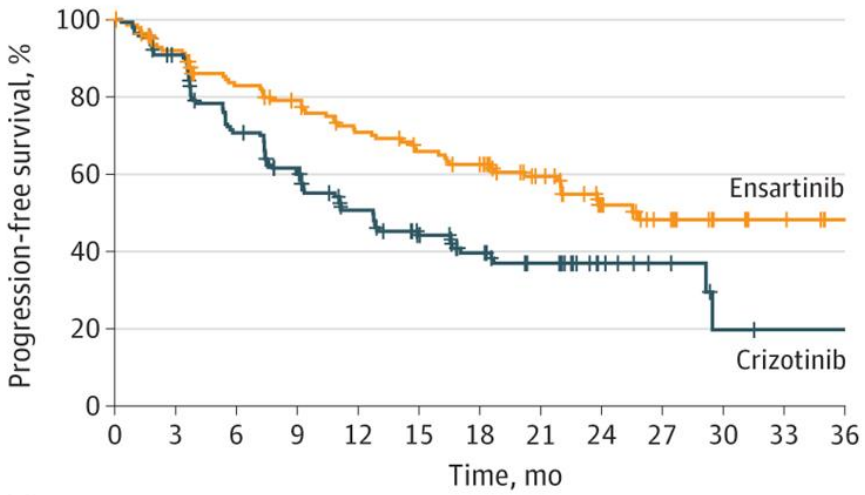


- Hazard: risk at time t
  - $h(t)$
- Risk/protective factor X_1
  - Experimental treatment vs Standard treatment
- Aim: to quantify the risk increase/reduction associated to X_1
- $\log(h(t)) = \lambda(t) + \beta X_1$

RISK AT BASELINE

COX REGRESSION MODEL

	Ensartinib (n = 143)	Crizotinib (n = 147)
mPFS (95% CI), mo	25.8 (21.8-NR)	12.7 (9.2-16.6)



No. at risk

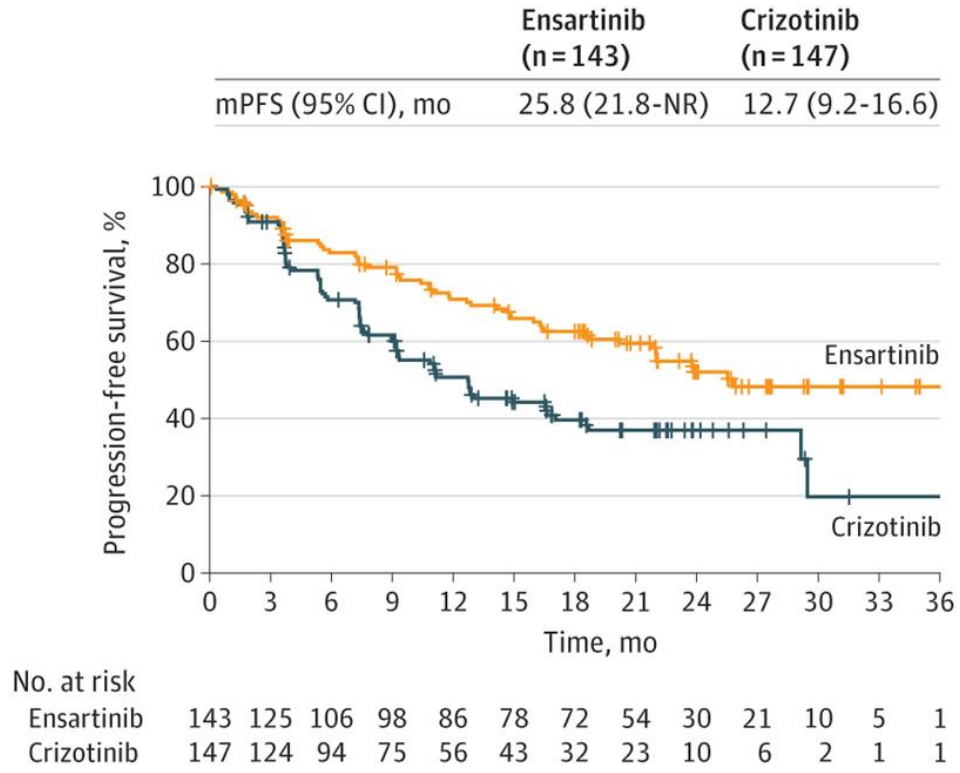
Ensartinib	143	125	106	98	86	78	72	54	30	21	10	5	1
Crizotinib	147	124	94	75	56	43	32	23	10	6	2	1	1

- Hazard: risk at time t
  - $h(t)$
- Risk/protective factor X_1
  - Experimental treatment vs Standard treatment
- Aim: to quantify the risk increase/reduction associated to X_1
- $\log(h(t)) = \lambda(t) + \beta X_1$

$X_1 := \begin{cases} 1 & \text{ENSARTINIB} \\ 0 & \text{CRIZOTINIB} \end{cases}$

$\lambda(t)$ → RISK AT BASELINE

COX REGRESSION MODEL

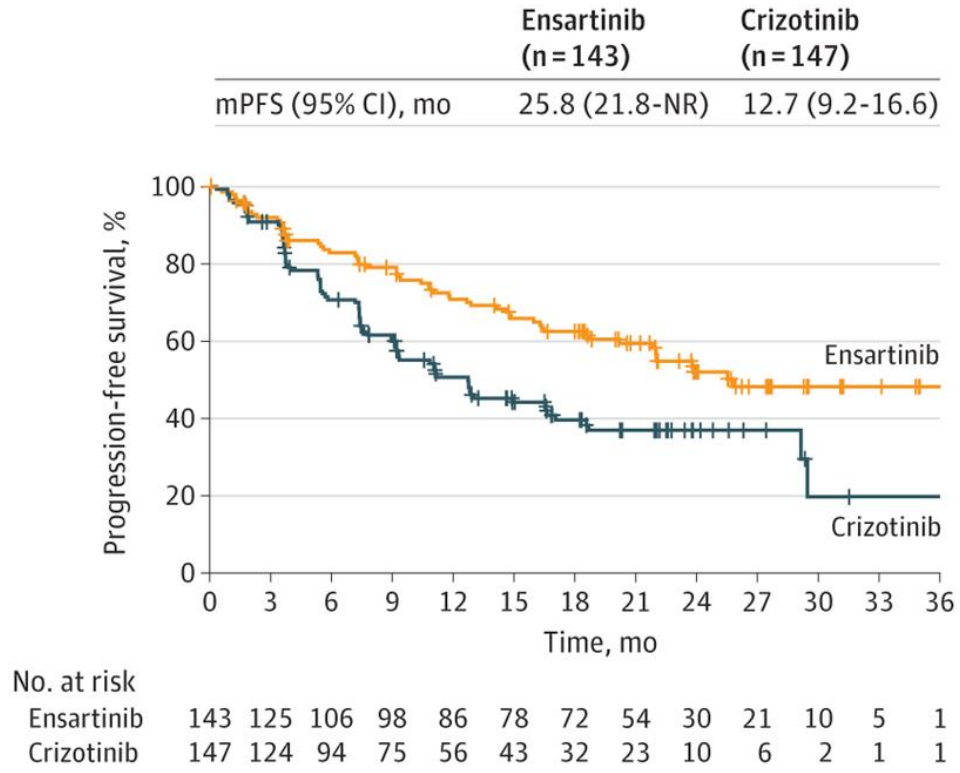


- Hazard: risk at time t
  - $h(t)$
- Risk/protective factor X_1
  - Experimental treatment vs Standard treatment
- Aim: to quantify the risk increase/reduction associated to X_1
- $\log(h(t)) = \lambda(t) + \beta X_1$

$X_1 := \begin{cases} 1 & \text{ENSARTINIB} \\ 0 & \text{CRIZOTINIB} \end{cases}$

$\lambda(t)$: RISK AT BASELINE (RISK OF PROGRESSION UNDER STANDARD TREATMENT)

COX REGRESSION MODEL



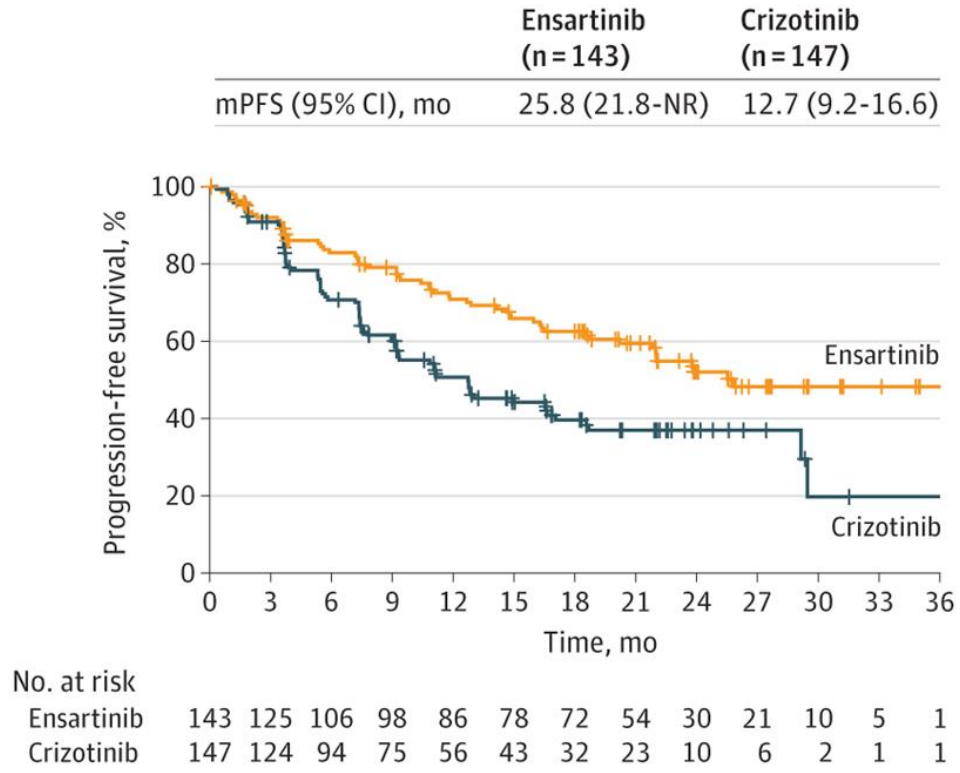
- Hazard: risk at time t
  - $h(t)$
- Risk/protective factor X_1
  - Experimental treatment vs Standard treatment
- Aim: to quantify the risk increase/reduction associated to X_1
- $\log(h(t)) = \lambda(t) + \beta X_1$

$X_1 := \begin{cases} 1 & \text{ENSARTINIB} \\ 0 & \text{CRIZOTINIB} \end{cases}$

$\lambda(t)$: RISK AT BASELINE UNDER STANDARD TREATMENT

β: QUANTIFIES RISK REDUCTION/INCREASE IN EXP. TREATMENT GROUP

COX REGRESSION MODEL



- Hazard: risk at time t
  - $h(t)$
- Risk/protective factor X_1
  - Experimental treatment vs Standard treatment
- Aim: to quantify the risk increase/reduction associated to X_1
- $\log(h(t)) = \lambda(t) + \beta X_1$
- $\lambda(t)$ is the risk in the standard treatment group
- β quantifies the risk increase/reduction in the experimental treatment group
  - $\beta > 0$ risk increase
  - $\beta < 0$ risk reduction

$X_1 = \begin{cases} 1 & \text{ENSARTINIB} \\ 0 & \text{CRIZOTINIB} \end{cases}$

$X_1 = 0 \Rightarrow \log(h(t)) = \lambda(t)$

$X_1 = 1 \Rightarrow \log(h(t)) = \lambda(t) + \beta$

COX REGRESSION MODEL

- Hazard: risk at time t
  - $h(t)$
- Risk/protective factor X_1
  - Experimental treatment vs Standard treatment
- Supposse we have a patient in the control group $(X_1 = 0)$
  - $\log(h(t; X_1 = 0)) = \lambda(t)$
- Supposse we have a patient in the experimetal group $(X_1 = 1)$
  - $\log\big(h(t; X_1 = 1)\big) = \lambda(t) + \beta$
- As we did for logistic regression model, compare the two patients
  - $\log\big(h(t; X_1 = 0)\big) - \log\big(h(t; X_1 = 1)\big) = \lambda(t) - (\lambda(t) + \beta)$

$$X_1 = \begin{cases} 1 & \text{ENSARTINIB} \\ 0 & \text{CRIZOTINIB} \end{cases}$$

COX REGRESSION MODEL

- Hazard: risk at time t
  - $h(t)$
- Risk/protective factor X_1
  - Experimental treatment vs Standard treatment
- Supposse we have a patient in the control group $(X_1 = 0)$
  - $\log(h(t; X_1 = 0)) = \lambda(t)$
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$$X_1 = \begin{cases} 1 & \text{ENSARTINIB} \\ 0 & \text{CRIZOTINIB} \end{cases}$$

COX REGRESSION MODEL

$$X_1 := \begin{cases} 1 & \text{ENSARTINIB} \\ 0 & \text{CRIZOTINIB} \end{cases}$$

- Hazard: risk at time t
  - $h(t)$
- Risk/protective factor X_1
  - Experimental treatment vs Standard treatment
- Supposse we have a patient in the control group $(X_1 = 0)$
  - $\log(h(t; X_1 = 0)) = \lambda(t)$
- Supposse we have a patient in the experimetal group $(X_1 = 1)$
  - $\log\big(h(t; X_1 = 1)\big) = \lambda(t) + \beta$
- As we did for logistic regression model, compare the two patients
  - $\log\big(h(t; X_1 = 0)\big) - \log\big(h(t; X_1 = 1)\big) = \beta$

COX REGRESSION MODEL

- Hazard: risk at time t
  - $h(t)$
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  - Experimental treatment vs Standard treatment
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- Supposse we have a patient in the experimetal group $(X_1 = 1)$
  - $\log\big(h(t; X_1 = 1)\big) = \lambda(t) + \beta$
- As we did for logistic regression model, compare the two patients
  - $\log\big(h(t; X_1 = 0)\big) - \log\big(h(t; X_1 = 1)\big) = \beta$

$X_i = \begin{cases} 1 & \text{ENSARTINIB} \\ 0 & \text{CRIZOTINIB} \end{cases}$

THE DIFFERENCE IN HAZARD ON A LOG SCALE IS CONSTANT

COX REGRESSION MODEL

- Hazard: risk at time t
  - $h(t)$
- Risk/protective factor X_1
  - Experimental treatment vs Standard treatment
- Supposne we have a patient in the control group $(X_1 = 0)$
  - $\log(h(t; X_1 = 0)) = \lambda(t)$
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  - $\log\big(h(t; X_1 = 1)\big) = \lambda(t) + \beta$
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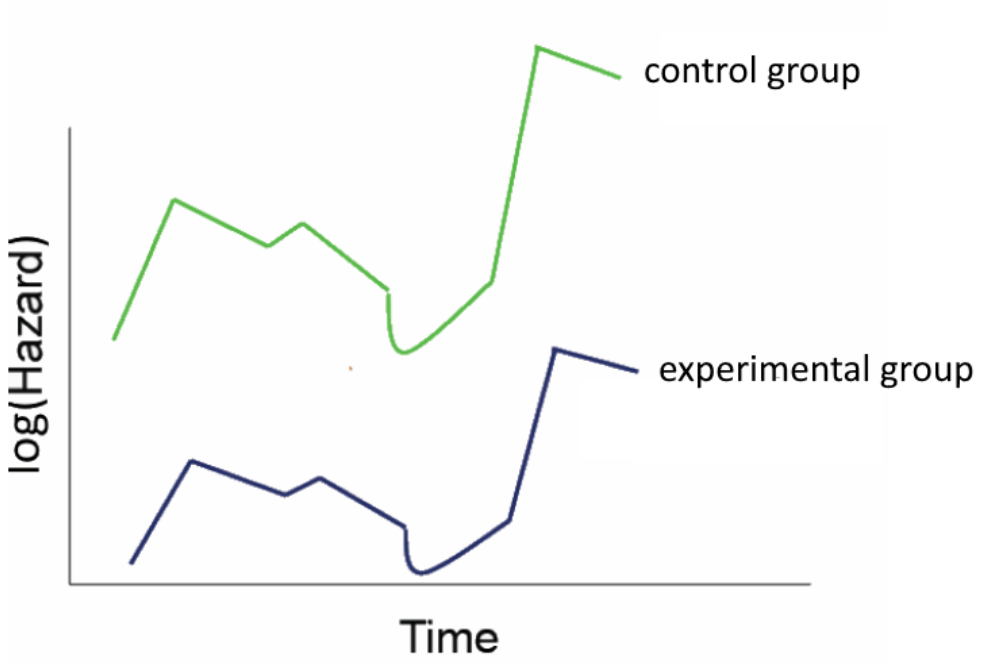
  - $\log\big(h(t; X_1 = 0)\big) - \log\big(h(t; X_1 = 1)\big) = \beta$

$X_1 = \begin{cases} 1 & \text{ENSARTINIB} \\ 0 & \text{CRIZOTINIB} \end{cases}$

THE DIFFERENCE IN HAZARDS ON A LOG SCALE IS CONSTANT



COX REGRESSION MODEL

$$X_1 = \begin{cases} 1 & \text{ENSARTINIB} \\ 0 & \text{CRIZOTINIB} \end{cases}$$

- Hazard: risk at time t
  - $h(t)$
- Risk/protective factor X_1
  - Experimental treatment vs Standard treatment
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  - $\log(h(t; X_1 = 0)) = \lambda(t)$
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  - $\log\big(h(t; X_1 = 1)\big) = \lambda(t) + \beta$
- As we did for logistic regression model, compare the two patients
  - $\log\big(h(t; X_1 = 0)\big) - \log\big(h(t; X_1 = 1)\big) = \beta \Longrightarrow \frac{\log\big(h(t; X_1 = 0)\big)}{\log\big(h(t; X_1 = 1)\big)} = \beta$

COX REGRESSION MODEL

$$X_1 = \begin{cases} 1 & \text{ENSARTINIB} \\ 0 & \text{CRIZOTINIB} \end{cases}$$

- Hazard: risk at time t
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  - $\log\big(h(t; X_1 = 1)\big) = \lambda(t) + \beta$
- As we did for logistic regression model, compare the two patients
  - $\log\big(h(t; X_1 = 0)\big) - \log\big(h(t; X_1 = 1)\big) = \beta \Longrightarrow \log\left(\frac{h(t;X_1=0)}{h(t;X_1=1)}\right) = \beta \Longrightarrow \frac{h(t;X_1=0)}{h(t;X_1=1)} = \exp\beta$

COX REGRESSION MODEL

- Hazard: risk at time t
  - $h(t)$
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- Supponse we have a patient in the control group $(X_1 = 0)$
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$X_1 = \begin{cases} 1 & \text{ENSARTINIB} \\ 0 & \text{CRIZOTINIB} \end{cases}$

#HAZARD RATIO

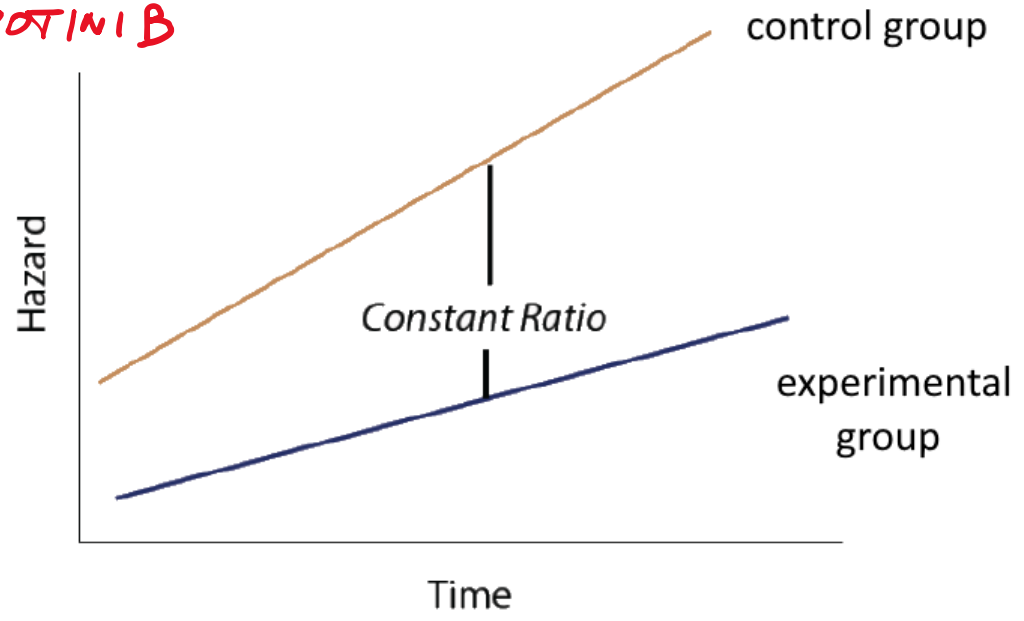
COX REGRESSION MODEL OR PROPORTIONAL HAZARDS REGRESSION MODEL

- Hazard: risk at time t
  - $h(t)$
- Risk/protective factor X_1
  - Experimental treatment vs Standard treatment
- Supponse we have a patient in the control group $(X_1 = 0)$
  - $\log(h(t; X_1 = 0)) = \lambda(t)$
- Supponse we have a patient in the experimetal group $(X_1 = 1)$
  - $\log\big(h(t; X_1 = 1)\big) = \lambda(t) + \beta$
- As we did for logistic regression model, compare the two patients
  - $\log\big(h(t; X_1 = 0)\big) - \log\big(h(t; X_1 = 1)\big) = \beta \Longrightarrow \log\left(\frac{h(t;X_1=0)}{h(t;X_1=1)}\right) = \beta \Longrightarrow \frac{h(t;X_1=0)}{h(t;X_1=1)} = \exp\beta$

$X_1 = \begin{cases} 1 & \text{ENSARTINIB} \\ 0 & \text{CRIZOTINIB} \end{cases}$

HAZARD RATIO

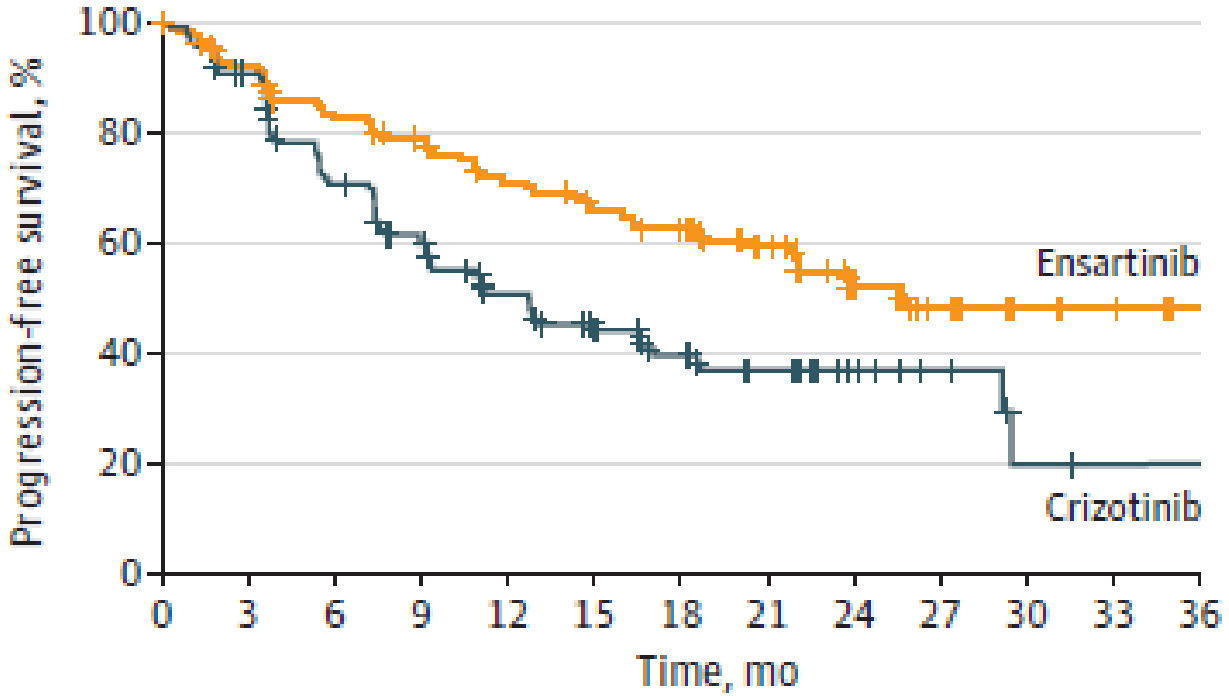
THE RATIO OF THE HAZARDS IS CONSTANT OVER TIME



HAZARD RATIO

- Hazard: risk at time t
  - $\log(h(t)) = \lambda(t) + \beta X_1$
  - $HR = \exp \beta$

	Ensartinib (n = 143)	Crizotinib (n = 147)
mPFS (95% CI), mo	25.8 (21.8-NR)	12.7 (9.2-16.6)
Hazard ratio (95% CI)	0.51 (0.35-0.72)	
P value (log-rank test)	<.001	



No. at risk

Ensartinib	143	125	106	98	86	78	72	54	30	21	10	5	1
Crizotinib	147	124	94	75	56	43	32	23	10	6	2	1	1

INTERPRETATION

- HR > 1: higher hazard (worse survival) associated with the risk factor
- HR < 1: lower hazard (better survival) associated with the risk factor (protective factor)
- HR = 1: no association between the hazard (and survival) and the risk factor

HAZARD RATIO

- Hazard: risk at time t
  - $\log(h(t)) = \lambda(t) + \beta X_1$
  - $HR = \exp \beta$
  - HR = 0.51
  - Treatment with Ensartinib is associated with a 49% reduction in the risk of progression

	Ensartinib (n = 143)	Crizotinib (n = 147)
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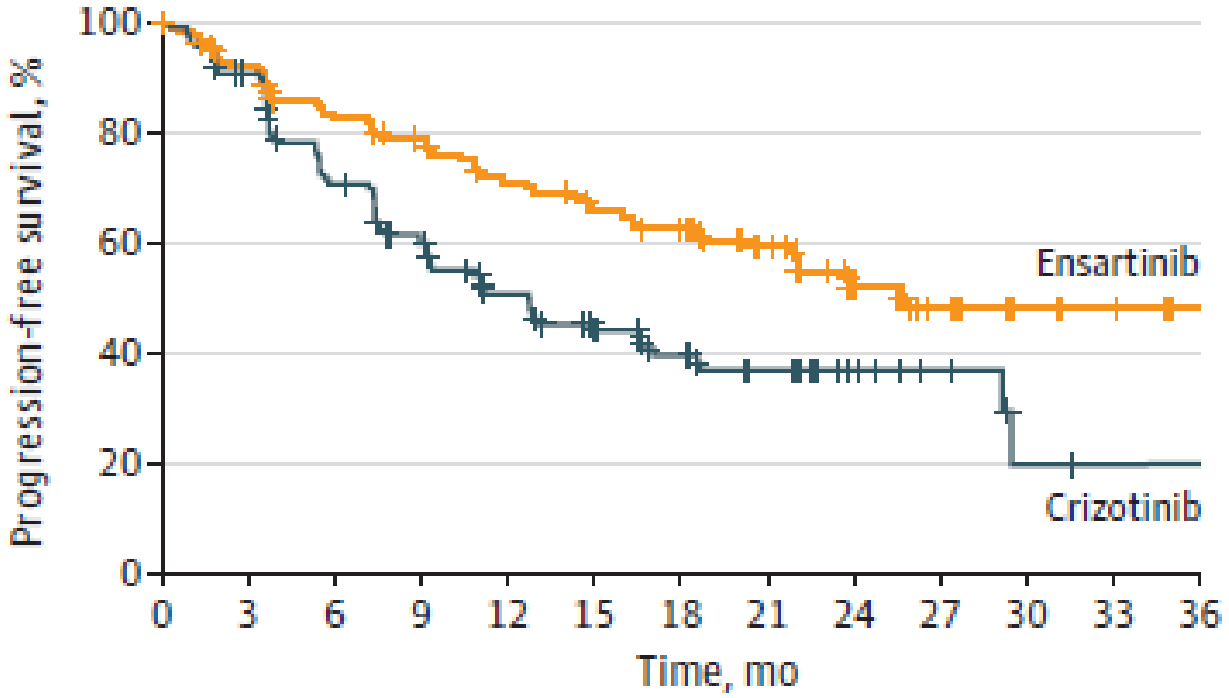

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HAZARD RATIO

- Hazard: risk at time t
  - $\log(h(t)) = \lambda(t) + \beta X_1$
  - $HR = \exp \beta$
  - HR = 0.51
  - Treatment with Ensartinib is associated with a 49% reduction in the risk of progression
  - Since the 95%CI does not contain unity therefore the risk of progression is significantly lower in the Ensartinib group than in the Crizotinib group

	Ensartinib (n = 143)	Crizotinib (n = 147)
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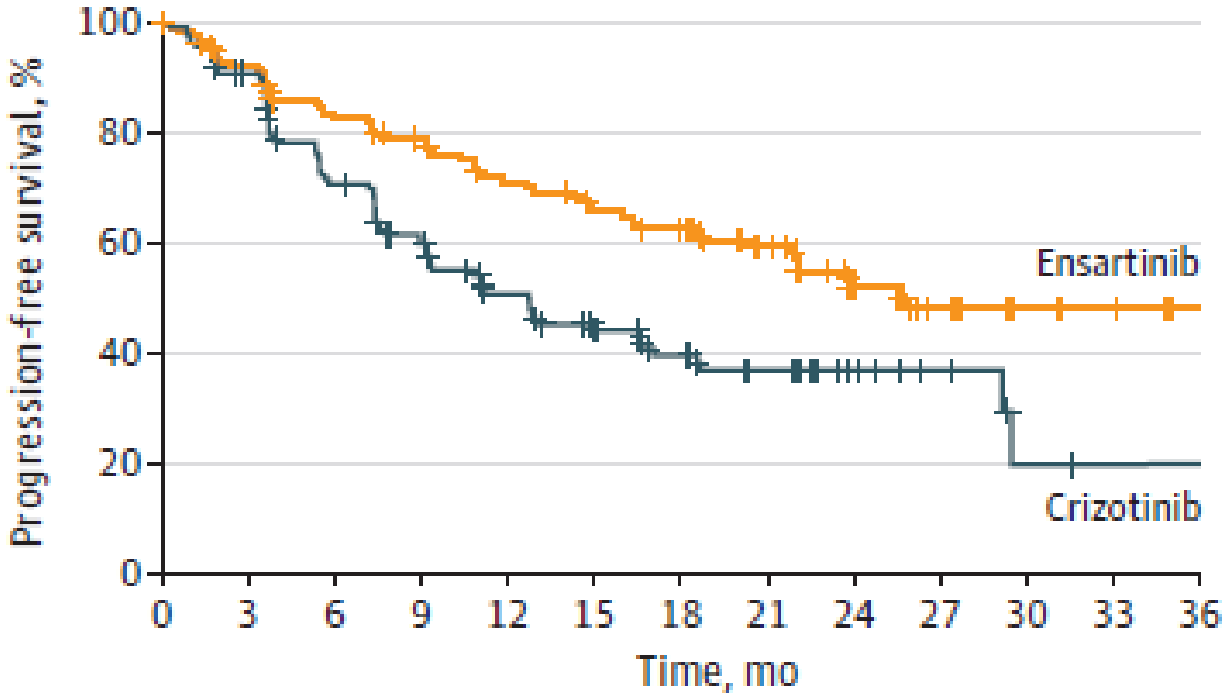

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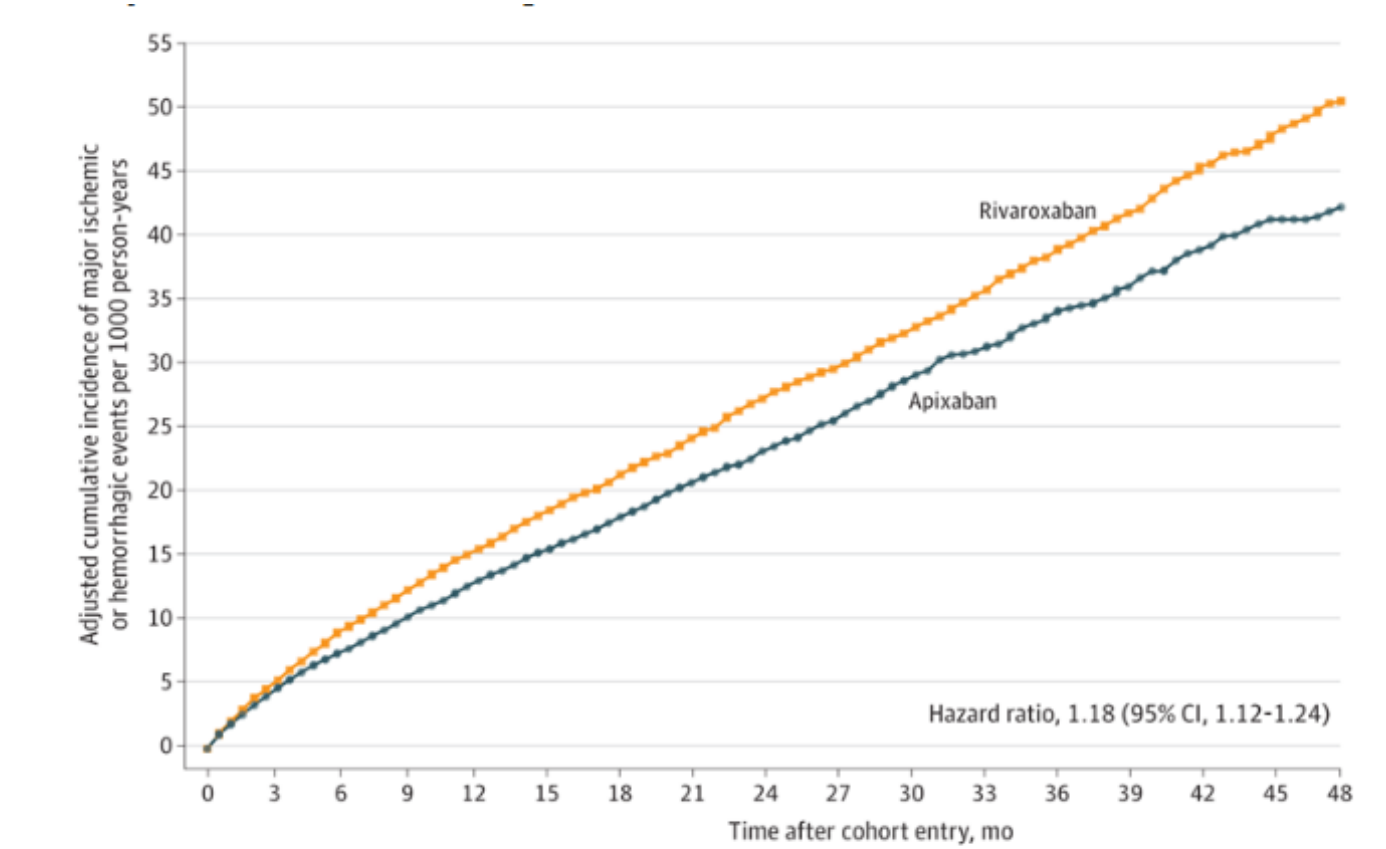
CUMULATIVE INCIDENCE

- Association of Rivaroxaban vs Apixaban With Major Ischemic or Hemorrhagic Events in Patients With Atrial Fibrillation



RESEARCH Open Access

Serum cholinesterase may independently predict prognosis in non-small-cell lung cancer

Abstract

Background: Serum cholinesterase (ChE) was found to be involved in cancer initiation and progression. However, the survival association between serum ChE and non-small cell lung cancer (NSCLC) has not been extensively discussed. In the present study, we aim to elevate the role of ChE in overall survival (OS) of NSCLC patients.

Methods: A total of 961 histologically confirmed NSCLC patients diagnosed between 2013 and 2018 in a provincial cancer hospital in southwestern China were retrospectively selected. Relevant information, such as histological type, clinical stage, chemotherapy, smoking status, body mass index (BMI), important serum indicators (albumin, neutrophil-to-lymphocyte ratio, ChE), date of death of the patients was extracted from the computerized hospital information system. Univariate and multivariate Cox proportional hazards models were used to determine the association between baseline serum ChE measured at the diagnosis and the OS of NSCLC patients.

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METHODS

- Descriptive statistics were used to illustrate and compare general characteristics of the participants. The survival curves for NSCLC patients of different baseline ChE levels were drawn and compared by using **Kaplan-Meier** method and the **log-rank** test.
- **Univariate** and **multivariate Cox proportional hazards** models were used to evaluate the crude and adjusted associations between baseline serum ChE and the OS of NSCLC patients
  - Variables that achieved a less strict significance ($p < 0.10$) in univariate analyses were included into the subsequent multivariate model.
- A two-tailed probability less than 0.05 was deemed statistically significant

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  - Variables that achieved a less strict significance ($p < 0.10$) in univariate analyses were included into the subsequent multivariate model.
- A two-tailed probability less than 0.05 was deemed statistically significant
- *Schoenfeld's global and individual test were used to estimate time-varying covariance for the assumption of the Cox proportional hazard regression analysis*

TABLE I

Table 1 General characteristics of 961 NSCLC patients

Characteristics	All patients (*N* = 961)	The lower group (ChE < 7700 U/L, *N* = 482)	The higher group (ChE > = 7700 U/L, *N* = 479)	*p* value
Sex				
Female	340 (35.40)[c]	136 (28.20)[c]	204 (42.60)[c]	< 0.001
Male	621 (64.60)[c]	346 (71.80)[c]	275 (57.40)[c]	
Age at diagnosis (Years)	61.15 (10.67)[a]	63.10 (10.92)[a]	59.18 (10.04)[a]	< 0.001
Ethnicity				
Minority	89 (9.30)[c]	55 (11.40)[c]	34 (7.10)[c]	0.041
Han majority	872 (90.70)[c]	427 (88.60)[c]	445 (92.90)[c]	
Smoking				
No	384 (40.00)[c]	169 (35.10)[c]	215 (44.90)[c]	0.003
Yes	577 (60.00)[c]	313 (64.90)[c]	264 (55.10)[c]	
BMI (kg/m^2)	23.74 (35.88)[a]	24.36 (50.63)[a]	23.14 (6.58)[a]	0.603
Chemotherapy				
No	443 (46.10)[c]	239 (49.60)[c]	204 (42.60)[c]	0.035
Yes	518 (53.90)[c]	243 (50.40)[c]	275 (57.40)[c]	
Complications				
No	521 (54.20)[c]	262 (54.40)[c]	259 (54.10)[c]	0.981
Yes	440 (45.80)[c]	220 (45.60)[c]	220 (45.90)[c]	
Histological type				
Adenocarcinoma	628 (65.30)[c]	283 (58.70)[c]	345 (72.00)[c]	< 0.001
Squamous cell carcinoma	291 (30.30)[c]	177 (36.70)[c]	114 (23.80)[c]	
Large cell carcinoma	8 (0.80)[c]	6 (1.20)[c]	2 (0.40)[c]	
Multiple types	34 (3.50)[c]	16 (3.30)[c]	18 (3.80)[c]	
Stage				
Early stage	84 (8.70)[c]	29 (6.00)[c]	55 (11.50)[c]	0.004
Advanced stage	877 (91.30)[c]	453 (94.00)[c]	424 (88.50)[c]	
Survival length (Day)	374.00 (147.00, 717.00)[b]	276.74 (107.00, 587.75)[b]	483.43 (219.00, 841.50)[b]	< 0.001
ALB (U/L)	42.50 (38.57, 45.20)[b]	39.95 (35.86, 42.99)[b]	44.19 (42.10, 46.60)[b]	< 0.001
NLR (Unit free)	2.95 (1.97, 4.36)[b]	3.43 (2.22, 5.20)[b]	2.53 (1.83, 3.46)[b]	< 0.001
ChE (U/L)	7700.00 (6287.00, 8900.00)[b]	–	–	

K-M CURVES

- Overall Survival (OS)

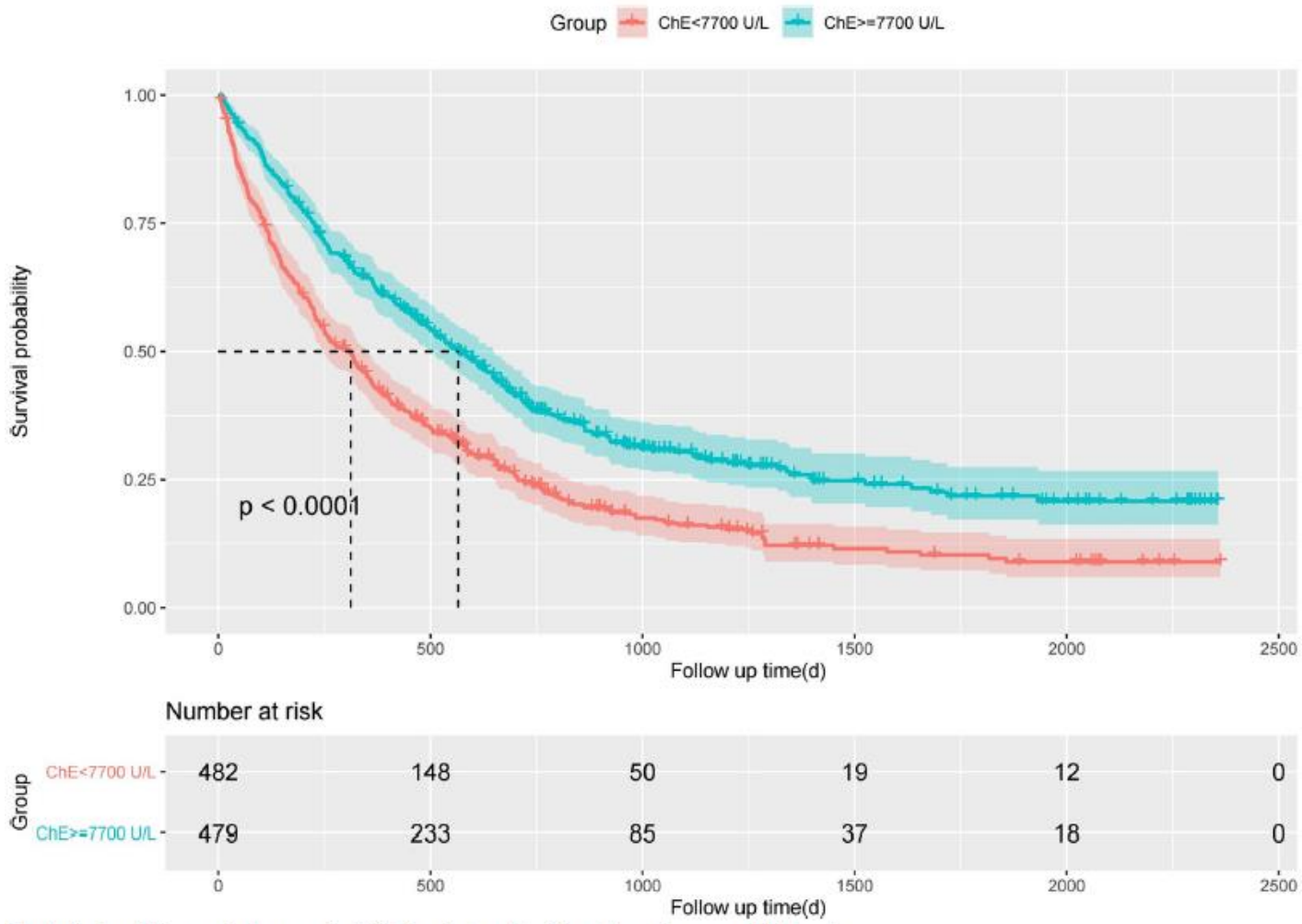

Fig. 1 Kaplan-Meier survival curves for NSCLC patients with different baseline serum ChE levels

UNIVARIABLE COX MODEL

Table 2 Univariate and multivariate Cox proportional hazards model results

Covariates	Univariate Cox model	
	Crude HR (90% CI)	***p* value**
Sex (Male)	1.63 (1.42, 1.86)	< 0.001
Age at diagnosis (+ 5 years)	1.08 (1.05, 1.12)	< 0.001
Smoking (Yes)	1.31 (1.15, 1.49)	< 0.001
BMI (+ 1)	1.00 (0.99, 1.01)	0.21
Chemotherapy (Yes)	0.60 (0.53, 0.68)	< 0.001
Comorbidities (Yes)	0.95 (0.85, 1.09)	0.57
Histological type		
Squamous cell carcinoma	1.36 (1.19, 1.55)	< 0.001
Large cell carcinoma	0.82 (0.39, 1.71)	0.65
Multiple types	1.76 (1.28, 2.41)	0.003
Stage (Advanced stage)	4.95 (3.40, 7.21)	< 0.001
Baseline serum ALB (> = 35 U/L)	0.40 (0.33, 0.48)	< 0.001
Baseline serum NLR (+ 5)	1.34 (1.28, 1.40)	< 0.001
Baseline serum ChE (> = 7700 U/L)	0.61 (0.53, 0.69)	< 0.001

UNIVARIABLE COX MODEL

Table 2 Univariate and multivariate Cox proportional hazards model results

Covariates	Univariate Cox model		Multivariate Cox model	
	Crude HR (90% CI)	*p* value	Adjusted HR (95% CI)	*p* value
Sex (Male)	1.63 (1.42, 1.86)	< 0.001	1.32 (1.07, 1.64)	0.01
Age at diagnosis (+ 5 years)	1.08 (1.05, 1.12)	< 0.001		
Smoking (Yes)	1.31 (1.15, 1.49)	< 0.001		
BMI (+ 1)	1.00 (0.99, 1.01)	0.21		
Chemotherapy (Yes)	0.60 (0.53, 0.68)	< 0.001	0.55 (0.47, 0.64)	< 0.001
Comorbidities (Yes)	0.95 (0.85, 1.09)	0.57		
Histological type				
Squamous cell carcinoma	1.36 (1.19, 1.55)	< 0.001		
Large cell carcinoma	0.82 (0.39, 1.71)	0.65		
Multiple types	1.76 (1.28, 2.41)	0.003	1.77 (1.20, 2.61)	0.017
Stage (Advanced stage)	4.95 (3.40, 7.21)	< 0.001	4.78 (3.18, 7.18)	< 0.001
Baseline serum ALB (> = 35 U/L)	0.40 (0.33, 0.48)	< 0.001	0.53 (0.42, 0.68)	< 0.001
Baseline serum NLR (+ 5)	1.34 (1.28, 1.40)	< 0.001	1.25 (1.17, 1.34)	< 0.001
Baseline serum ChE (> = 7700 U/L)	0.61 (0.53, 0.69)	< 0.001	0.77 (0.67, 0.93)	0.006

MULTIVARIABLE (MULTIVARIATE) COX REGRESSION MODEL

- We want to estimate the effect of several risk factors on the hazard
  - $h(t)$ is the hazar of the event over time (outcome variable)
    - $X_1, X_2, \ldots, X_n$ are risk factors

$$\ln h(t) = \lambda(t) + \beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_n X_n$$

$$h_1(t) = P(Y = 1, t | X_1 = 1 \,\&\, X_2 = 1, \ldots, X_n = 1)$$
$$h_0(t) = P(Y = 1, t | X_1 = 0 \,\&\, X_2 = 1, \ldots, X_n = 1)$$

$$\ln HR = \ln h_{1(t)} - \ln h_{0(t)} = (\lambda(t) + \beta_1 + \beta_2 X_2 + \cdots + \beta_n X_n) - (\lambda(t) + \beta_2 X_2 + \cdots + \beta_n X_n) = \beta_1$$

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$\exp \beta_1$ is the HR of X_1 adjusted by $X_2, \ldots, X_n$

We are comparing two group of patients that share the same risk factors $X_2, \ldots, X_n$ and differ only in X_1

UNIVARIABLE COX MODEL

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Delirium as a Predictor of Mortality in Mechanically Ventilated Patients in the Intensive Care Unit

E. Wesley Ely, MD, MPH
Ayumi Shintani, PhD, MPH
Brenda Truman, RN, MSN
Theodore Speroff, PhD
Sharon M. Gordon, PsyD
Frank E. Harrell, Jr, PhD
Sharon K. Inouye, MD, MPH
Gordon R. Bernard, MD
Robert S. Dittus, MD, MPH

Context In the intensive care unit (ICU), delirium is a common yet underdiagnosed form of organ dysfunction, and its contribution to patient outcomes is unclear.

Objective To determine if delirium is an independent predictor of clinical outcomes, including 6-month mortality and length of stay among ICU patients receiving mechanical ventilation.

Design, Setting, and Participants Prospective cohort study enrolling 275 consecutive mechanically ventilated patients admitted to adult medical and coronary ICUs of a US university-based medical center between February 2000 and May 2001. Patients were followed up for development of delirium over 2158 ICU days using the Confusion Assessment Method for the ICU and the Richmond Agitation-Sedation Scale.

YET ANOTHER EXAMPLE

comes in critically ill ICU patients.

Management of patients with sepsis and multiorgan failure has tradition-

See also Patient Page.

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Caring for the Critically Ill Patient Section Editor: Deborah J. Cook, MD, Consulting Editor, *JAMA*. **Advisory Board:** David Bihari, MD; Christian Brun-Buisson, MD; Timothy Evans, MD; John Heffner, MD; Norman Paradis, MD; Adrienne Randolph, MD.

VARIABLES

- Age
- Men
- Race
- Charlson Comorbidity Index
- Vision/Hearing deficits
- mBDRS scale
- APACHE score
- SOFA score
- ICU admission diagnosis

Table 1. Baseline Characteristics of the Patients*

Characteristic	No. (%)†	
	No Delirium (n = 41)	Delirium (n = 183)
Age, mean (SD), y	54 (17)	56 (17)
Men	18 (44)	95 (52)
Race		
White	32 (78)	145 (79)
Black	9 (22)	38 (21)
Charlson Comorbidity Index, mean (SD)	3.2 (2.8)	3.2 (2.8)
Vision deficits, No./total (%)‡	23/33 (70)	104/153 (68)
Hearing deficits, No./total (%)‡	5/32 (16)	29/152 (19)
mBDRS score, mean (SD)	0.14 (0.6)	0.23 (0.8)
Activities of daily living, mean (SD)	0.81 (2.4)	0.91 (2.3)
APACHE II score, mean (SD)	23.2 (9.6)	25.6 (8.1)
SOFA score, mean (SD)	9.5 (2.9)	9.6 (3.4)
ICU admission diagnosis§		
Sepsis and/or acute respiratory distress syndrome	24 (59)	78 (43)
Pneumonia	6 (15)	35 (19)
Myocardial infarction/congestive heart failure	4 (10)	15 (8)
Hepatic or renal failure	0	11 (6)
Chronic obstructive pulmonary disease	2 (5)	18 (10)
Gastrointestinal bleeding	2 (5)	18 (10)
Malignancy	0	7 (4)
Drug overdose	3 (7)	8 (4)
Other	14 (34)	53 (29)

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit; mBDRS, modified Blessed Dementia Rating Scale; SOFA, Sequential Organ Failure Assessment.
*All comparisons between the no delirium and delirium groups were nonsignificant ($P > .05$). See "Methods" section for descriptions of scales and for scale ranges.
†Except where noted otherwise.
‡Denominators indicate number of patients with available information.
§Recorded by the patients' medical team as the diagnoses most representative of the reason for admission to the ICU. Patients were sometimes given more than 1 admission diagnosis by the medical team, resulting in column totals >100%.

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DELIRIUM IN ICU AND MORTALITY

STATISTICAL ANALYSIS

- Six-month mortality, overall hospital length of stay, and length of stay after first ICU discharge were analyzed using **time-to-event analyses**
  - For 6-month mortality analyses, patients were censored at the time of last contact alive or at 6 months from enrollment, whichever was first.
  - Censoring for length-of-stay analyses occurred at time of hospital death
- **Kaplan-Meier** survival curves were used for graphical presentation of time to death or hospital discharge, and **log-rank statistics** were used to assess difference by overall delirium status
- **Cox proportional hazard regression** models were used to obtain **hazard ratios (HRs)** of death up to 6 months from enrollment and HRs of remaining in hospital

RESULTS

- Six-month mortality, overall hospital length of stay, and length of stay after first ICU discharge were analyzed using **time-to-event analyses**
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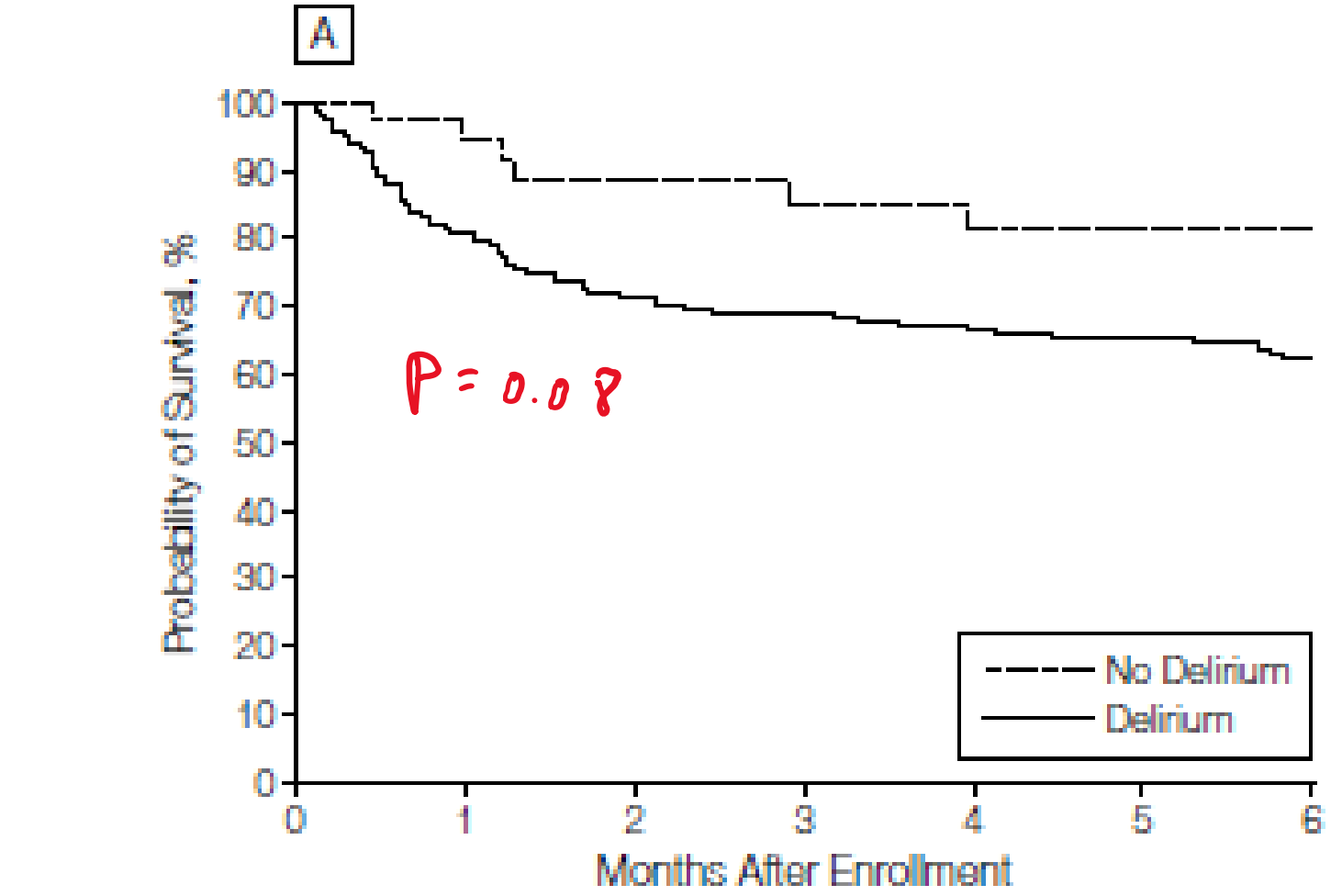

No. at Risk

No Delirium	41	34	28	25	22	21	19
Delirium	183	138	116	111	104	98	88