Great & Crazy Things We Do in Oncology: Truth hiding in plain sight

Vinay Prasad MD MPH

Hematologist Oncologist SFGH

Professor

UCSF

Disclosure

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Disclosures. (Research funding) Arnold Ventures (Royalties) Johns Hopkins Press, MedPage, YouTube, Substack (Consulting) Optum Health. (Other) Plenary Session podcast has Patreon backers.

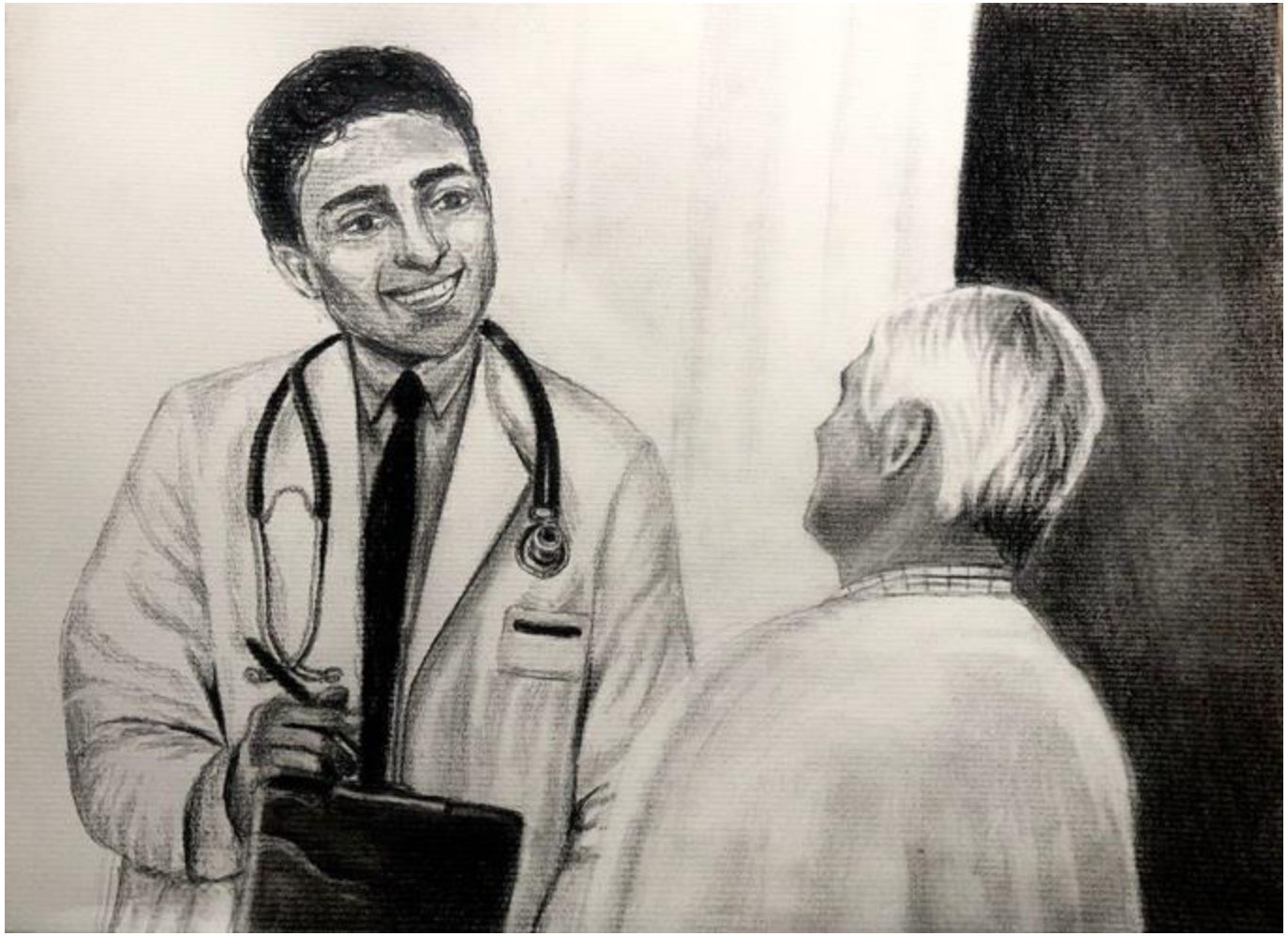
Thanks for having me back

Great things we do

- Provide comfort
- Provide guidance
- Give good drugs

One day I was in clinic….

One day I was in clinic….



Visiting student rendition

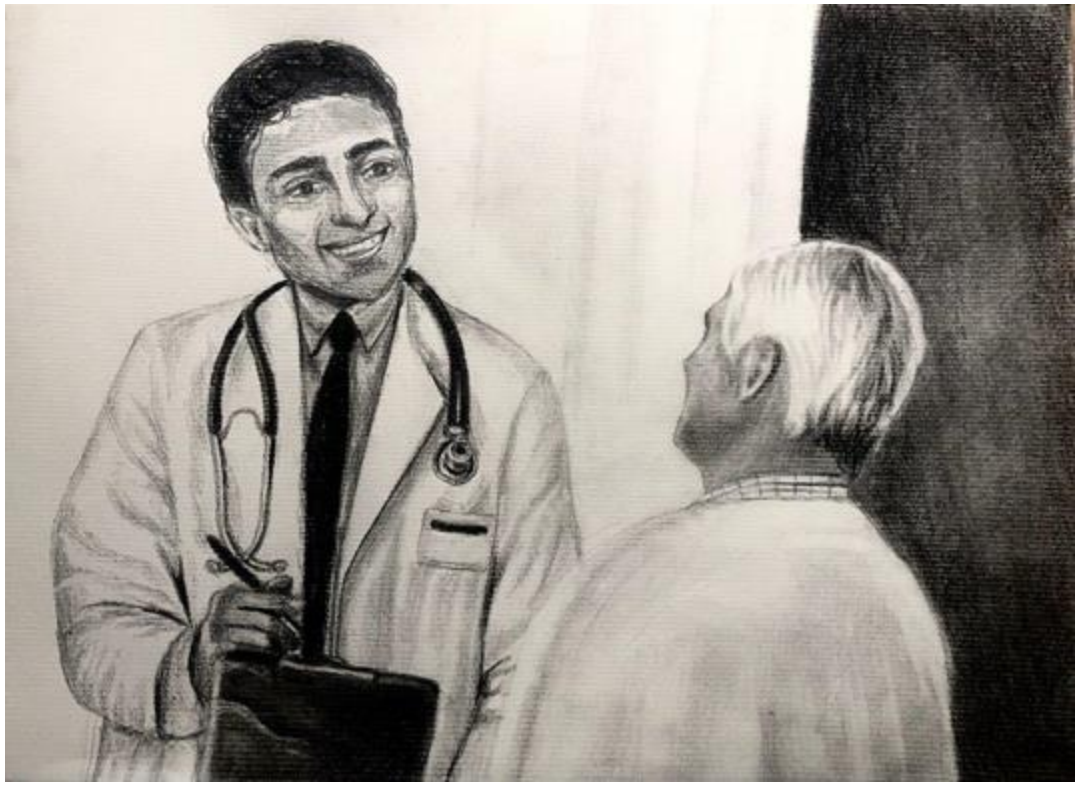
Should I Drink Coffee to Prevent Colorectal Cancer?

Share

By Jim Stallard, **Friday, March 22, 2019**

Coffee is made up of more than 1,000 chemical compounds.

I always advise my patients nearly anything in moderation is fine. I wouldn't take up drinking coffee to prevent colon cancer, but if you enjoy doing it, as I do, I wouldn't stop



Visiting student rendition

- “Didn’t you read the new study, doctor?”

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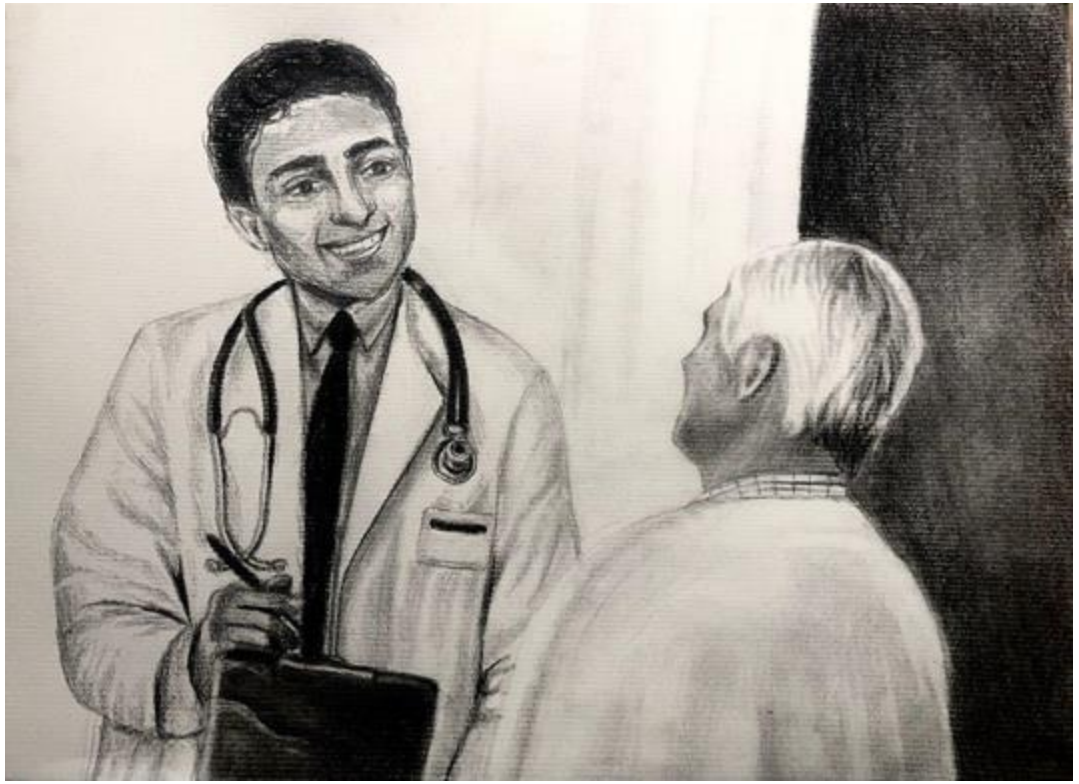

- Didn’t you read the new study?

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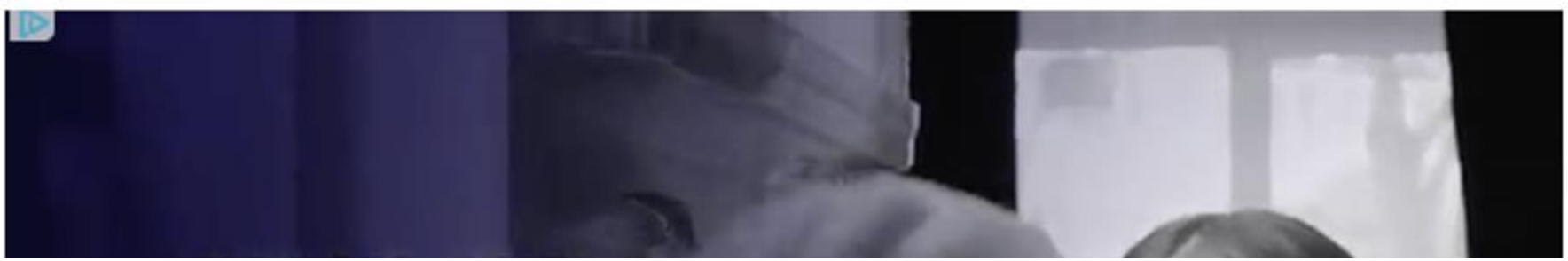
Coffee linked to longer survival in patients with colorectal cancer, study says

Adrianna Rodriguez
USA TODAY

Published 11:01 a.m. ET Sept. 17, 2020 | Updated 6:18 p.m. ET Sept. 17, 2020



Harvard researchers link coffee with reduced colon cancer recurrence

October 17, 2015

You may drink coffee because it tastes good or helps you wake up. But the popular brew is also associated with health benefits, such as reducing the risk for heart disease, stroke, and type 2 diabetes. Now a study from Harvard-affiliated Dana-Farber Cancer Institute published Aug. 17, 2015, in *the Journal of Clinical Oncology* suggests that regular consumption of caffeinated coffee may be associated with a reduced recurrence of colon cancer, and even a reduced risk of death. The study

Daily coffee consumption associated with improved survival in patients with metastatic colorectal cancer

- **Data from a large observational study suggests coffee consumption associated with lower risk of cancer progression and death**
- **Benefit pertains to caffeinated and decaffeinated coffee**

In a large group of patients with metastatic colorectal cancer, consumption of a few cups of coffee a day was associated with longer survival and a lower risk of the cancer worsening, researchers at Dana-Farber Cancer Institute and other organizations report in a new study.

The findings, based on data from a large observational study nested in a clinical trial, are in line with earlier studies showing a connection between regular coffee consumption and improved outcomes in patients with non-metastatic colorectal cancer. The study is being published today by *JAMA Oncology*.

Posted on

SEPTEMBER 17, 2020

EMAIL

Research

Kimmie Ng, MD, MPH

Rectal Cancer

Dana-Farber Cancer Institute

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Daily coffee consumption associated with improved survival in patients with metastatic colorectal cancer

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Benefit pertains to caffeinated and decaffeinated coffee

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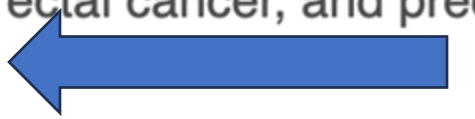
"This study adds to the large body of literature supporting the importance of diet and other modifiable factors in the treatment of patients with colorectal cancer," Ng adds. "Further research is needed to determine if there is indeed a causal connection between coffee consumption and improved outcomes in patients with colorectal cancer, and precisely which compounds within coffee are responsible for this benefit."



JAMA Oncology | Original Investigation

Association of Coffee Intake With Survival in Patients With Advanced or Metastatic Colorectal Cancer

Christopher Mackintosh, MLA; Chen Yuan, ScD; Fang-Shu Ou, PhD; Sui Zhang, MS; Donna Niedzwiecki, PhD; I-Wen Chang, MD; Bert H. O'Neil, MD; Brian C. Mullen, MS; Heinz-Josef Lenz, MD; Charles D. Blanke, MD; Alan P. Venook, MD; Robert J. Mayer, MD; Charles S. Fuchs, MD; Federico Innocenti, MD, PhD; Andrew B. Nixon, PhD; Richard M. Goldberg, MD; Eileen M. O'Reilly, MD; Jeffrey A. Meyerhardt, MD, MPH; Kimmie Ng, MD, MPH

IMPORTANCE Several compounds found in coffee possess antioxidant, anti-inflammatory, and insulin-sensitizing effects, which may contribute to anticancer activity. Epidemiological studies have identified associations between increased coffee consumption and decreased recurrence and mortality of colorectal cancer. The association between coffee consumption and survival in patients with advanced or metastatic colorectal cancer is unknown.

OBJECTIVE To evaluate the association of coffee consumption with disease progression and death in patients with advanced or metastatic colorectal cancer.

DESIGN, SETTING, AND PARTICIPANTS This prospective observational cohort study included 1171 patients with previously untreated locally advanced or metastatic colorectal cancer who were enrolled in Cancer and Leukemia Group B (Alliance)/SWOG 80405, a completed phase 3 clinical trial comparing the addition of cetuximab and/or bevacizumab to standard chemotherapy. Patients reported dietary intake using a semiquantitative food frequency questionnaire at the time of enrollment. Data were collected from October 27, 2005, to January 18, 2018, and analyzed from May 1 to August 31, 2018.

Invited Commentary
page 1721

Supplemental content

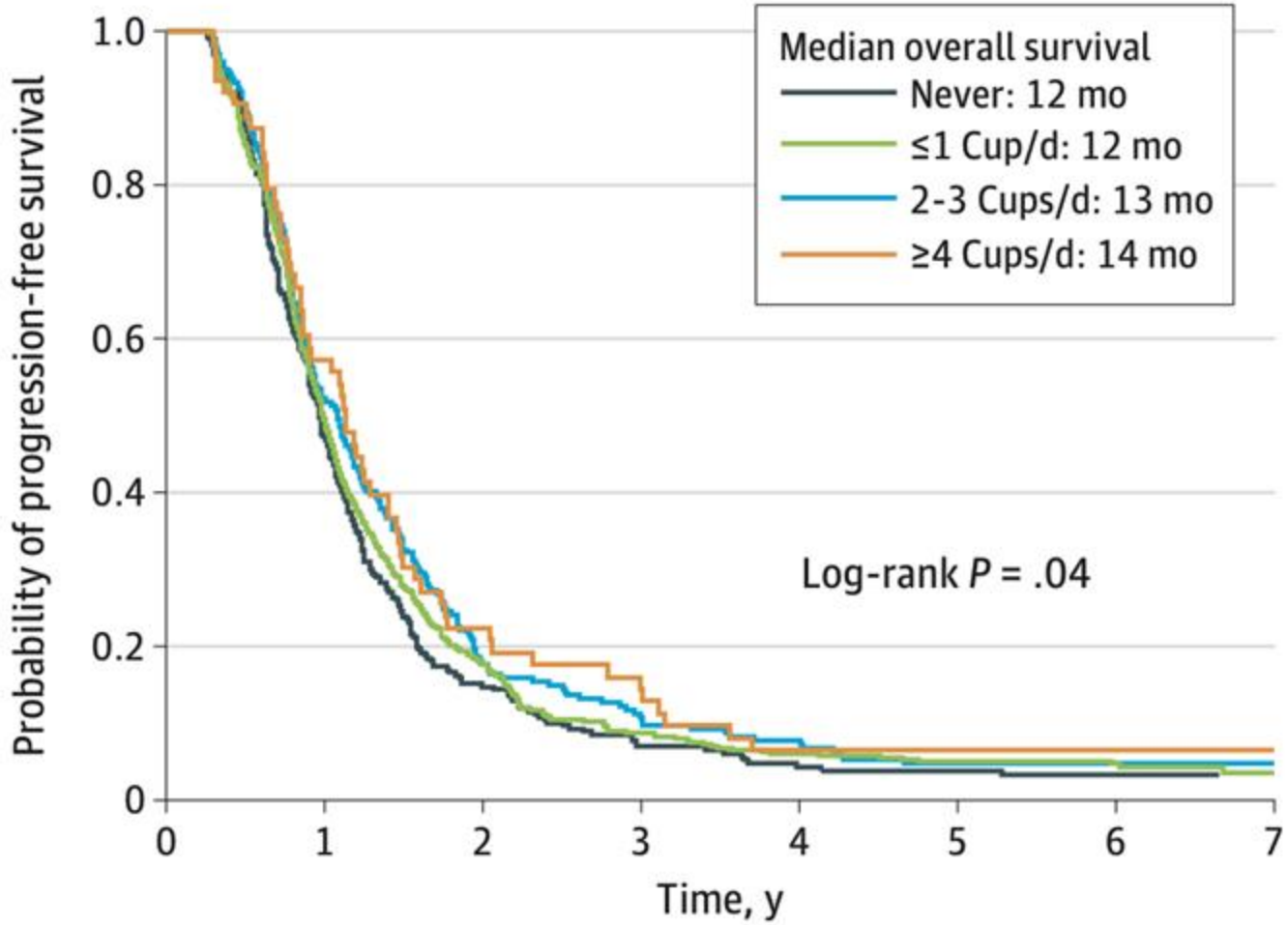
Mackintosh C, Yuan C, Ou FS, Zhang S, Niedzwiecki D, Chang IW, O'Neil BH, Mullen BC, Lenz HJ, Blanke CD, Venook AP. Association of coffee intake with survival in patients with advanced or metastatic colorectal cancer. JAMA oncology. 2020 Nov 1;6(11):1713-21.

What did they do?

- Took 1171 patients with previously untreated locally advanced or metastatic colorectal cancer who were enrolled in Cancer and Leukemia Group B (Alliance)/SWOG 80405
- Compared people who drank 1,2,3, and 4+ cups of coffee
- Here is what they found

Mackintosh C, Yuan C, Ou FS, Zhang S, Niedzwiecki D, Chang IW, O'Neil BH, Mullen BC, Lenz HJ, Blanke CD, Venook AP. Association of coffee intake with survival in patients with advanced or metastatic colorectal cancer. JAMA oncology. 2020 Nov 1;6(11):1713-21.

B Progression-free survival



No. at risk

Never	280	235	40	17	9	7	2	0
≤1 Cup/d	599	283	98	47	32	23	13	4
2-3 Cups/d	229	116	39	22	15	9	2	2
≥4 Cups/d	63	36	14	9	4	4	3	3

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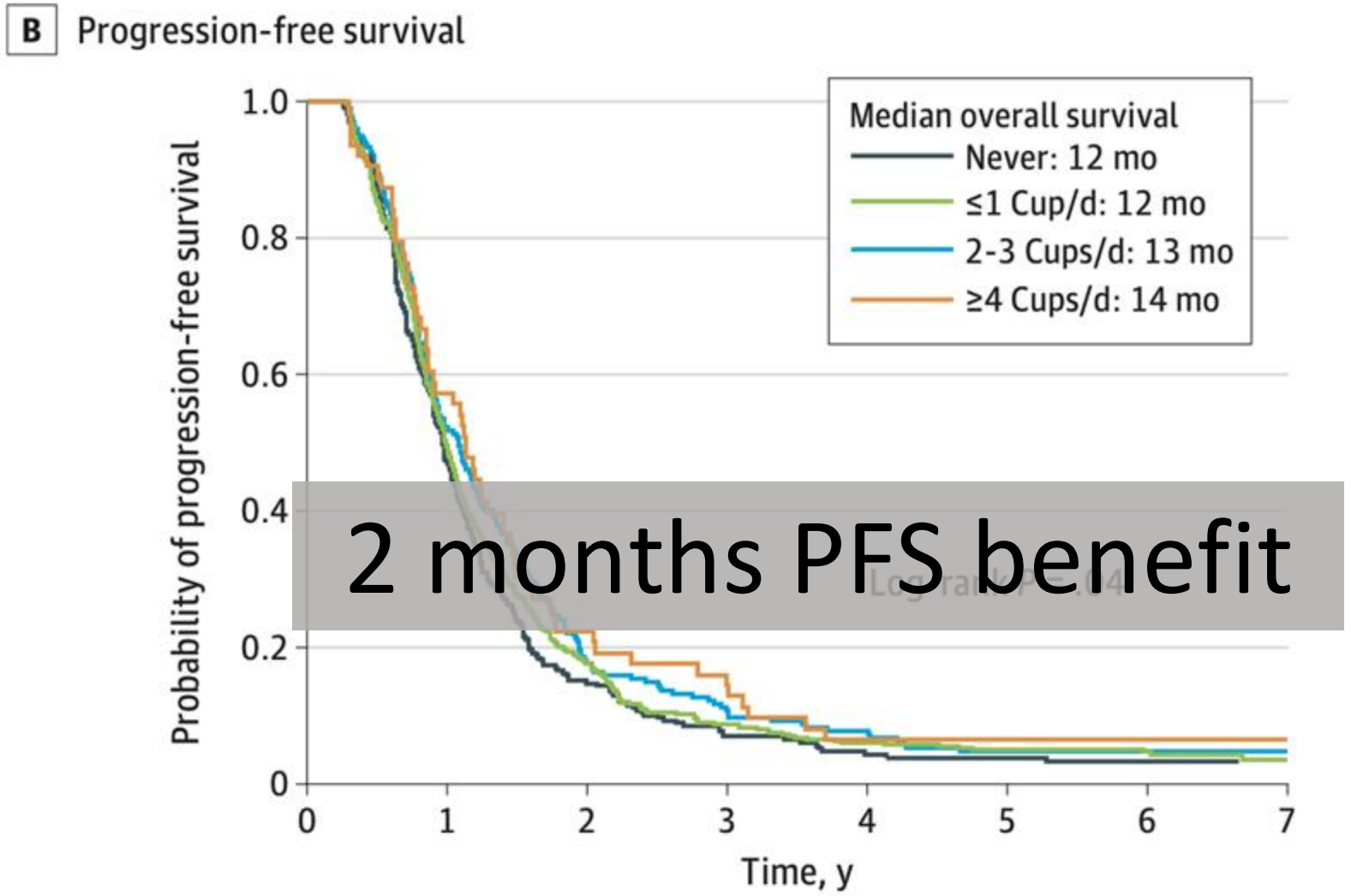

2 months PFS benefit

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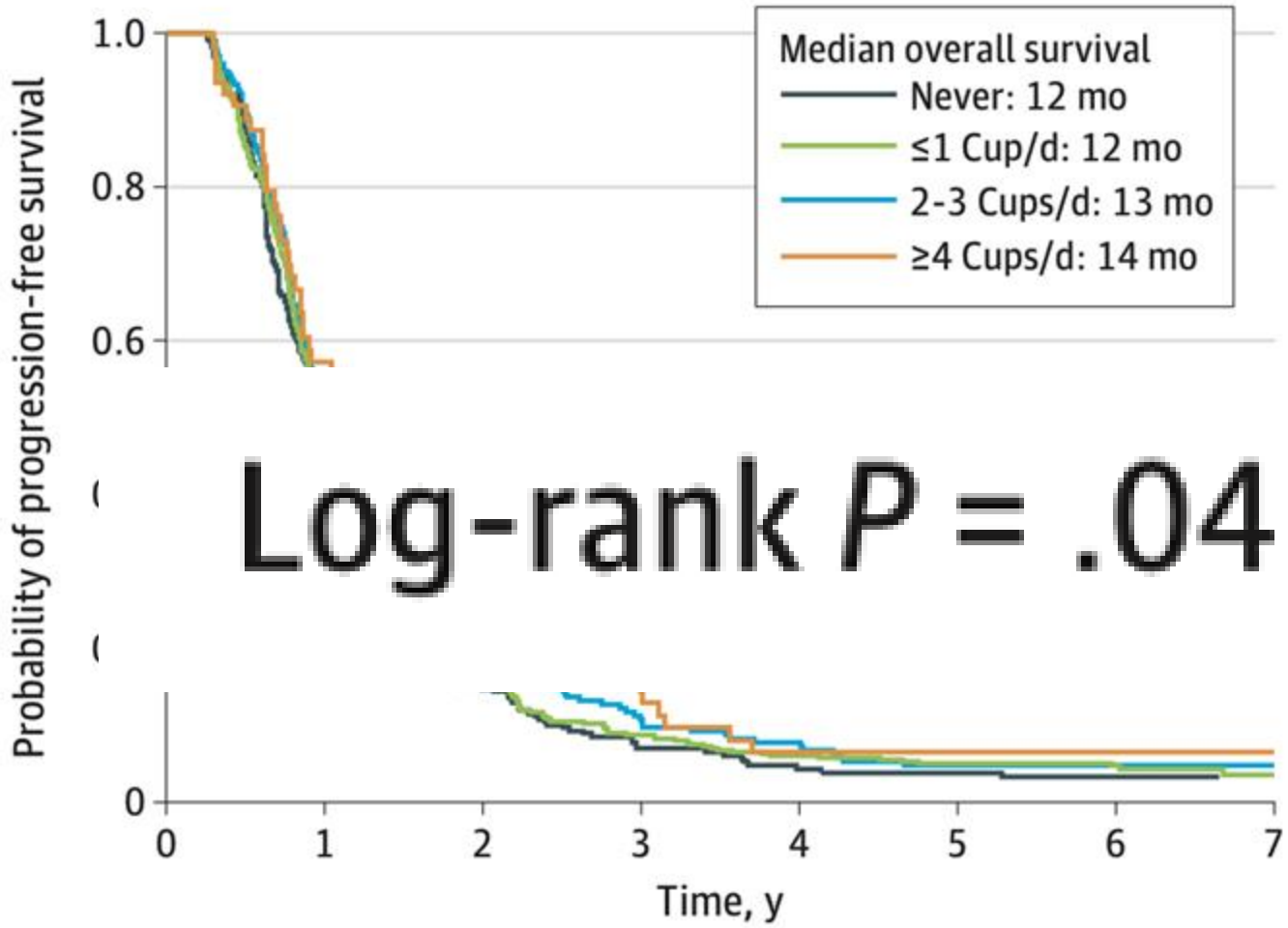

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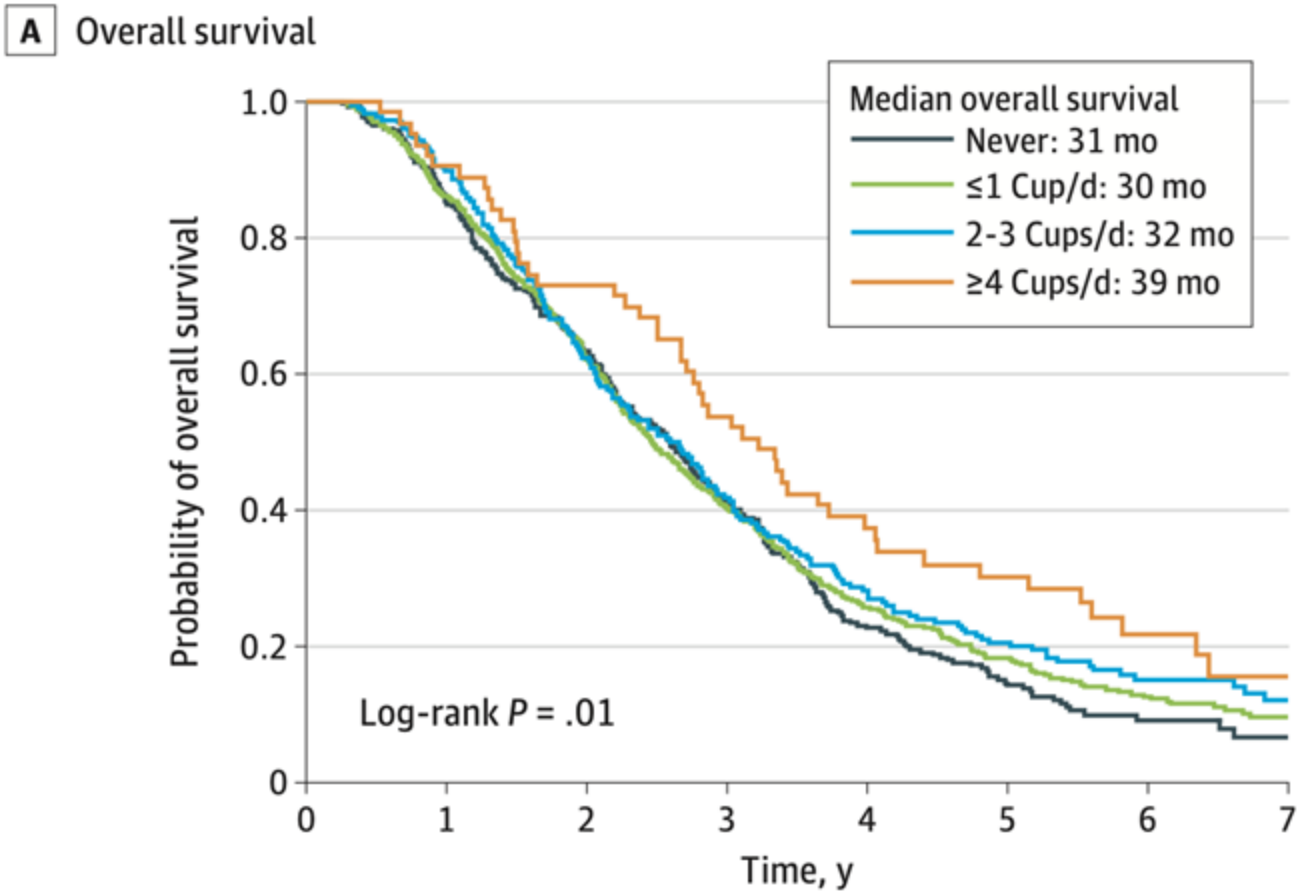

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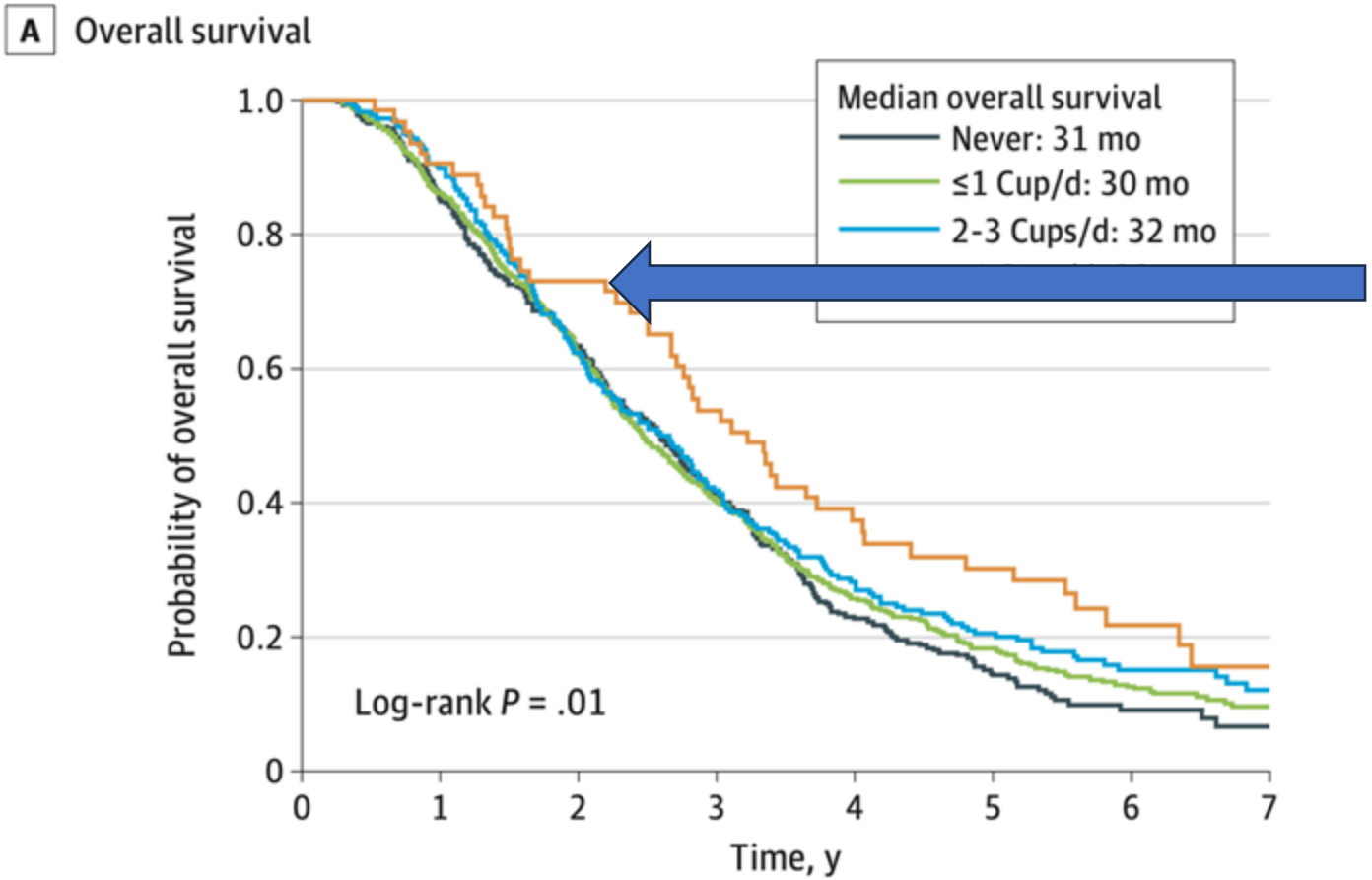

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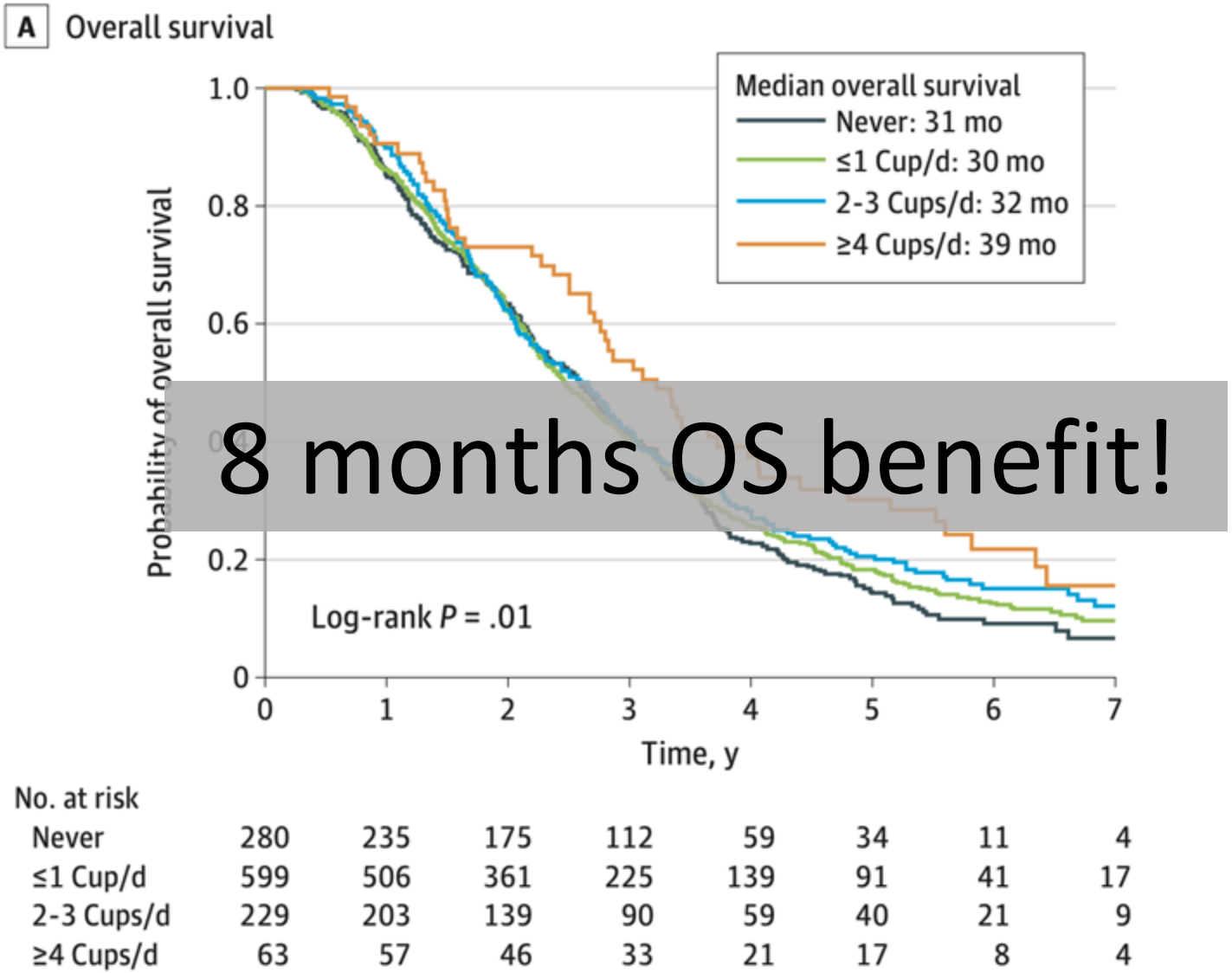

8 months OS benefit!

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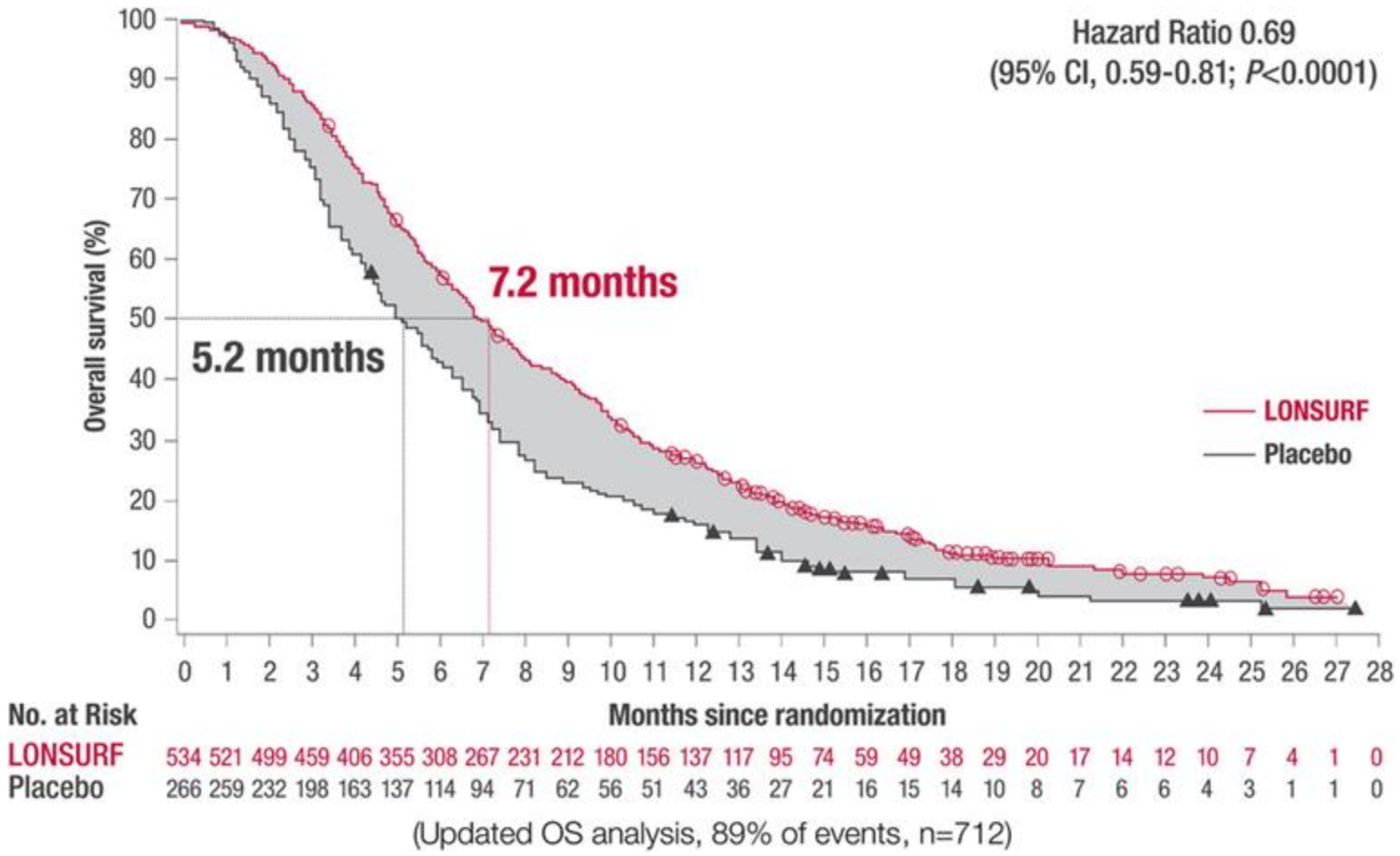
8 month survival benefit from coffee?



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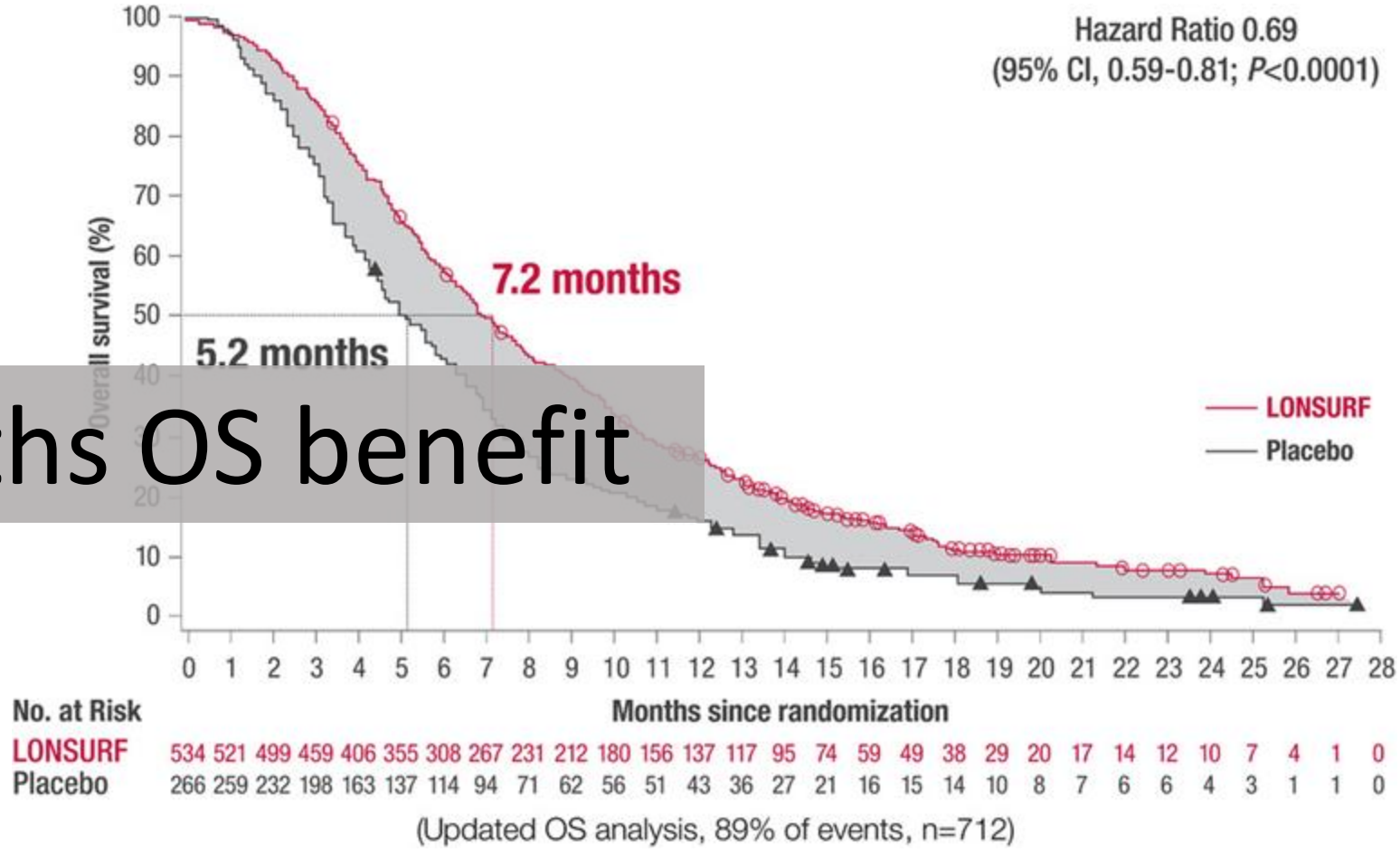

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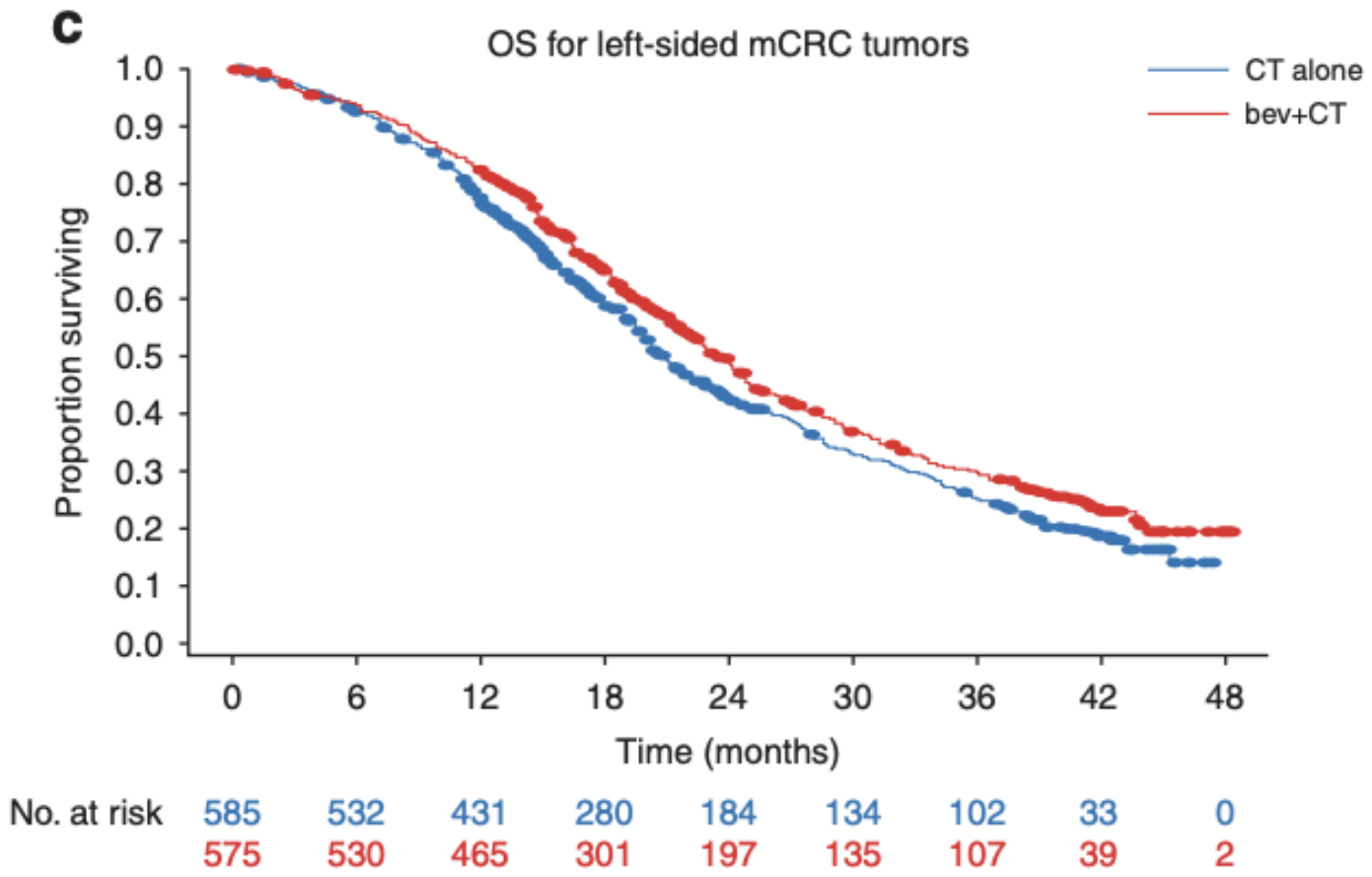

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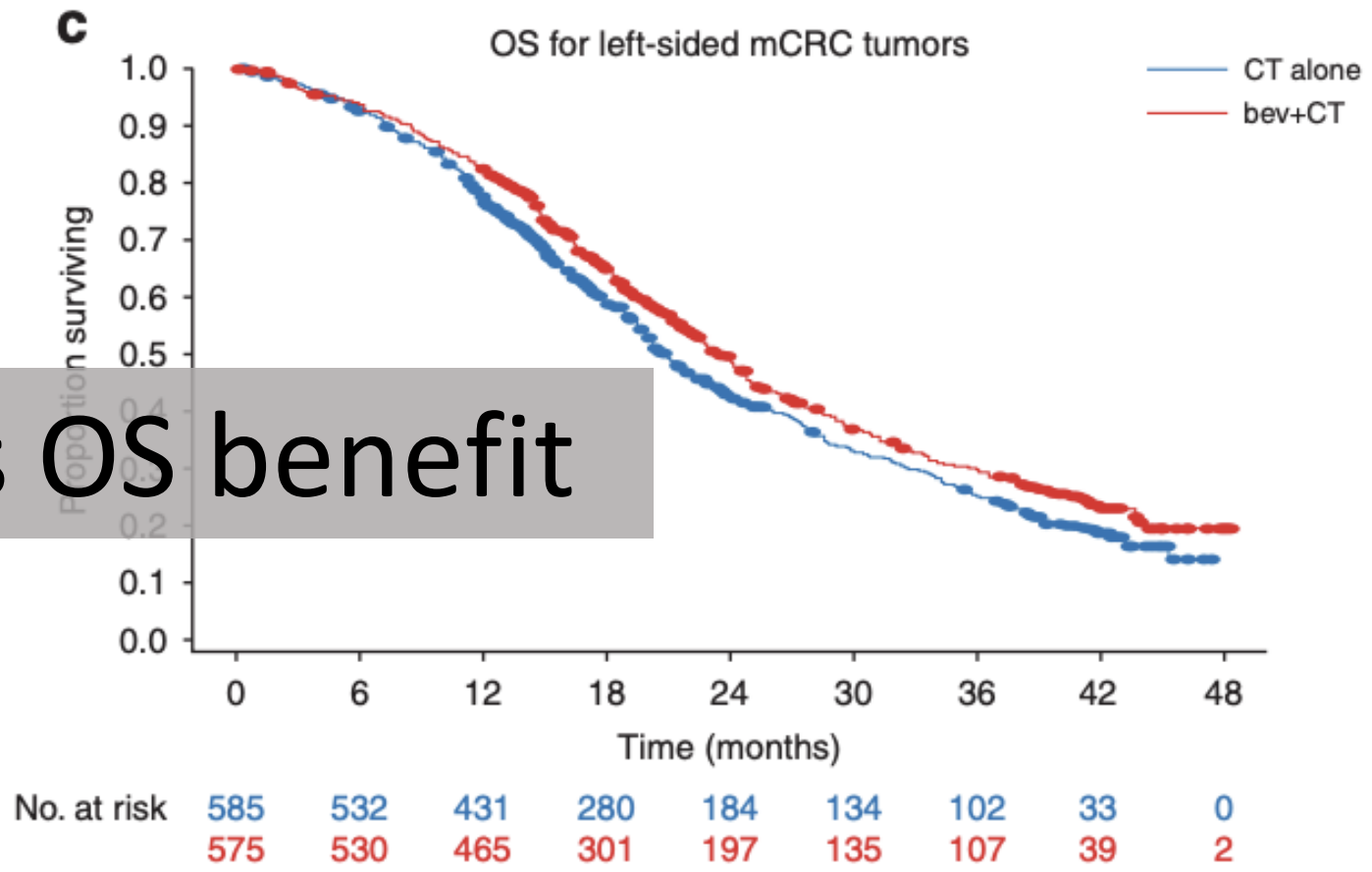

3 months OS benefit

Mackintosh C, Yuan C, Ou FS, Zhang S, Niedzwiecki D, Chang IW, O'Neil BH, Mullen BC, Lenz HJ, Blanke CD, Venook AP. Association of coffee intake with survival in patients with advanced or metastatic colorectal cancer. JAMA oncology. 2020 Nov 1;6(11):1713-21.

Table. Associations of Total, Caffeinated, and Decaffeinated Coffee Consumption With Overall and Progression-Free Su

Variable	Frequency of consumption				
	Never	<1 Cup/d	1 Cup/d	2-3 Cups/d	≥4 Cups/d
Total coffee consumption					
Overall survival					
No. of events/ No. of patients	246/280	248/301	253/298	191/229	49/63
Adjusted HR (95% CI)[b]	1 [Reference]	0.88 (0.74-1.06)	0.89 (0.74-1.07)	0.82 (0.67-0.99)	0.64 (0.47-0.88)
Multivariable HR (95% CI)[c]	1 [Reference]	0.89 (0.75-1.07)	0.91 (0.76-1.09)	0.82 (0.67-1.00)	0.64 (0.46-0.87)

8 months OS benefit!

Pooled				
N	585	575	585	575
Median (95% CI)	8.2 (7.9, 8.5)	10.0 (9.4, 10.8)	20.8 (19.6, 22.4)	23.5 (21.6, 24.8)
HR (95% CI)	0.76 (0.67, 0.86)		0.85 (0.74, 0.98)	
p value	<0.001		0.028	

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COFFEE IS WAY BETTER THAN ACTUAL DRUGS!

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Other clues?

Figure 3. Multivariable-Adjusted Hazard Ratios (HRs) and 95% CIs for Overall and Progression-Free Survival

Body mass index	
<25.0	0.87 (0.80-0.95)
≥25.0	0.96 (0.91-1.02)

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It only works in thin people?

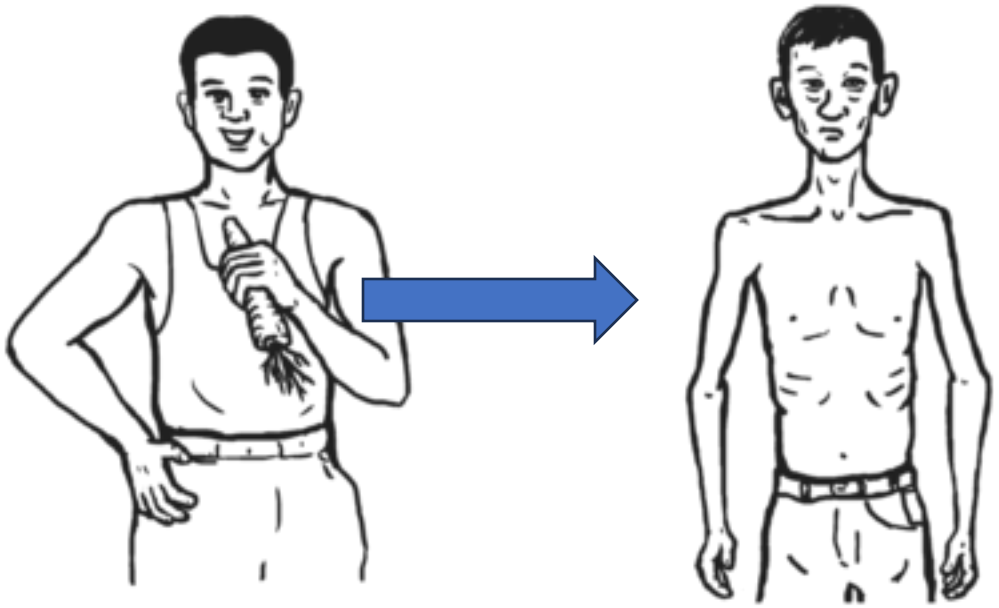
Mackintosh C, Yuan C, Ou FS, Zhang S, Niedzwiecki D, Chang IW, O'Neil BH, Mullen BC, Lenz HJ, Blanke CD, Venook AP. Association of coffee intake with survival in patients with advanced or metastatic colorectal cancer. JAMA oncology. 2020 Nov 1;6(11):1713-21.

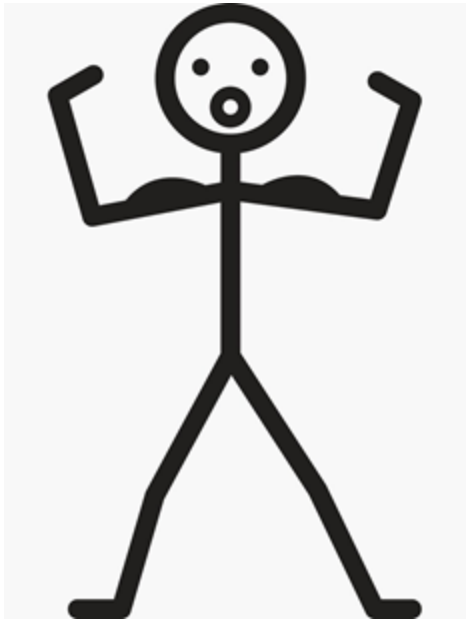
Why?

- Possibility 1: smells spurious

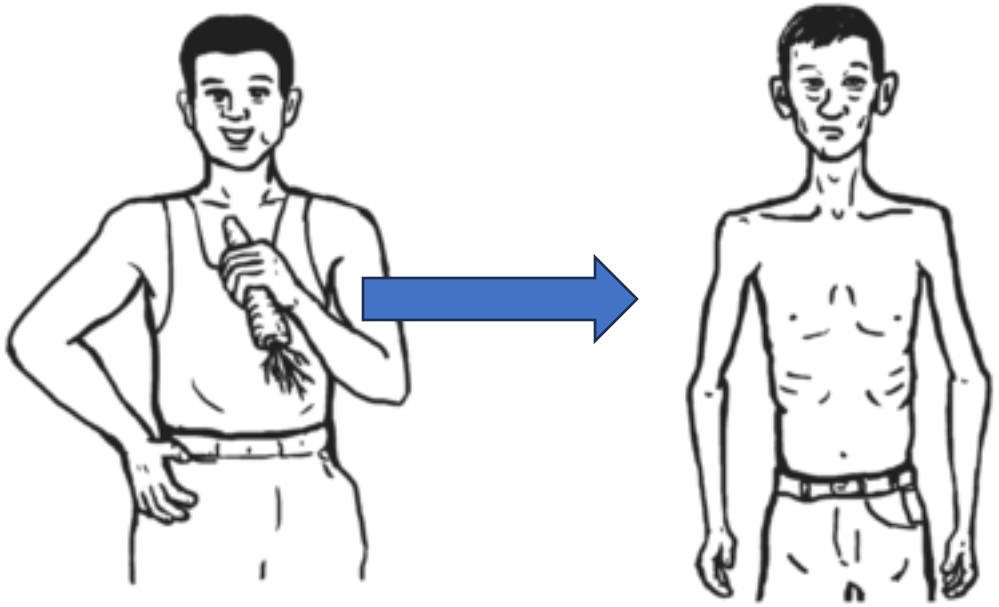
Why?

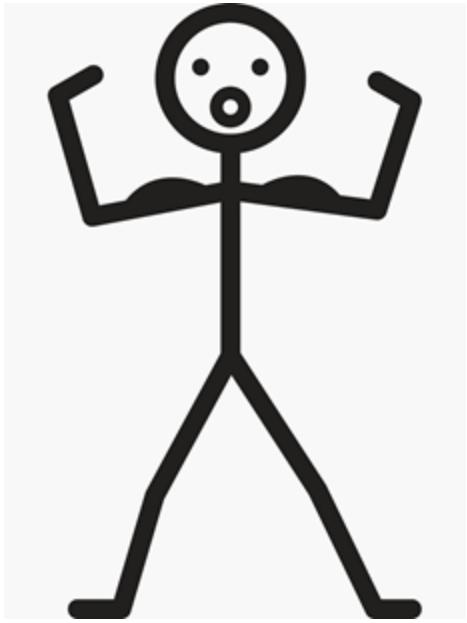
- Possibility 1: smells spurious
- Two reasons to be thin



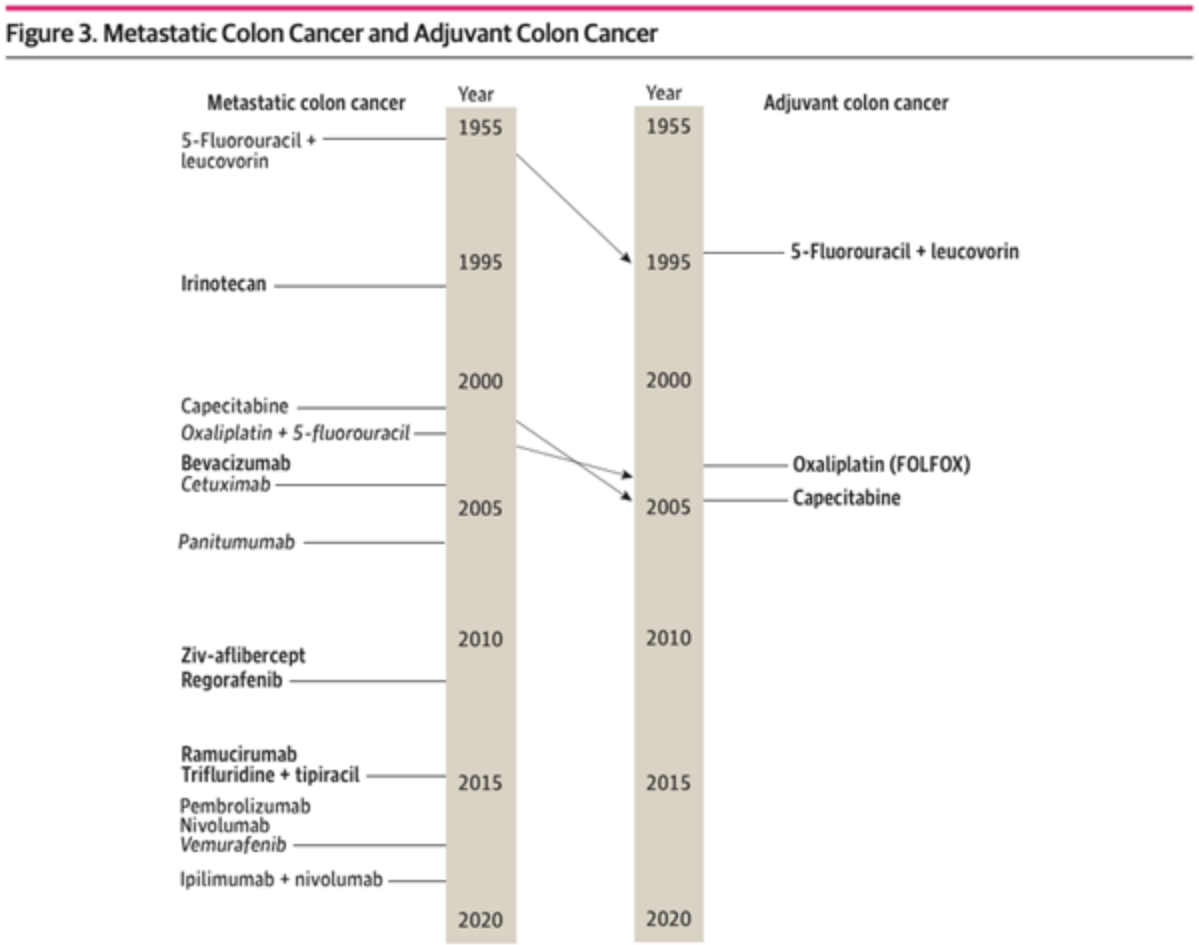


- Who drinks 4 cups of coffee?





Every substance that improves outcomes in colon cancer in metastatic & adjuvant setting



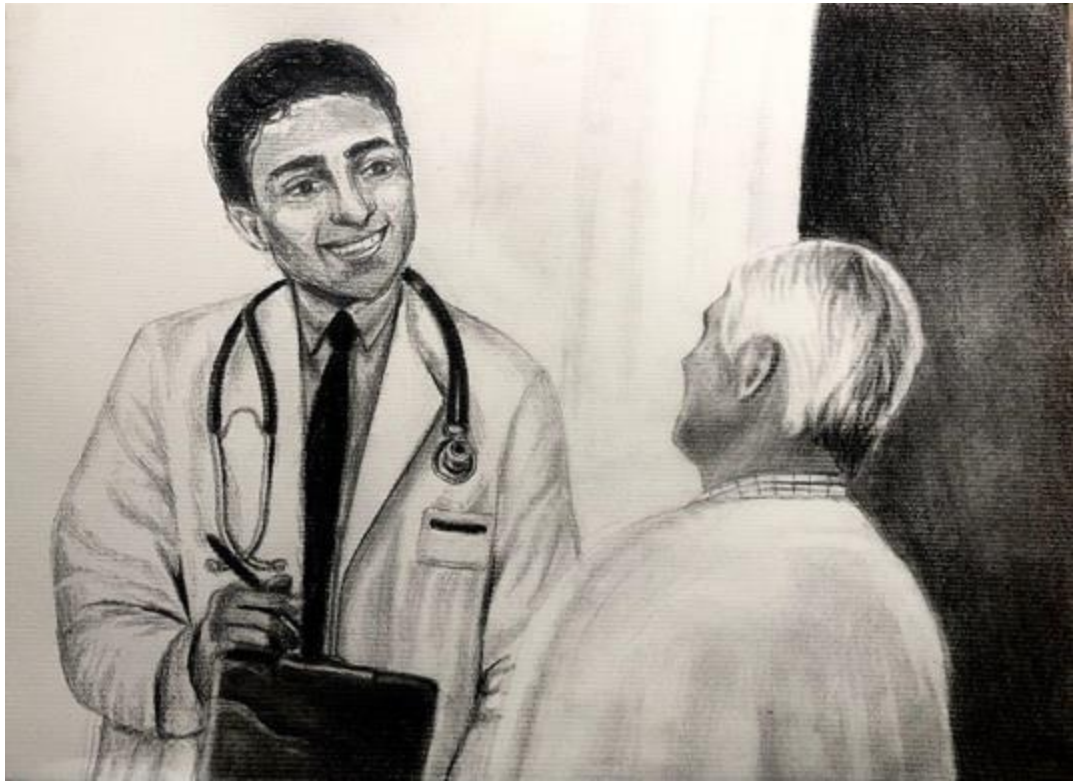
Parsons S, Maldonado EB, Prasad V. Comparison of drugs used for adjuvant and metastatic therapy of colon, breast, and non–small cell lung cancers. JAMA network open. 2020 Apr 1;3(4):e202488-.

Overall take

- Too large effect size
- Small PFS -> large OS (inconsistent effects)
- Larger benefit than actual anti-cancer drugs! (8 vs 2-3 mo; better HR)
- A few random events drive OS curve
- Among thin people, cachectic patients may lose the desire to drink coffee
- No substance that has 0% activity has ever worked in metastatic and adjuvant setting (not biologically plausible)

Overall take

- How did I feel?




Plenary Session

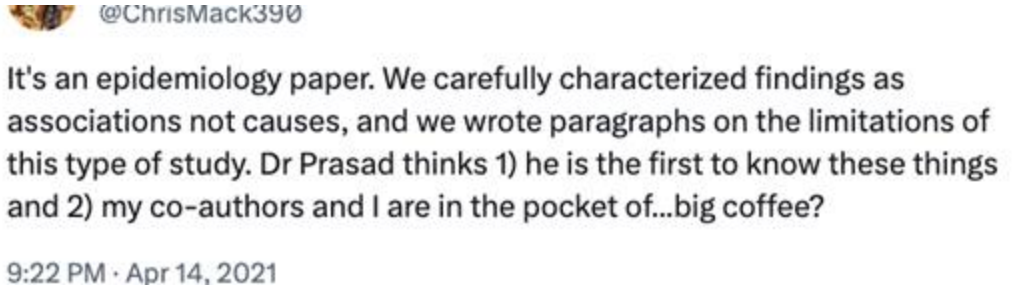
Actually angry b/c people who do this work make it harder to take care of patients

Actually angry b/c people who do this work make it harder to take care of patients

@ChrisMack390

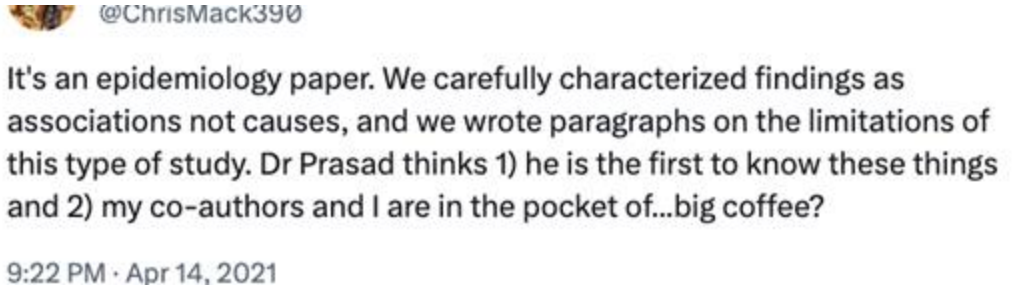
It's an epidemiology paper. We carefully characterized findings as associations not causes, and we wrote paragraphs on the limitations of this type of study. Dr Prasad thinks 1) he is the first to know these things and 2) my co-authors and I are in the pocket of...big coffee?

9:22 PM · Apr 14, 2021



It is not personal, but doing useless research makes it harder to

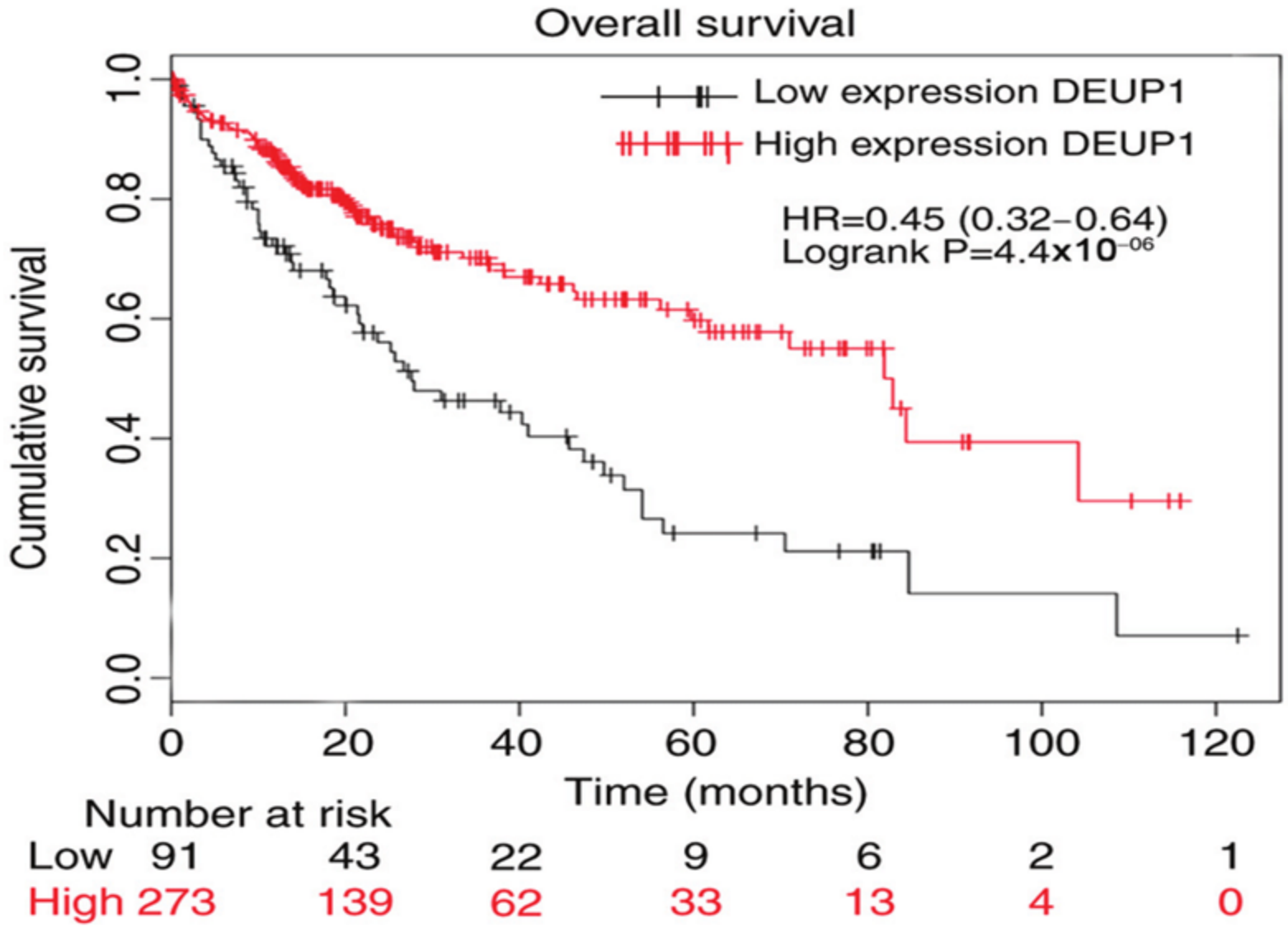
Be a doctor
Teach the public about science
Build trust in science



Great thing
Research
Crazy thing we do in medicine
Careers > truth

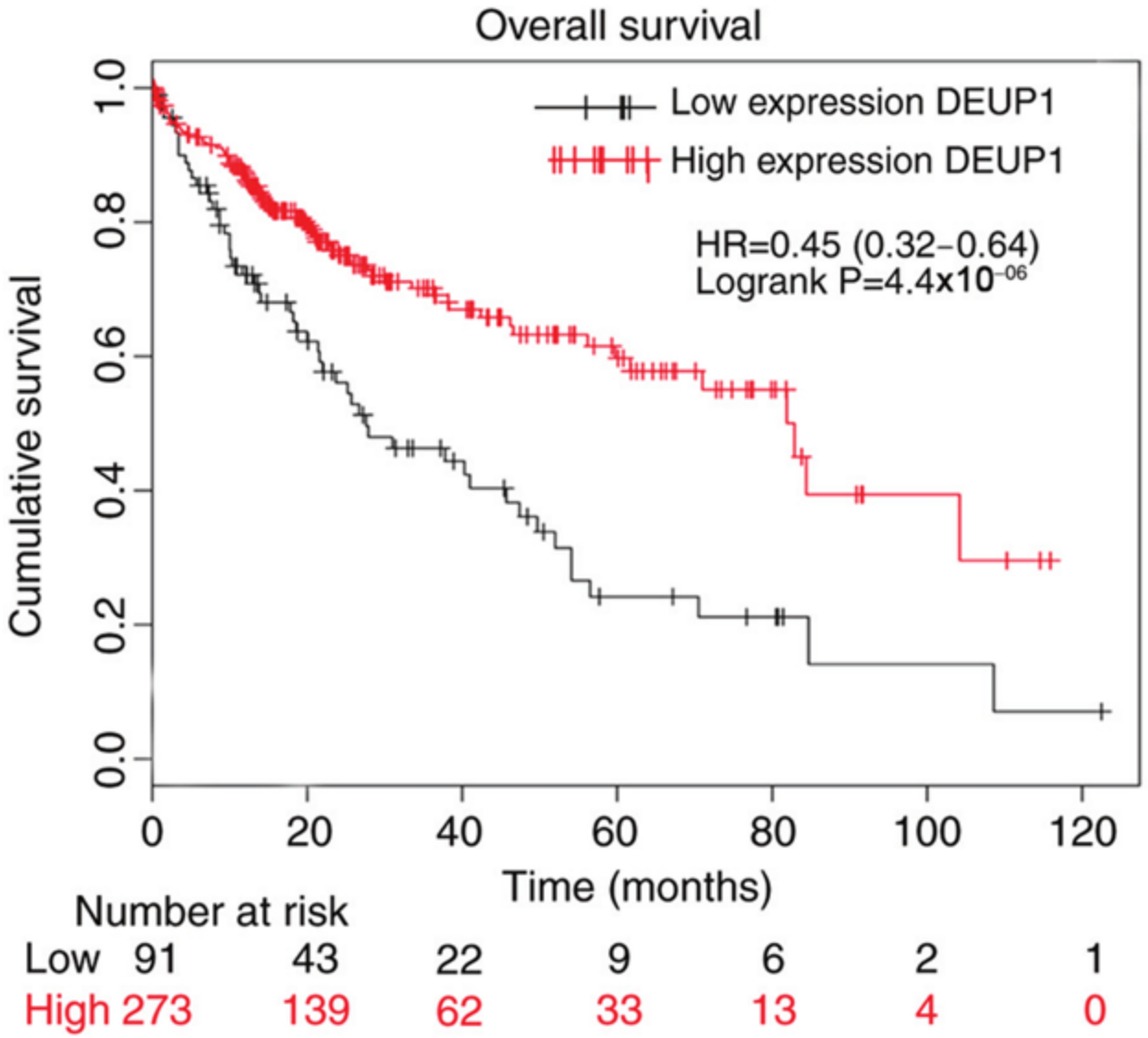
Education

K-M plot



Yu Q, Cao S, Tang H, Li J, Guo W, Zhang S. Clinical significance of aberrant DEUP1 promoter methylation in hepatocellular carcinoma. Oncology Letters. 2019 Aug 1;18(2):1356-64.

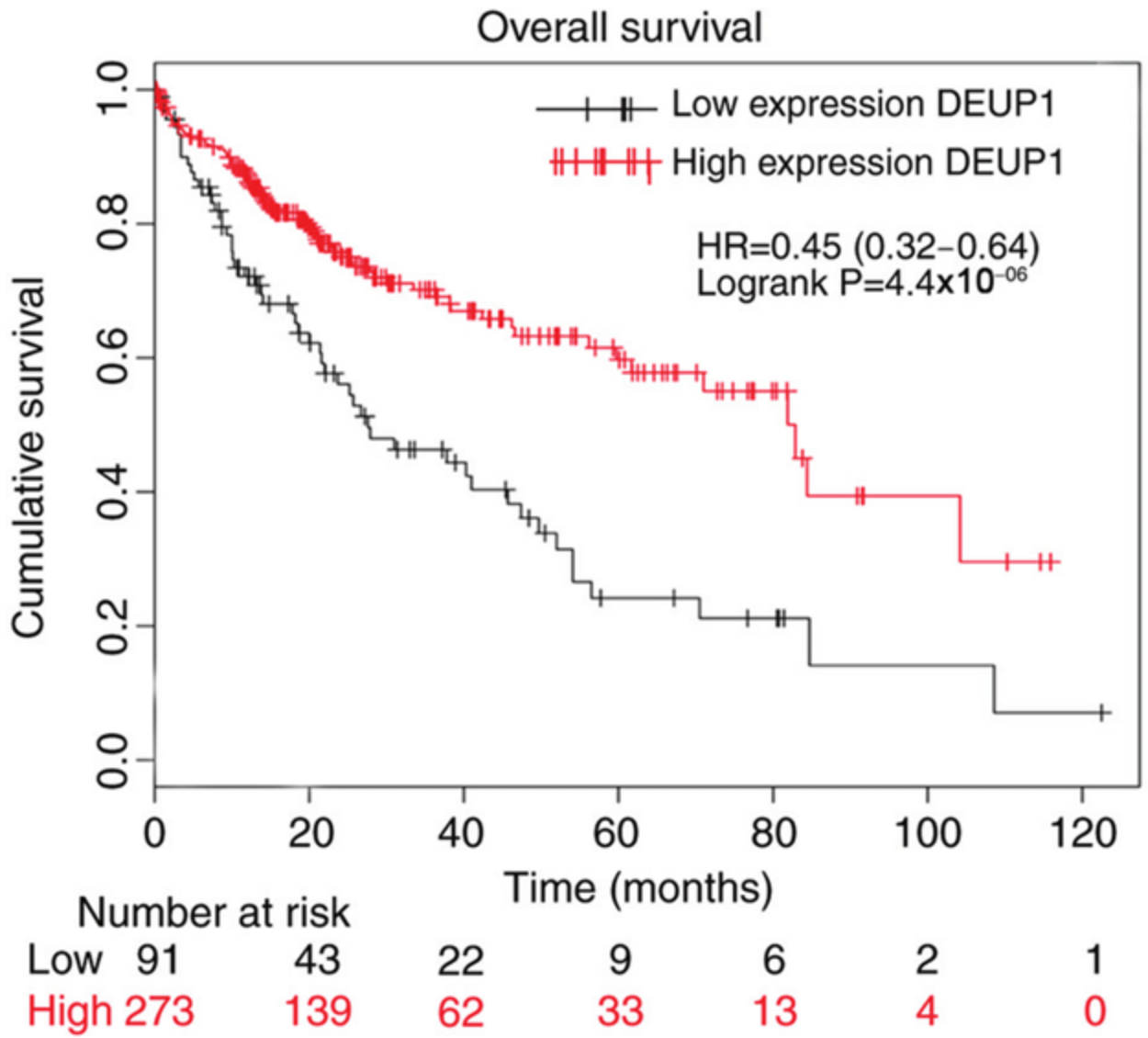
K-M plot



- Every time the curve dips, that means an event occurred
- Numbers at bottom show number of ppl at risk
- Larger steps at the end of the curve is because fewer people are at risk

Yu Q, Cao S, Tang H, Li J, Guo W, Zhang S. Clinical significance of aberrant DEUP1 promoter methylation in hepatocellular carcinoma. Oncology Letters. 2019 Aug 1;18(2):1356-64.

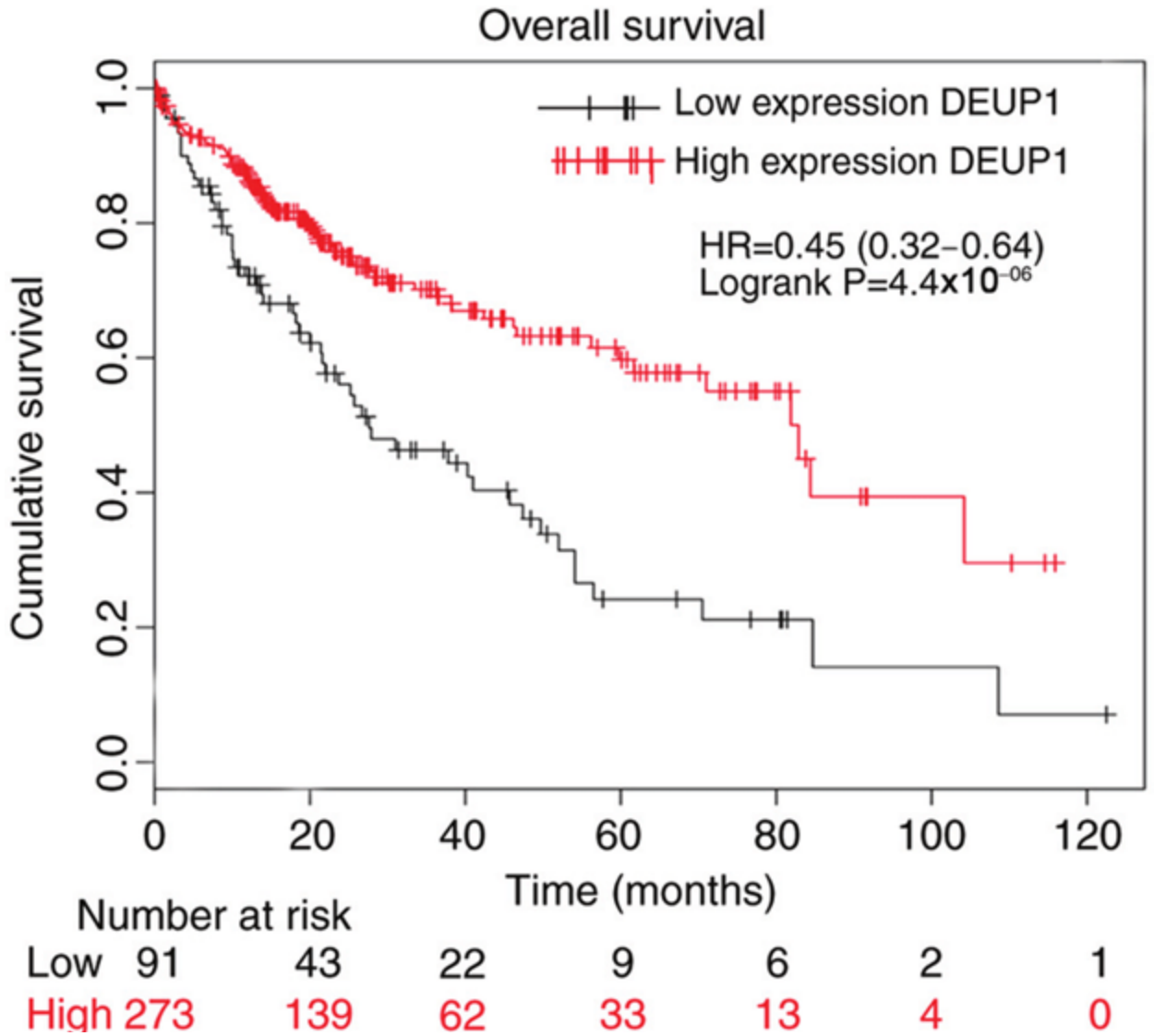
K-M plot



- Vertical tics indicate a patient is censored – we don't know what happened to that person beyond that time
- Estimate of survival beyond tics is avg. people in whom we do know survival

Yu Q, Cao S, Tang H, Li J, Guo W, Zhang S. Clinical significance of aberrant DEUP1 promoter methylation in hepatocellular carcinoma. Oncology Letters. 2019 Aug 1;18(2):1356-64.

K-M plot



- Maximum information harvesting
- Key assumption is uninformative censoring

Yu Q, Cao S, Tang H, Li J, Guo W, Zhang S. Clinical significance of aberrant DEUP1 promoter methylation in hepatocellular carcinoma. Oncology Letters. 2019 Aug 1;18(2):1356-64.

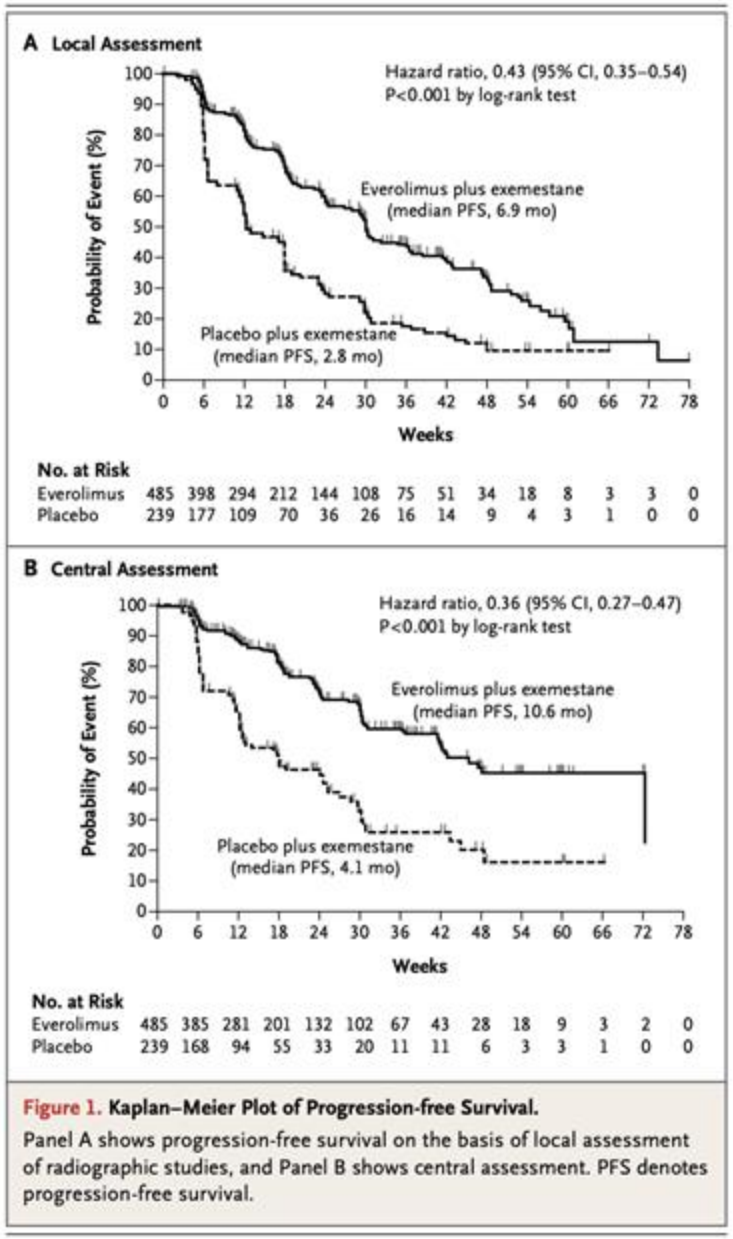
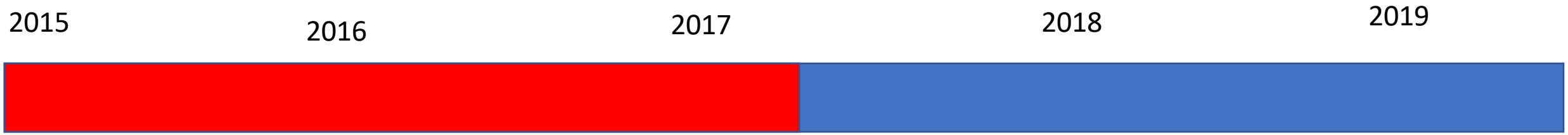


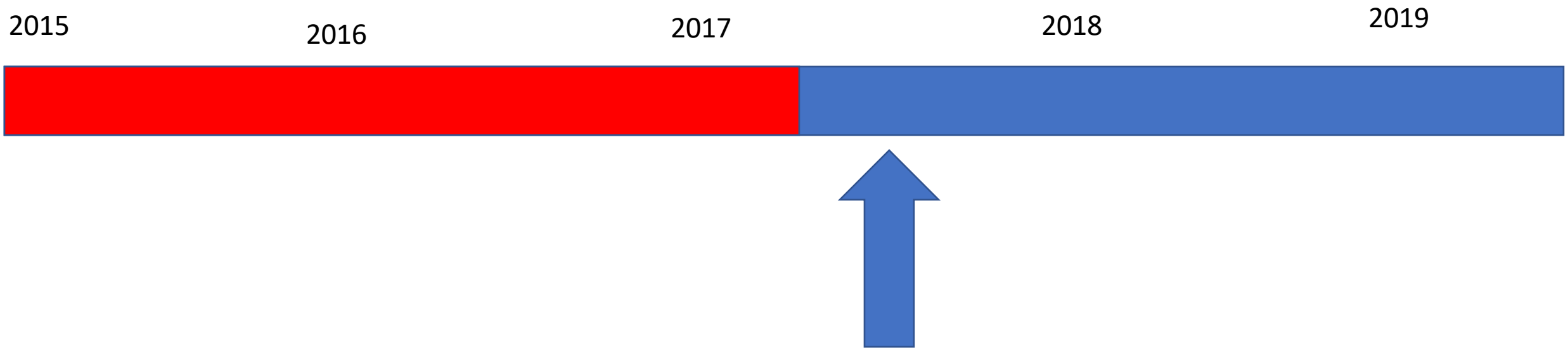
Figure 1. Kaplan–Meier Plot of Progression-free Survival.

Panel A shows progression-free survival on the basis of local assessment of radiographic studies, and Panel B shows central assessment. PFS denotes progression-free survival.

- OS is ascertained continuously
- PFS is binned (why?)

Baselga J, Campone M, Piccart M, Burris III HA, Rugo HS, Sahmoud T, Noguchi S, Gnant M, Pritchard KI, Lebrun F, Beck JT. Everolimus in postmenopausal hormone-receptor–positive advanced breast cancer. New England Journal of Medicine. 2012 Feb 9;366(6):520-9.


2015
2016
2017
2018
2019


2015
2016
2017
2018
2019

What are the reasons someone is censored

- OS
- They enrolled recently
- Lost to follow up

- PFS
- They enrolled recently
- Lost to follow up

What are the reasons someone is censored

- OS
- They enrolled recently
- Lost to follow up

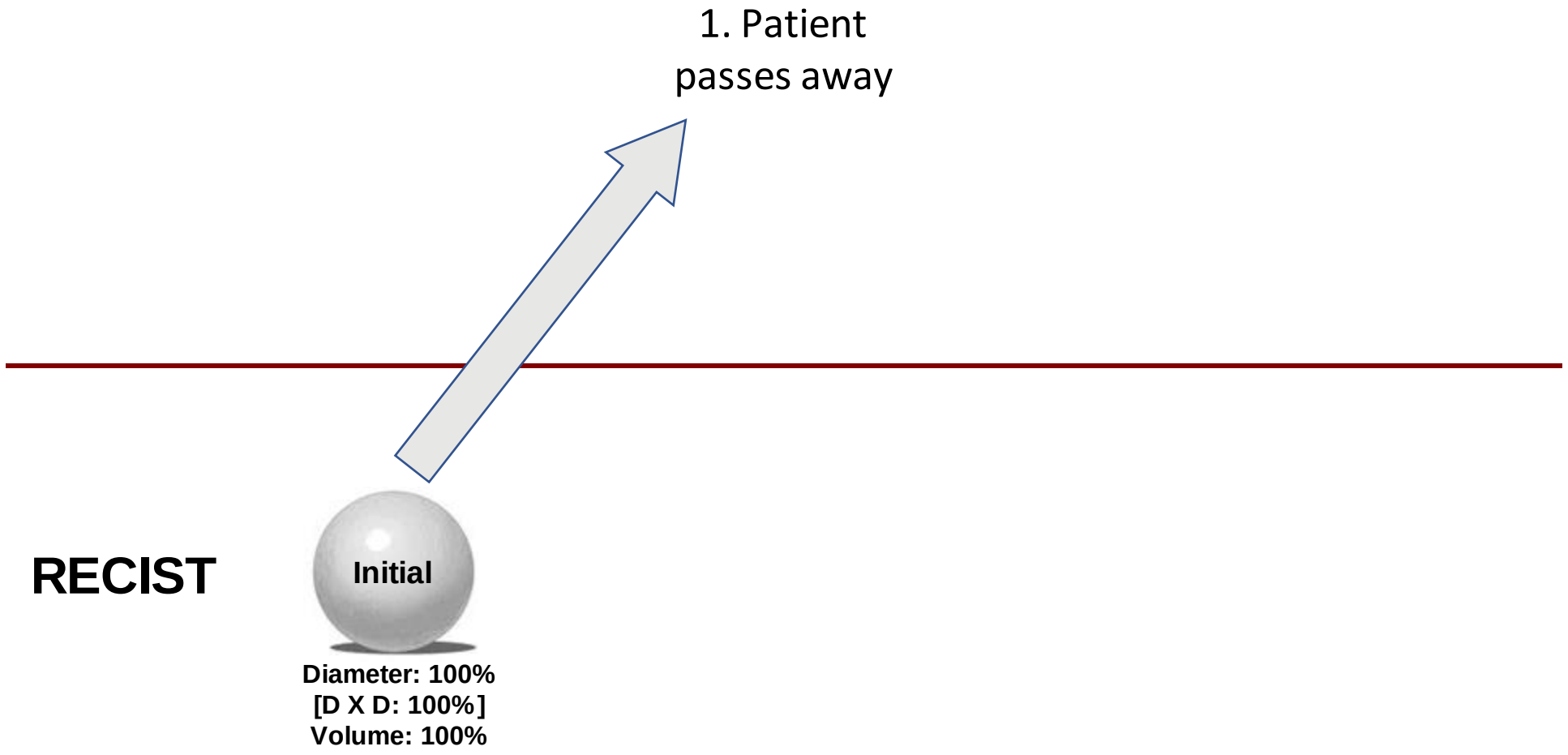
- PFS
- They enrolled recently
- Lost to follow up
- ?????

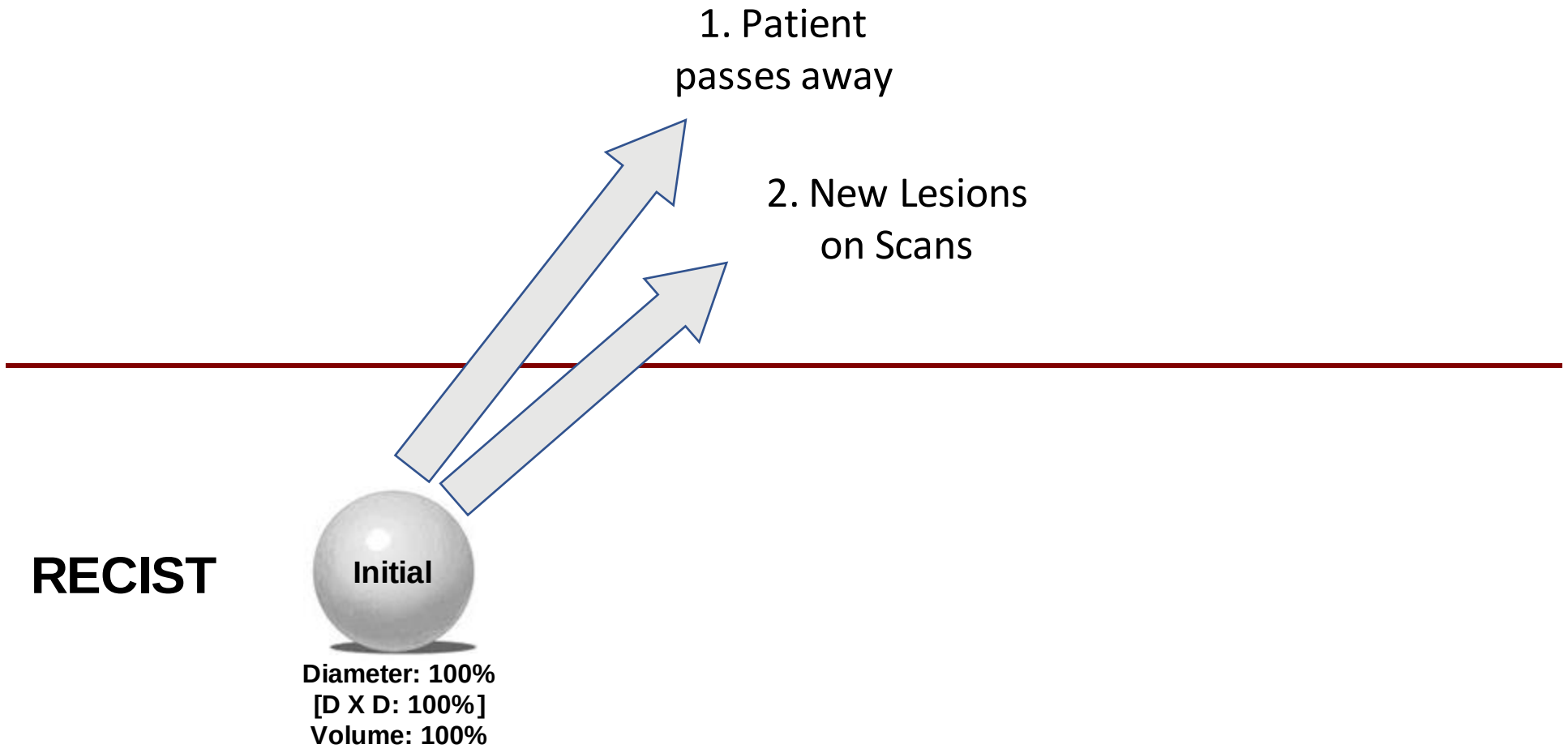
What do you need for PFS that you don’t need for OS

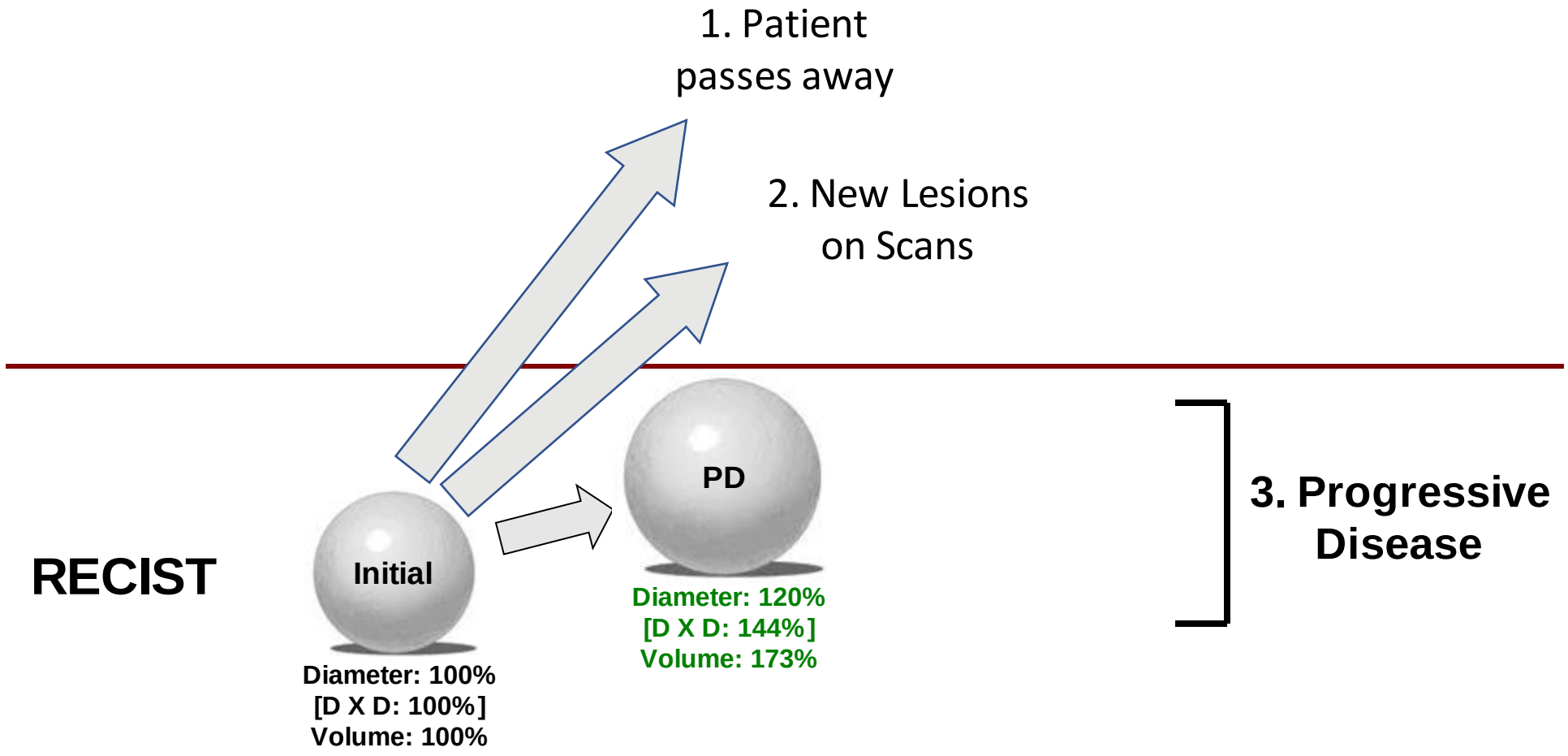

ONE
Aquilion

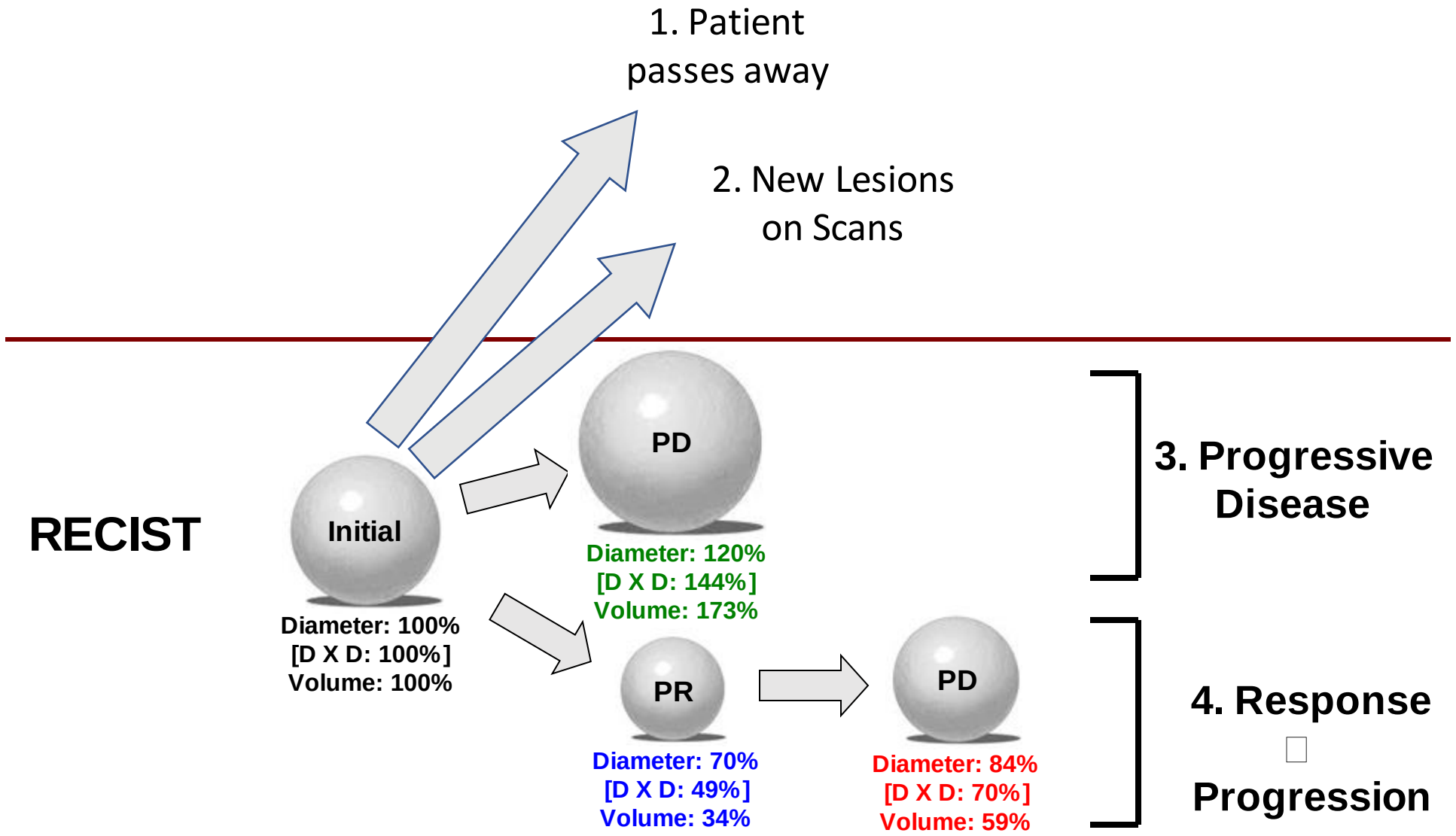
RECIST

Diameter: 100%
[D X D: 100%]
Volume: 100%


1. Patient
passes away
RECIST
Initial
Diameter: 100%
[D X D: 100%]
Volume: 100%


1. Patient
passes away
2. New Lesions
on Scans
RECIST
Initial
Diameter: 100%
[D X D: 100%]
Volume: 100%


1. Patient
passes away
2. New Lesions
on Scans
RECIST
Initial
Diameter: 100%
[D X D: 100%]
Volume: 100%
PD
Diameter: 120%
[D X D: 144%]
Volume: 173%
3. Progressive
Disease


1. Patient passes away
2. New Lesions on Scans
RECIST
Initial
Diameter: 100%
[D X D: 100%]
Volume: 100%
PD
Diameter: 120%
[D X D: 144%]
Volume: 173%
PR
Diameter: 70%
[D X D: 49%]
Volume: 34%
PD
Diameter: 84%
[D X D: 70%]
Volume: 59%
3. Progressive Disease
4. Response
Progression

What are the reasons someone is censored

- OS
- They enrolled recently
- Lost to follow up

- PFS
- They enrolled recently
- Lost to follow up
- Patient has to get the scan

ORIGINAL ARTICLE

Everolimus in Postmenopausal Hormone-Receptor–Positive Advanced Breast Cancer

José Baselga, M.D., Ph.D., Mario Campone, M.D., Ph.D., Martine Piccart, M.D., Ph.D., Howard A. Burris III, M.D., Hope S. Rugo, M.D., Tarek Sahmoud, M.D., Ph.D., Shinzaburo Noguchi, M.D., Michael Gnant, M.D., Kathleen I. Pritchard, M.D., Fabienne Lebrun, M.D., J. Thaddeus Beck, M.D., Yoshinori Ito, M.D., Denise Yardley, M.D., Ines Deleu, M.D., Alejandra Perez, M.D., Thomas Bachelot, M.D., Ph.D., Luc Vittori, M.Sc., Zhiying Xu, Ph.D., Pabak Mukhopadhyay, Ph.D., David Lebwohl, M.D., and Gabriel N. Hortobagyi, M.D.

From Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston (J.B.); Institut de Cancérologie de l'Ouest/René Gauducheau, Nantes Saint Herblain, France (M.C.); Institute Jules Bordet, Brussels (M.P., F.L.); Sarah Cannon Research Institute, Nashville (H.A.B., D.Y.); University of California, San Francisco, Helen Diller Family Comprehensive Cancer Center, San Francisco (H.S.R.); Novartis, East Hanover, NJ (T.S., Z.X., P.M., D.L.); Osaka University, Department of Breast and Endocrine Surgery, Osaka, Japan (S.N.); the Department of Surgery, Comprehensive Cancer Center, Medical University of Vienna, Vienna (M.G.); Sunnybrook Odette Cancer Centre and the University of Toronto, Toronto (K.I.P.); Highlands Oncology Group, Fayetteville, AR (J.T.B.); Cancer Institute Hospital of Japanese Foundation for Cancer Research, Ariake, Tokyo (Y.I.); Oncology Center, AZ Nikolass, Sint-Niklaas, Belgium (I.D.); Memorial Cancer Institute, Hollywood, FL (A.P.); Centre Léon-Bérard, Lyon, France (T.B.); Novartis Pharma, Basel, Switzerland (L.V.); and the University of Texas M.D. Anderson Cancer Center, Houston (G.N.H.). Address reprint requests to Dr. Baselga at the Division of Hematology/Oncology, Massachusetts General Hospital Cancer Center, 55 Fruit St., Lawrence House 108, Boston, MA 02114, or at jbaselga@partners.org.

This article (10.1056/NEJMoa1109653) was published on December 7, 2011, and updated on December 13, 2011, at NEJM.org.

N Engl J Med 2012;366:520-9.

ABSTRACT

BACKGROUND

Resistance to endocrine therapy in breast cancer is associated with activation of the mammalian target of rapamycin (mTOR) intracellular signaling pathway. In early studies, the mTOR inhibitor everolimus added to endocrine therapy showed antitumor activity.

METHODS

In this phase 3, randomized trial, we compared everolimus and exemestane versus exemestane and placebo (randomly assigned in a 2:1 ratio) in 724 patients with hormone-receptor–positive advanced breast cancer who had recurrence or progression while receiving previous therapy with a nonsteroidal aromatase inhibitor in the adjuvant setting or to treat advanced disease (or both). The primary end point was progression-free survival. Secondary end points included survival, response rate, and safety. A preplanned interim analysis was performed by an independent data and safety monitoring committee after 359 progression-free survival events were observed.

RESULTS

Baseline characteristics were well balanced between the two study groups. The median age was 62 years, 56% had visceral involvement, and 84% had hormone-sensitive disease. Previous therapy included letrozole or anastrozole (100%), tamoxifen (48%), fulvestrant (16%), and chemotherapy (68%). The most common grade 3 or 4 adverse events were stomatitis (8% in the everolimus-plus-exemestane group vs. 1% in the placebo-plus-exemestane group), anemia (6% vs. <1%), dyspnea (4% vs. 1%), hyperglycemia (4% vs. <1%), fatigue (4% vs. 1%), and pneumonitis (3% vs. 0%). At the interim analysis, median progression-free survival was 6.9 months with everolimus plus exemestane and 2.8 months with placebo plus exemestane, according to assessments by local investigators (hazard ratio for progression or death, 0.43; 95% confidence interval [CI], 0.35 to 0.54; P<0.001). Median progression-free survival was 10.6 months and 4.1 months, respectively, according to central assessment (hazard ratio, 0.36; 95% CI, 0.27 to 0.47; P<0.001).

CONCLUSIONS

Everolimus combined with an aromatase inhibitor improved progression-free survival in patients with hormone-receptor–positive advanced breast cancer previously treated with nonsteroidal aromatase inhibitors. (Funded by Novartis; BOLERO-2 ClinicalTrials.gov number, NCT00863655.)

Baselga J, Campone M, Piccart M, Burris III HA, Rugo HS, Sahmoud T, Noguchi S, Gnant M, Pritchard KI, Lebrun F, Beck JT. Everolimus in postmenopausal hormone-receptor–positive advanced breast cancer. New England Journal of Medicine. 2012 Feb 9;366(6):520-9.

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FDA Approves Everolimus for Advanced Breast Cancer

Ben Leach
Published: Monday, Jul 23, 2012

The FDA has approved everolimus (Afinitor, Novartis) for treating patients with hormone receptor-positive, HER2-negative breast cancer, when given in combination with the aromatase inhibitor exemestane.

José Baselga, MD, PhD

The interim analysis of the study by local investigators found that median PFS in the everolimus plus exemestane arm was 6.9 months compared with 2.8 months in the placebo plus exemestane arm (hazard ratio [HR]=0.43; CI 95%, 0.35-0.54; *P* <.001). A separate central assessment also found that median PFS was 10.6 months in the everolimus arm and 4.1 months in the control arm (HR=0.36; 95% CI, 0.27-0.47; *P* < .001).

Related Articles

NewYork-Presbyterian/Columbia University Breast Cancer Faculty Share 2020 Resolutions to Improve Patient Care

Immunotherapy

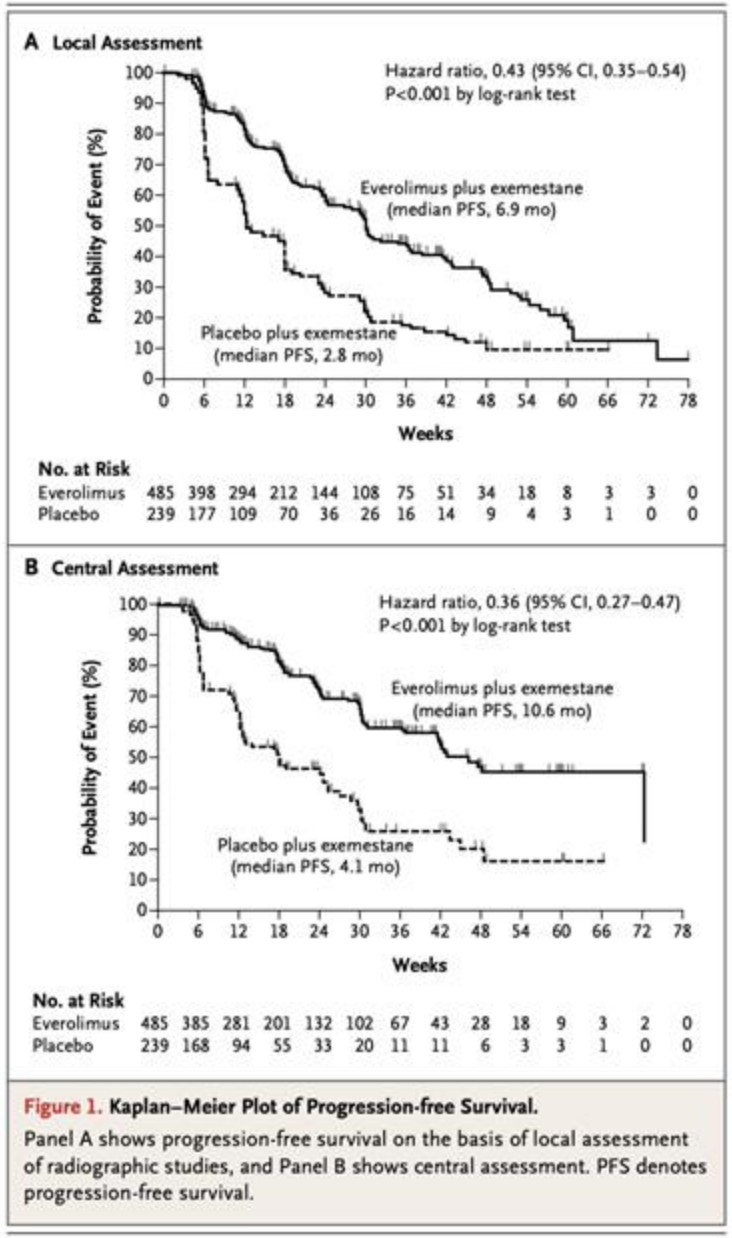

Figure 1. Kaplan–Meier Plot of Progression-free Survival.

Panel A shows progression-free survival on the basis of local assessment of radiographic studies, and Panel B shows central assessment. PFS denotes progression-free survival.

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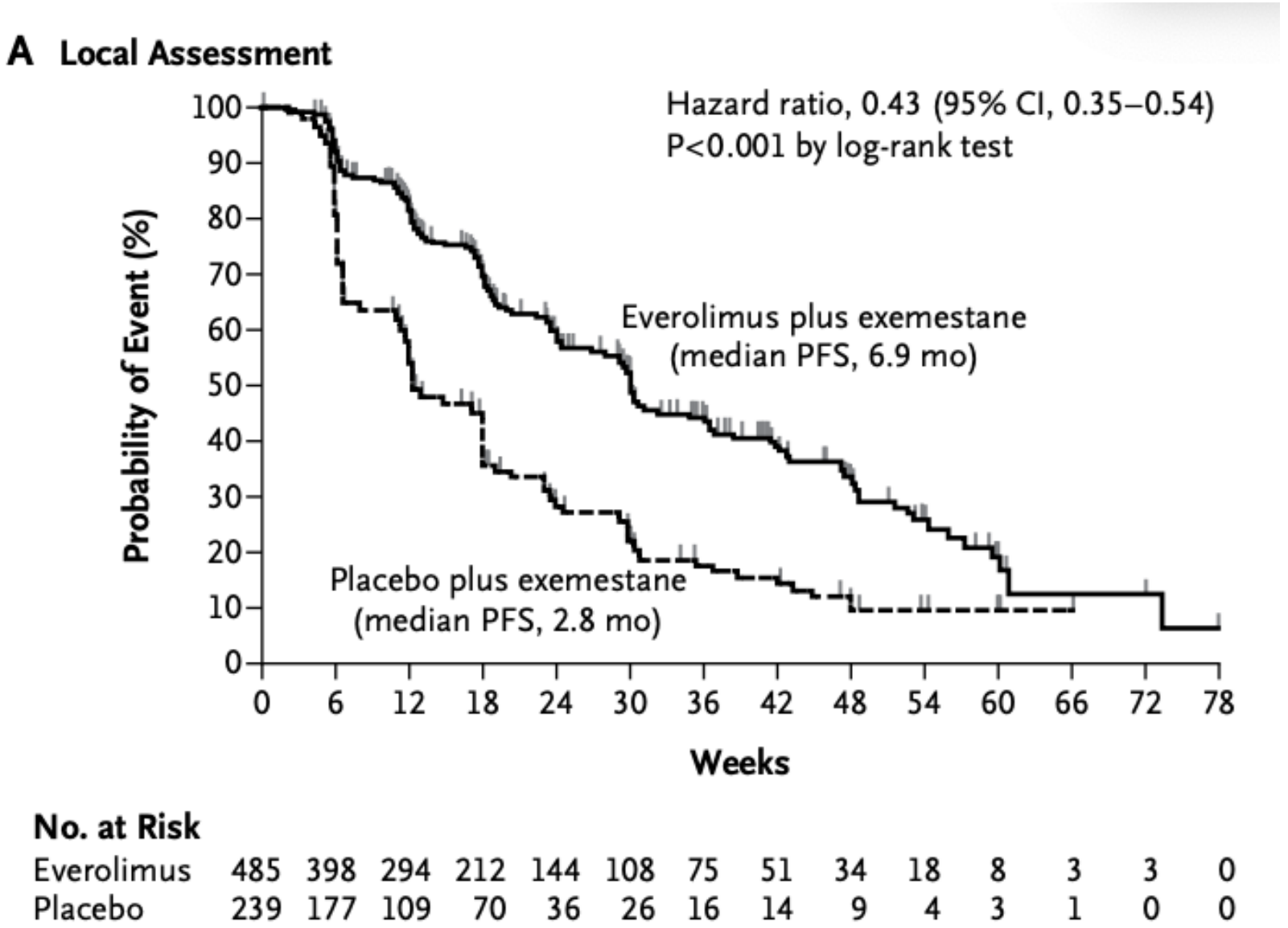

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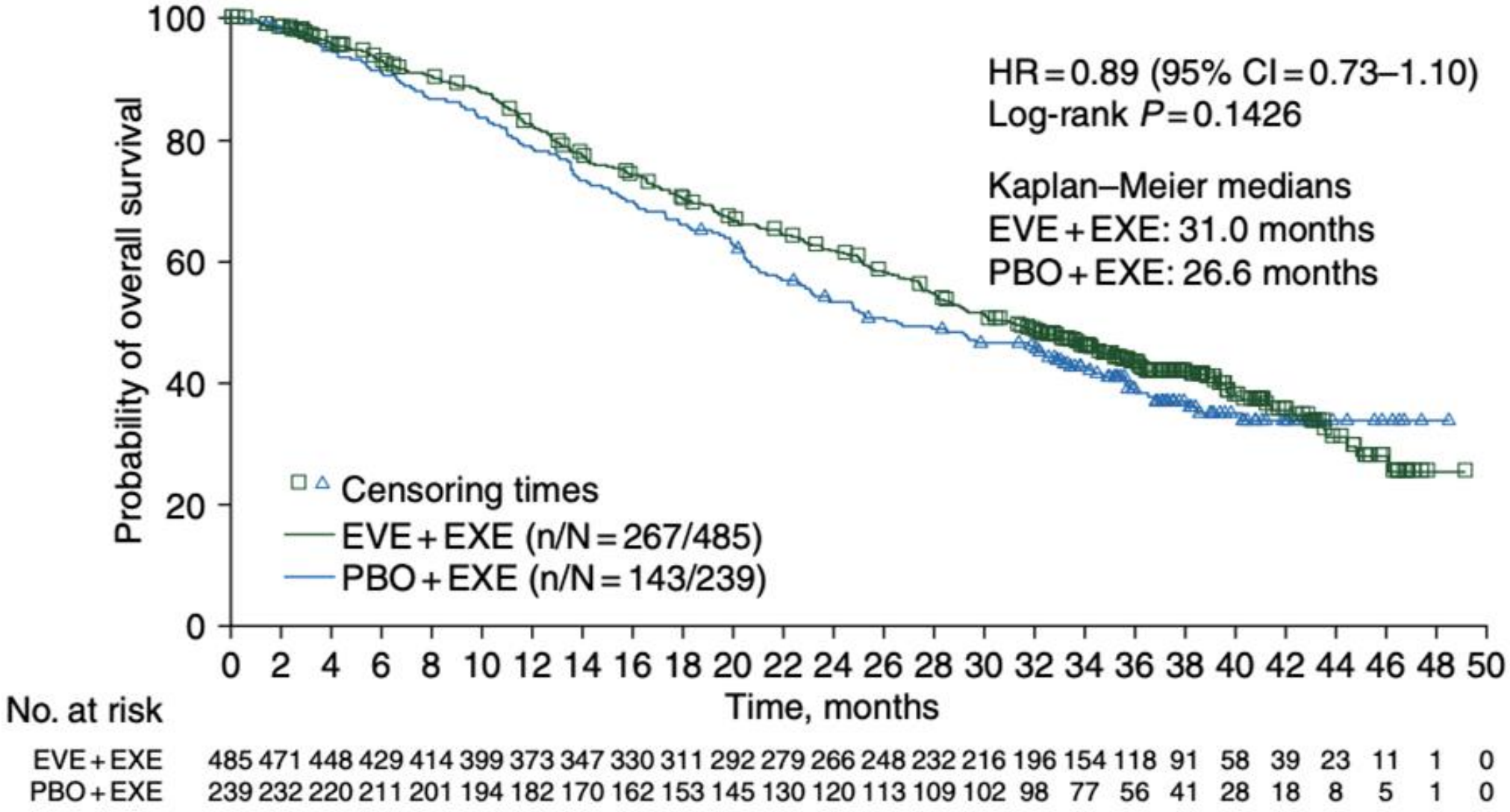
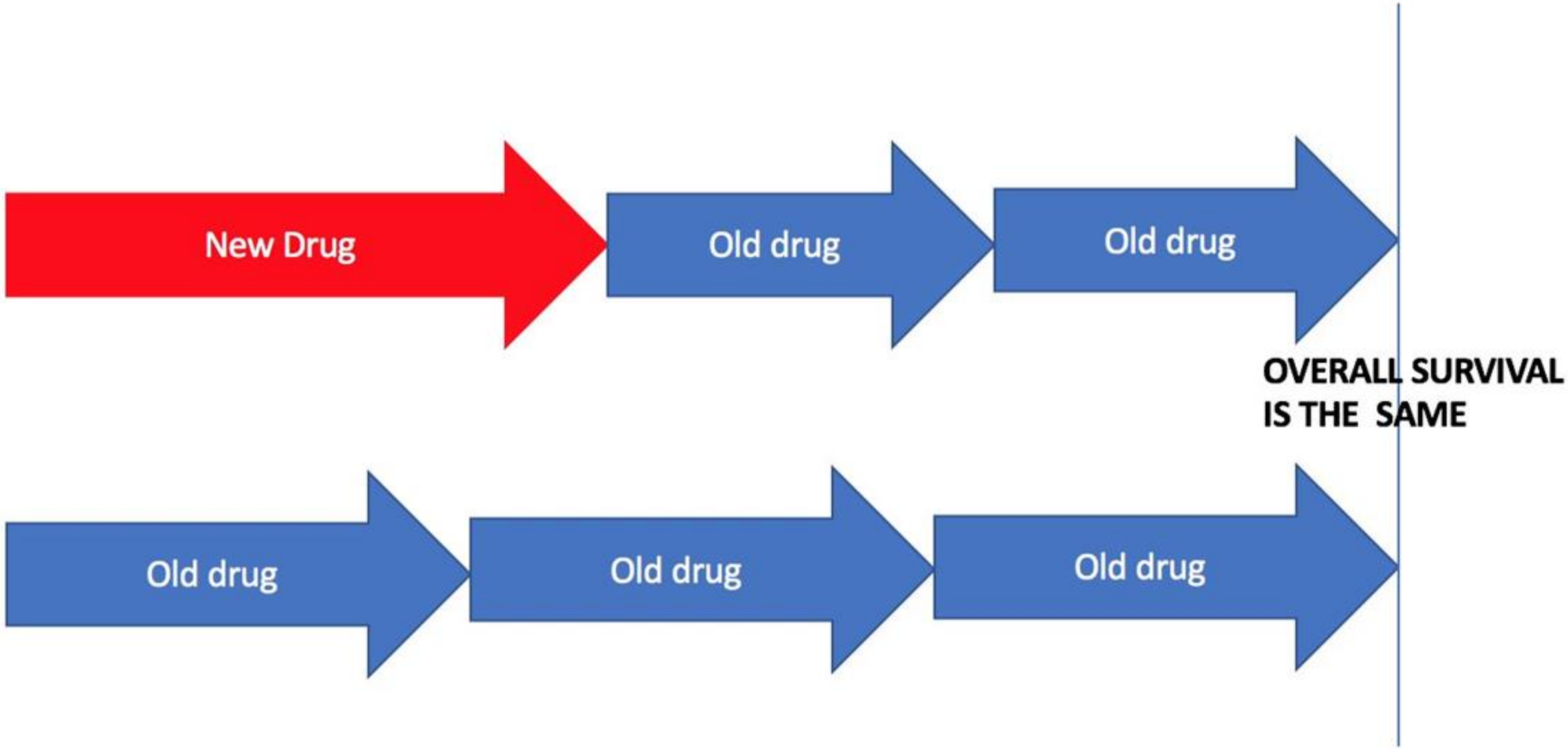
Piccart M, Hortobagyi GN, Campone M, Pritchard KI, Lebrun F, Ito Y, Noguchi S, Perez A, Rugo HS, Deleu I, Burris III HA. Everolimus plus exemestane for hormone-receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: overall survival results from BOLERO-2. Annals of oncology. 2014 Dec 1;25(12):2357-62.



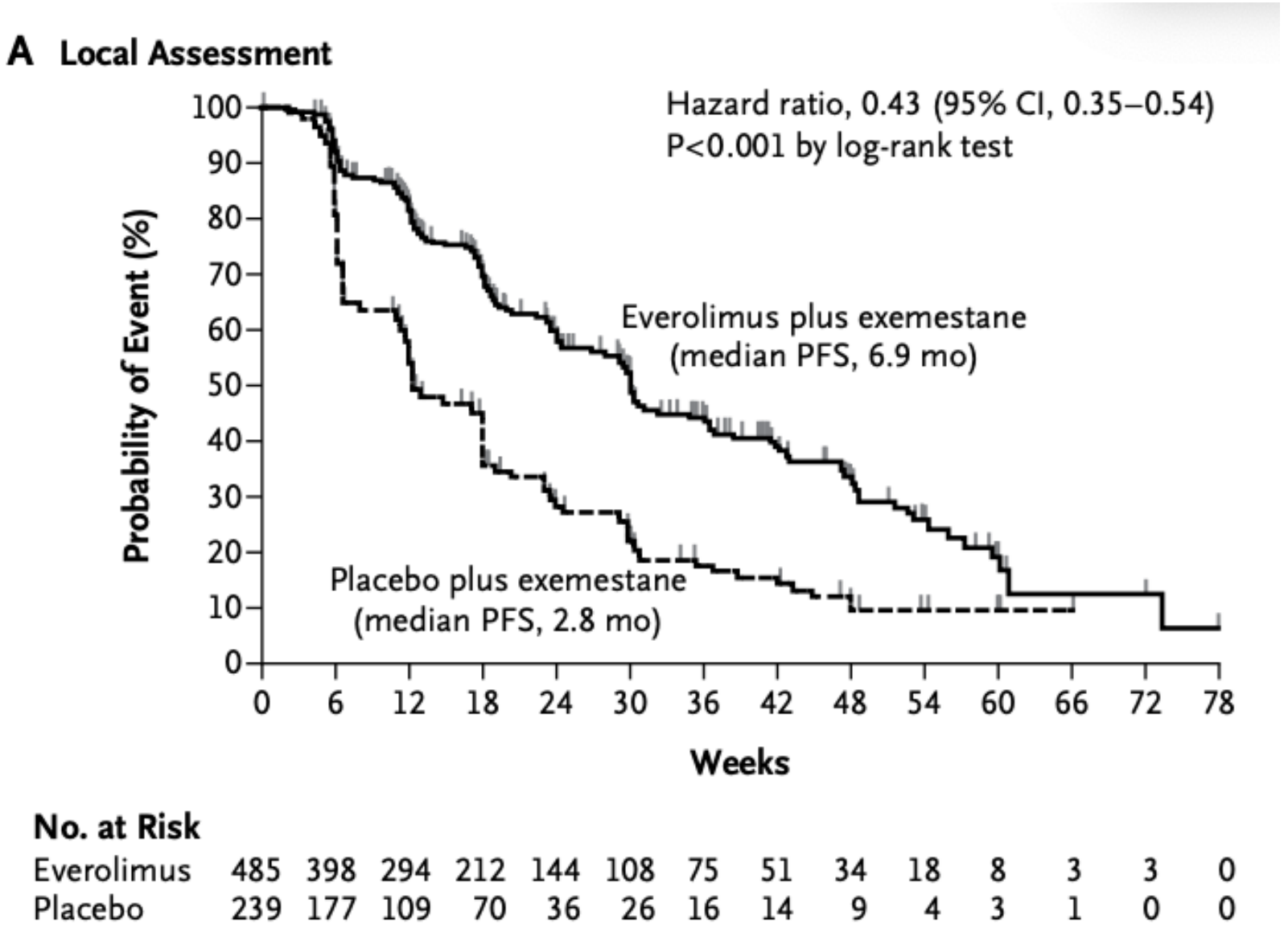
Kaplan–Meier estimates of overall survival. CI, confidence interval; EVE, everolimus; EXE, exemestane; HR, hazard ratio; PBO, placebo.

Why does this happen?



@vprasadmdmph

Is that the only reason?



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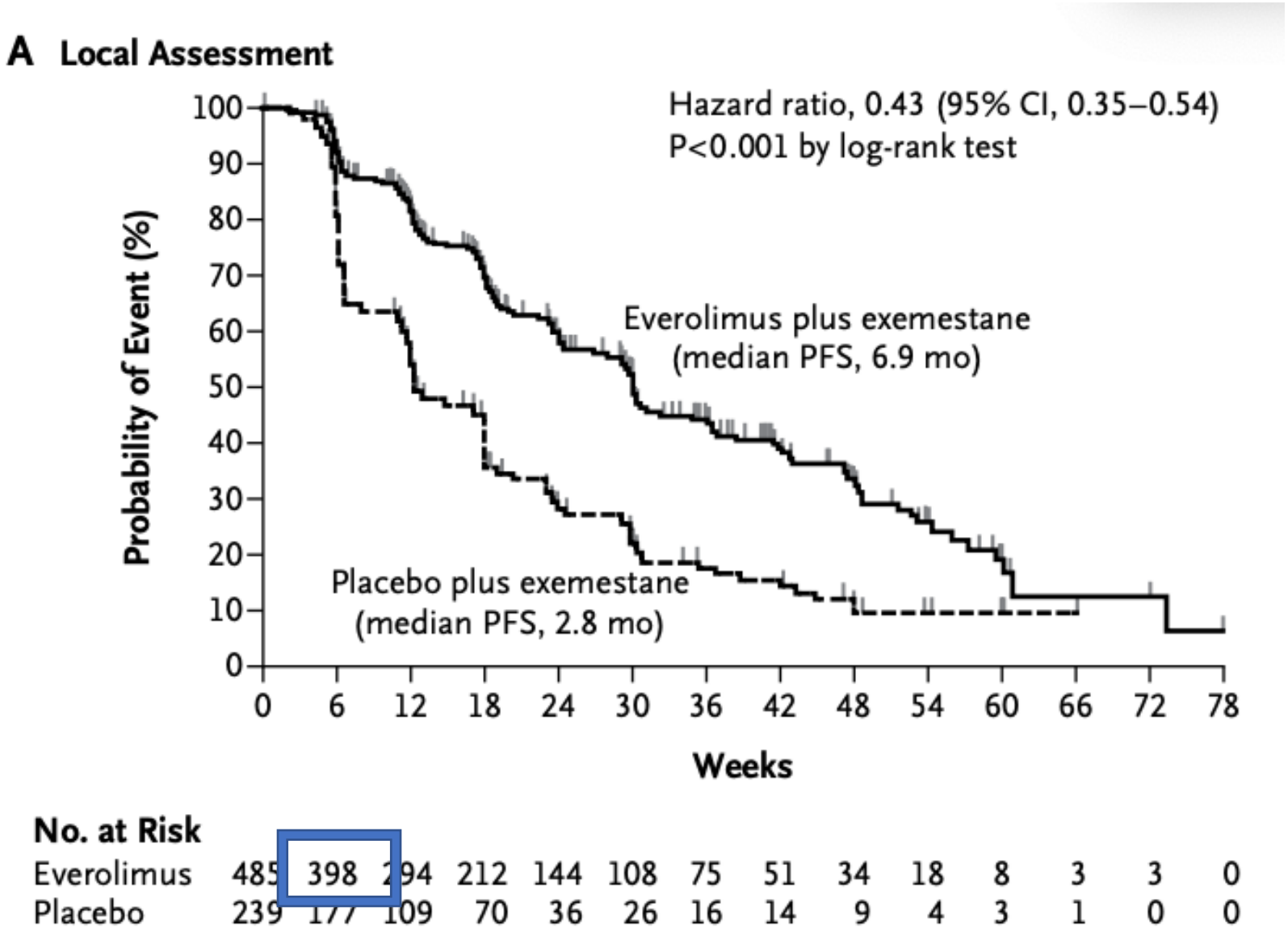

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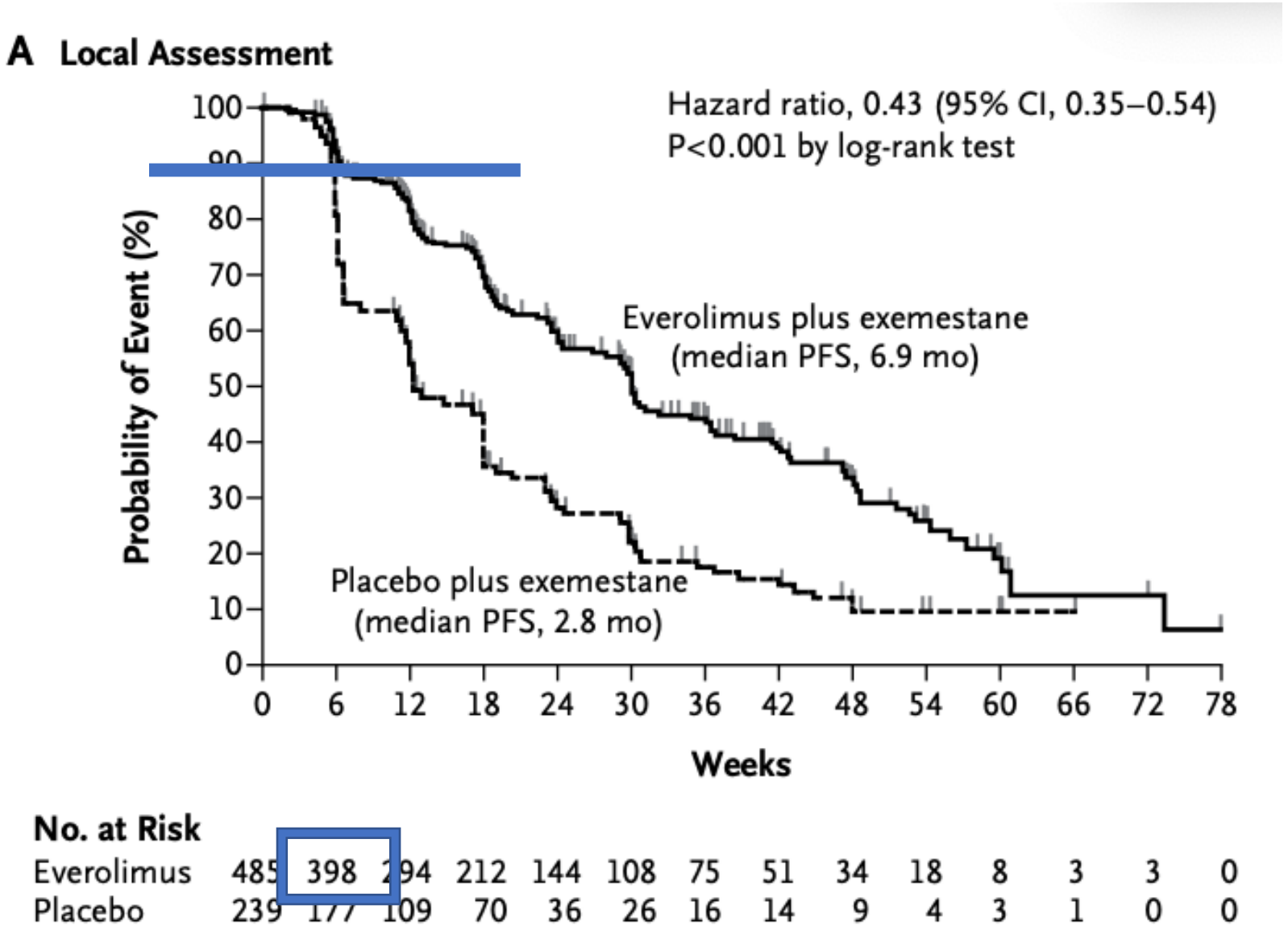

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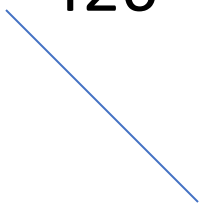
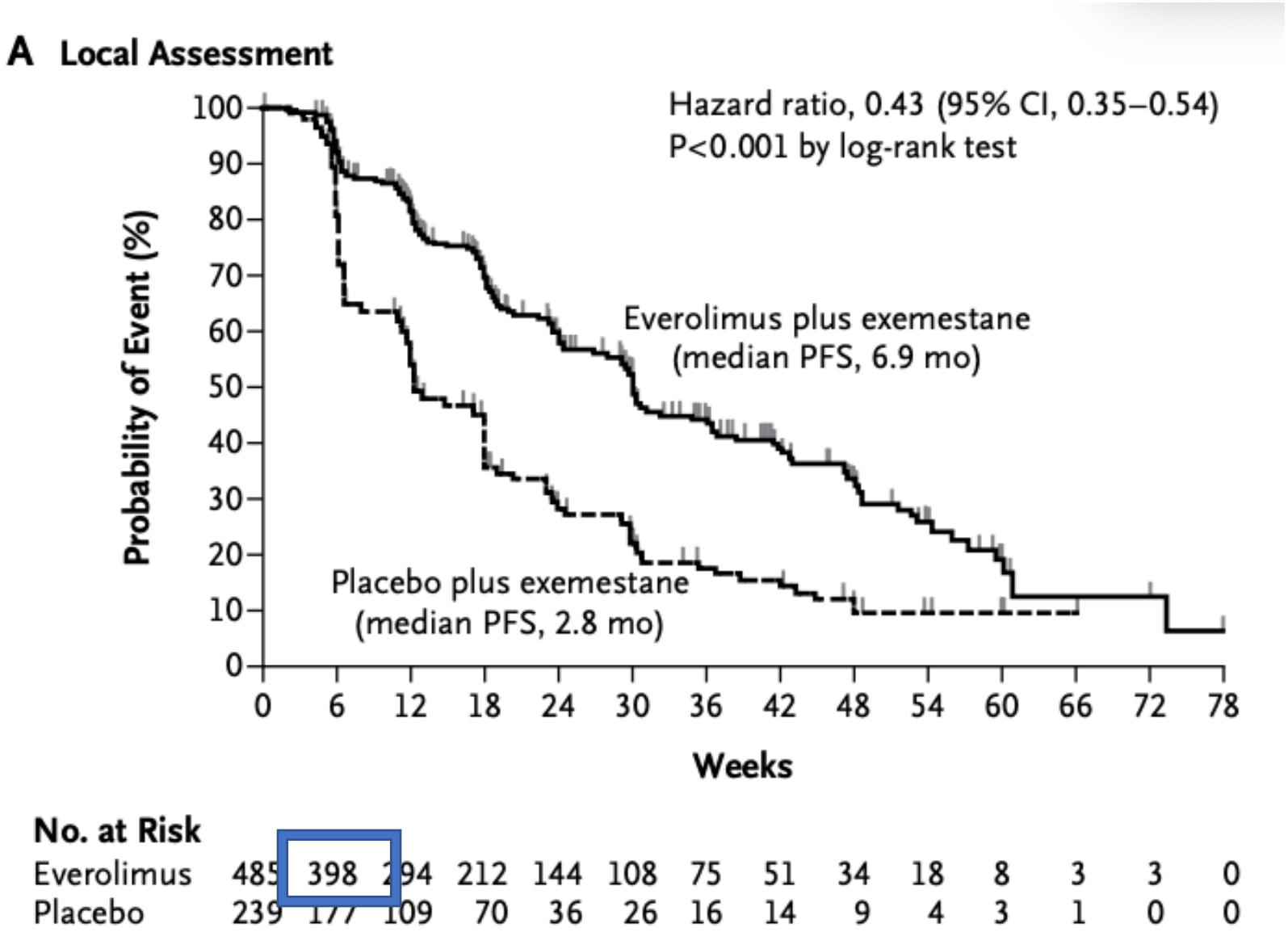
- 485 *.12 = 59
- 485-59 = 426





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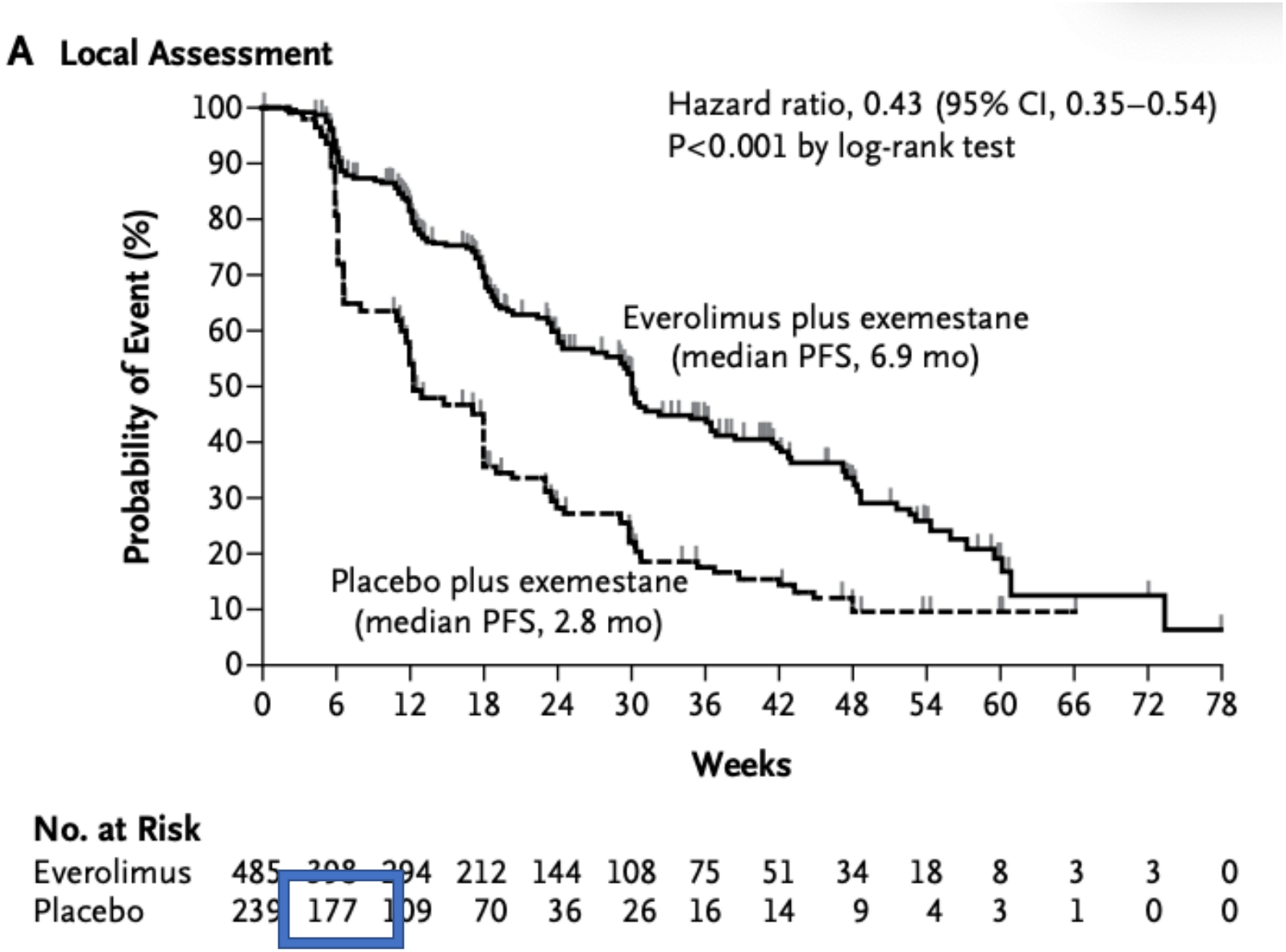
- 426-398 = 28 people censored (28/426 -= 7%)



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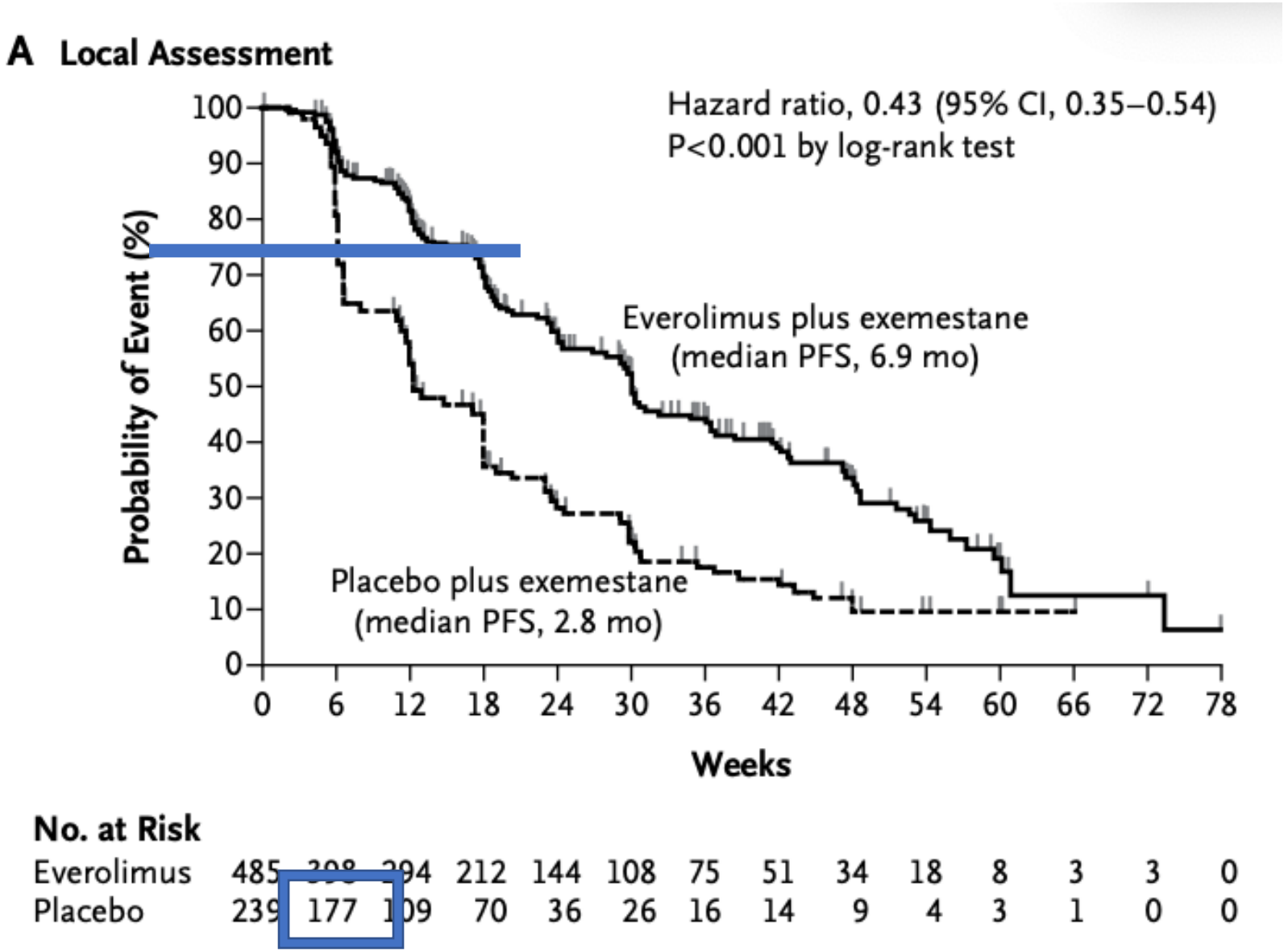

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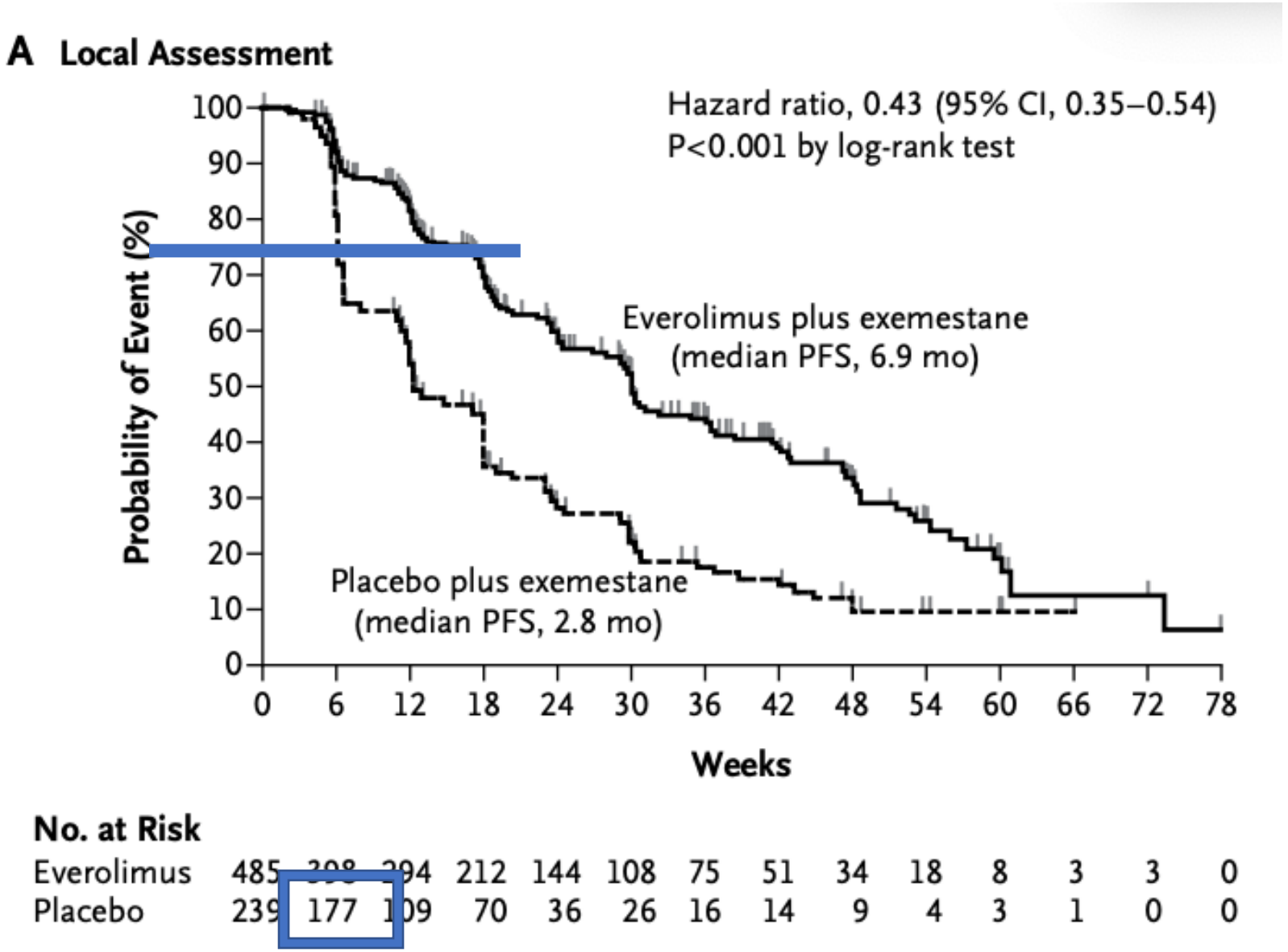
- 239 *.25 = 60
- 239 – 60 = 179



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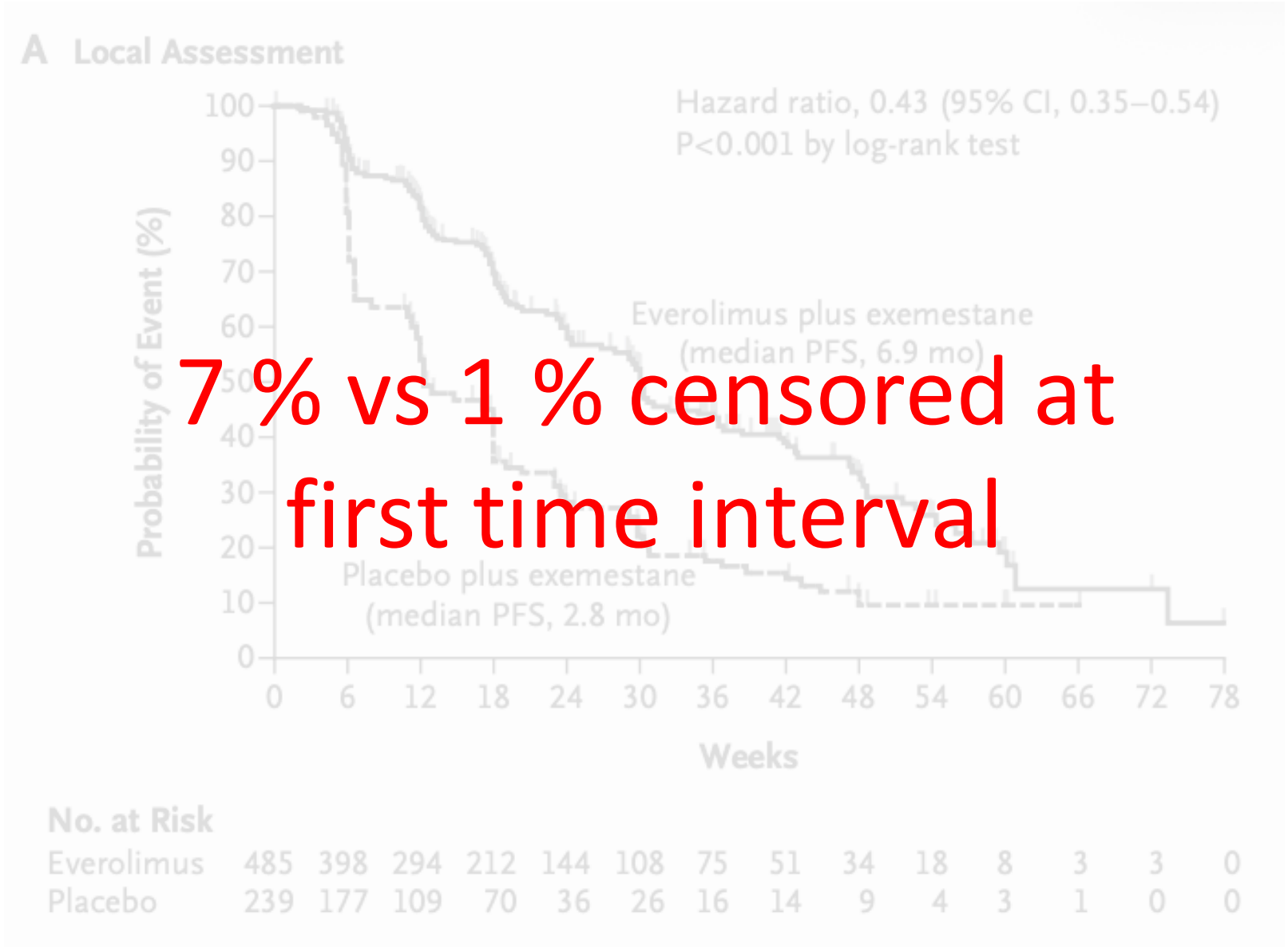
- 2 people censored = 2/239 = <1%



7 % vs 1 % censored at first time interval

Baselga J, Campone M, Piccart M, Burris III HA, Rugo HS, Sahmoud T, Noguchi S, Gnant M, Pritchard KI, Lebrun F, Beck JT. Everolimus in postmenopausal hormone-receptor–positive advanced breast cancer. New England Journal of Medicine. 2012 Feb 9;366(6):520-9.

Why?

Why?

- OS
- They enrolled recently
- Lost to follow up

- PFS
- They enrolled recently
- Lost to follow up
- Patient has to get the scan

Why?

- OS
- They enrolled recently
- Lost to follow up

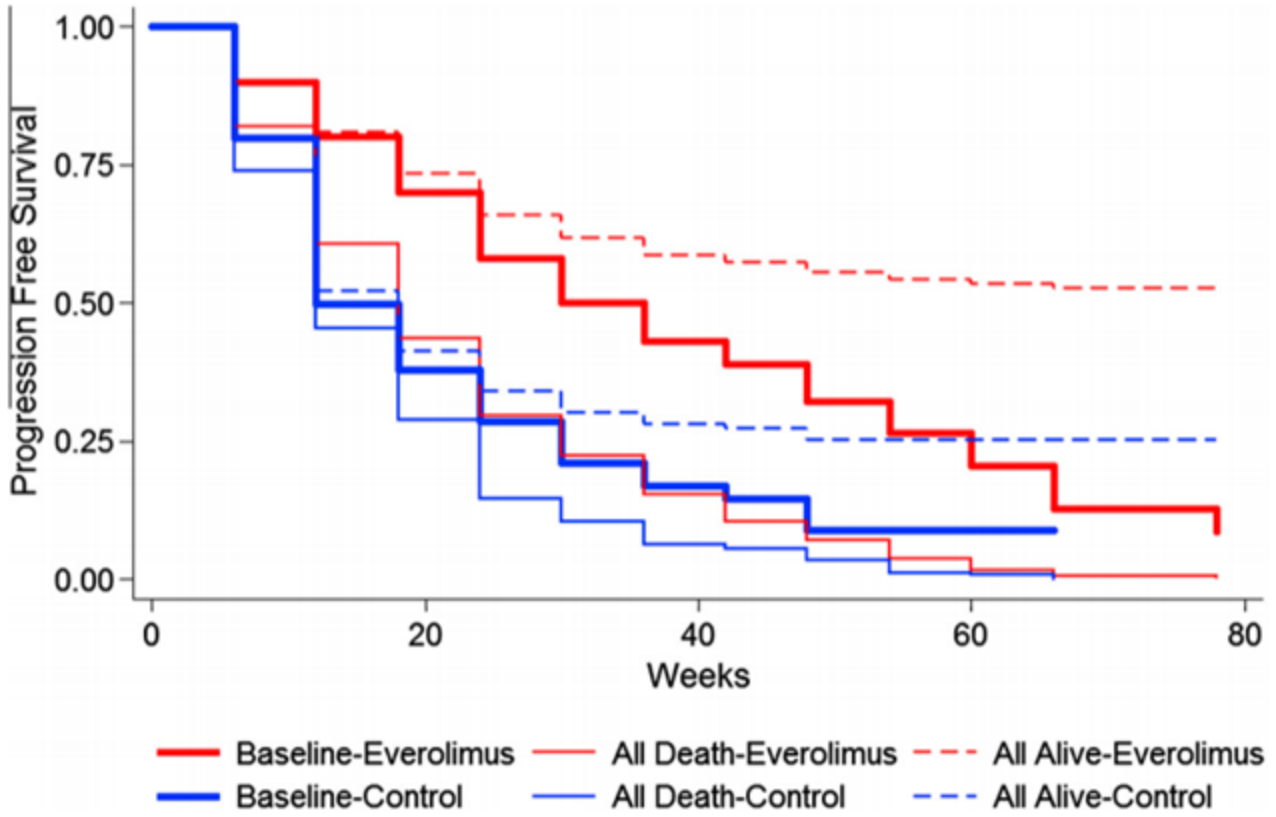
- PFS
- They enrolled recently
- Lost to follow up
- Patient has to get the scan

Why so much censoring on Intervention arm?

- B/c toxicity
- Is the assumption of uninformative censoring met?

The role of censoring on progression free survival: Oncologist discretion advised

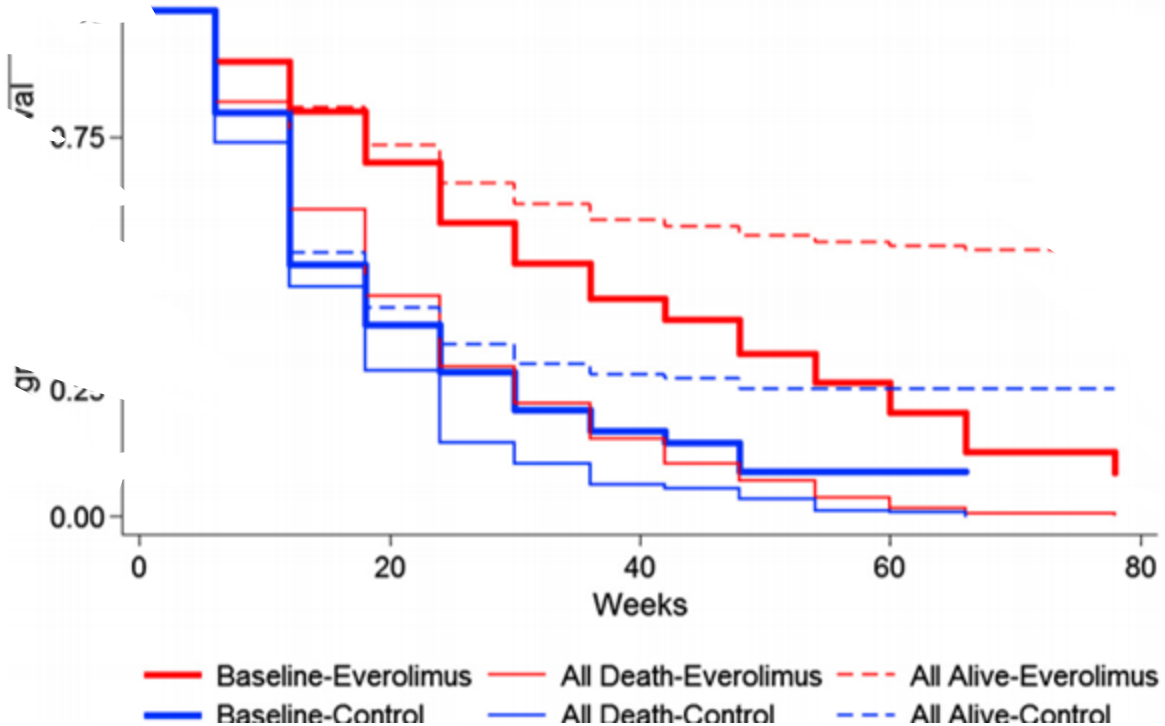
Vinay Prasad [a,*], Usama Bilal [b]

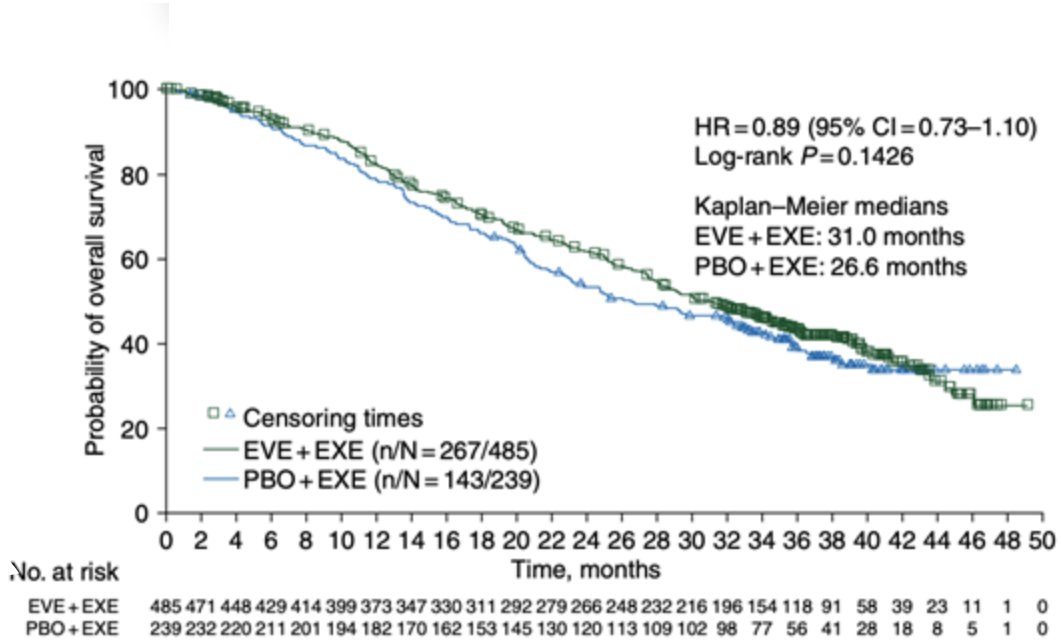


Prasad V, Bilal U. The role of censoring on progression free survival: oncologist discretion advised. European Journal of Cancer. 2015 Nov 1;51(16):2269-71.

The role of censoring on progression free survival: Oncologist discretion advised

Vinay Prasad [a,*], Usama Bilal [b]





...tes of overall survival. CI, confidence interval; EVE, everolimus; EXE, exemestane; HR, hazard ratio; PBO, placebo.

Prasad V, Bilal U. The role of censoring on progression free survival: oncologist discretion advised. European Journal of Cancer. 2015 Nov 1;51(16):2269-71.; Piccart M, Hortobagyi GN, Campone M, Pritchard KI, Lebrun F, Ito Y, Noguchi S, Perez A, Rugo HS, Deleu I, Burris III HA. Everolimus plus exemestane for hormone-receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: overall survival results from BOLERO-2. Annals of oncology. 2014 Dec 1;25(12):2357-62.

Tito Fojo, MD PhD

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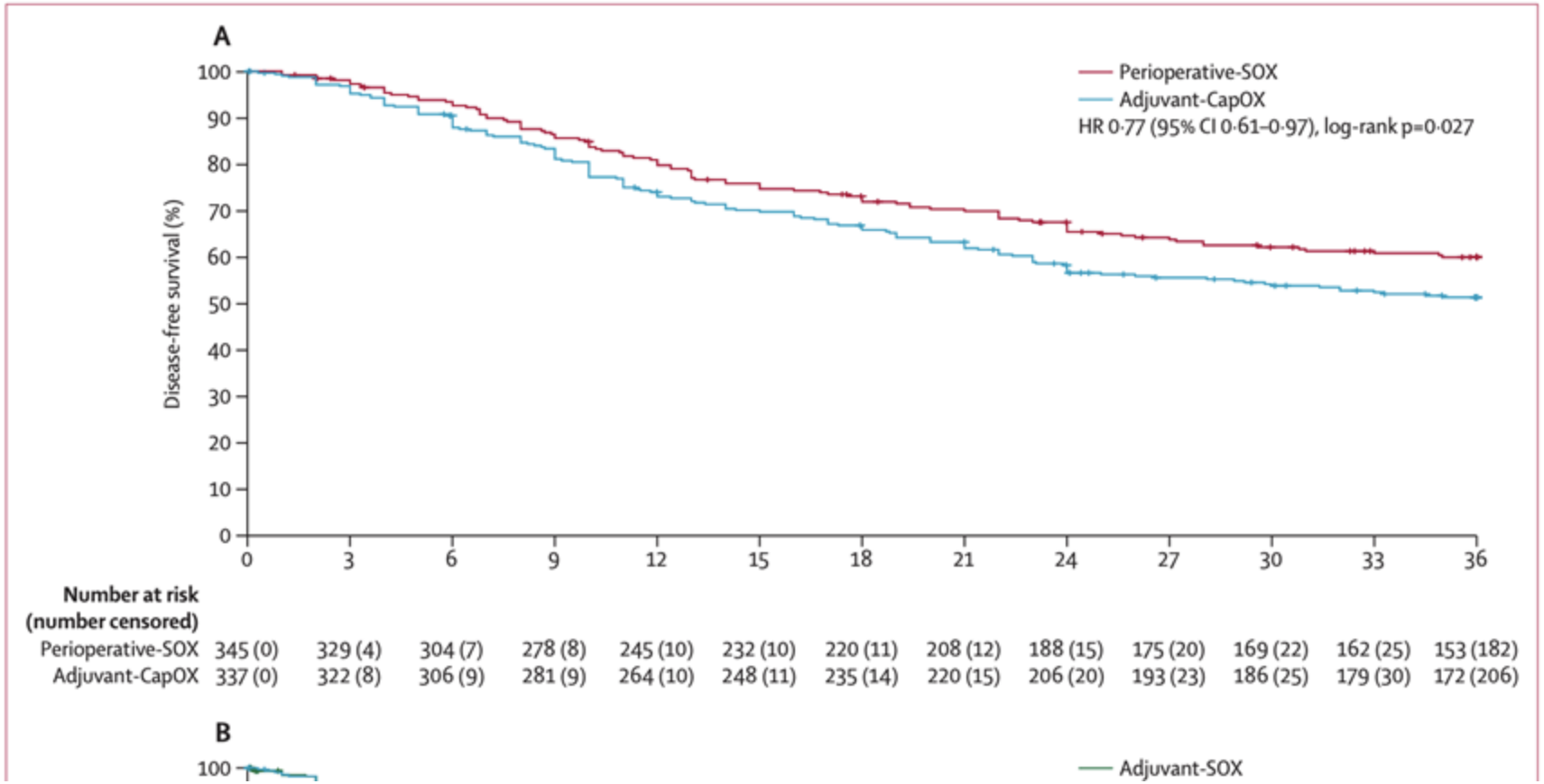

Zhang X, Liang H, Li Z, Xue Y, Wang Y, Zhou Z, Yu J, Bu Z, Chen L, Du Y, Wang X. Perioperative or postoperative adjuvant oxaliplatin with S-1 versus adjuvant oxaliplatin with capecitabine in patients with locally advanced gastric or gastro-oesophageal junction adenocarcinoma undergoing D2 gastrectomy (RESOLVE): an open-label, superiority and non-inferiority, phase 3 randomised controlled trial. The Lancet Oncology. 2021 Aug 1;22(8):1081-92.

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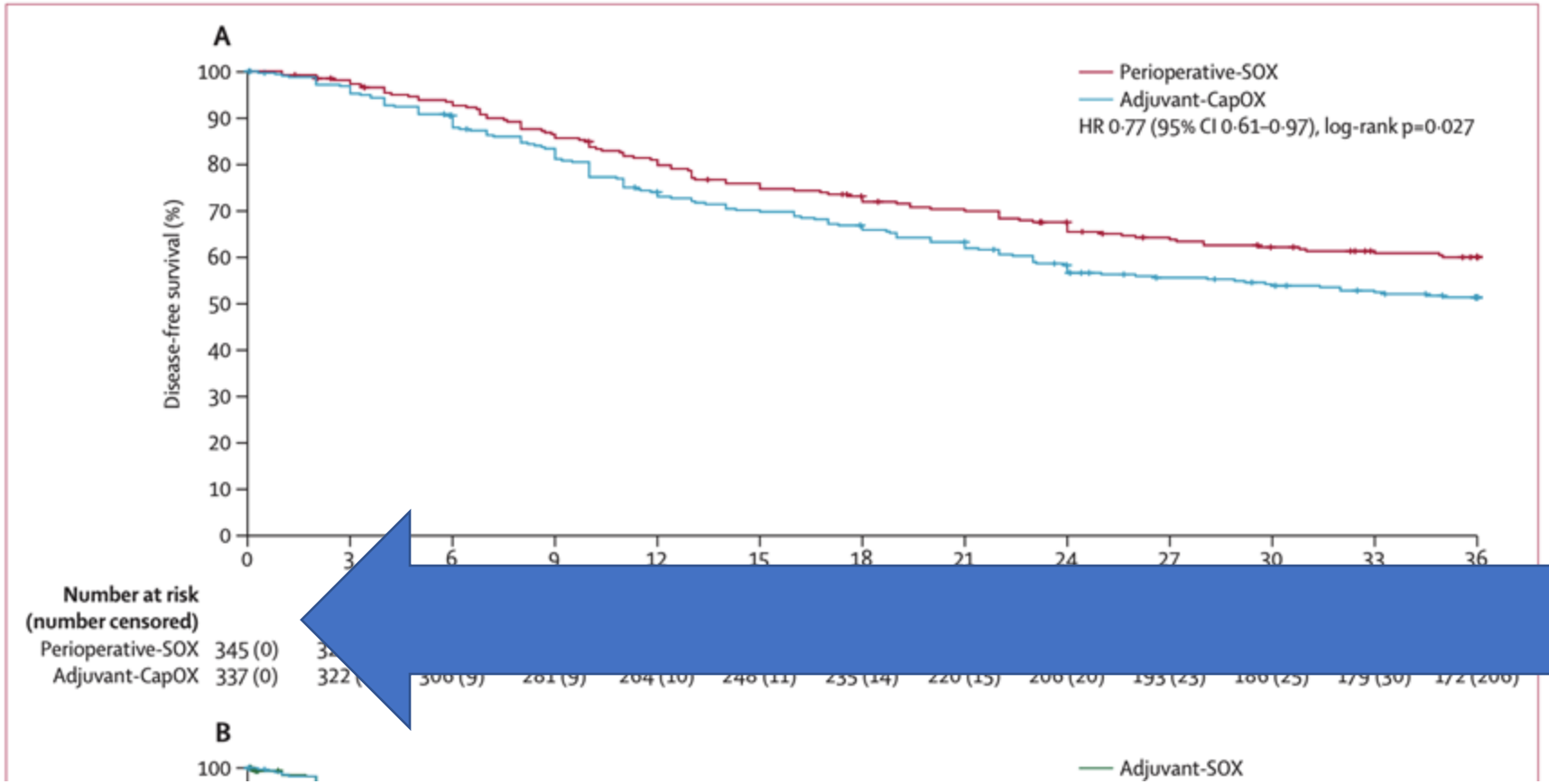
Oncology



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Following

Kate Rosen

@KateKateRosen Follows you

Medical student with a lot of questions. #KateforResident2022 #Neurosurgery

Original Research

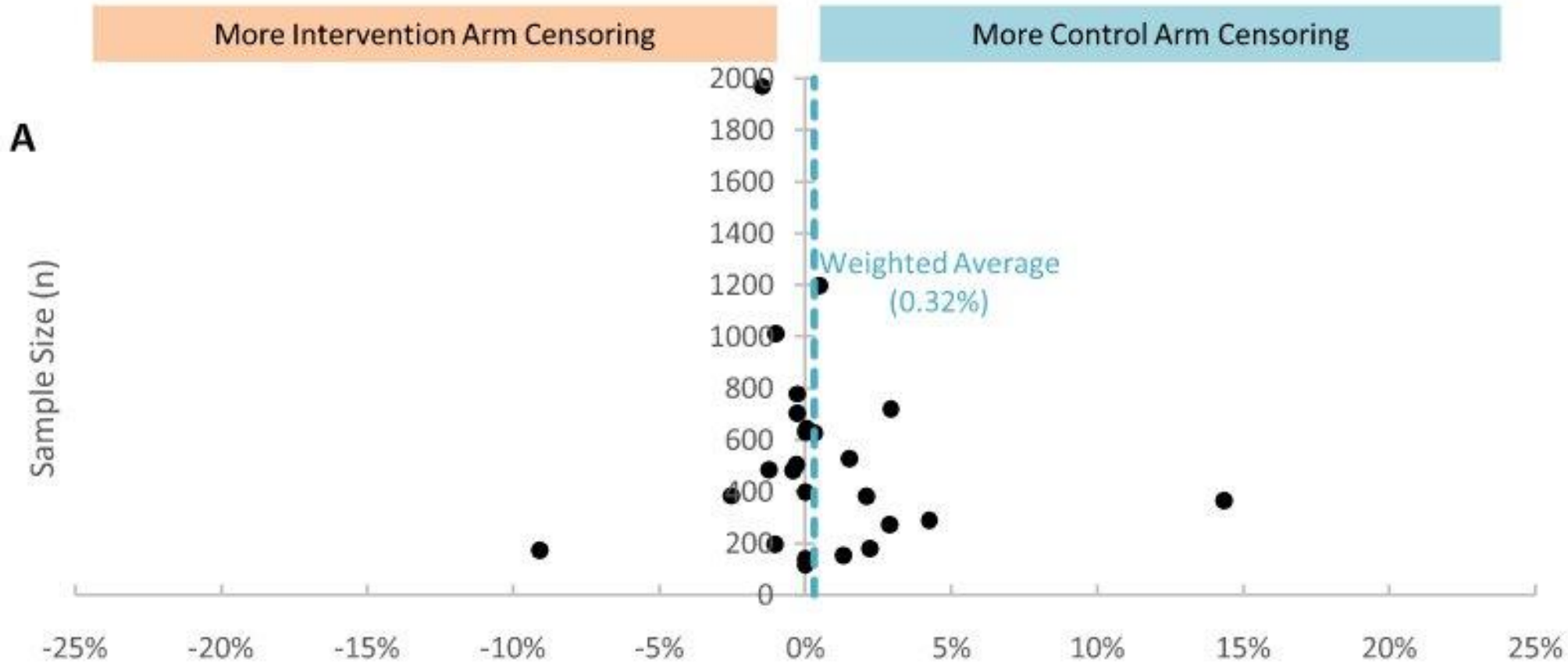
Censored patients in Kaplan–Meier plots of cancer drugs: An empirical analysis of data sharing

Kate Rosen [a], Vinay Prasad [b], Emerson Y. Chen [c,*]

[a] *School of Medicine, Oregon Health & Science University, Portland, OR, USA*
[b] *Department of Epidemiology and Biostatistics, University of California, San Francisco, CA, USA*
[c] *Division of Hematology Oncology, Oregon Health & Science University, Knight Cancer Institute, Portland, OR, USA*

Received 24 July 2020; received in revised form 8 September 2020; accepted 25 September 2020

Rosen K, Prasad V, Chen EY. Censored patients in Kaplan–Meier plots of cancer drugs: an empirical analysis of data sharing. European Journal of Cancer. 2020 Dec 1;141:152-61.



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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Cancer

O. Sartor, J. de Bono, K.N. Chi, K. Fizazi, K. Herrmann, K. Rahbar, S.T. Tagawa, L.T. Nordquist, N. Vaishampayan, G. El-Haddad, C.H. Park, T.M. Beer, A. Armour, W.J. Pérez-Contreras, M. DeSilvio, E. Kpamegan, G. Gericke, R.A. Messmann, M.J. Morris, and B.J. Krause, for the VISION Investigators*

ABSTRACT

Sartor O, De Bono J, Chi KN, Fizazi K, Herrmann K, Rahbar K, Tagawa ST, Nordquist LT, Vaishampayan N, El-Haddad G, Park CH. Lutetium-177–PSMA-617 for metastatic castration-resistant prostate cancer. New England Journal of Medicine. 2021 Sep 16;385(12):1091-103.

Eligible patients had PSMA-positive metastatic castration-resistant prostate cancer, which was defined as at least one PSMA-positive metastatic lesion and no PSMA-negative lesions that would be excluded according to the protocol criteria; PSMA-positive status was determined with the use of centrally read gallium-68 (^{68}Ga)–labeled PSMA-11 (^{68}Ga-PSMA-11) PET–CT imaging at baseline.[27] Diagnostic-grade CT scans were also available for all the patients. The presence of PSMA-positive lesions was defined in the protocol as ^{68}Ga-PSMA-11 uptake greater than that of liver parenchyma in one or more metastatic lesions of any size in any organ system. The presence of PSMA-negative lesions was de-

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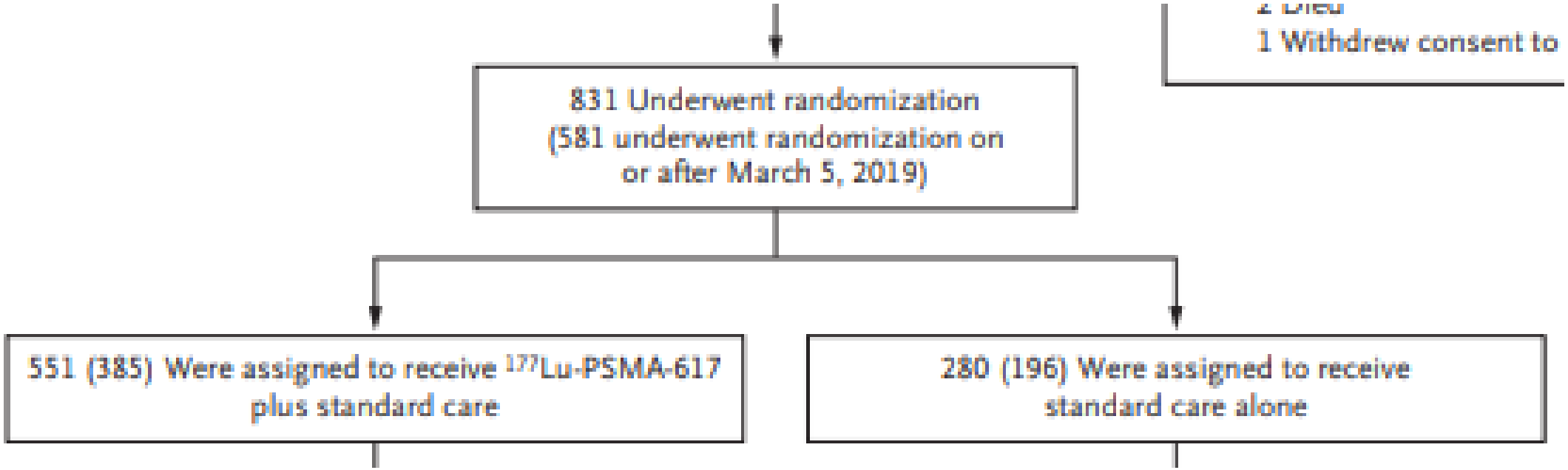
Of the 1003 patients who underwent scanning, 831 (82.9%) were judged to have met all the trial eligibility criteria, including the PSMA imaging criteria, and were randomly assigned,



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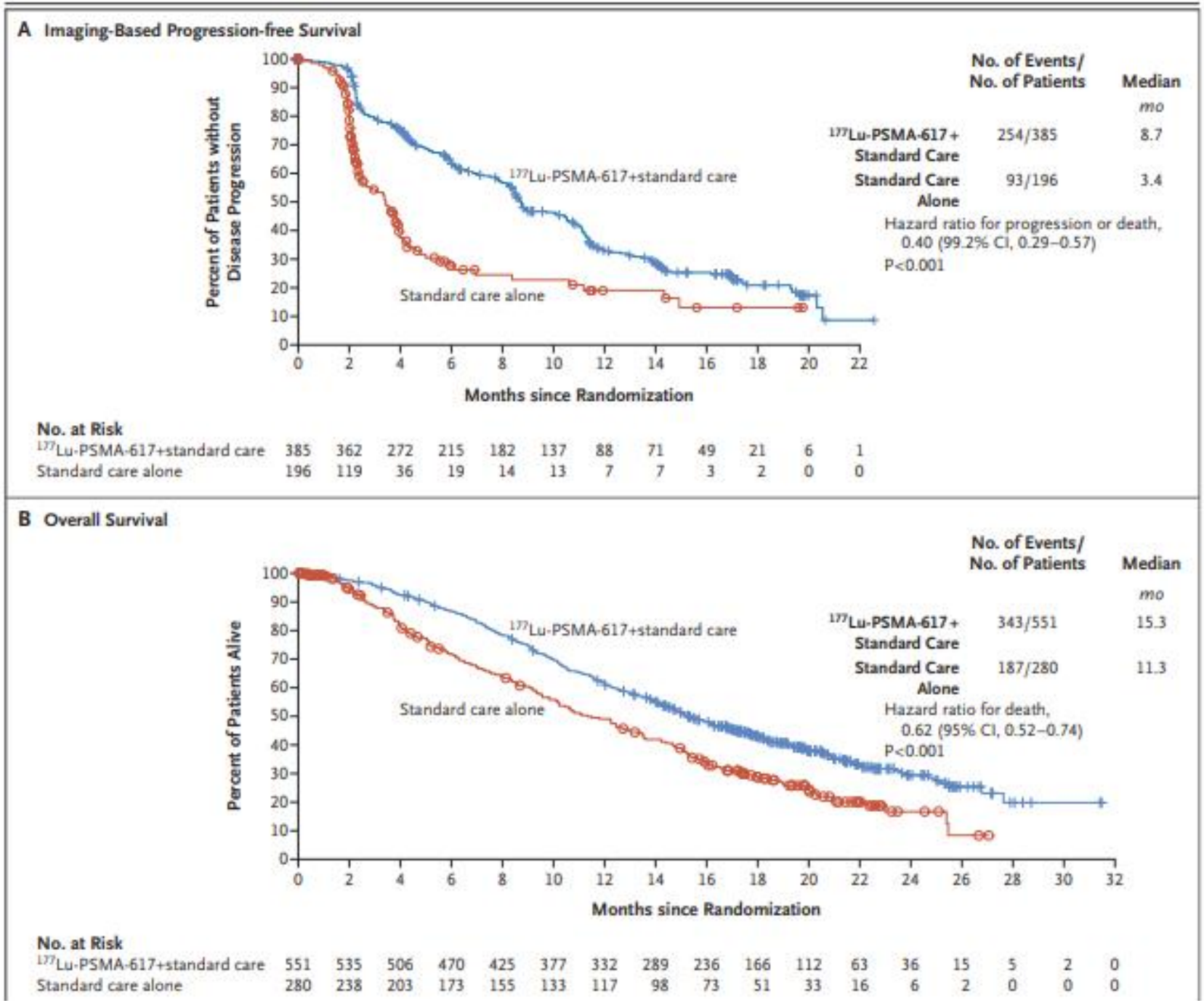

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What’s the problem?

What's the problem?

Standard-care therapy that was permitted by the trial protocol had to be agreed on and assigned by the physician–investigator before randomization, but it could be modified at the discretion of the treating physician. Standard-care therapies could not include cytotoxic chemotherapy, systemic radioisotopes (e.g., radium-223 [^{223}Ra]), immunotherapy, or drugs that were investigational when the trial was designed (e.g., olaparib). These constraints were used because of a lack of safety data on combining the investigational drug with these agents. Permitted treatments included but were not restricted to the approved hormonal treatments (including abiraterone and enzalutamide), bisphosphonates, radiation therapy, denosumab, or glucocorticoid at any dose. Castrate testosterone levels had to be maintained throughout the trial.

Sartor O, De Bono J, Chi KN, Fizazi K, Herrmann K, Rahbar K, Tagawa ST, Nordquist LT, Vaishampayan N, El-Haddad G, Park CH. Lutetium-177–PSMA-617 for metastatic castration-resistant prostate cancer. New England Journal of Medicine. 2021 Sep 16;385(12):1091-103.

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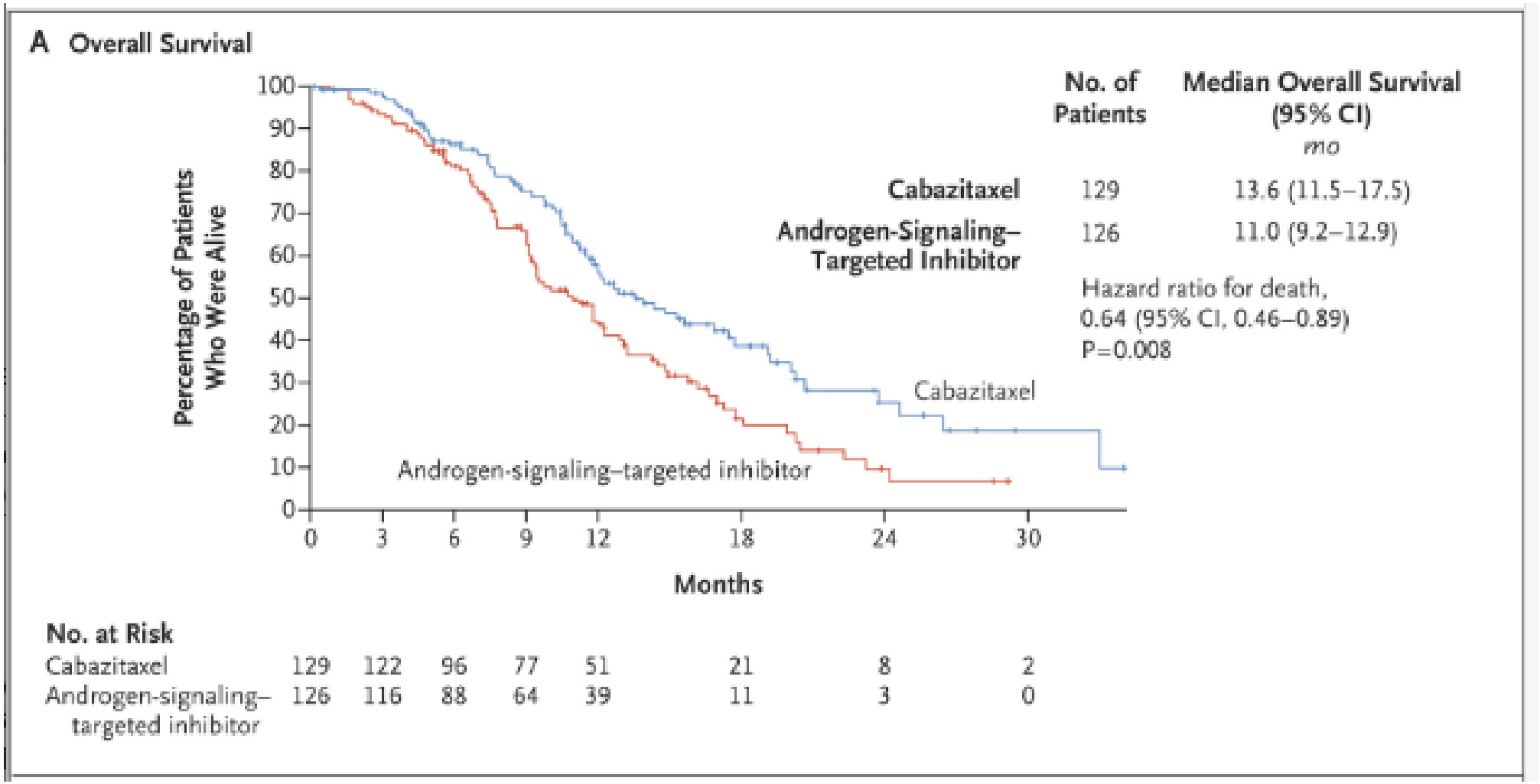
	^{177}Lu-PSMA-617 plus Standard Care (N=385)	Standard Care Alone (N=196)
Previous androgen-receptor–pathway inhibitor — no. (%)‖		
One regimen	213 (55.3)	98 (50.0)
Two regimens	150 (39.0)	86 (43.9)
More than two regimens	22 (5.7)	12 (6.1)
Previous taxane therapy — no. (%)**		
One regimen	207 (53.8)	102 (52.0)
Two regimens	173 (44.9)	92 (46.9)
Docetaxel	377 (97.9)	191 (97.4)
Cabazitaxel	161 (41.8)	84 (42.9)

Sartor O, De Bono J, Chi KN, Fizazi K, Herrmann K, Rahbar K, Tagawa ST, Nordquist LT, Vaishampayan N, El-Haddad G, Park CH. Lutetium-177–PSMA-617 for metastatic castration-resistant prostate cancer. New England Journal of Medicine. 2021 Sep 16;385(12):1091-103.

CARD Trial



de Wit R, de Bono J, Sternberg CN, Fizazi K, Tombal B, Wülfing C, Kramer G, Eymard JC, Bamias A, Carles J, Iacovelli R. Cabazitaxel versus abiraterone or enzalutamide in metastatic prostate cancer. New England Journal of Medicine. 2019 Dec 26;381(26):2506-18.

Choice of control group in randomised trials of cancer medicine: are we testing trivialities?

Several trials in cancer medicine over the past 5 years share two common features: first, they were used—or were intended to be used—to seek marketing authorisation from the US Food and Drug Administration (FDA) or European Medicines Agency, and second, they test an experimental group against a weak comparator that is infrequently used in practice. The choices of comparators in four trials—those of ibrutinib and rituximab versus rituximab in Waldenström's macroglobulinaemia,[1] ibrutinib versus chlorambucil in

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prasad@ohsu.edu

Tao D, Prasad V. Choice of control group in randomised trials of cancer medicine: are we testing trivialities?. The Lancet Oncology. 2018 Sep 1;19(9):1150-2.

JAMA Oncology | Original Investigation

Analysis of Control Arm Quality in Randomized Clinical Trials Leading to Anticancer Drug Approval by the US Food and Drug Administration

Talal Hilal, MD; Mohamad Bassam Sonbol, MD; Vinay Prasad, MD, MPH

IMPORTANCE To date, an empirical evaluation of the quality of control arms in randomized clinical trials (RCTs) leading to anticancer drug approvals by the US Food and Drug Administration (FDA) has not been undertaken.

OBJECTIVE We sought to estimate the percentage of RCTs that used a control arm deemed suboptimal and led to FDA approval of anticancer drugs from January 1, 2013, to July 31, 2018.

DESIGN, SETTING, AND PARTICIPANTS This quality improvement study included 143 anticancer drug approvals granted by the FDA from January 1, 2013, to July 31, 2018. All approvals based on single-arm studies (48 approvals) were excluded. Approvals based on RCTs were further investigated and each trial was analyzed for design, time of patient accrual, control arm, and primary end point. Standard-of-care therapy was determined by evaluating the literature and published guidelines 1 year prior to the start of trial enrollment. The percentage of approvals based on RCTs that used suboptimal control arms was then calculated. The quality of the control arm was deemed suboptimal if the choice of control agent was restricted to exclude a recommended agent, the control arm was specified but the recommended agent was unspecified, and if prior RCT data had demonstrated that the control agent was inferior to an available alternative.

MAIN OUTCOMES AND MEASURES Estimated percentage of RCTs that used suboptimal control arms that led to FDA approval of anticancer agents between January 1, 2013, to July 31, 2018.

RESULTS A total of 145 studies that led to 143 drug approvals between January 1, 2013, and July 31, 2018, were included. Of these studies, 48 single-arm studies were excluded. The remaining 97 studies led to 95 drug approvals. Of these 95 approvals, 16 (17%) were based on RCTs with suboptimal control arms; 15 were international trials, and 1 was conducted in the United States. The type of approval was regular in 15 trials and accelerated in 1 trial. When categorized by the nature of suboptimal control, 4 (25%) trials omitted active treatment in control arm by limiting investigator's choice, 11 (63%) trials omitted active treatment in the control arm by using a control agent known to be inferior to other available agents or not allowing combinations, and 1 (13%) trial used a previously used treatment in the control arm with a known lack of benefit associated with reexposure.

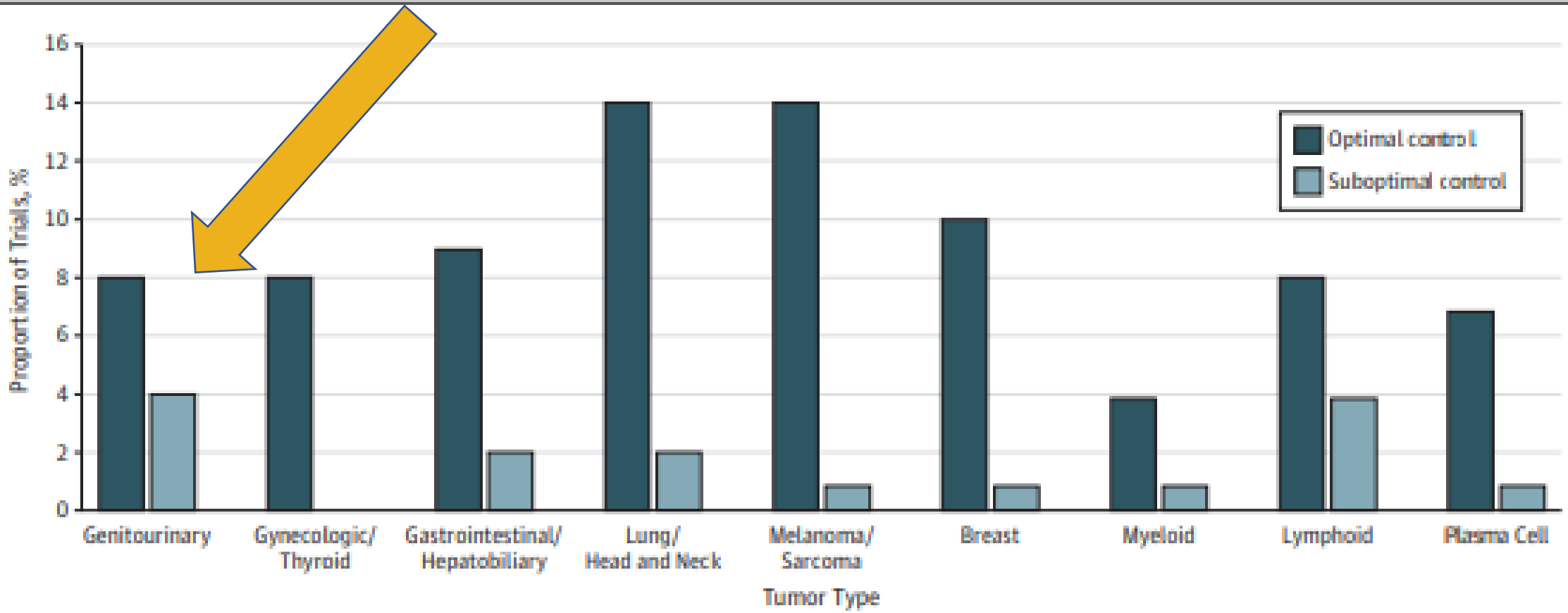
CONCLUSIONS AND RELEVANCE Although anticancer drug approvals are increasing, a proportion of these drugs are reaching the market without proven superiority to what is considered the standard of care at the time of patient enrollment in pivotal trials. The choice of control arm should be optimized to ensure that new anticancer agents being marketed are

Supplemental content

Author Affiliations: Division of Hematology and Oncology, Mayo Clinic, Phoenix, Arizona (Hilal, Sonbol); Division of Hematology Oncology, Knight Cancer Institute,

Hilal T, Sonbol MB, Prasad V. Analysis of control arm quality in randomized clinical trials leading to anticancer drug approval by the US Food and Drug Administration. JAMA oncology. 2019 Jun 1;5(6):887-92.

Figure 2. Proportion of Trials That Used a Suboptimal Control Arm by Tumor Type



Hilal T, Sonbol MB, Prasad V. Analysis of control arm quality in randomized clinical trials leading to anticancer drug approval by the US Food and Drug Administration. JAMA oncology. 2019 Jun 1;5(6):887-92.

What happened?

undergone randomization, whereas imaging-based progression-free survival and key secondary efficacy outcomes were analyzed in a subgroup of patients who had undergone randomization, for the following reason. After the trial started (May 29, 2018), a high incidence of withdrawal from the trial was noted in the control group at certain sites and was attributed principally to patient disappointment (see the Supplementary Methods section). After discussion with regulatory authorities, we implemented enhanced trial-site education measures on March 5, 2019 to reduce the incidence of withdrawal. The high incidence of withdrawal could have affected the interpretability of radiographic end points. Therefore, the primary analysis of imaging-based progression-free survival and the analyses of key secondary end points were amended to include only the patients who had undergone randomization on or after March 5, 2019. To maintain

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were implemented (on or after March 5, 2019). The percentage of patients in the control group who discontinued the trial without receiving the randomly assigned treatment was 56% (47 of 84 patients) before the implementation of these measures and 16.3% (32 of 196 patients) after implementation, as compared with 1.2% (2 of 166 patients) and 4.2% (16 of 385 patients), respectively, in the ^{177}Lu-PSMA-617 group. The data-

Sartor O, De Bono J, Chi KN, Fizazi K, Herrmann K, Rahbar K, Tagawa ST, Nordquist LT, Vaishampayan N, El-Haddad G, Park CH. Lutetium-177–PSMA-617 for metastatic castration-resistant prostate cancer. New England Journal of Medicine. 2021 Sep 16;385(12):1091-103.

European Journal of Cancer 141 (2020) 152–161

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Original Research

Censored patients in Kaplan–Meier plots of cancer drugs: An empirical analysis of data sharing

Kate Rosen [a], Vinay Prasad [b], Emerson Y. Chen [c,*]

[a] *School of Medicine, Oregon Health & Science University, Portland, OR, USA*
[b] *Department of Epidemiology and Biostatistics, University of California, San Francisco, CA, USA*
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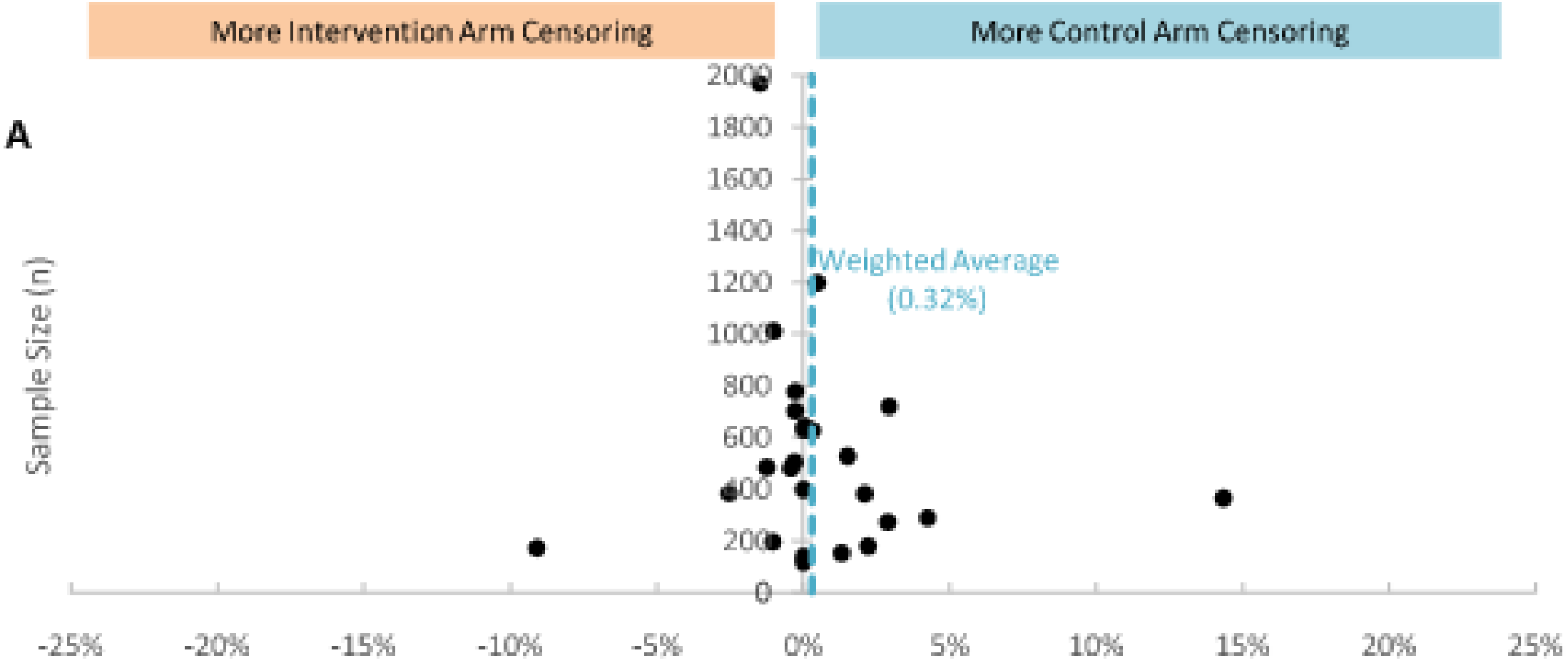

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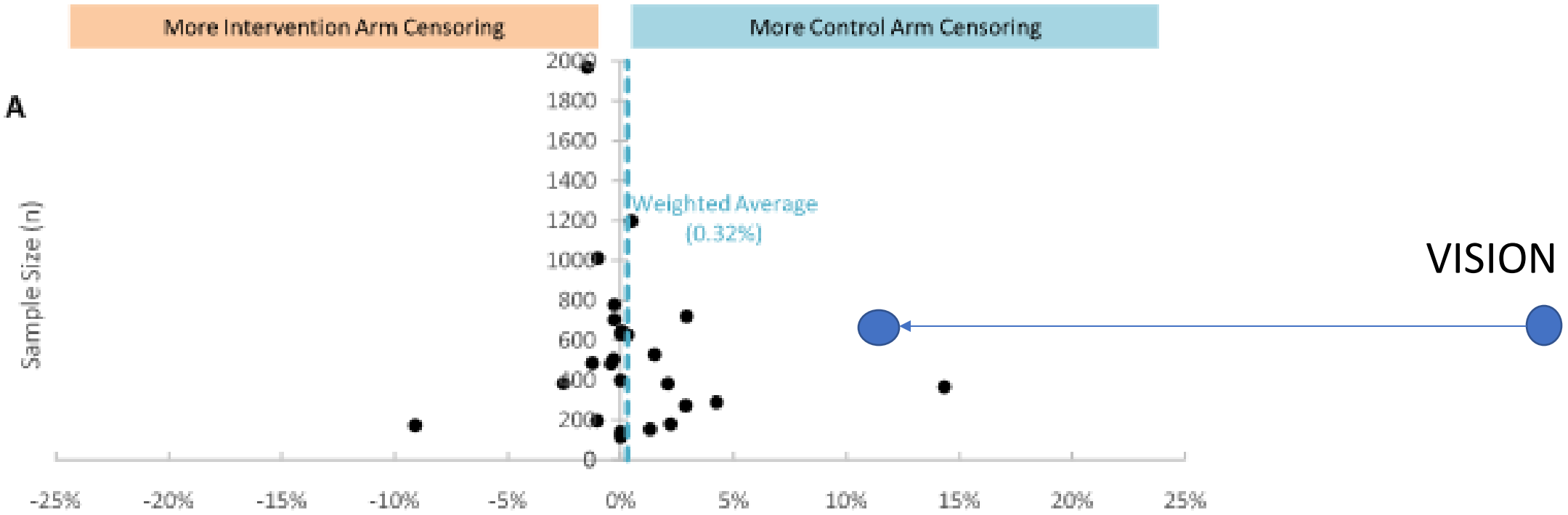

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second-line cabazitaxel chemotherapy.[25] Rather, in this trial, we investigated the use of ^{177}Lu-PSMA-617 as an addition to existing standard care at the time the trial was designed. The rationale for the exclusion of certain treatments was that the safety profile of these therapies had not been established in combination with ^{177}Lu-PSMA-617. The trial aimed to assess the efficacy of ^{177}Lu-PSMA-617 plus standard-care therapies that could safely be combined in order to provide physicians with a broad permitted range of concomitant treatment options. Patients who had received only one taxane were ineligible if they were deemed at baseline to be candidates for receiving a second taxane. Approximately one fifth of the patients in the imaging-based progression-free survival analysis set received a second taxane postprotocol, with a slightly higher percentage in the control group than in the ^{177}Lu-PSMA-617 group. Although the TheraP trial of ^{177}Lu-PSMA-

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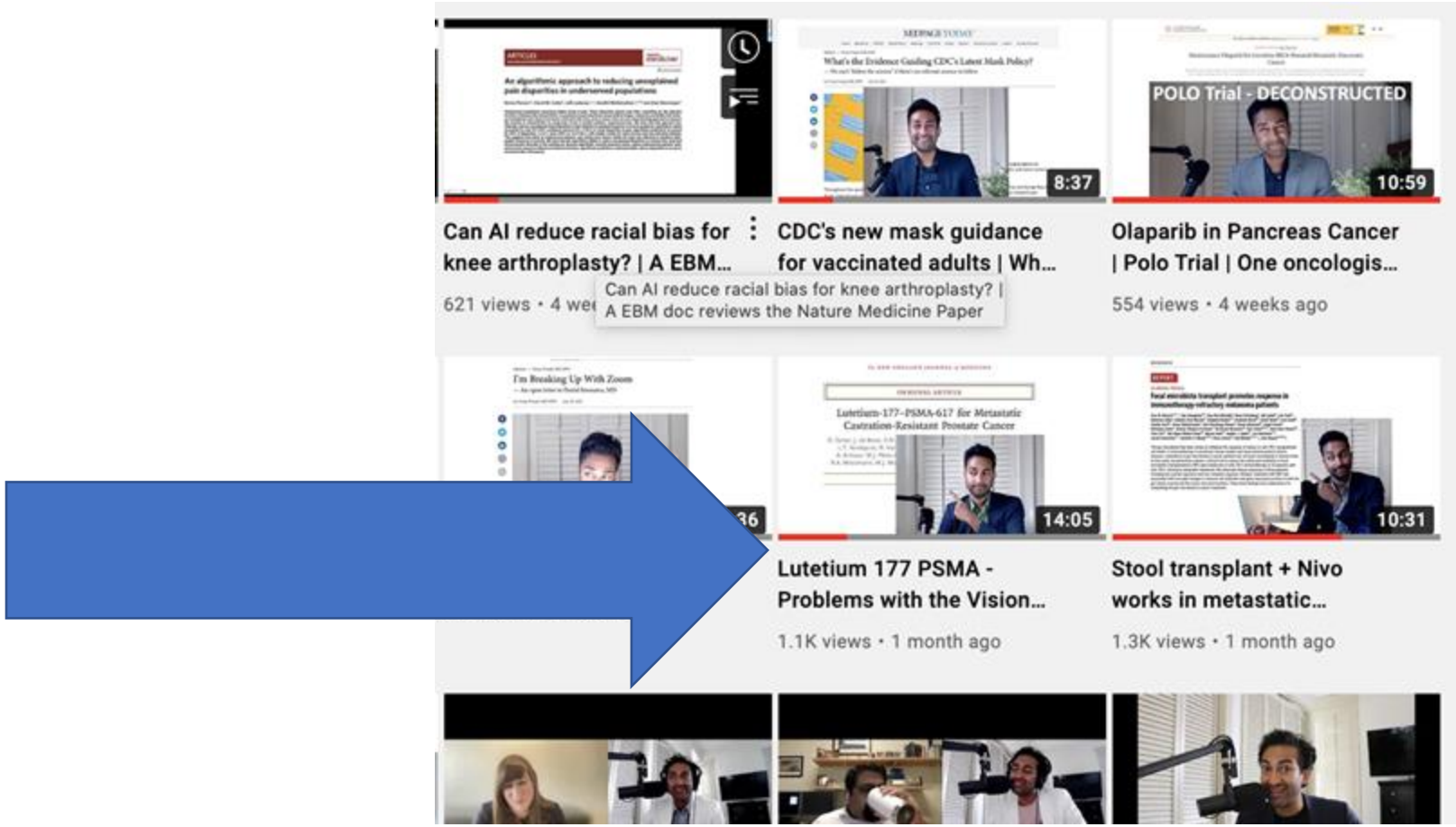
Table S4. Cancer-related therapy after discontinuation of randomized treatment in the imaging-based progression-free survival analysis set

Treatment*	^{177}Lu-PSMA-617 plus standard care (n=385)	Standard care alone (n=196)	Overall (n=581)
Radiotherapy – no. (%)	25 (6.5)	22 (11.2)	47 (8.1)
Medication – no. (%)	97 (25.2)	63 (32.1)	160 (27.5)
Medications received by ≥1% of patients overall – no. (%)†			
Taxanes	64 (16.6)	44 (22.4)	108 (18.6)
Cabazitaxel	51 (13.2)	38 (19.4)	89 (15.3)
Docetaxel	17 (4.4)	8 (4.1)	25 (4.3)
Paclitaxel	2 (0.5)	2 (1.0)	4 (0.7)
Paclitaxel albumin	1 (0.3)	0	1 (0.2)

Sartor O, De Bono J, Chi KN, Fizazi K, Herrmann K, Rahbar K, Tagawa ST, Nordquist LT, Vaishampayan N, El-Haddad G, Park CH. Lutetium-177–PSMA-617 for metastatic castration-resistant prostate cancer. New England Journal of Medicine. 2021 Sep 16;385(12):1091-103.

YouTube – Vinay Prasad MD MPH



- We do great and crazy things
- Truth is in plain sight

- We do great and crazy things
- Truth is in plain sight
  - Low credibility research
  - Trials with design issues/ bad control arms
  - Goal is to help patients/ not our careers
  - Many forget

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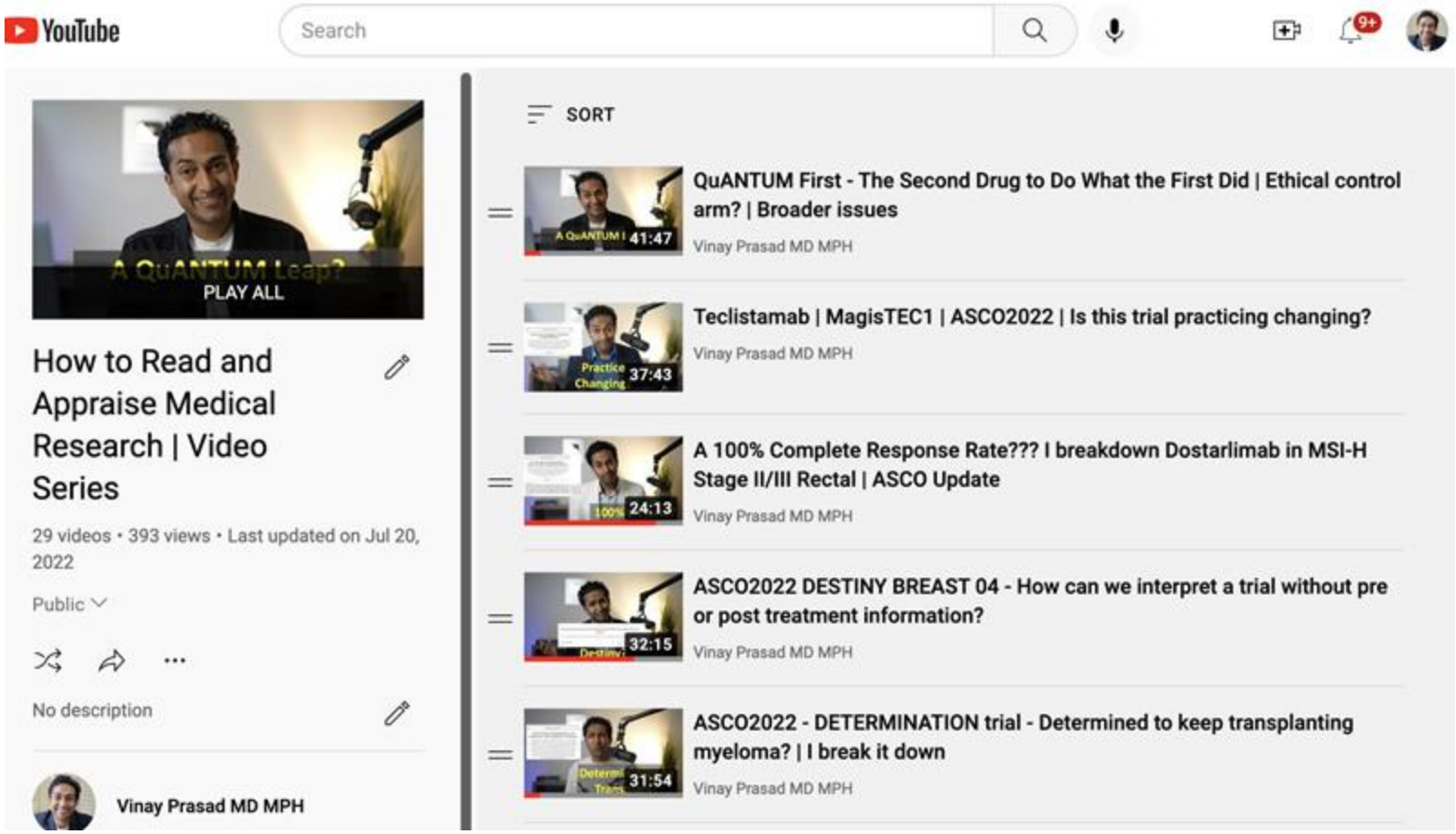

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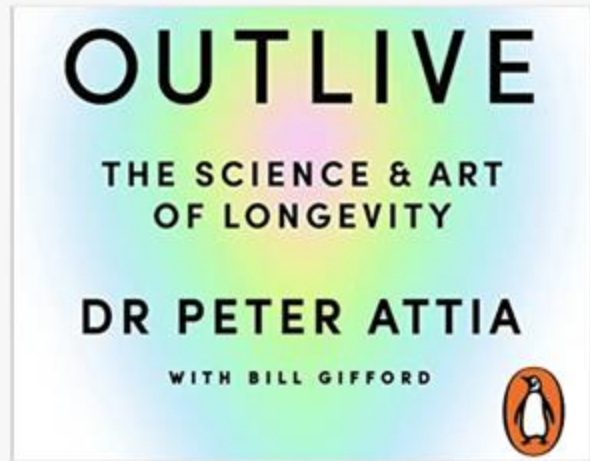

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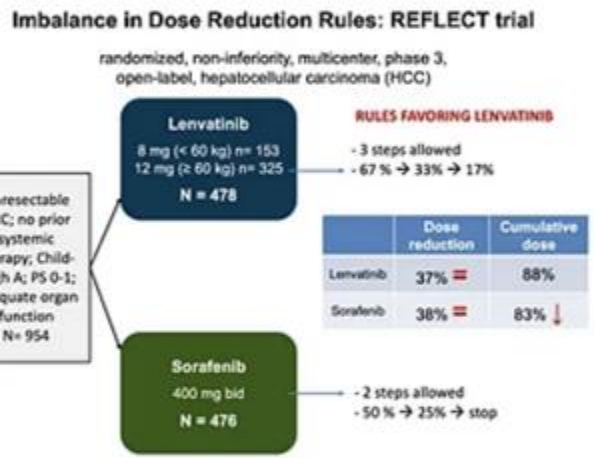

e starting dose is fair, but that about it

se modification rules plague cancer trials

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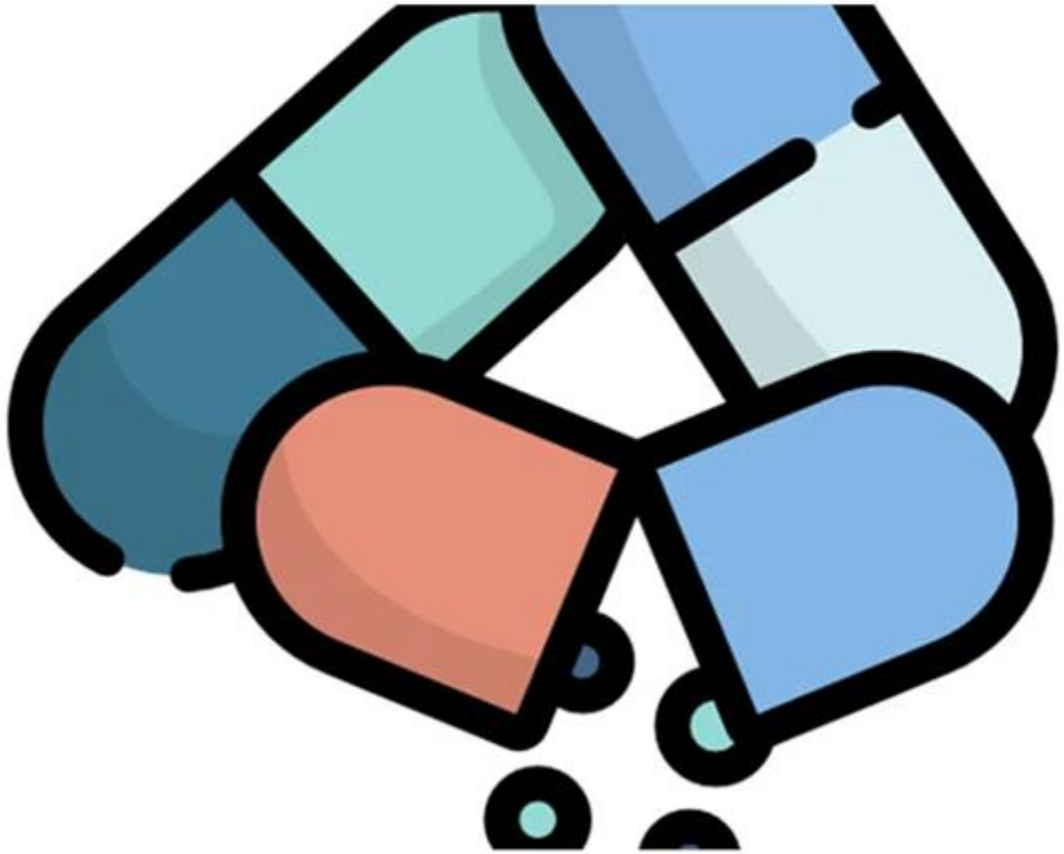

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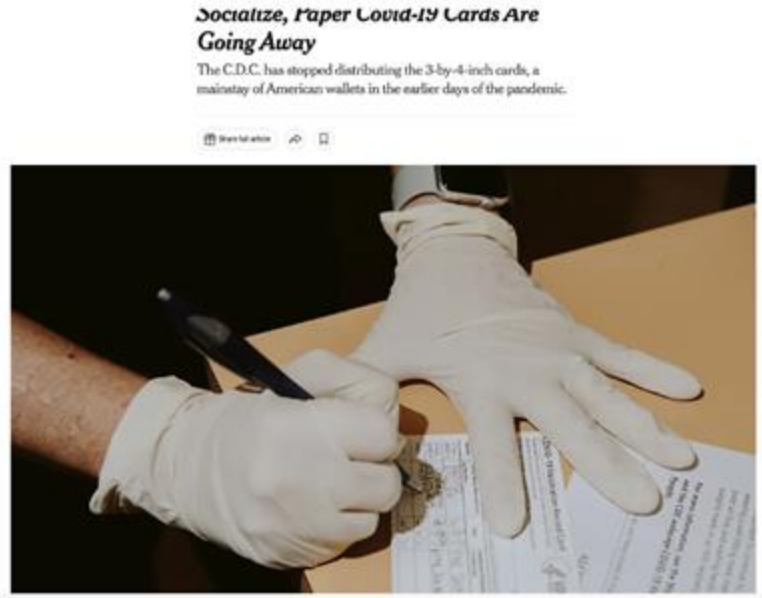

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▶ PLAY 1 hr 29 min

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5.11 - Malignant Book Club - Part 5 E

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