Complexities in Heme Malignancy Literature

Vinay Prasad MD MPH

Associate Prof of Medicine

UCSF

Disclosure of Conflicts of Interest

Vinay Prasad, MD, MPH, has the following financial relationships to disclose:

- Grant Research Support - Arnold Ventures
- Consultant – UnitedHealthcare, OptumRX
- Royalties – John Hopkins Press, Medscape
- Subscriber fees – YouTube, Substack, Patreon

Case Presentation

- 60 year old sister of a 65 year old patient with multiple myeloma

Case Presentation

- 60 year old sister of a 65 year old patient with multiple myeloma

- “Doctor, should I increase the amount of exercise I do to protect against myeloma?”

Case Presentation

- 60 year old sister of a 65 year old patient with multiple myeloma
- “Doctor, should I increase the amount of exercise I do to protect against myeloma?”
- “Didn’t you read the new study?”

Study: Getting Enough Exercise Lowers Risk of 7 Cancers

January 9, 2020

Getting recommended amounts of physical activity is linked to a lower risk for 7 cancer types, according to a study from the American Cancer Society, the National Cancer Institute, and the Harvard T.H. Chan School of Public Health.

original reports abstract

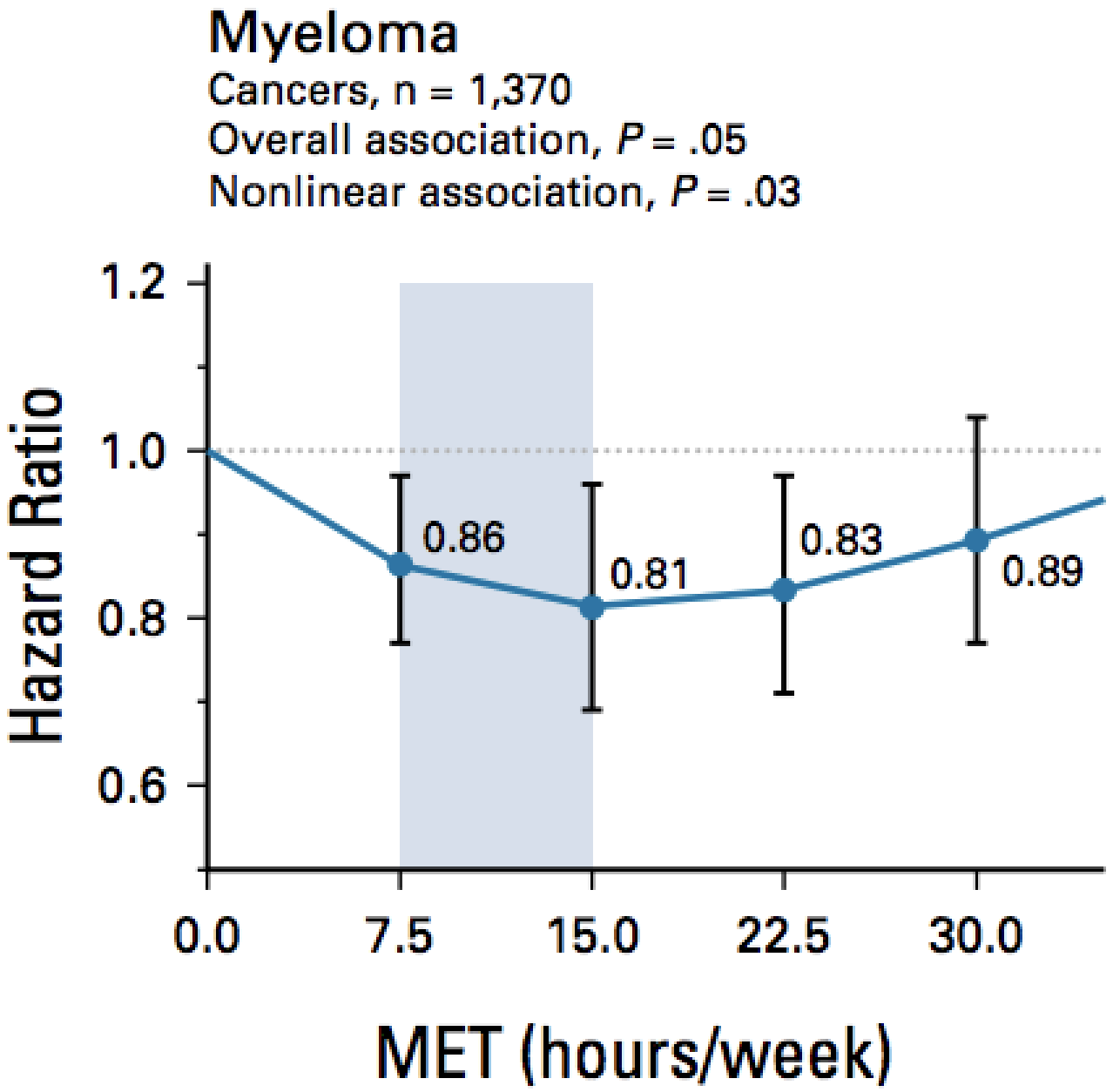
Amount and Intensity of Leisure-Time Physical Activity and Lower Cancer Risk

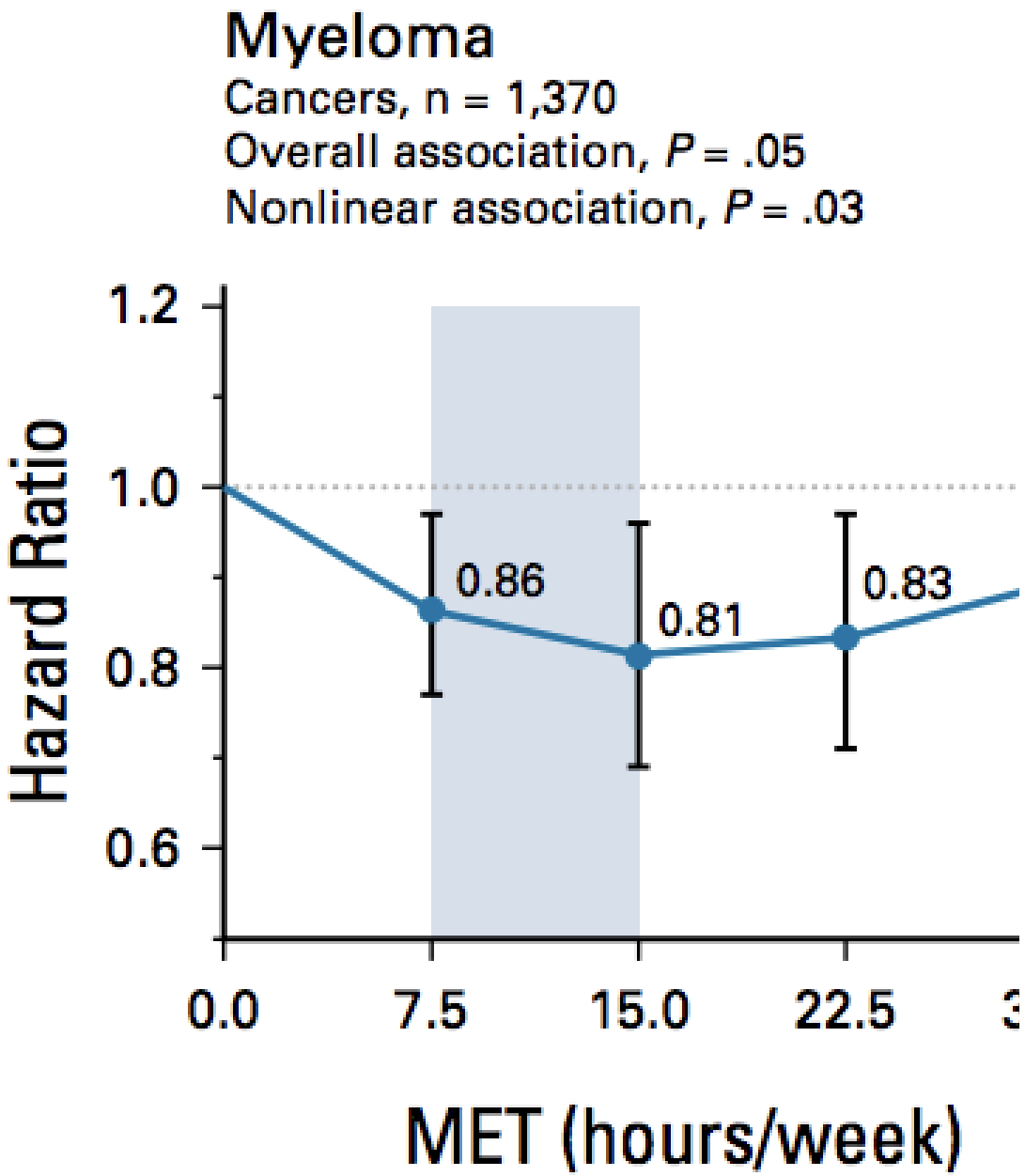
Charles E. Matthews, PhD[1]; Steven C. Moore, PhD[1]; Hannah Arem, PhD[2]; Michael B. Cook, PhD[1]; Britton Trabert, PhD[1]; Niclas Håkansson, PhD[3]; Susanna C. Larsson, PhD[3,4]; Alicja Wolk, DrMedSci[3,4]; Susan M. Gapstur, PhD[5]; Brigid M. Lynch, PhD[6,7]; Roger L. Milne, PhD[6,8]; Neal D. Freedman, PhD[1]; Wen-Yi Huang, PhD[1]; Amy Berrington de Gonzalez, DPhil[9]; Cari M. Kitahara, PhD[9]; Martha S. Linet, MD[9]; Eric J. Shiroma, ScD[10]; Sven Sandin, PhD[11,12]; Alpa V. Patel, PhD[5]; and I-Min Lee, ScD[13]

PURPOSE To determine whether recommended amounts of leisure-time physical activity (ie, 7.5-15 metabolic equivalent task [MET] hours/week) are associated with lower cancer risk, describe the shape of the dose-response relationship, and explore associations with moderate- and vigorous-intensity physical activity.

METHODS Data from 9 prospective cohorts with self-reported leisure-time physical activity and follow-up for cancer incidence were pooled. Multivariable Cox regression was used to estimate adjusted hazard ratios (HRs) and 95% CIs of the relationships between physical activity with incidence of 15 types of cancer. Dose-response relationships were modeled with restricted cubic spline functions that compared 7.5, 15.0, 22.5, and 30.0 MET hours/week to no leisure-time physical activity, and statistically significant associations were determined using tests for trend ($P < .05$) and 95% CIs (< 1.0).

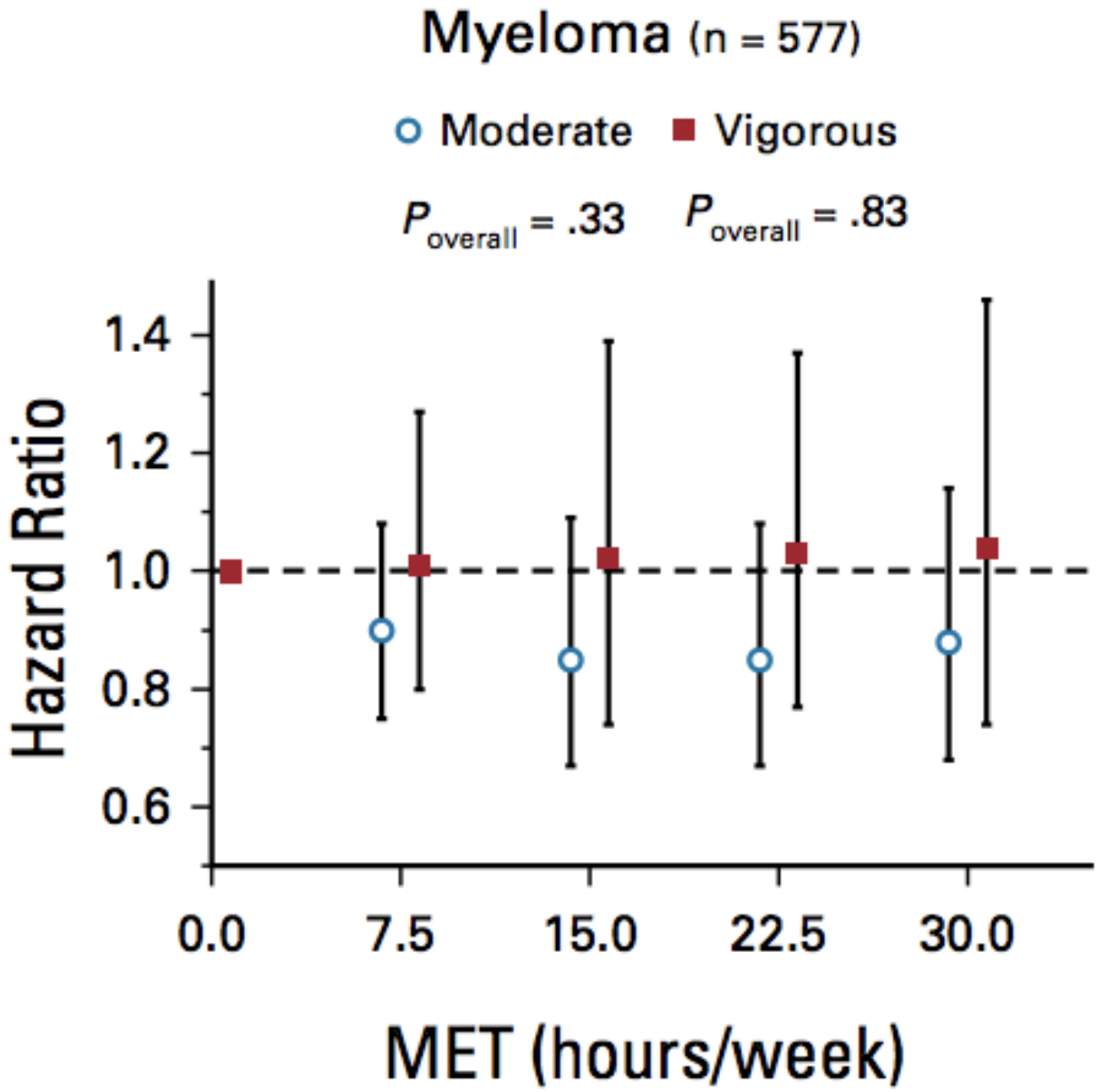
RESULTS A total of 755,459 participants (median age, 62 years [range, 32-91 years]; 53% female) were followed for 10.1 years, and 50,620 incident cancers accrued. Engagement in recommended amounts of activity (7.5-15 MET hours/week) was associated with a statistically significant lower risk of 7 of the 15 cancer types studied, including colon (8%-14% lower risk in men), breast (6%-10% lower risk), endometrial (10%-18% lower risk), kidney (11%-17% lower risk), myeloma (14%-19% lower risk), liver (18%-27% lower risk), and non-Hodgkin lymphoma (11%-18% lower risk in women). The dose response was linear in shape for half of the associations and nonlinear for the others. Results for moderate- and vigorous-intensity leisure-time physical activity were mixed. Adjustment for body mass index eliminated the association with endometrial cancer but had limited effect on other cancer types.


Myeloma
Cancers, n = 1,370
Overall association, P = .05
Nonlinear association, P = .03
Hazard Ratio
1.2
1.0
0.8
0.6
0.86
0.81
0.83
0.89
0.0
7.5
15.0
22.5
30.0
MET (hours/week)



Physical activity	MET
Light intensity activities	**< 3**
writing, desk work, using computer	1.5[10]
walking slowly	2.0[10]
Moderate intensity activities	**3 to 6**
walking, 3.0 mph (4.8 km/h)	3.0[10]
sweeping or mopping floors, vacuuming carpets	3 to 3.5[10]
yoga session with asanas and pranayama	3.3[11]
Tennis doubles	5.0[10]
sexual activity, aged 22	5.8[12]
Vigorous intensity activities	**>= 6**
bicycling, on flat, 10–12 mph (16–19 km/h), light effort	6.0[10]
sun salutation (Surya Namaskar, vigorous with transition jumps)	7.4[11]
basketball game	8.0[10]
swimming moderately to hard	8 to 11[10]
jogging, 5.6 mph (9.0 km/h)	8.8[13]
rope jumping (66/min)	9.8[13]
rope jumping (84/min)	10.5[13]
rope jumping (100/min)	11.0[13]
jogging, 6.8 mph (10.9 km/h)	11.2[13]

Physical activity	MET
Light intensity activities	**< 3**
writing, desk work, using computer	1.5[10]
walking slowly	2.0[10]
Moderate intensity activities	**3 to 6**
walking, 3.0 mph (4.8 km/h)	3.0[10]
sweeping or mopping floors, vacuuming carpets	3 to 3.5[10]
yoga session with asanas and pranayama	3.3[11]
Tennis doubles	5.0[10]
sexual activity, aged 22	5.8[12]
bicycling, on flat, 10–12 mph (16–19 km/h), light effort	6.0[10]
sun salutation (Surya Namaskar, vigorous with transition jumps)	7.4[11]
basketball game	8.0[10]
swimming moderately to hard	8 to 11[10]
jogging, 5.6 mph (9.0 km/h)	8.8[13]
rope jumping (66/min)	9.8[13]
rope jumping (84/min)	10.5[13]
rope jumping (100/min)	11.0[13]
jogging, 6.8 mph (10.9 km/h)	11.2[13]


Myeloma (n = 577)
Moderate
Vigorous
$P_{overall}$ = .33
$P_{overall}$ = .83
Hazard Ratio
1.4
1.2
1.0
0.8
0.6
0.0
7.5
15.0
22.5
30.0
MET (hours/week)

How did I feel?


Plenary Session

- Implausible finding
- Potential for multiple hypothesis testing
- Confounding – being ill makes you both less likely to exercise and more likely to develop cancer
- Measurement error – self reported is not true

- “Do I believe staying active is part of a healthy life? Yes

Would I do it specifically to avoid myeloma? I would do it as part of general and cardiovascular health

- “Do I believe staying active is part of a healthy life? Yes

Would I do it specifically to avoid myeloma? I would do it as part of general and cardiovascular health

- But have you read the paper?”

- No!

Key objectives

- 1. What are the best techniques to keep up with the literature?
- 2. What are e.g. of studies that are commonly misinterpreted?
- 3. How can you be a better reader of medical information?

50 million scientific articles

Publication pile-up

Science and engineering articles published annually worldwide, m

Source: National Science Foundation

Replication, Duplication, and Waste in a Quarter Million Systematic Reviews and Meta-Analyses

Replication, Duplication, and Waste in a Quarter Million Systematic Reviews and Meta-Analyses

The Mass Production of Redundant, Misleading, and Conflicted Systematic Reviews and Meta-analyses

Replication, Duplication, and Waste in a Quarter Million Systematic Reviews and Meta-Analyses

The Mass Production of Redundant, Misleading, and Conflicted Systematic Reviews and Meta-analyses

SPECIAL | 18 OCTOBER 2018

Challenges in irreproducible research

COMMENTARY

21st Century Physician: Triaging the Tsunami of Medical Information

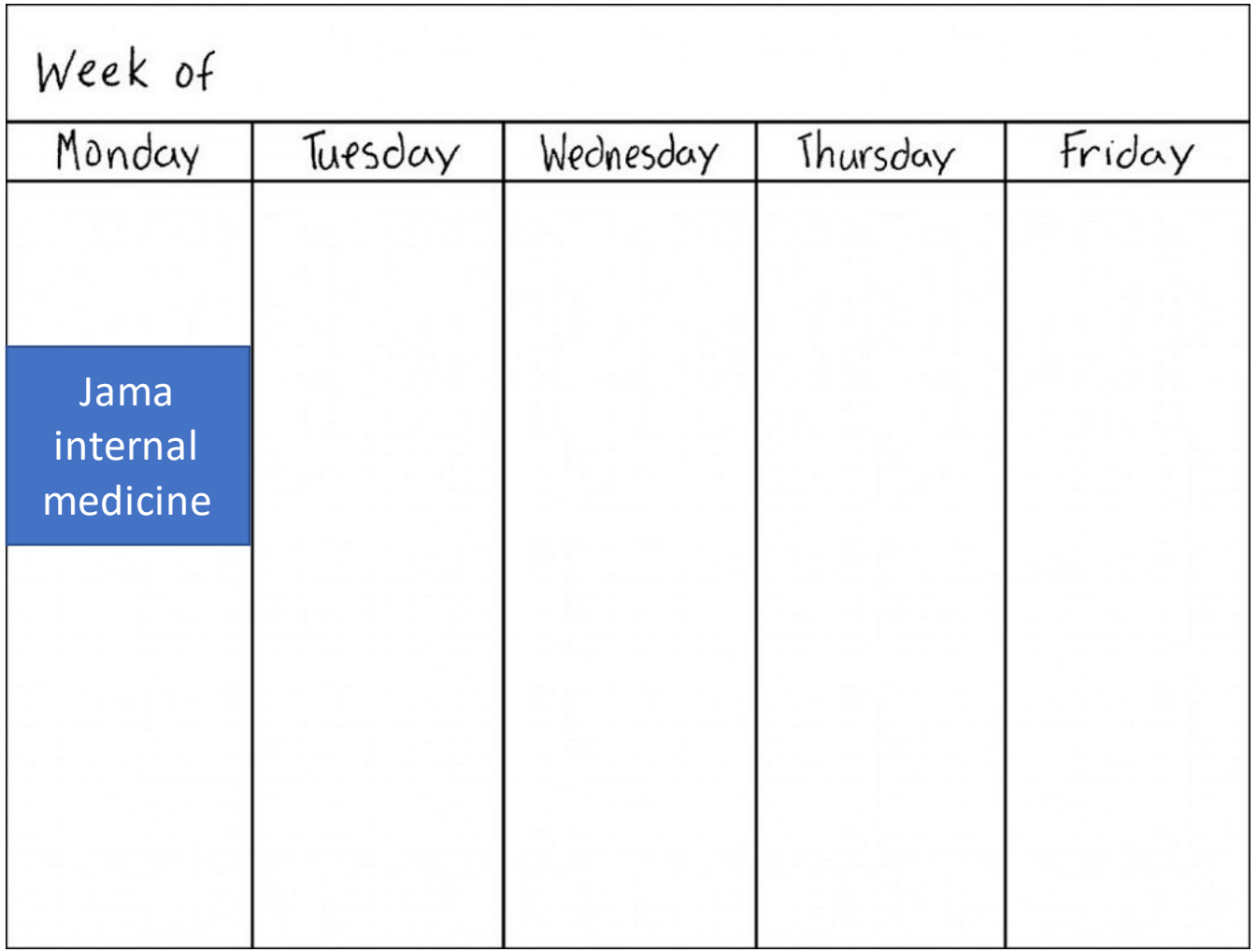
Vinay Prasad, MD, MPH

DISCLOSURES | September 25, 2018

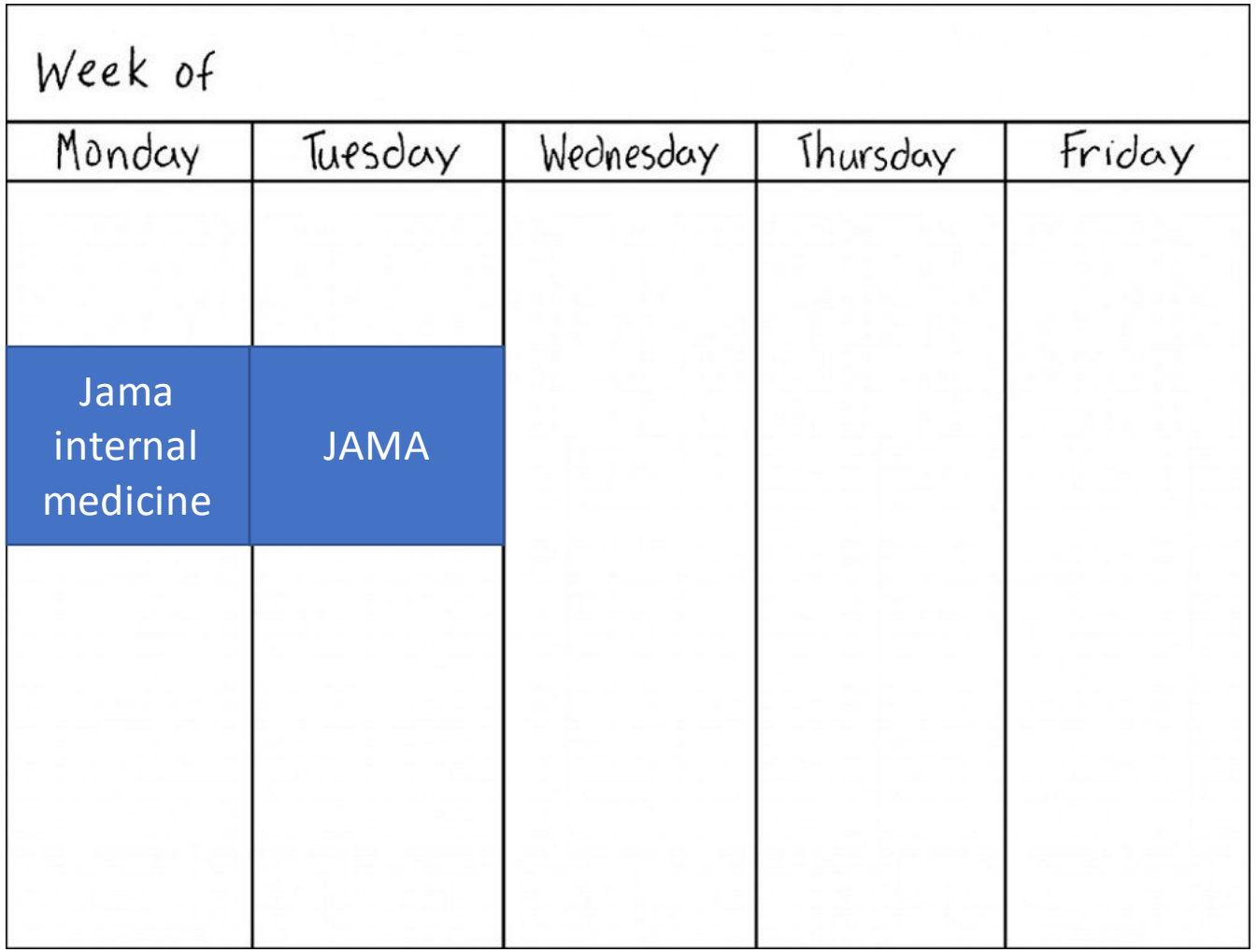
Timing is everything

Week of				
Monday	Tuesday	Wednesday	Thursday	Friday

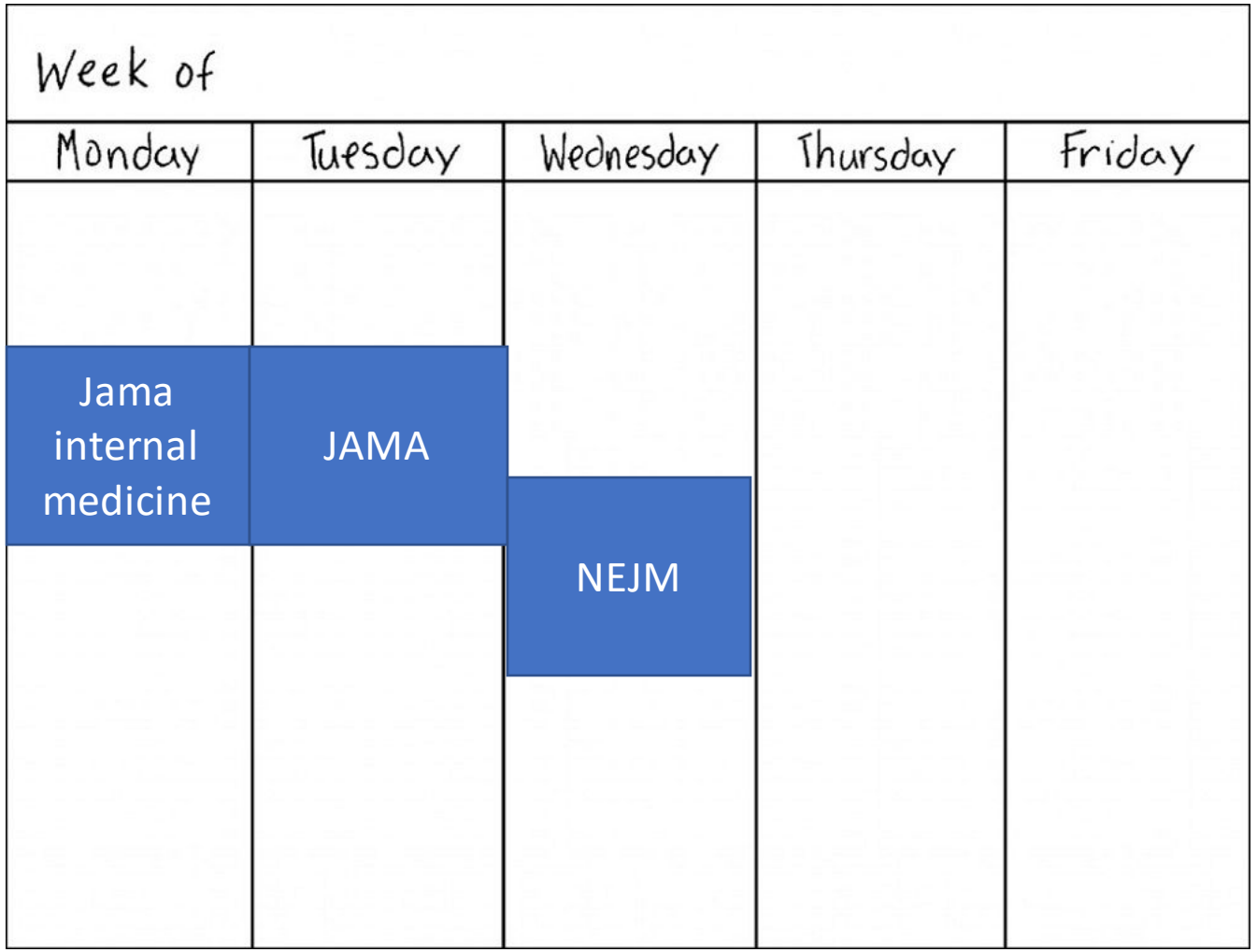
Timing is everything



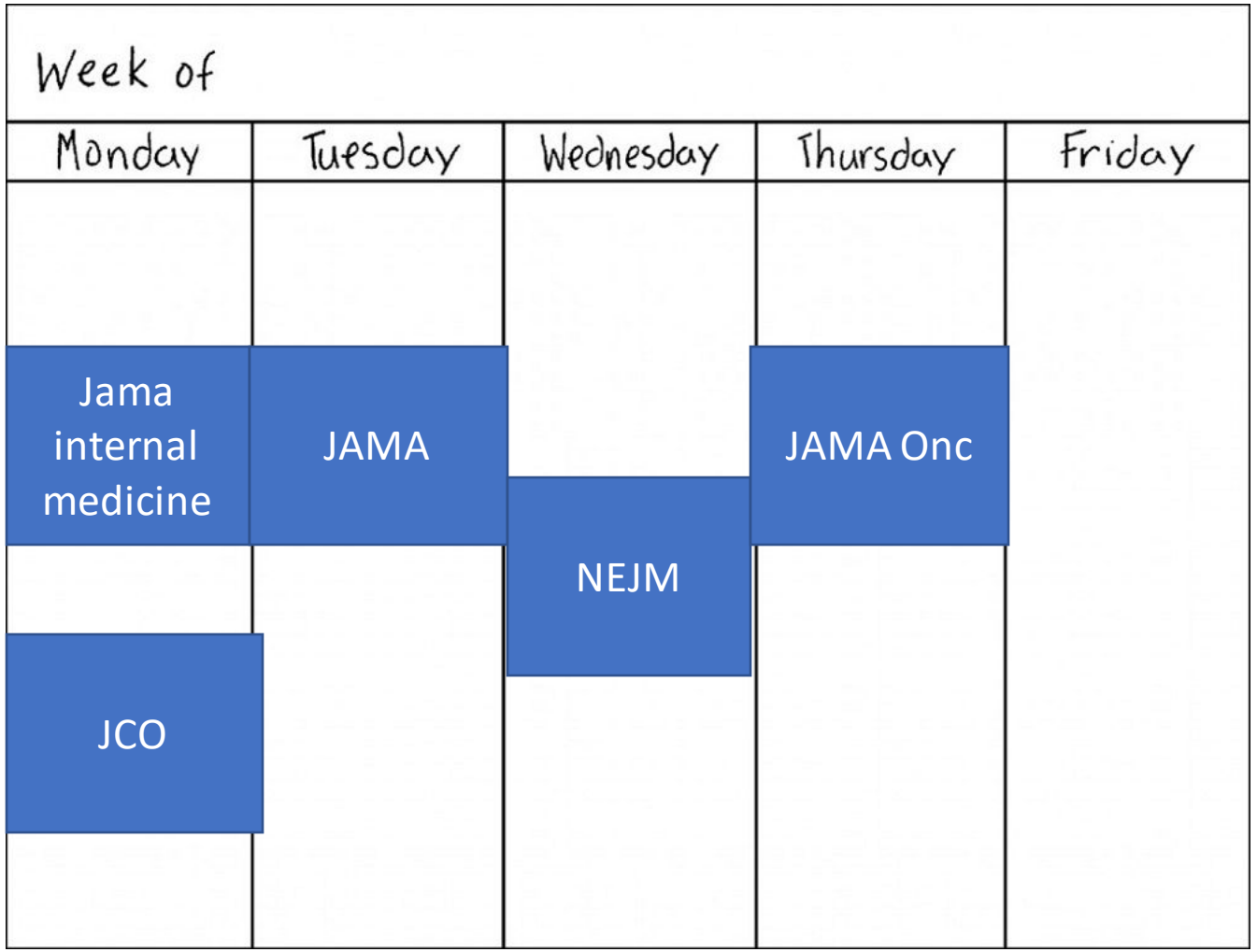
Timing is everything



Timing is everything



Timing is everything



Home

Explore

Notifications

Messages

Bookmarks

Top Articles

Profile

More

Tweet

Vinay Prasad, MD MPH

31.9K Tweets

Edit profile

Vinay Prasad, MD MPH

@VPrasadMDMPH

Professor @ucsf, Physician-Scientist, Writer; More at @vkprasadlab @plenary_session, YouTube, #vpzd podcast & @Sensible_Med; Views are mine

Science & Technology ⓘ Bay Area, Ca

vinayprasadmdmph.substack.com Joined February 2013

2,727 Following **211.6K** Followers

Location

https://profiles.ucsf.edu/vinayak.prasad

1001 Potrero Ave San Francisco CA 94110

No hours available

Get directions **Contact**

Tweets Tweets & replies Media Likes


A FAVOR FOR
A RIVETING WIN
Obama: 10 days to reach debt deal
SUMMER GAMES FAMILIAR NAMES
THE INDIANAPOLIS STAR
Obama: 'If not now, when?'
President says he won't agree to temporary debt deal
PARTISAN DEADLOCK: WHERE THEY STAND
School shooter awaits sentence
FELT LIKE 108°
(and today will be another scorcher)

News

Vitamin E increases all-cause mortality

Shelley Wood

November 10, 2004

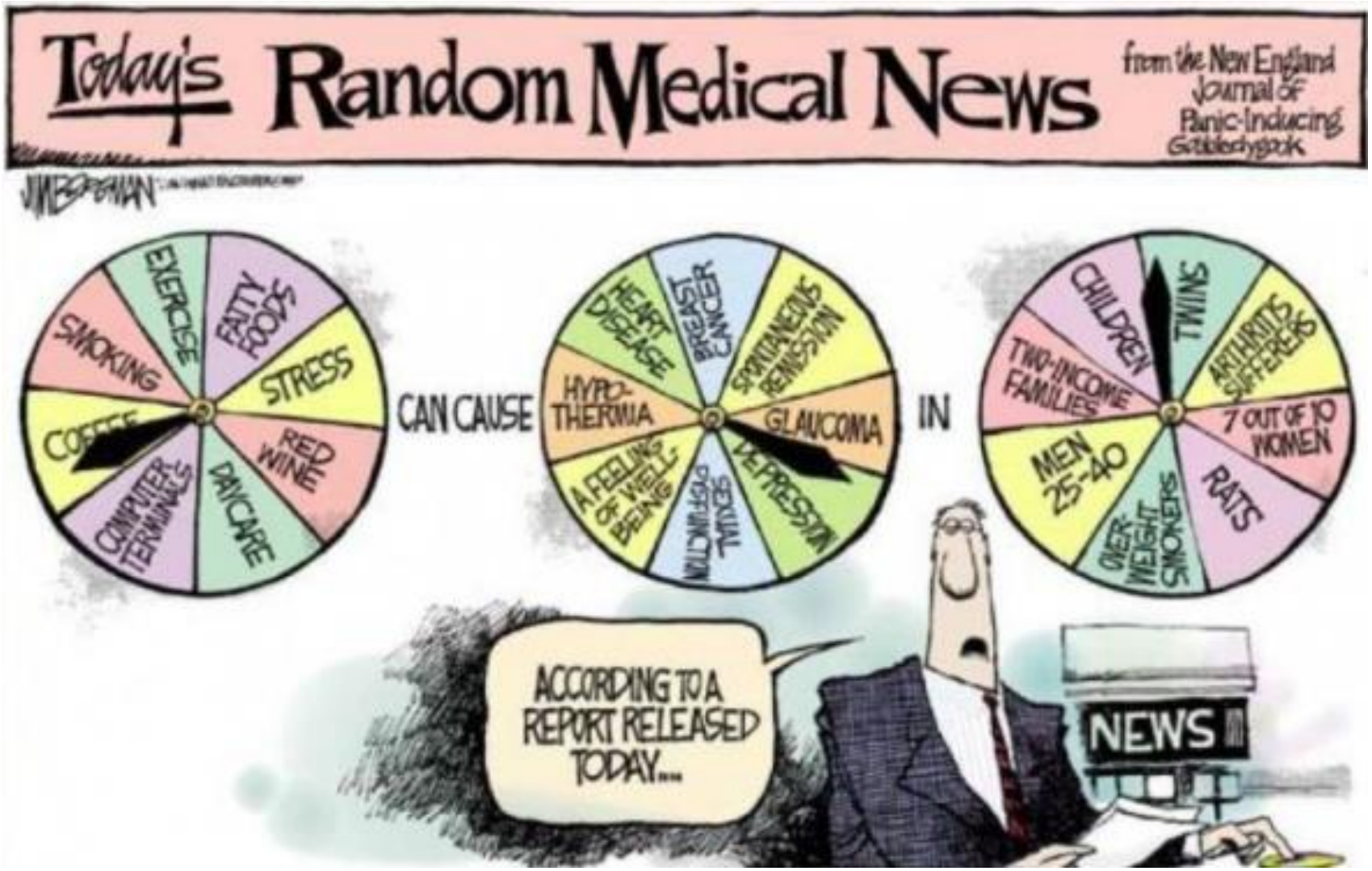
New Orleans, LA - Driving a final nail in the coffin for vitamin E, a meta-analysis of the popular supplement indicates that doses >400 IU/day can increase the risk of death from any cause. Vitamin-E capsules typically contain 400 to 800 IU.

NEWS

VITAMIN E MORTALITY STUDY CHALLENGED

MEGAN HAGGAN — 29/08/2017

A new study questions whether Vitamin E supplements are really correlated with an increased mortality risk


Today's Random Medical News
from the New England Journal of Panic-Inducing Gobbledygook
JIM BORGMAN
EXERCISE
FATTY FOODS
SMOKING
STRESS
COFFEE
RED WINE
COMPUTER TERMINALS
DAYCARE
CAN CAUSE
HEART DISEASE
BREAST CANCER
HYPO-THERMIA
SPONTANEOUS REMISSION
GLAUCOMA
A FEELING OF WELL-BEING
SEXUAL DYSFUNCTION
DEPRESSION
IN
CHILDREN
TWINS
TWO-INCOME FAMILIES
ARTHRITIS SUFFERERS
MEN 25-40
7 OUT OF 10 WOMEN
OVER-WEIGHT SMOKERS
RATS
ACCORDING TO A REPORT RELEASED TODAY...
NEWS

- Y = Mortality

- X1 = Vitamin E exposure
- X2 = Age
- X3 = Sex
- X4 = Race

- Y = Mortality

- X1 = Vitamin E exposure
- X2 = Age
- X3 = Sex
- X4 = Race
- X5 = Income

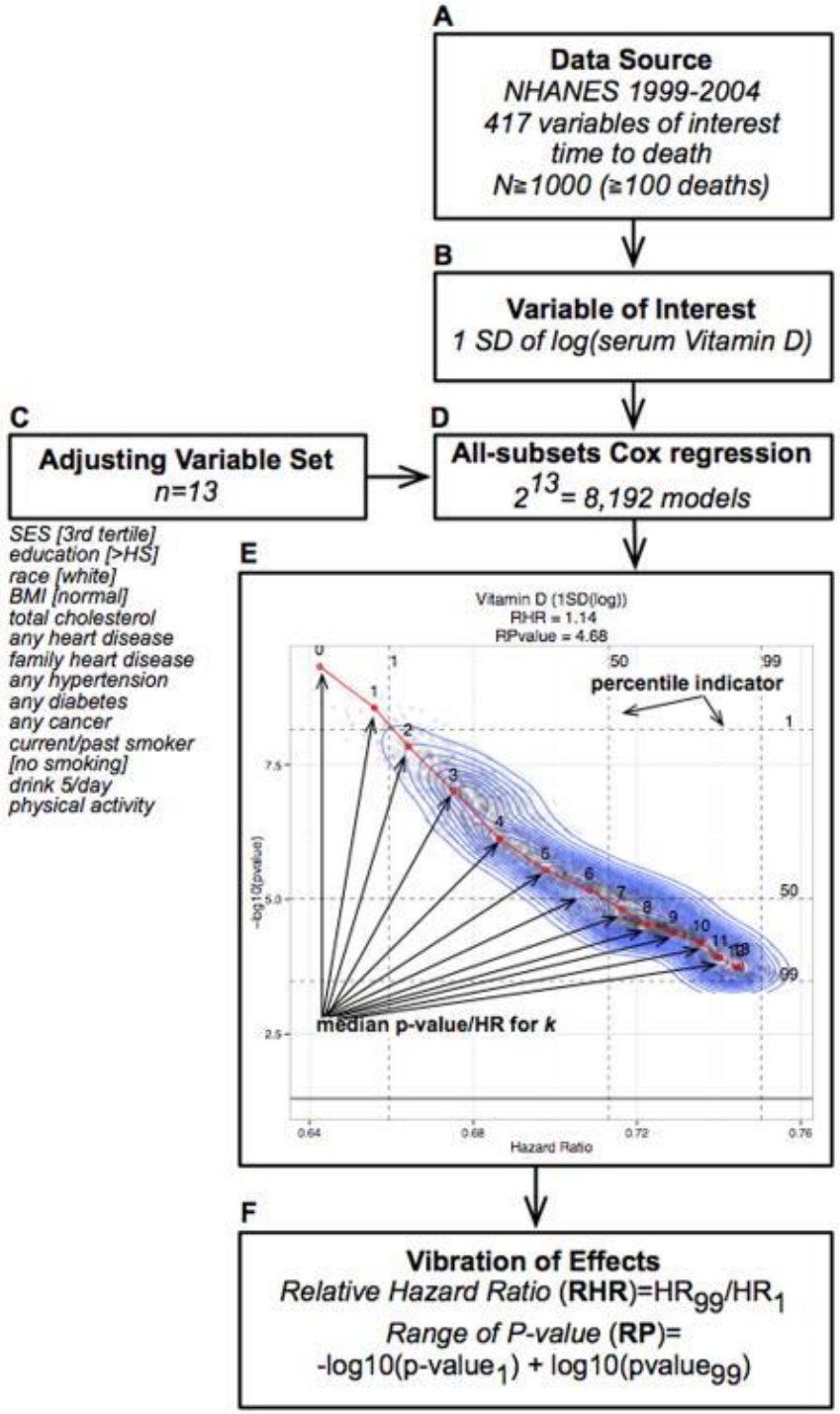
- Y = Mortality

- X1 = Vitamin E exposure
- X2 = Age
- X3 = Sex
- X4 = Race
- X5 = Income
- X6 = Smoking

- Y = Mortality

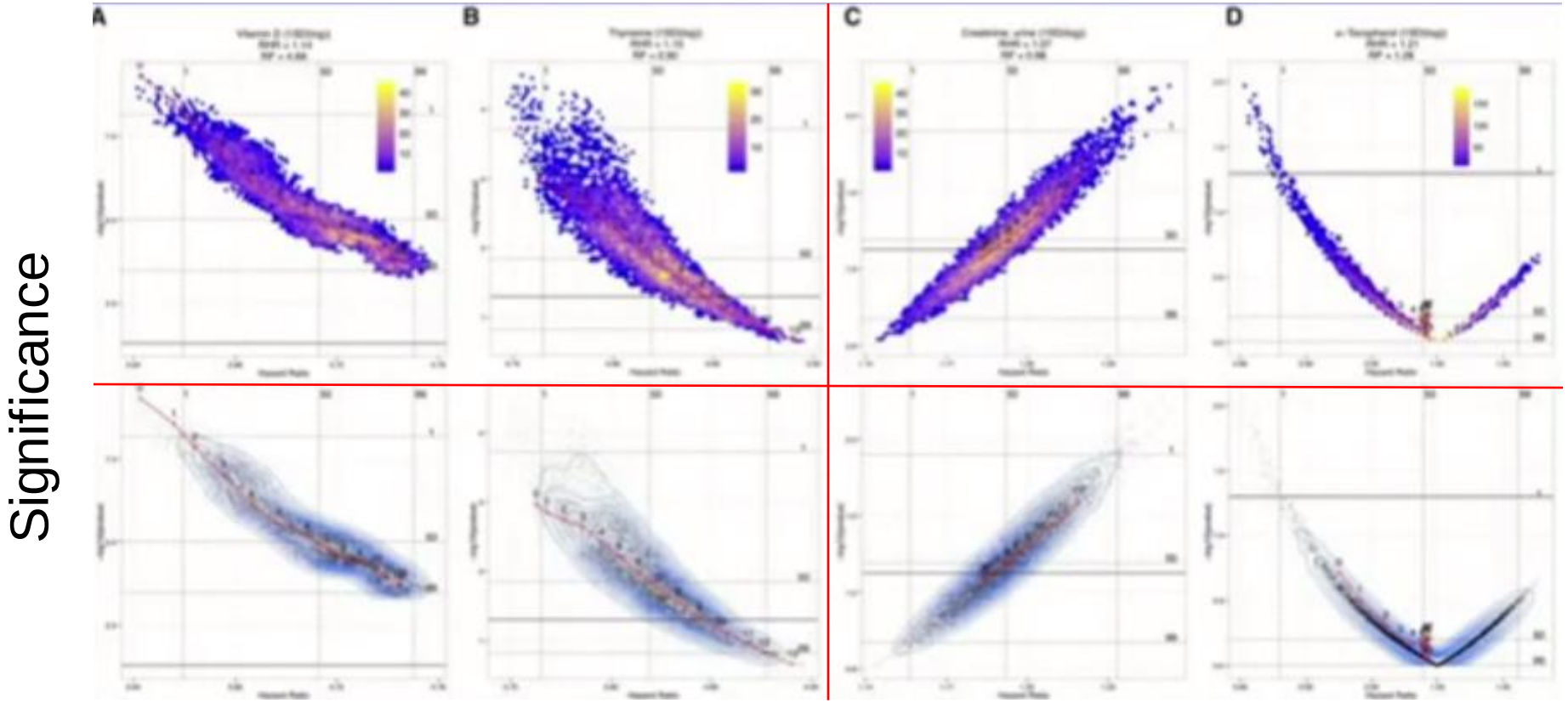
- X1 = Vitamin E exposure
- X2 = Age
- X3 = Sex
- X4 = Income
- X5 = Smoking
- X6 = body mass index (BMI), hypertension, diabetes, cholesterol, alcohol consumption, education, family history of heart disease, heart disease, any cancer, physical activity) and race/ethnicity

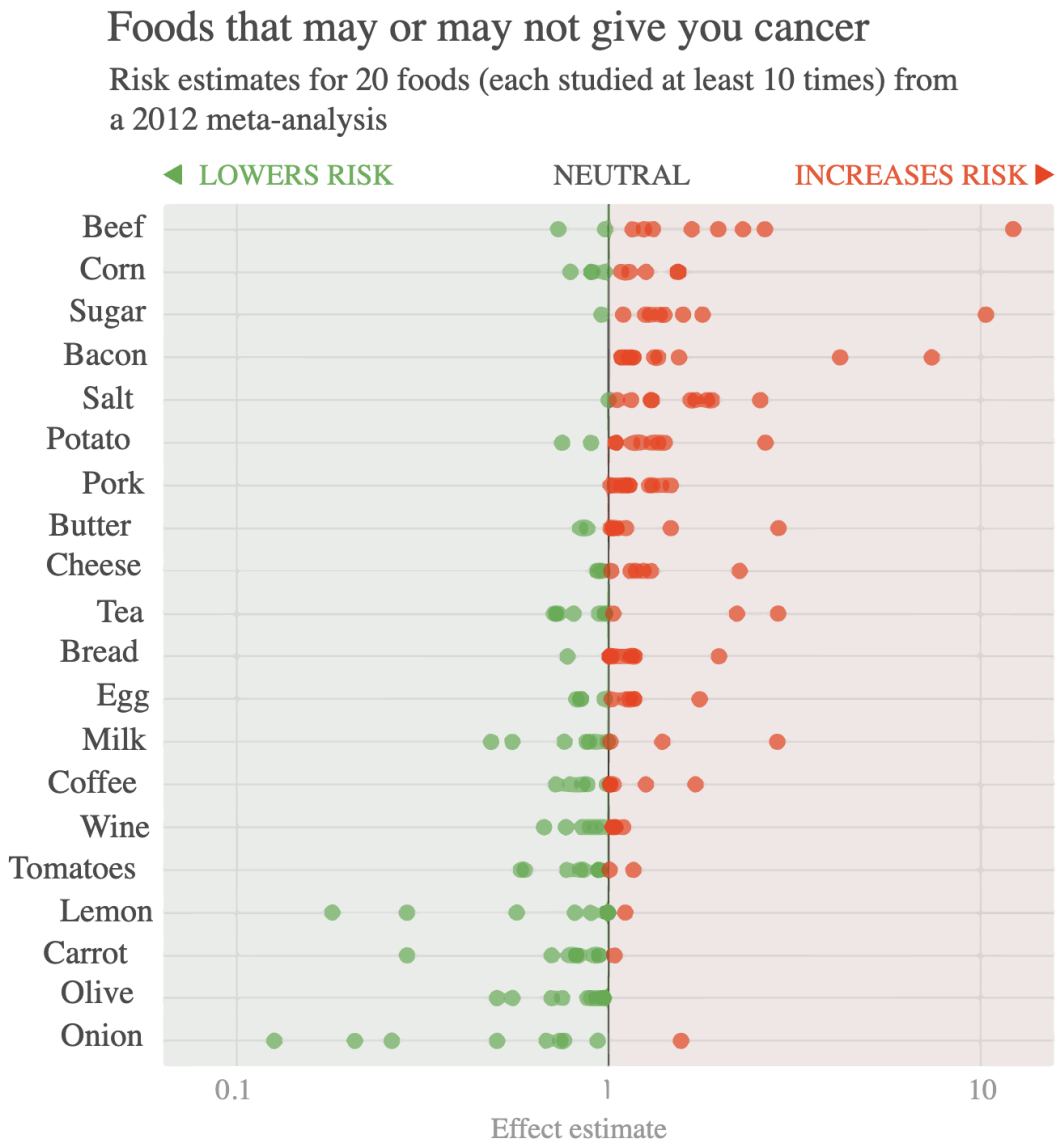
- Many investigators with access to the data, probing these relationships
- Each adjust for some set of covariates that make sense to them
- What if you simulate the entire research community?



Buford Patel
Ioannidis, JCE

Observational/ Epidemiology studies can say anything





Ioannidis, AJCN

Schoenfeld JD, Ioannidis JP. Is everything we eat associated with cancer? A systematic cookbook review. The American Journal of Clinical Nutrition. 2013;97(1):127-134. doi:10.3945/ajcn.112.047142

Triage

- Pertain to my practice/ interest vs. No
- Randomized vs. observational
- Multicenter vs. single center
- Large sample vs. small
- Clinical endpoint vs. surrogate

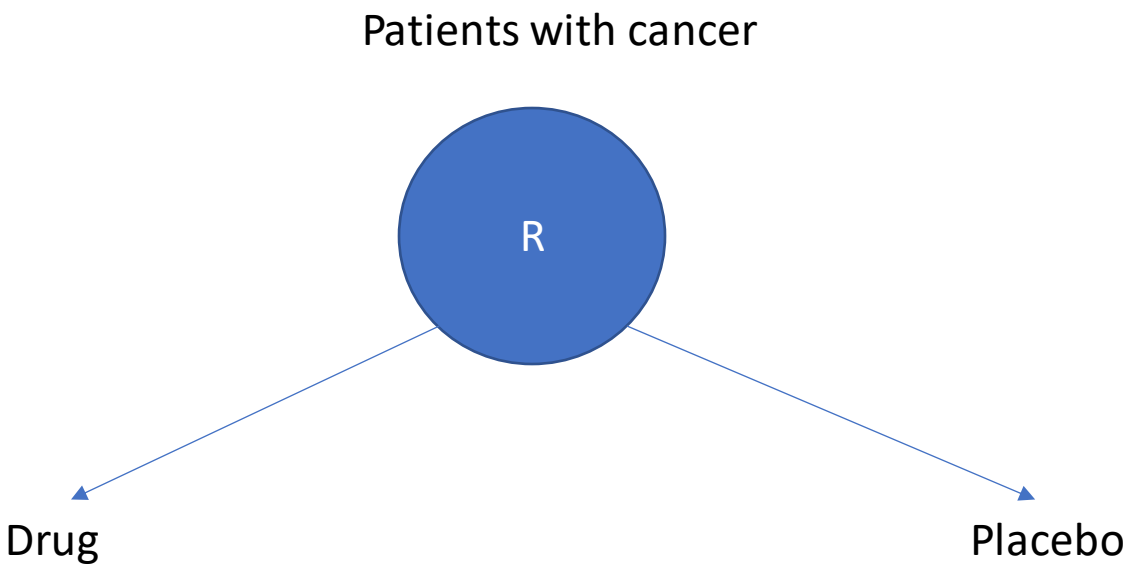
Ask questions and find answer first

- What was the intervention?
- Is the control arm what you would have done?
- What was the effect size?
- Clinical or surrogate endpoint?
- What happened after the trial ended?
- Any games with patient selection?

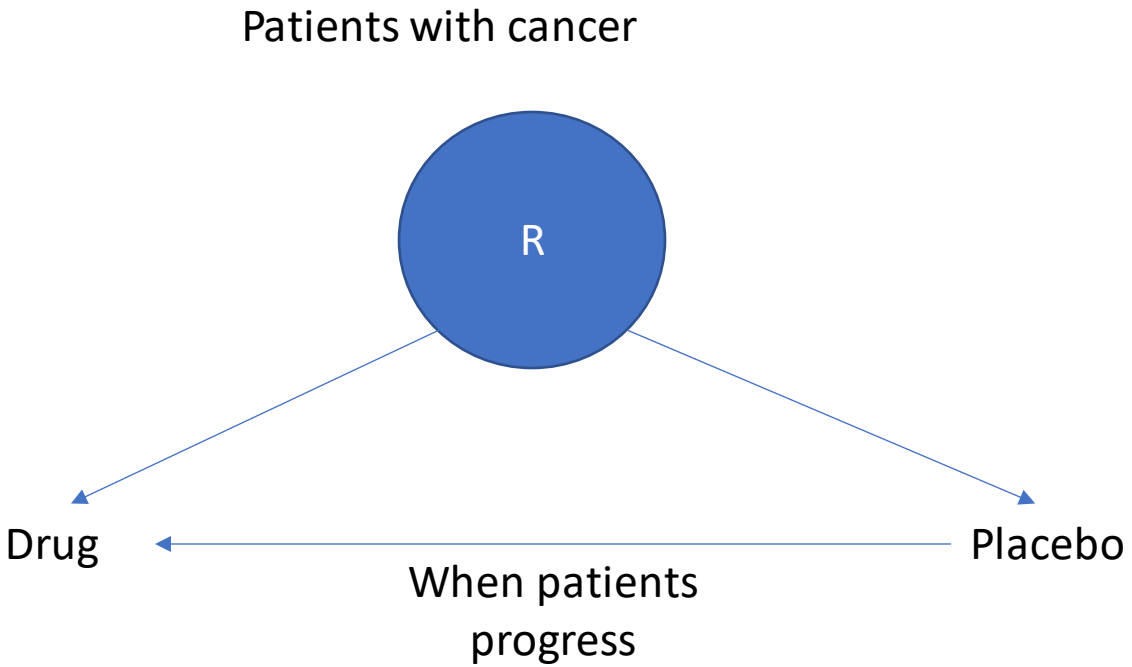
Key objectives

- 1. What are the best techniques to keep up with the literature?
- 2. What are e.g. of studies that are commonly misinterpreted?
- 3. How can you be a better reader of medical information?

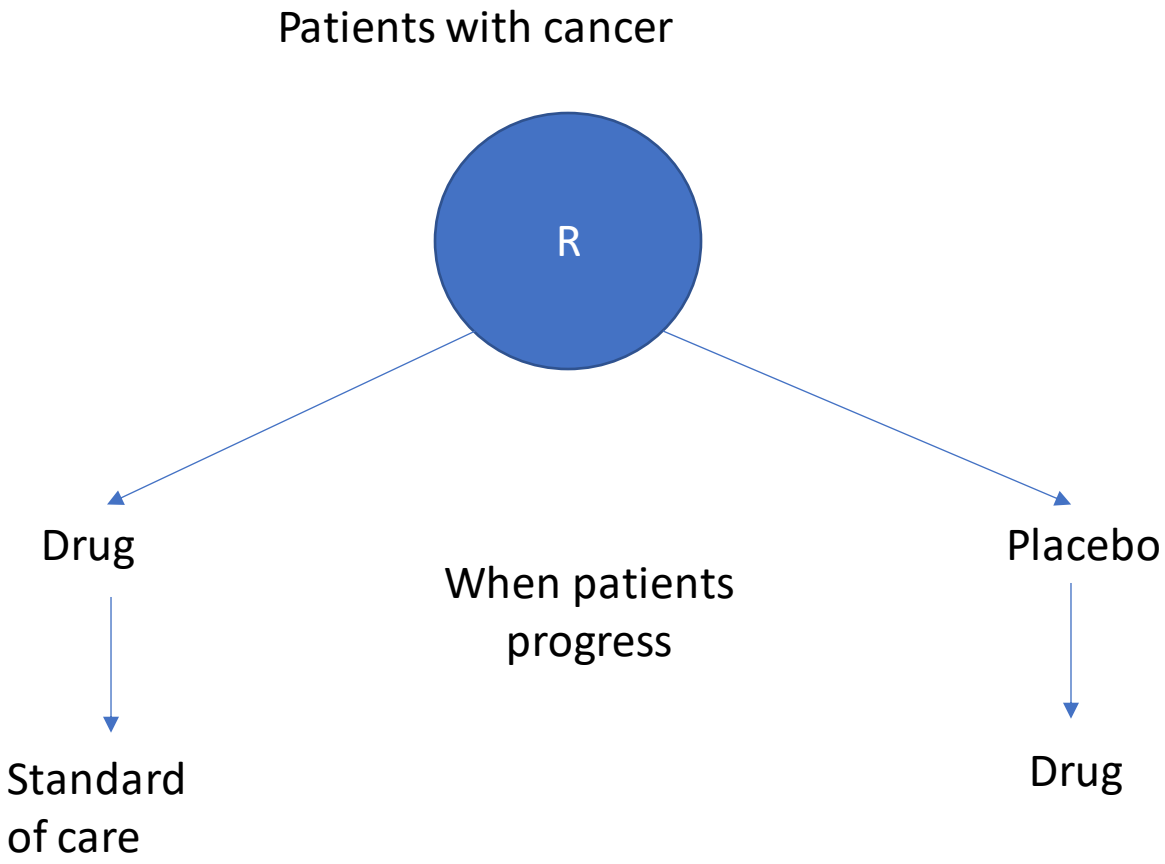
Crossover



Crossover


Patients with cancer
R
Drug
Placebo
When patients progress

Crossover


Patients with cancer
R
Drug
When patients progress
Placebo
Standard of care
Drug

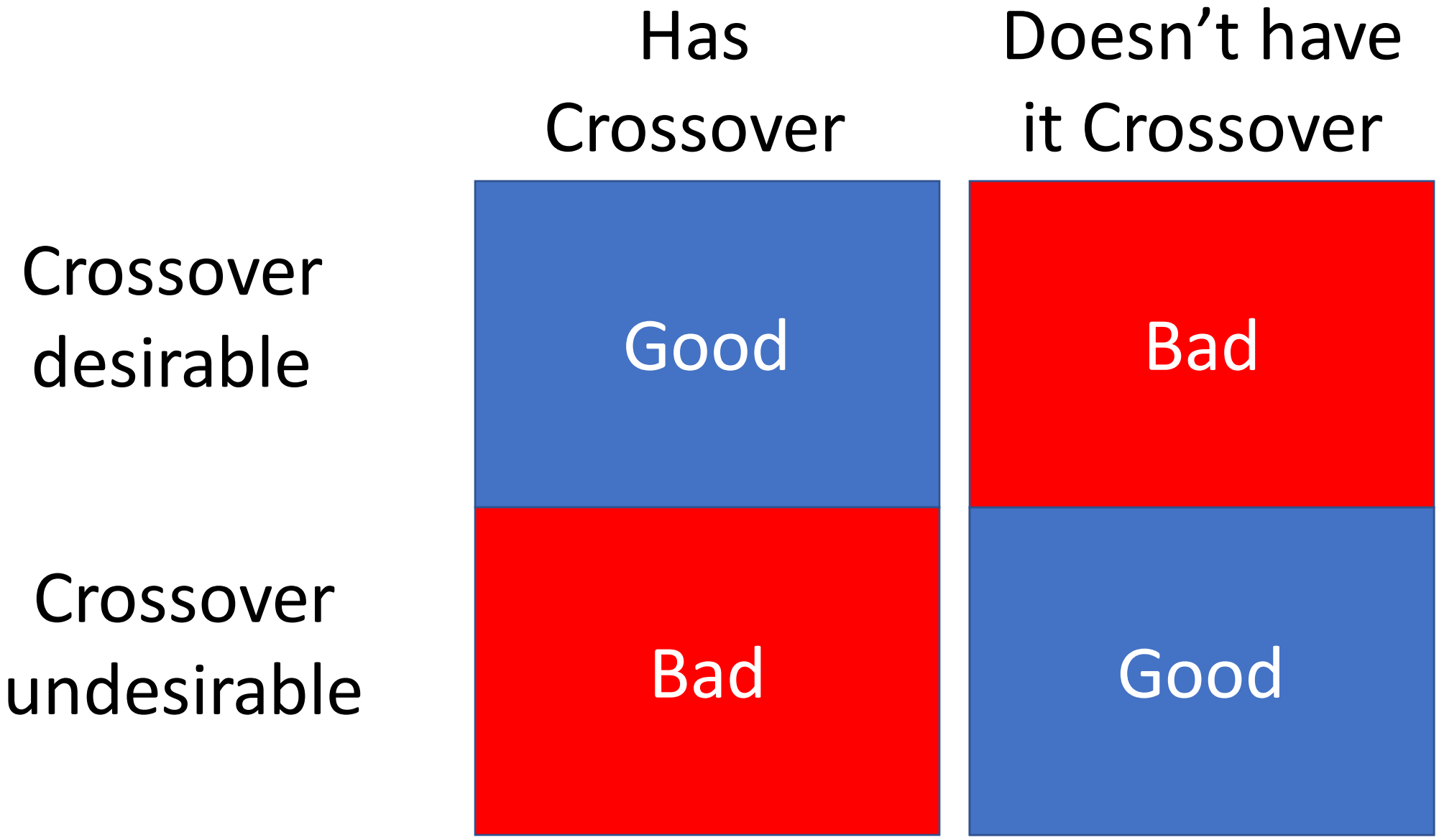
Crossover desirable

Crossover desirable

Crossover undesirable

	Has Crossover	Doesn't have it Crossover
Crossover desirable		
Crossover undesirable		

	Has Crossover	Doesn't have it Crossover
Crossover desirable	Good	
Crossover undesirable		Good


Has Crossover
Doesn't have it Crossover
Crossover desirable
Crossover undesirable
Good
Bad
Bad
Good

Everolimus Has Crossover

Crossover desirable

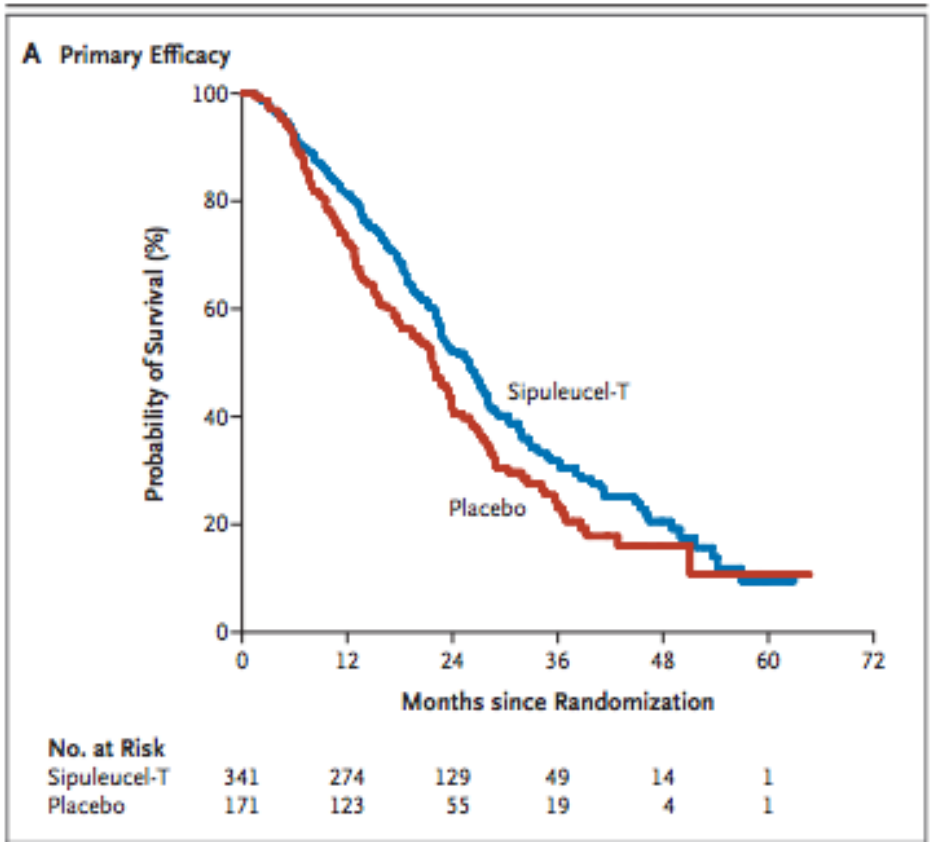
Crossover undesirable

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 29, 2010 VOL. 363 NO. 5

Sipuleucel-T Immunotherapy for Castration-Resistant Prostate Cancer

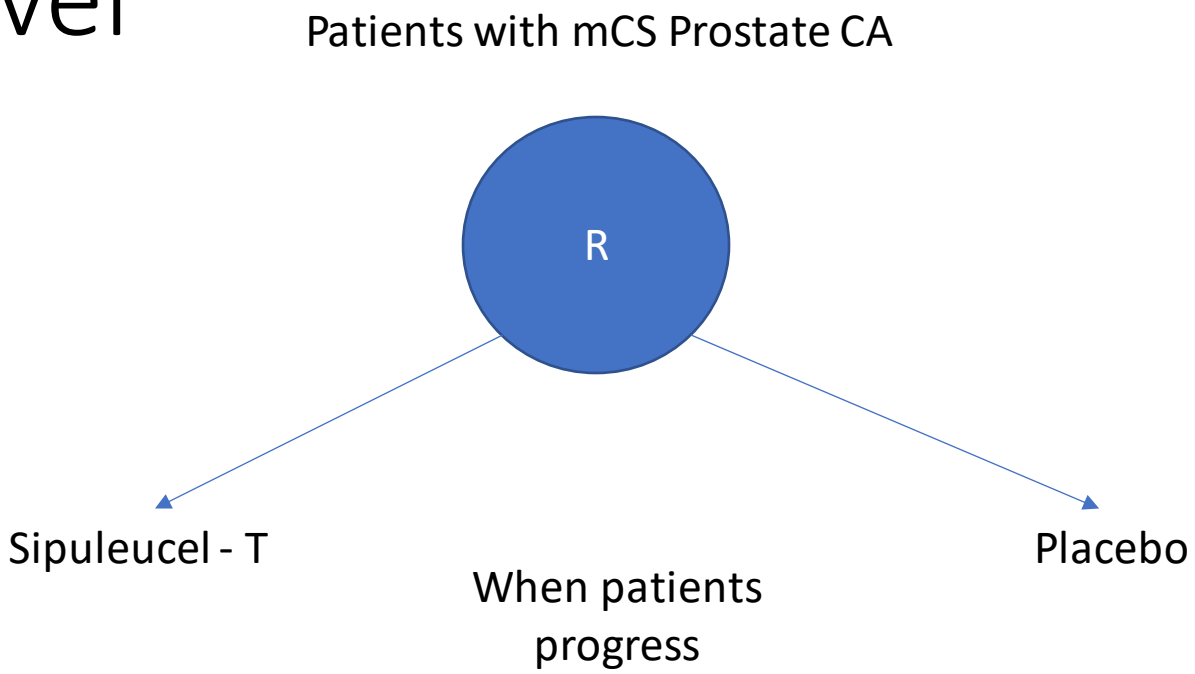
Philip W. Kantoff, M.D., Celestia S. Higano, M.D., Neal D. Shore, M.D., E. Roy Berger, M.D., Eric J. Small, M.D., David F. Penson, M.D., Charles H. Redfern, M.D., Anna C. Ferrari, M.D., Robert Dreicer, M.D., Robert B. Sims, M.D., Yi Xu, Ph.D., Mark W. Frohlich, M.D., and Paul F. Schellhammer, M.D., for the IMPACT Study Investigators*


A Primary Efficacy
Probability of Survival (%)
100
80
60
40
20
0
Sipuleucel-T
Placebo
0
12
24
36
48
60
72
Months since Randomization
No. at Risk
Sipuleucel-T 341 274 129 49 14 1
Placebo 171 123 55 19 4 1

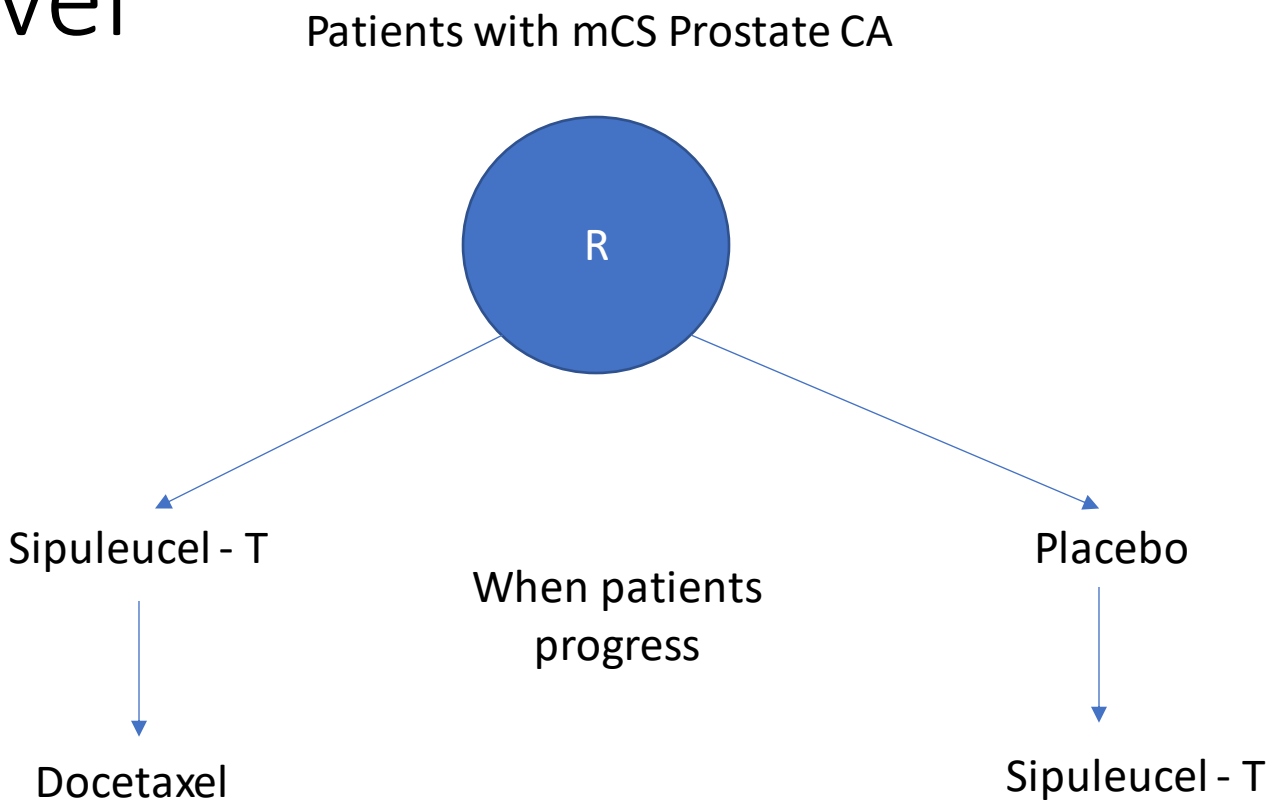
Sipleucel-T

- Only cancer therapeutic vaccine in history to be approved
- No responses, No change in time to progression (no activity)
- But 4 month OS gain (22->26 mo)

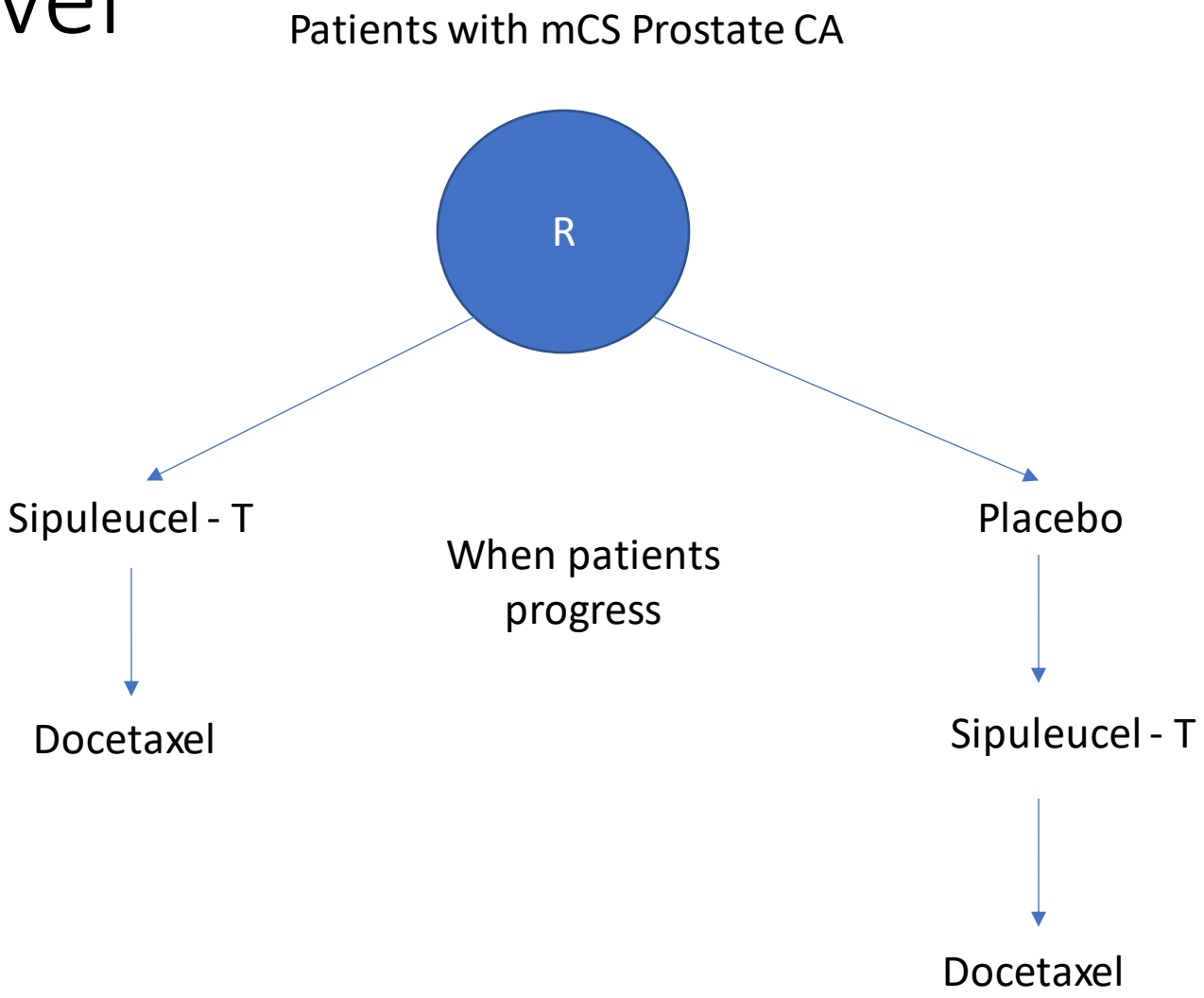
Crossover


Patients with mCS Prostate CA
R
Sipuleucel - T
Placebo
When patients progress

Crossover

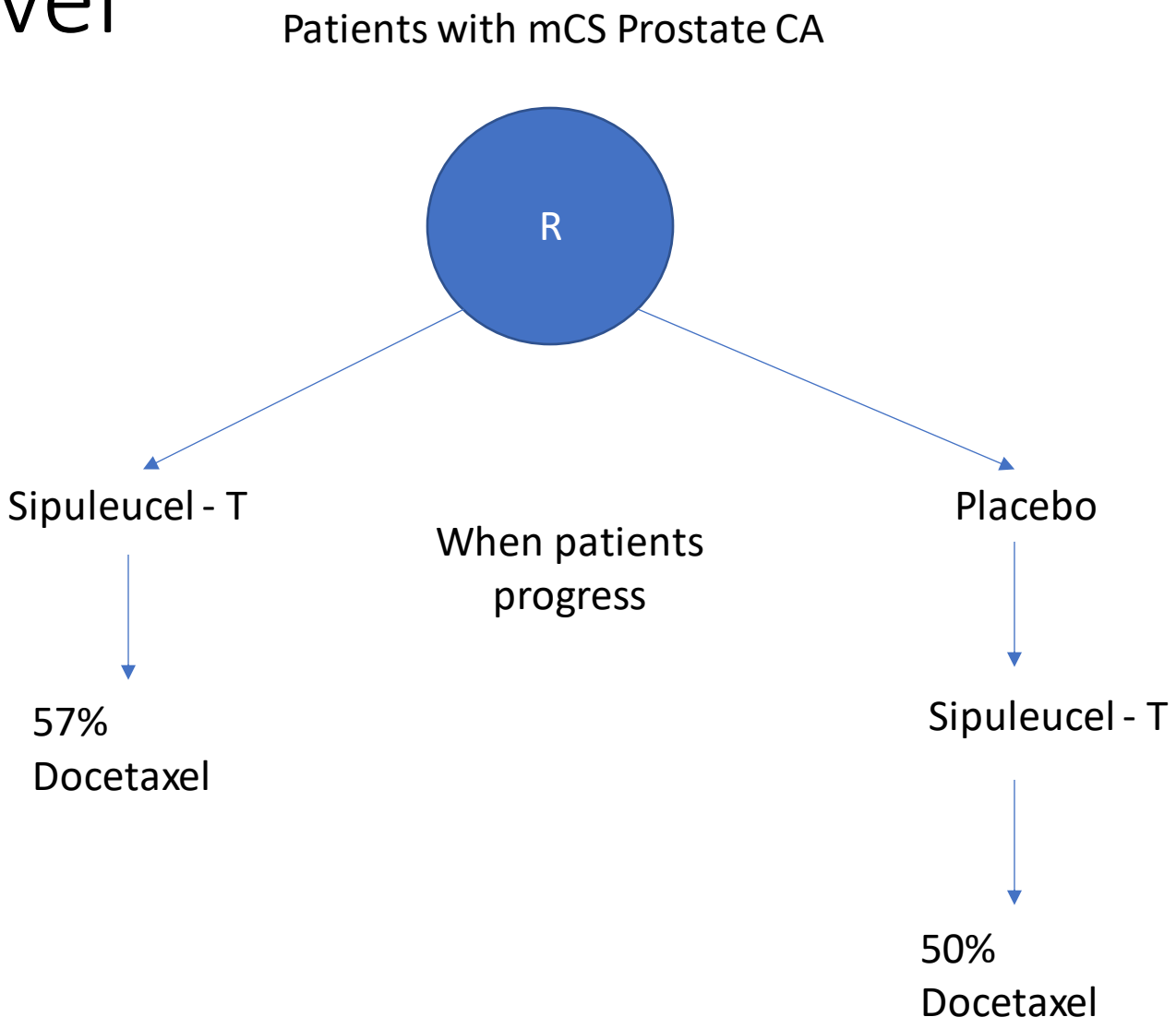

Patients with mCS Prostate CA
R
Sipuleucel - T
When patients progress
Placebo
Docetaxel
Sipuleucel - T

Crossover

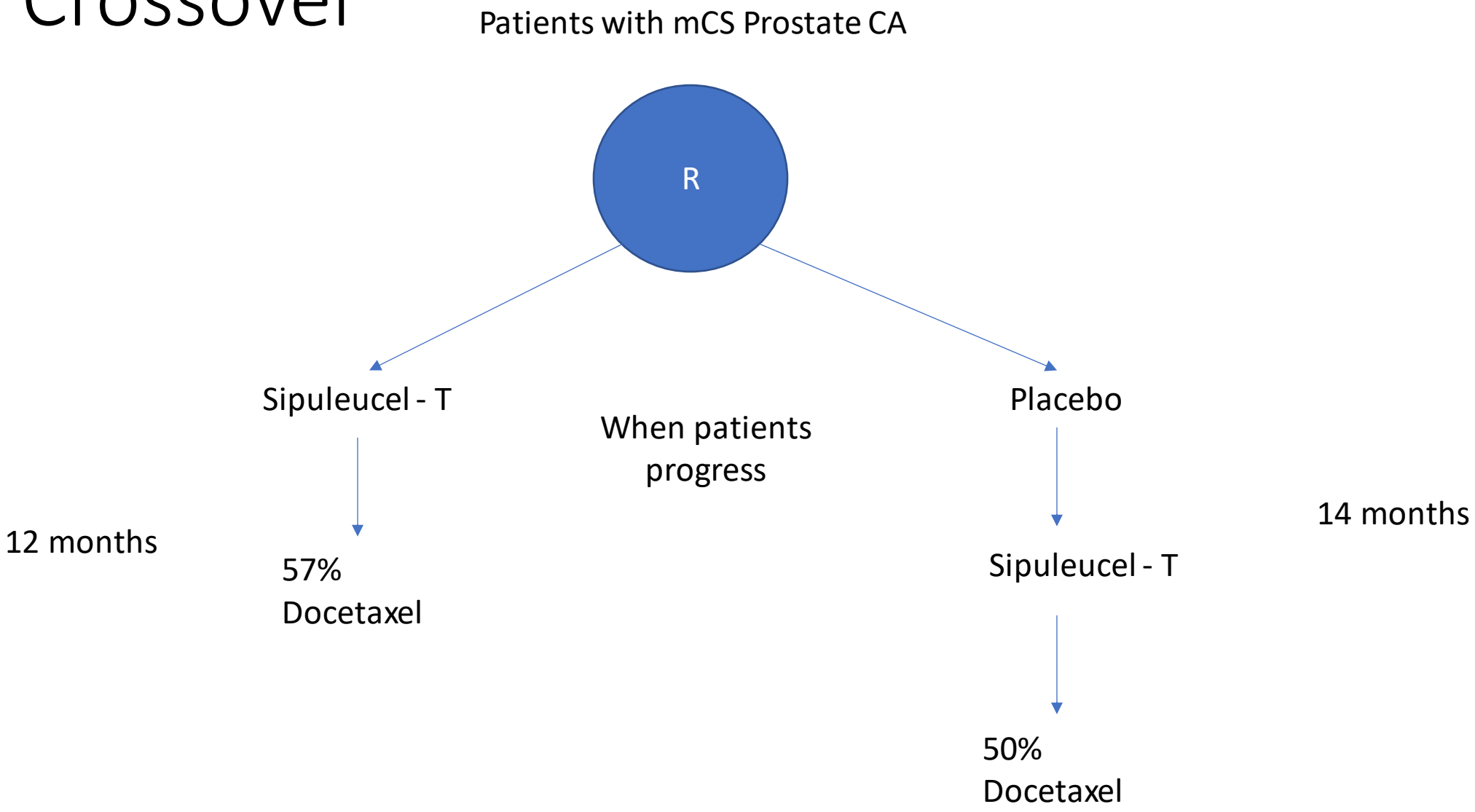

Patients with mCS Prostate CA
R
Sipuleucel - T
When patients progress
Placebo
Docetaxel
Sipuleucel - T
Docetaxel

Overall, additional anticancer treatments (other than APC8015F) were administered in 279 of the 341 patients (81.8%) in the sipuleucel-T group and 125 of the 171 patients (73.1%) in the placebo group. These therapies included docetaxel, received by 195 patients (57.2%) in the sipuleucel-T group and 86 patients (50.3%) in the placebo group. The Kaplan–Meier estimate of the median time to docetaxel use was 12.3 months in the sipuleucel-T group and 13.9 months in the placebo group.

Crossover


Patients with mCS Prostate CA
R
Sipuleucel - T
When patients progress
Placebo
57% Docetaxel
Sipuleucel - T
50% Docetaxel

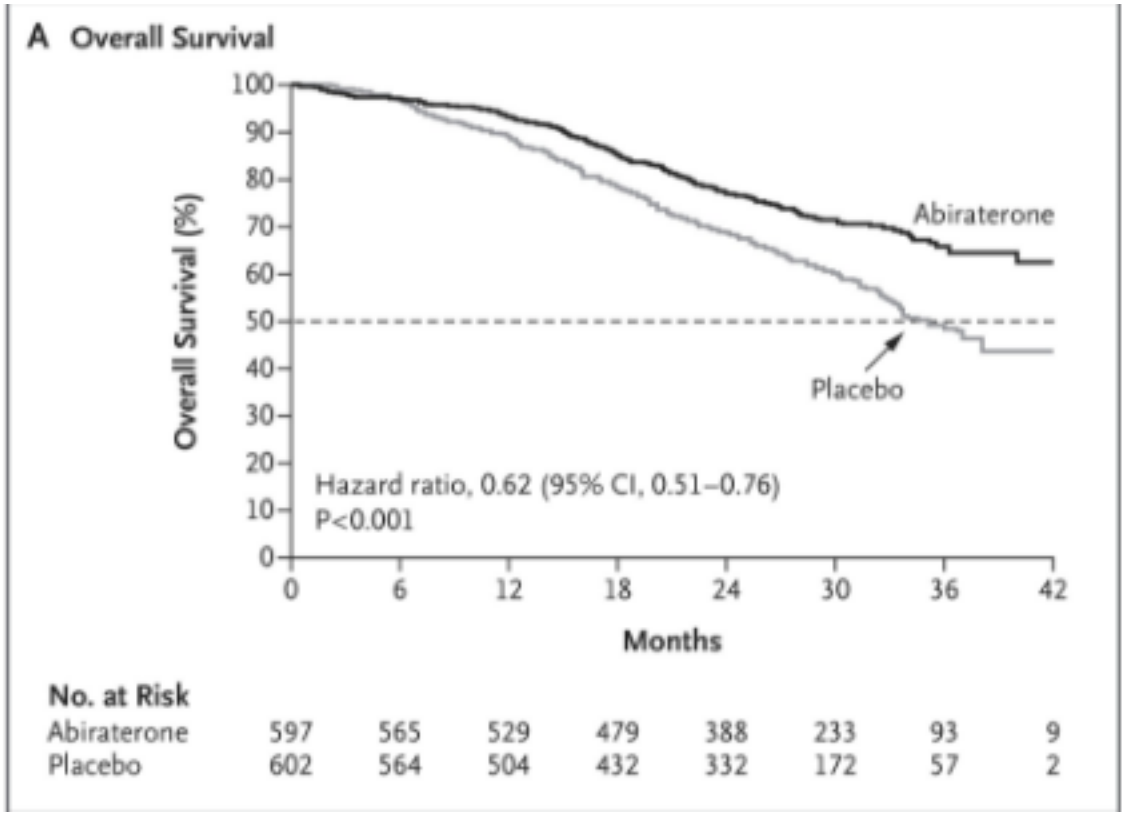
Crossover


Patients with mCS Prostate CA
R
Sipuleucel - T
When patients progress
Placebo
12 months
57% Docetaxel
Sipuleucel - T
14 months
50% Docetaxel

Cannot exclude the fact that OS in absence of RR or PFS is actually due to harm towards the control group from delay in chemotherapy due to getting an ineffective frozen salvage product

	Has Crossover	Doesn't have it Crossover
Crossover desirable	Good	Bad
Crossover undesirable: Trials assessing fundamental efficacy	Bad	Good

METASTATIC, CASTRATION-SENSITIVE PROSTATE CANCER ACCOUNTS FOR approximately 3% of all new prostate-cancer diagnoses in the United States.[1] Historically androgen-deprivation therapy consisting of bilateral orchiectomy or luteinizing hormone releasing hormone analogues, with or without first-generation androgen-receptor inhibitors, has bee

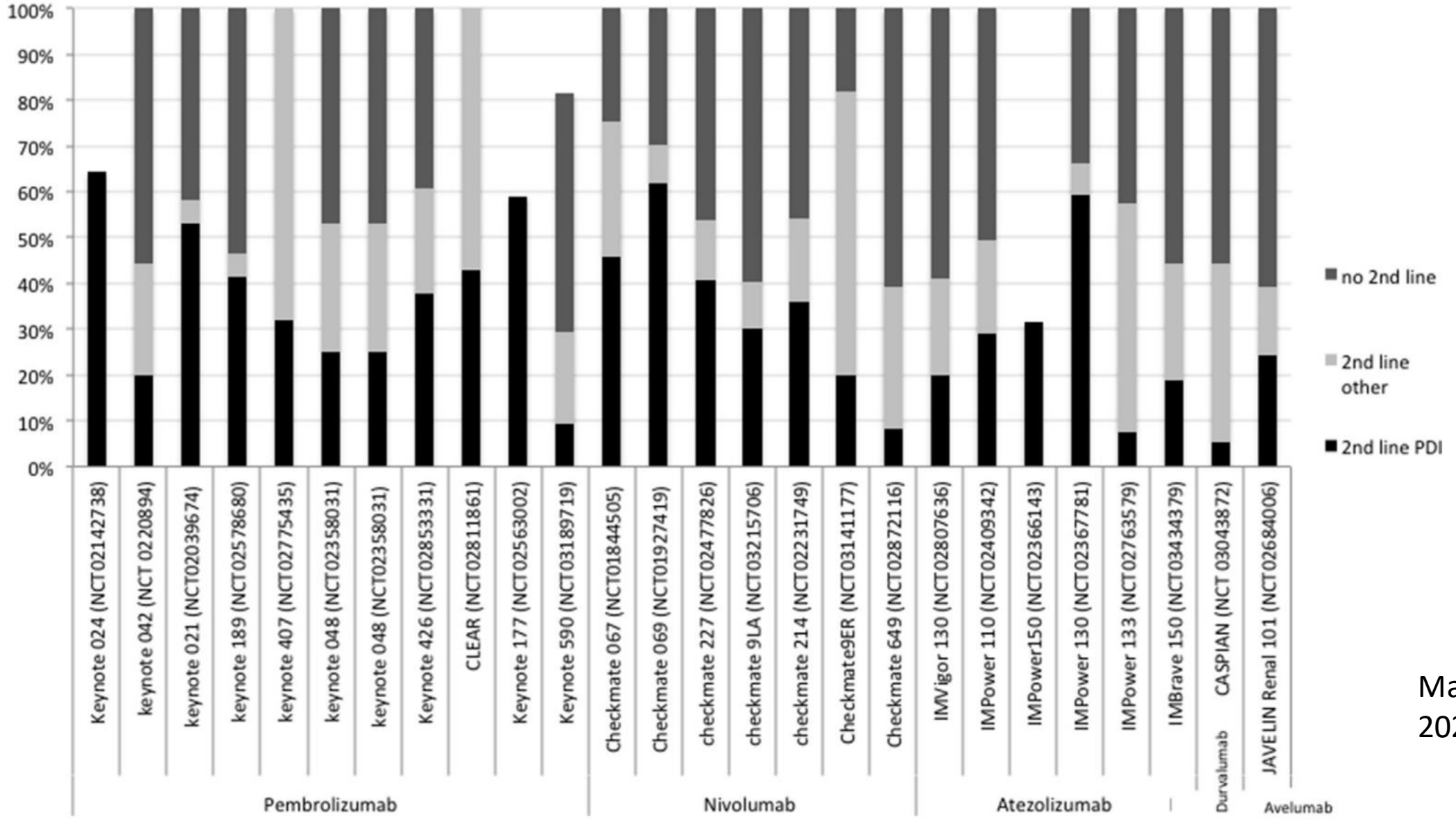


NEJM Stampede and Latitude

Fizazi et al. (July 27 issue)[1] report on the LATITUDE trial, and in the same issue, James et al.[2] report on the Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) trial. These phase 3 trials involving a total of more than 3000 men with advanced prostate cancer were designed after abiraterone was proved to prolong survival among patients with advanced prostate cancer. Before these trials, the standard of care for patients with advanced prostate cancer included sequential androgen suppression with various life-prolonging therapies (e.g., taxanes, abiraterone, or enzalutamide).

However, the control regimens in the STAMPEDE and LATITUDE trials were not designed to include the current sequential standard of care with life-prolonging crossover treatments; these treatments were not specified in the protocols (available with the full text of the articles at NEJM.org). This is critical, since the majority of men in the control groups in the STAMPEDE and LATITUDE trials died without exposure to abiraterone or enzalutamide. Thus, the drugs used in these control groups were inconsistent with current prevailing standards of care. This has implications for the conclusions of the trials and raises questions regarding whether or not there was a benefit for all trial participants.

Discussions between patients and physicians regarding the results of these trials should be made in the context of the above considerations. Physicians must reflect on the urgent need to better define and use surrogate end points so that death is not needed to conclude that a regimen is active.



Maniar, EJC 2021

Fig. 2. Subsequent treatment exposure for the control arm patients in first-line PD-1 and PD-L1 drug trials, where the same drug had been FDA approved in the 2nd line/refractory setting. This Figure is a visual representation of subsequent treatment exposure for the control arm patients in each respective trial. Missing data are left blank.

Determination

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Triplet Therapy, Transplantation, and Maintenance until Progression in Myeloma

P.G. Richardson, S.J. Jacobus, E.A. Weller, H. Hassoun, S. Lonial, N.S. Raje, E. Medvedova, P.L. McCarthy, E.N. Libby, P.M. Voorhees, R.Z. Orlowski, L.D. Anderson, Jr., J.A. Zonder, C.P. Milner, C. Gasparetto, M.E. Agha, A.M. Khan, D.D. Hurd, K. Gowin, R.T. Kamble, S. Jagannath, N. Nathwani, M. Alsina, R.F. Cornell, H. Hashmi, E.L. Campagnaro, A.C. Andreescu, T. Gentile, M. Liedtke, K.N. Godby, A.D. Cohen, T.H. Openshaw, M.C. Pasquini, S.A. Giralt, J.L. Kaufman, A.J. Yee, E. Scott, P. Torka, A. Foley, M. Fulciniti, K. Hebert, M.K. Samur, K. Masone, M.E. Maglio, A.A. Zeytoonjian, O. Nadeem, R.L. Schlossman, J.P. Laubach, C. Paba-Prada, I.M. Ghobrial, A. Perrot, P. Moreau, H. Avet-Loiseau, M. Attal, K.C. Anderson, and N.C. Munshi, for the DETERMINATION Investigators*

ABSTRACT

Determination

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Triplet Therapy, Transplantation, and Maintenance until Progression in Myeloma

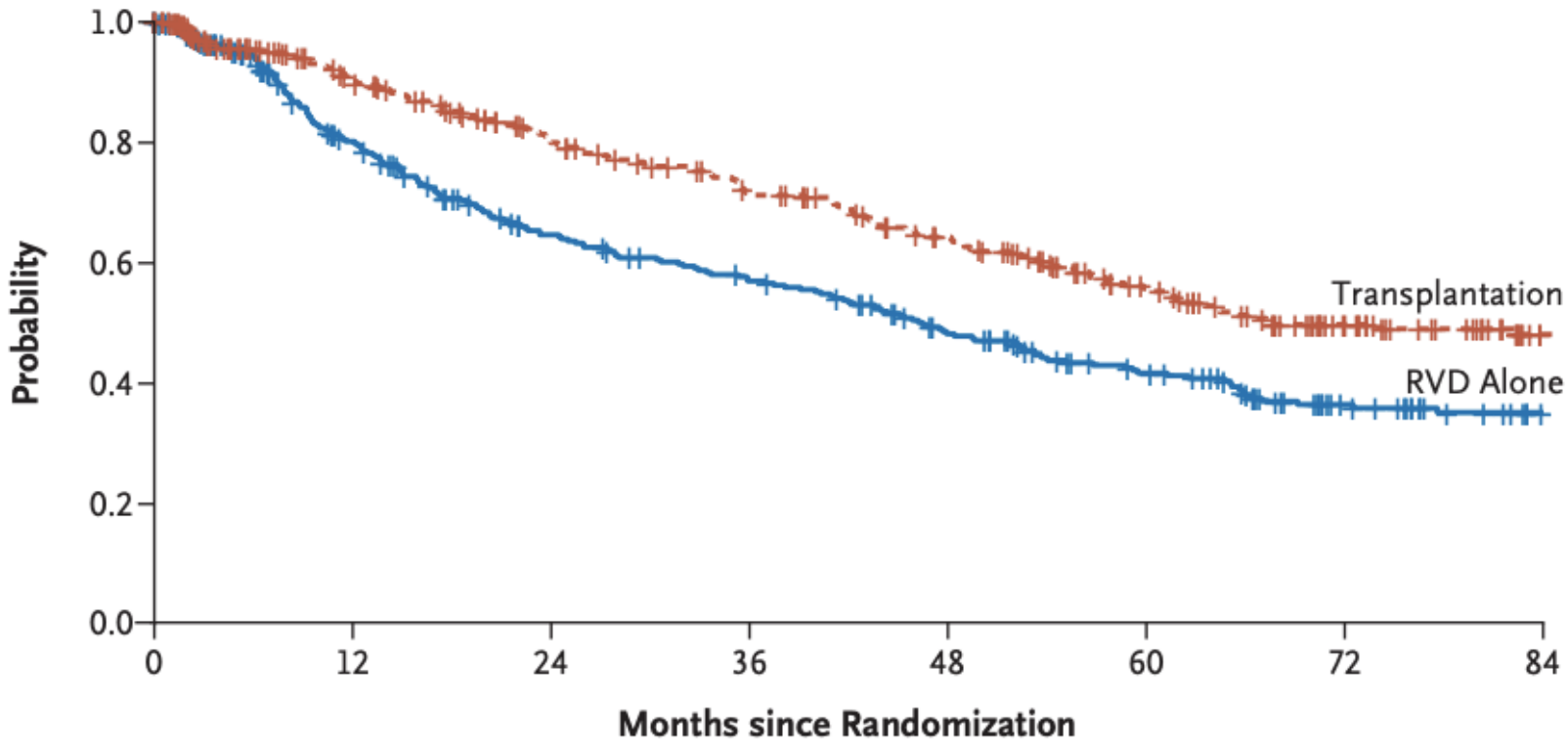
P.G. Richardson, S.J. Jacobus, E.A. Weller, H. Hassoun, S. Lonial, N.S. Raje, E. Medvedova, P.L. McCarthy, E.N. Libby, P.M. Voorhees, R.Z. Orlowski, L.D. Anderson, Jr., J.A. Zonder, C.P. Milner, C. Gasparetto, M.E. Agha, A.M. Khan, D.D. Hurd, K. Gowin, R.T. Kamble, S. Jagannath, N. Nathwani, M. Alsina, R.F. Cornell, H. Hashmi, E.L. Campagnaro, A.C. Andreescu, T. Gentile, M. Liedtke, K.N. Godby, A.D. Cohen, T.H. Openshaw, M.C. Pasquini, S.A. Giralt, J.L. Kaufman, A.J. Yee, E. Scott, P. Torka, A. Foley, M. Fulciniti, K. Hebert, M.K. Samur, K. Masone, M.E. Maglio, A.A. Zeytoonjian, O. Nadeem, R.L. Schlossman, J.P. Laubach, C. Paba-Prada, I.M. Ghobrial, A. Perrot, P. Moreau, H. Avet-Loiseau, M. Attal, K.C. Anderson, and N.C. Munshi, for the DETERMINATION Investigators*

ABSTRACT

coordinators, nursing teams, and administrative staff at all the trial sites; the following persons for their contributions: Steve Hill, Ph.D., of Ashfield MedComms, an Ashfield Health company, for medical writing and editing assistance with an earlier version of the manuscript; the data and safety monitoring committee (Joan Bladé, M.D., Robert Kyle, M.D., Christian Straaker, M.D., Ralph D'Agostino, Ph.D., Joe Massarro, Ph.D., and Jean Pearlstein, B.A.); Jack Sparacino, B.S., and Ashley Ford, B.A., for administrative assistance to the response review

participating site. All the patients provided written informed consent before treatment. The trial was designed by the senior academic investigators. The authors vouch for the accuracy and completeness of the data and for the adherence of the trial to the protocol. Preparation of an earlier version of the manuscript was paid for by the Dana–Farber Cancer Institute and the R.J. Corman Multiple Myeloma Research Fund. Information on trial oversight is provided in the Oversight section in the Supplementary Appendix, available at NEJM.org.

A **Progression-free Survival**

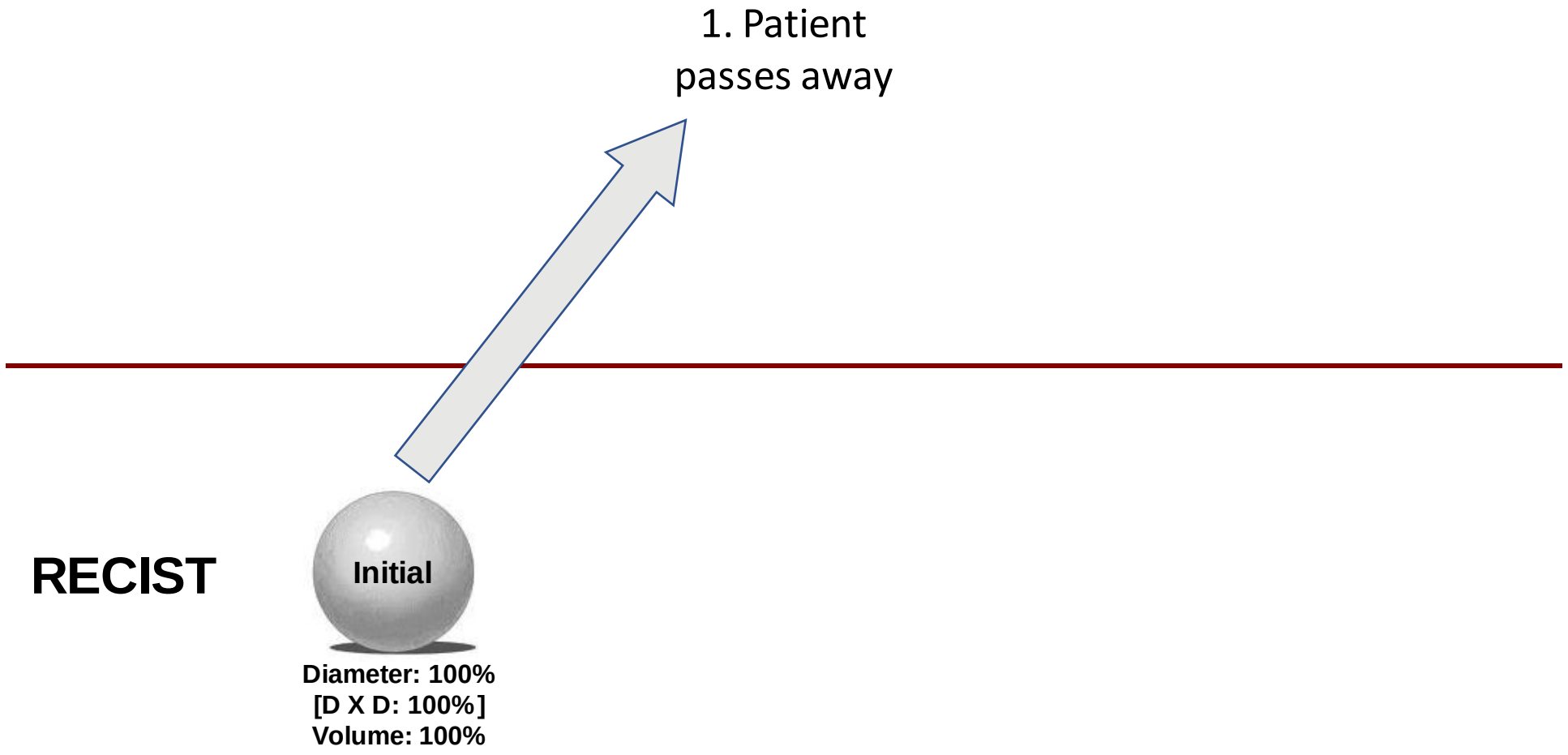


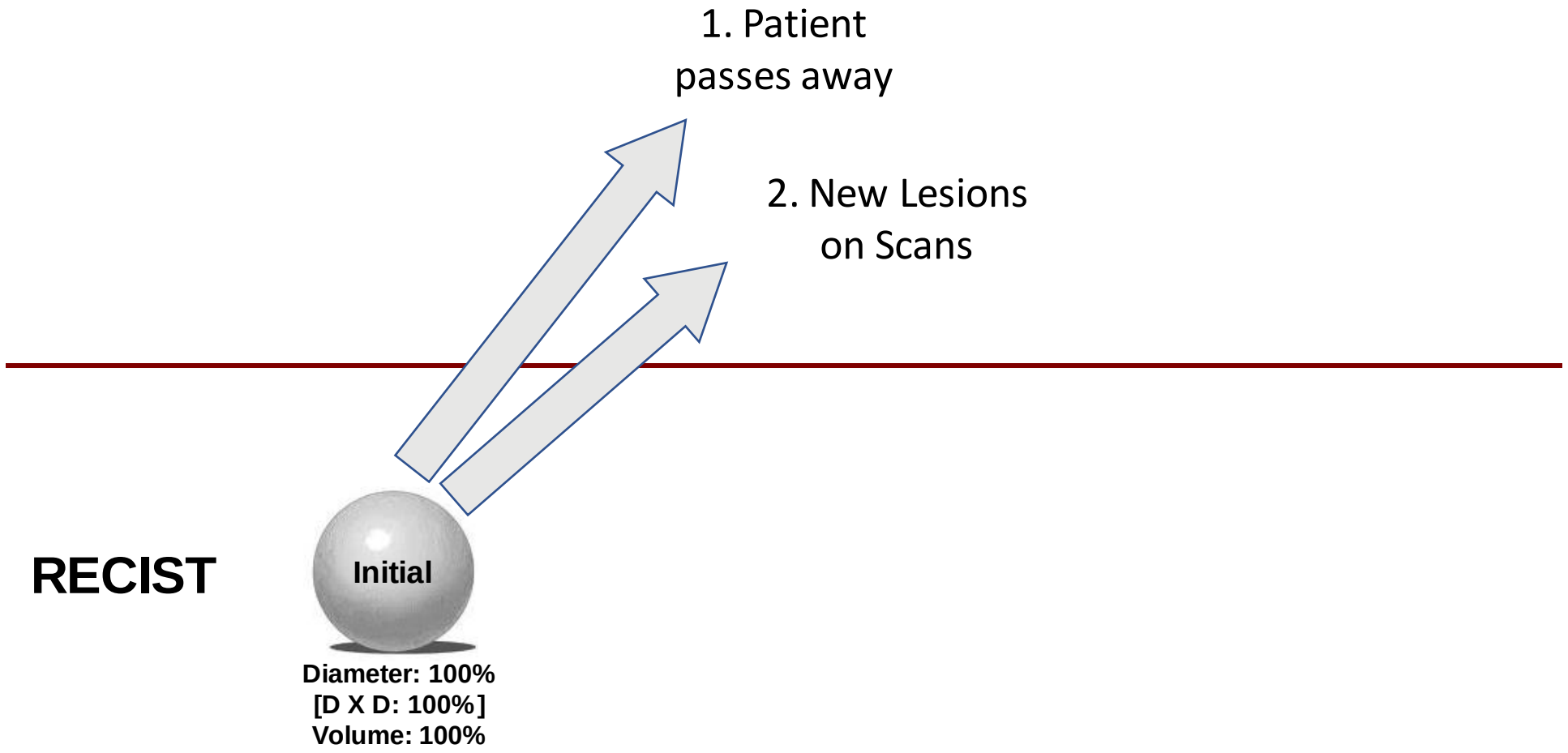
No. at Risk								
Transplantation	365	276	226	191	160	118	77	42
RVD Alone	357	250	187	160	126	96	60	40

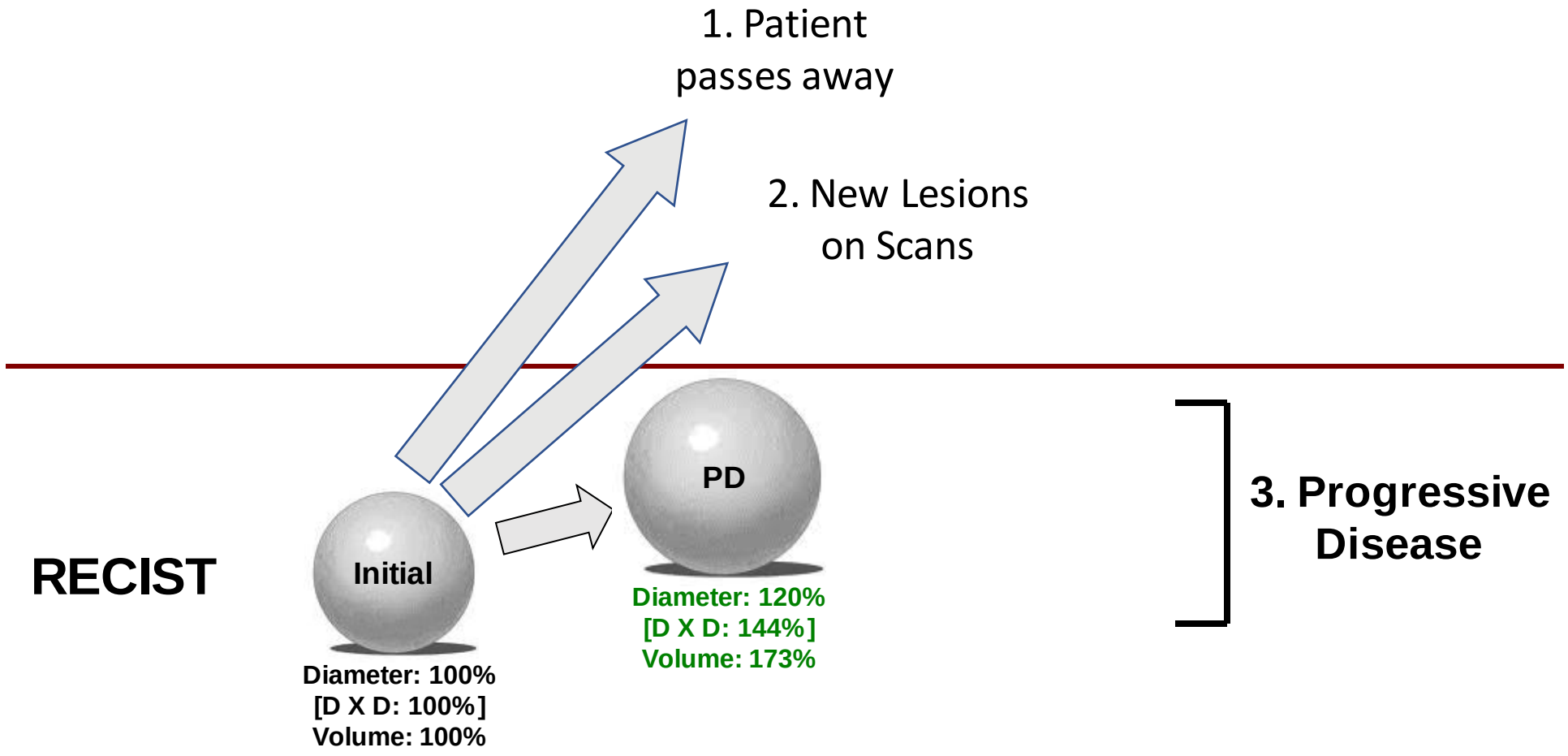
“What is PFS?”

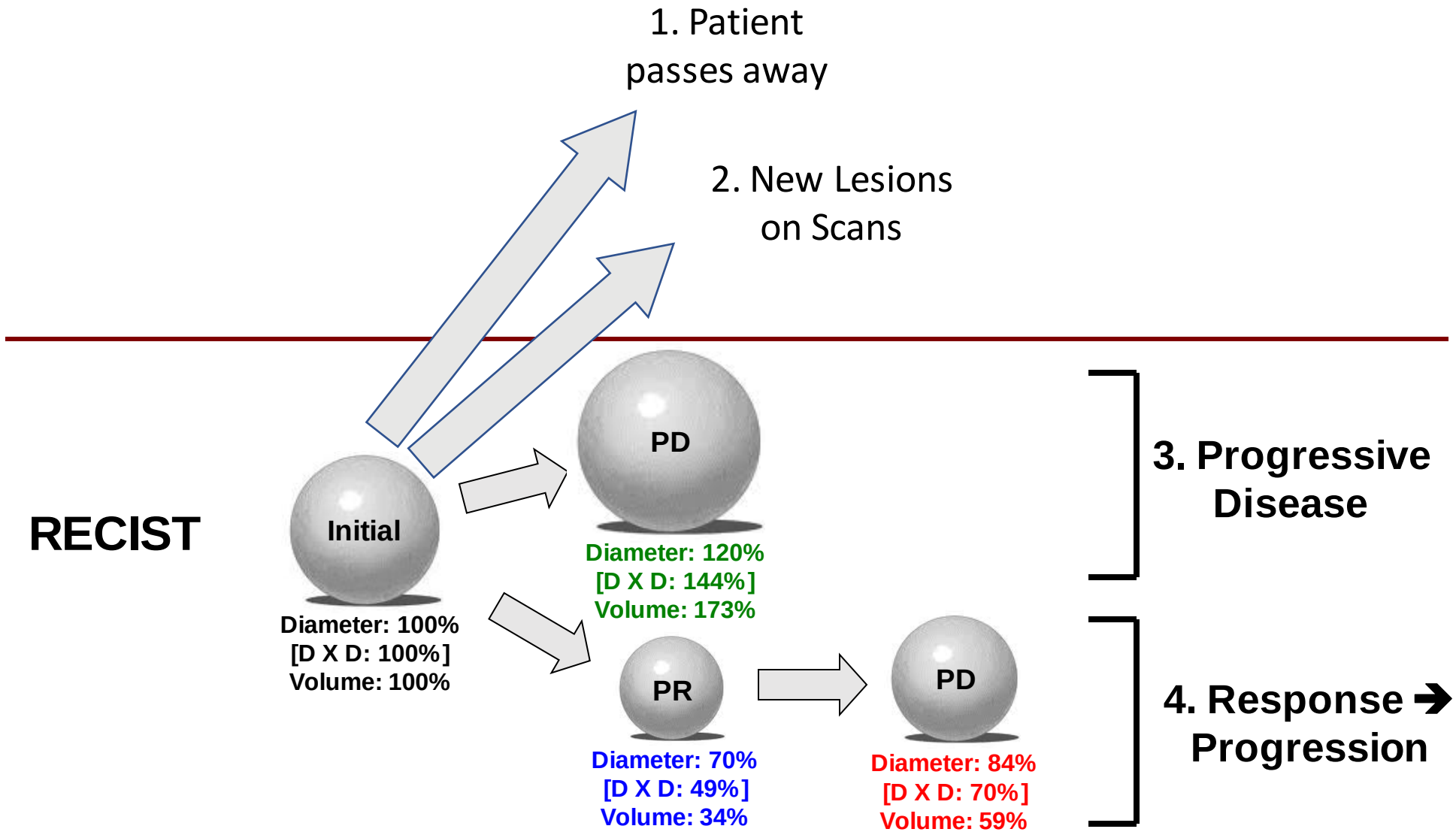
RECIST

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

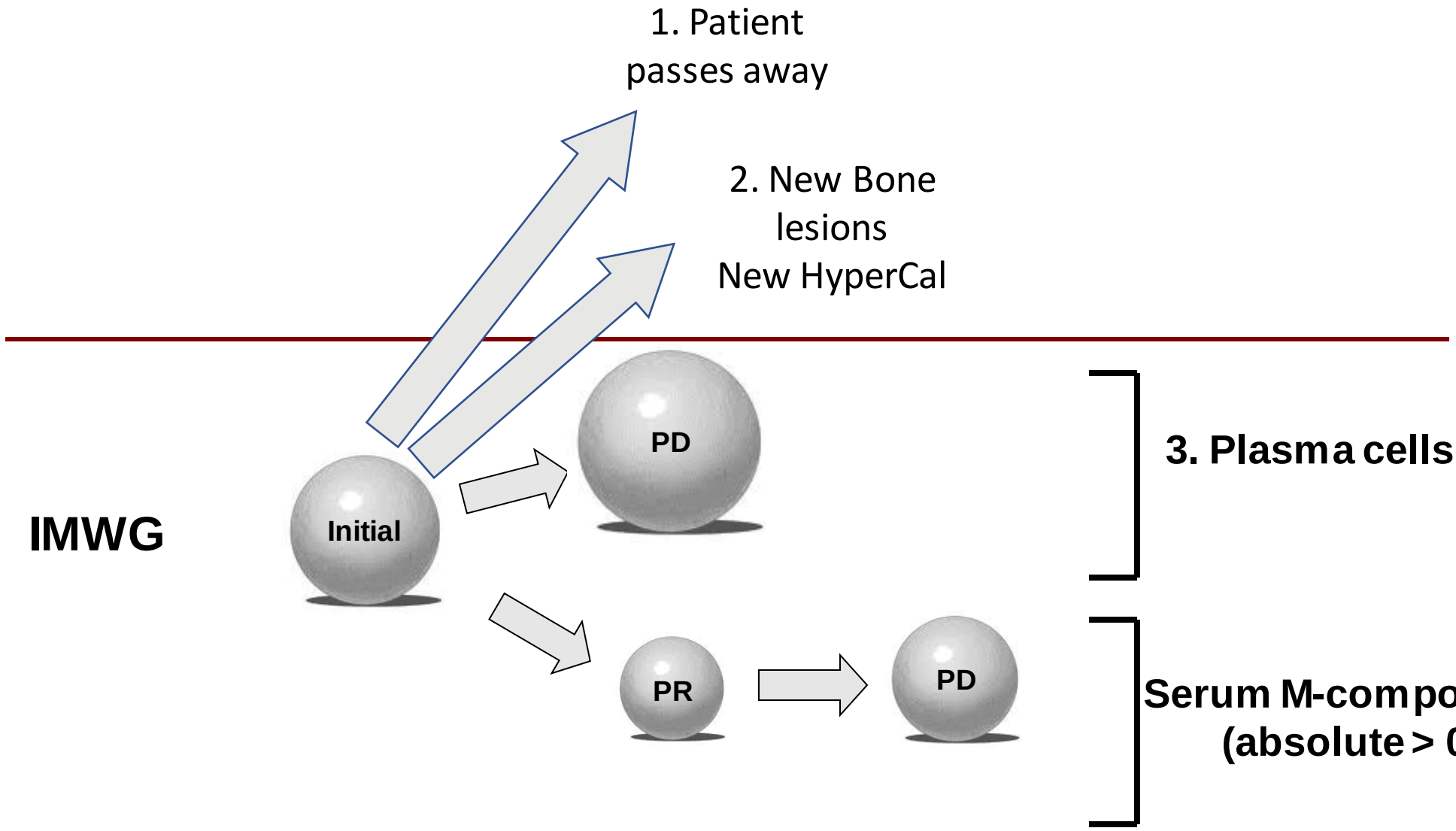

1. Patient
passes away
RECIST
Initial
Diameter: 100%
[D X D: 100%]
Volume: 100%


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%
3. Progressive Disease
PR
Diameter: 70%
[D X D: 49%]
Volume: 34%
PD
Diameter: 84%
[D X D: 70%]
Volume: 59%
4. Response ➔ Progression

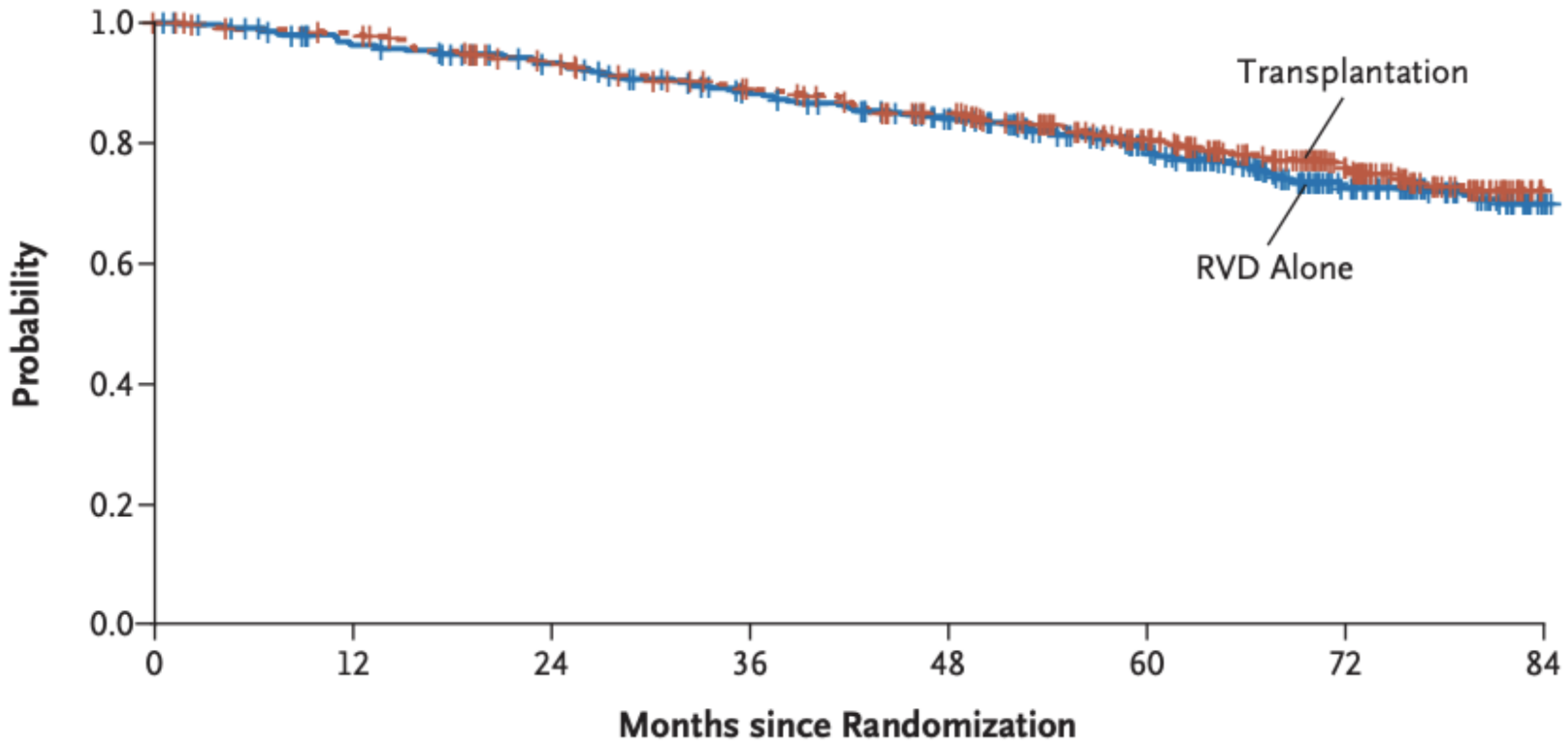
Myeloma


1. Patient
passes away
2. New Bone
lesions
New HyperCal
IMWG
Initial
PD
PR
PD
3. Plasma cells up 10%
Serum M-component up 25%
(absolute > 0.5 g/dL)

If this is so meaningful

- PFS will yield OS
- Kovics 2017 no correlation

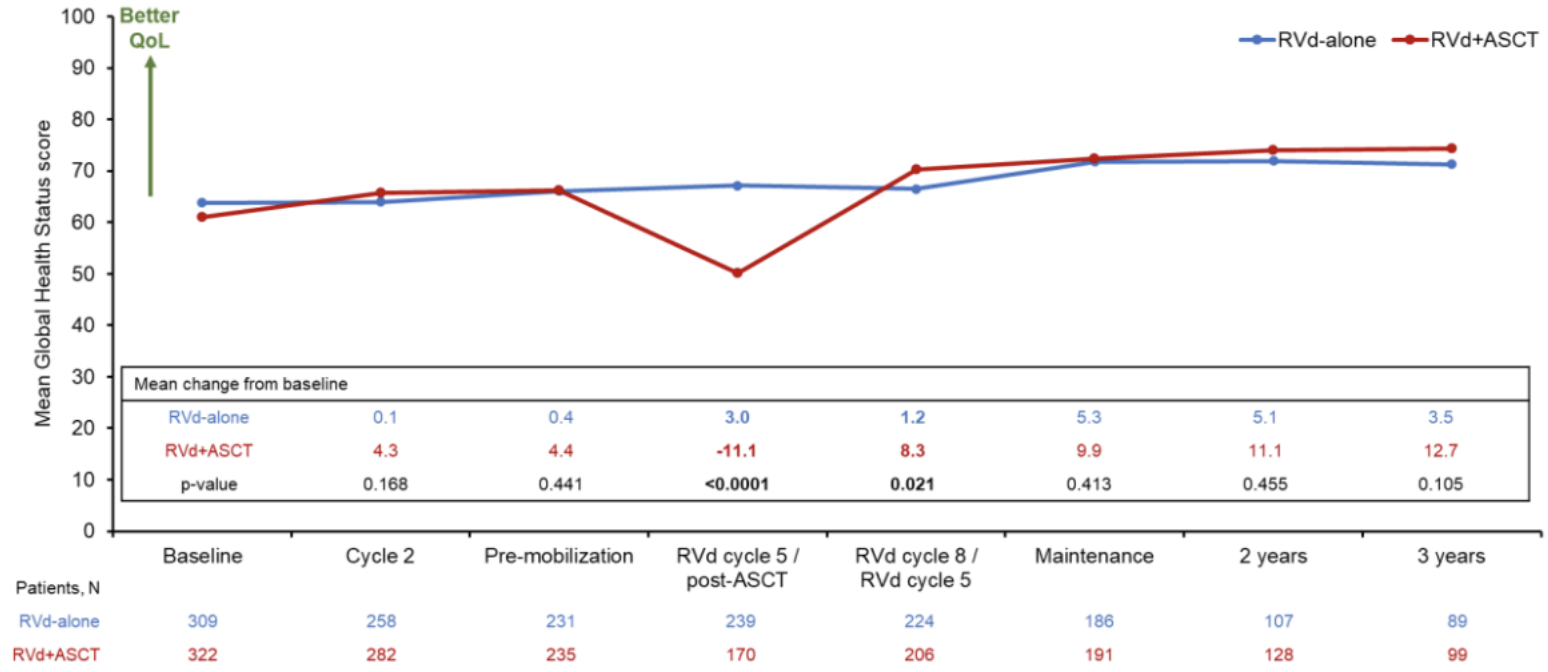
B **Overall Survival**



No. at Risk								
Transplantation	365	353	324	300	275	228	165	95
RVD Alone	357	332	313	285	258	214	143	88

Global QoL

A



Mean change from baseline							
RVd-alone	0.1	0.4	3.0	1.2	5.3	5.1	3.5
RVd+ASCT	4.3	4.4	**-11.1**	**8.3**	9.9	11.1	12.7
p-value	0.168	0.441	**<0.0001**	**0.021**	0.413	0.455	0.105

Patients, N	Baseline	Cycle 2	Pre-mobilization	RVd cycle 5 / post-ASCT	RVd cycle 8 / RVd cycle 5	Maintenance	2 years	3 years
RVd-alone	309	258	231	239	224	186	107	89
RVd+ASCT	322	282	235	170	206	191	128	99

But there was 20% crossover

patients (69.6%) in the transplantation group (Table S7). Of the 279 patients in the RVD-alone group who discontinued trial treatment, 78 (28.0%) underwent ASCT (35.1% of those who received subsequent post-protocol therapy). A post hoc sensitivity analysis of event-free survival was conducted to evaluate the effect of censoring for therapy outside the trial protocol. Median event-free survival (for

My Interpretation

- You don’t need to do transplant in CR1
- You don’t increase QoL
- You don’t increase OS
- 70% of people will never need an transplant
- Rates of auto should fall

AGILE

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ivosidenib and Azacitidine in *IDH1*-Mutated Acute Myeloid Leukemia

Pau Montesinos, M.D., Ph.D., Christian Recher, M.D., Ph.D., Susana Vives, M.D., Ewa Zarzycka, M.D., Jianxiang Wang, M.D., Giambattista Bertani, M.D., Michael Heuser, M.D., Rodrigo T. Calado, M.D., Ph.D., Andre C. Schuh, M.D., Su-Peng Yeh, M.D., Scott R. Daigle, M.S., Jianan Hui, Ph.D., Shuchi S. Pandya, M.D., Diego A. Gianolio, Ph.D., Stephane de Botton, M.D., Ph.D., and Hartmut Döhner, M.D.

ABSTRACT

BACKGROUND

The combination of ivosidenib — an inhibitor of mutant isocitrate dehydrogenase 1 (IDH1) — and azacitidine showed encouraging clinical activity in a phase 1b trial involving patients with newly diagnosed *IDH1*-mutated acute myeloid leukemia.

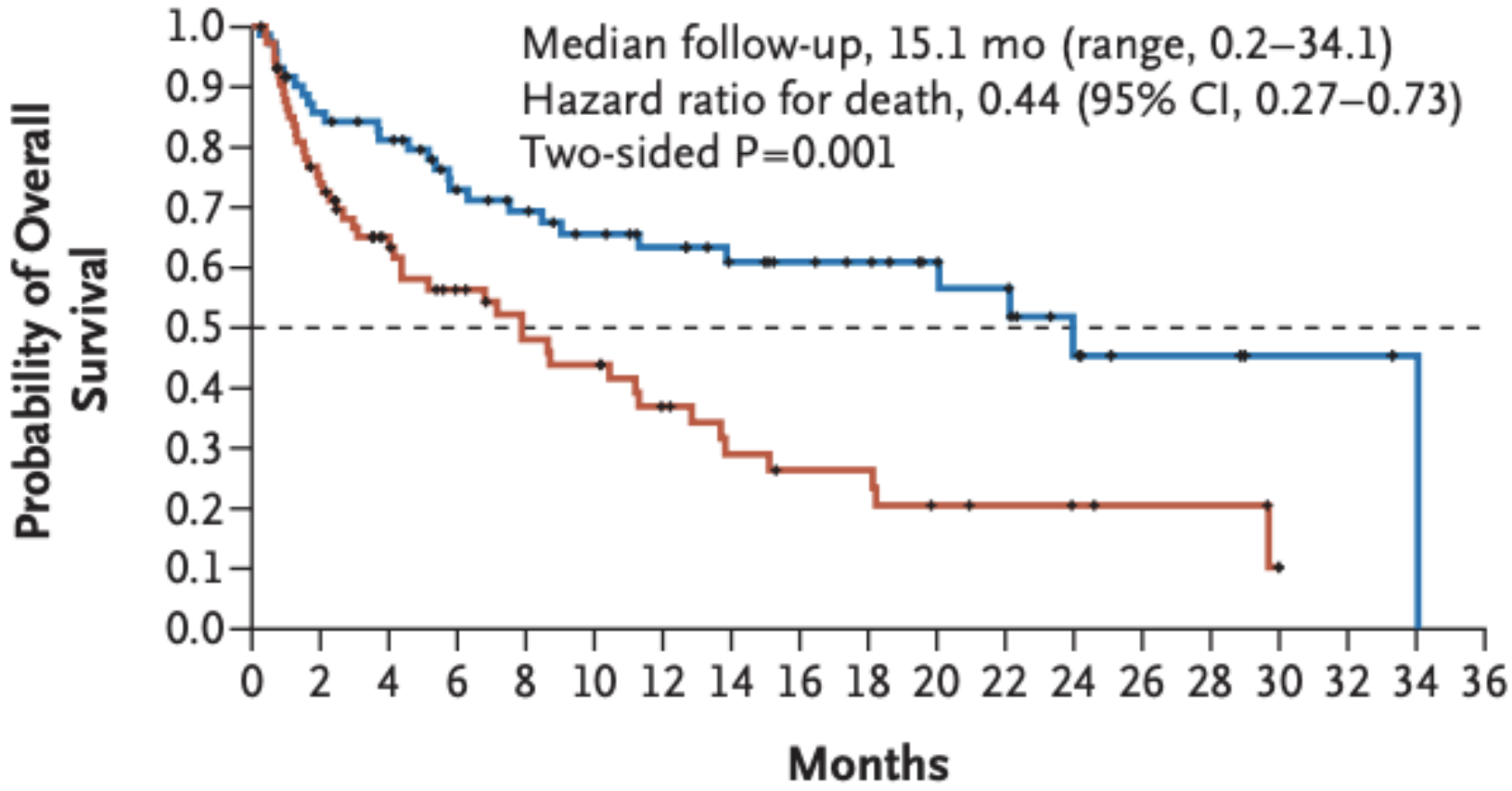
METHODS

In this phase 3 trial, we randomly assigned patients with newly diagnosed *IDH1*-mutated acute myeloid leukemia who were ineligible for intensive induction chemotherapy to receive oral ivosidenib (500 mg once daily) and subcutaneous or intravenous azacitidine (75 mg per square meter of body-surface area for 7 days in 28-day cycles) or to receive matched placebo and azacitidine. The primary end point was event-free survival, defined as the time from randomization until treatment failure (i.e., the patient did not have complete remission by week 24), relapse from remission, or death from any cause, whichever occurred first.

RESULTS

From Hospital Universitari i Politècnic La Fe, Valencia (P.M.), and Hospital Universitario Germans Trias i Pujol–Institut Català d'Oncologia Badalona, Josep Carreras Research Institute, Universitat Autònoma de Barcelona, Badalona (S.V.) — both in Spain; Institut Universitaire du Cancer de Toulouse Oncopole, Centre Hospitalier Universitaire de Toulouse, Toulouse (C.R.), and Institut Gustave Roussy, Villejuif (S.B.) — both in France; Klinika Hematologii i Transplantologii, Uniwersyteckie Centrum Kliniczne, Gdansk, Poland (E.Z.); the Institute of Hematology and Hospital of Blood Disease, Peking Union Medical College, Tianjin, China (J.W.); Azienda Socio Sanitaria Territoriale Grande Ospedale Metropolitano Niguarda,

B **Overall Survival**



No. at Risk

Ivosidenib+ azacitidine	72	58	53	42	38	33	29	24	21	19	15	13	7	4	4	2	2	1
Placebo+ azacitidine	74	53	38	29	23	21	15	11	9	9	6	5	4	3	3	0		

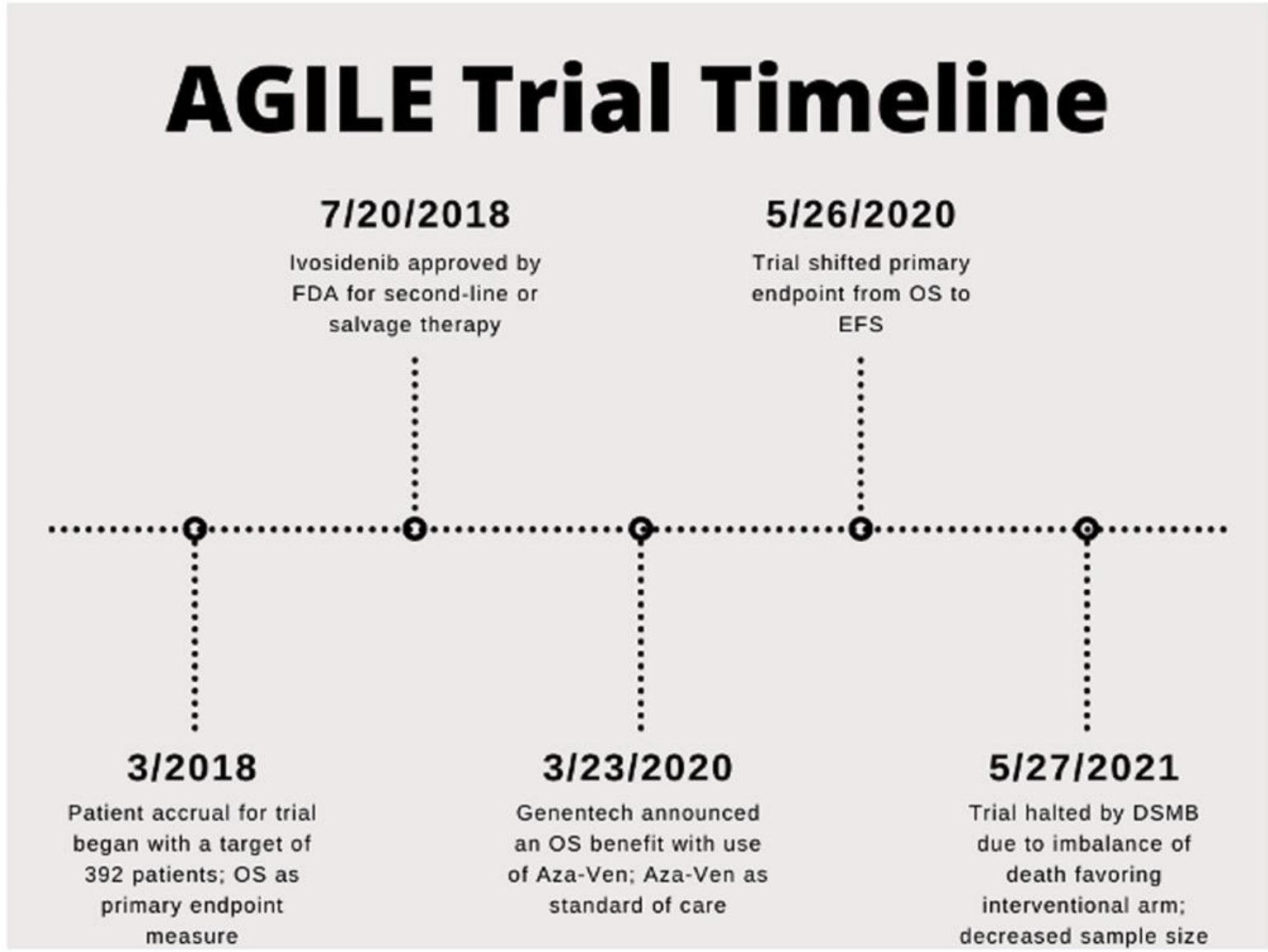


Fig. 1. Timeline of events pertinent to the AGILE trial.
Abbreviation: FDA, US Food and Drug Administration; OS, overall survival; EFS, event-free survival; Ven, venetoclax; Aza, azacitidine; DSMB, Data and Safety Monitoring Board; PFS, Progression-free survival.

AGILE

The AGILE trial of ivosidenib plus azacitidine versus azacitidine alone: How many limitations is too many?

Anjali Bhatt [a], Kerrington Powell [a], Vinay Prasad [b,*]

[a] College of Medicine, Texas A&M Health Science Center, Bryan, TX 77807, United States
[b] Department of Epidemiology and Biostatistics, University of California San Francisco, 550 16th St, 2nd Fl, San Francisco, CA 94158, United States

ARTICLE INFO

Keywords:
AGILE
IDH1-mutant acute myeloid leukemia
Ivosidenib
Azacitidine

ABSTRACT

The AGILE trial compared ivosidenib and azacitidine versus azacitidine for IDH1-mutant acute myeloid leukemia (AML) in elderly patients who were ineligible to receive intensive chemotherapy. While the results of this trial appear encouraging, various concerns become evident from the study design and methodology. First, the AGILE trial did not use post-protocol therapy that met the current standard of care. Second, researchers continued patient enrollment despite knowledge of the survival benefit of azacitidine plus venetoclax shown in the VIALE-A trial, resulting in an inferior control arm. Third, the primary endpoint of AGILE was changed from overall survival (OS) to event-free survival (EFS), and the sample size was reduced to expedite the results. Finally, the trial was halted early based on a non-primary endpoint, which likely led to exaggerated effect size or misleading results. We discuss these limitations and continue to advocate for careful analysis of study design to ensure that appropriate and accurate outcomes are implemented in future studies.

The AGILE trial (NCT03173248) compared ivosidenib and azacitidine against placebo and azacitidine among elderly patients diagnosed with isocitrate dehydrogenase 1 (IDH1) mutant acute myeloid leukemia (AML) who are ineligible to receive intensive chemotherapy [1]. AGILE exemplifies the challenges of conducting a clinical trial in a therapeutic environment that is both shifting and expanding. Expanding treatment options for patients with AML is focusing on innovative targeted therapies. Recently, the VIALE-A trial of azacitidine + venetoclax produced an OS benefit when compared to azacitidine alone (median OS of 14.7 months for Aza-Ven vs. 9.6 months for azacitidine + placebo), changing the standard of care to Aza-Ven [4,5].

AGILE continued to enroll patients over the ensuing year. On May 26th, 2020, two months after the VIALE-A results, AGILE investigators modified their primary endpoint from OS to event-free survival (EFS) [1]. This would lower the necessary sample size to demonstrate a sig-

which limits data interpretation in some pre-planned subgroup analyses. In addition, overall survival has traditionally been regarded as a standard primary end point for trials in acute myeloid leukemia; however, event-free survival has been proposed as an important end point for assessing the antileukemic potential of a precision drug, before the confounding effects of subsequent therapies. The high incidences of response and the superior event-free survival observed in this trial with ivosidenib and azaciti-

We wish to highlight troublesome characteristics of the AGILE trial. First, the control treatment of azacitidine is inferior to venetoclax plus azacitidine in patients with AML who are ineligible for intensive induction.[1] Trial recruitment (including U.S. centers) continued through May 2021, after the inferiority of azacitidine to azacitidine plus venetoclax had been shown. We are unaware of any data suggesting that ivosidenib plus azacitidine would be superior to venetoclax plus azacitidine. Unfortunately, substandard control groups are frequent in industry-sponsored randomized trials.[2]

Second, ivosidenib was approved by the Food and Drug Administration in 2018[3] and is used as a salvage therapy when progression occurs. However, only two patients in the control group received ivosidenib at progression, and only 21.6% received any subsequent targeted therapy for AML. This lack of adequate postprotocol therapy (that has previously proved to be effective) is also common among contemporary randomized trials in oncology.[4]

Third, the trial switched end points and was halted early — tactics that can exaggerate the effect size.[5] Given these limitations, we do not believe this trial to be a practice-changing trial.

Aaron M. Goodman, M.D.
University of California San Diego, La Jolla, CA
a1goodman@ucsd.edu

Ghulam Rehman Mohyuddin, M.D.
University of Utah, Salt Lake City, UT

Vinay Prasad, M.D., M.P.H.
University of California San Francisco, San Francisco, CA

In response to Goodman et al., we object to the statement that the control group of the AGILE trial was substandard. In the United States, venetoclax–azacitidine became an approved treatment option for patients who are ineligible for intensive chemotherapy in November 2018. Two patients from the United States were enrolled before this date, and enrollment in the United States was stopped in October 2018. The AGILE trial was a global trial that enrolled patients almost exclusively in Europe, Asia, and Brazil, where venetoclax–azacitidine had not been approved and was not an available treatment option. Regarding salvage therapy within the AGILE trial, ivosidenib could not be considered a postprotocol salvage therapy because the agent has also not been approved by the European Medicines Agency. Other salvage therapies were used on the basis of the investigators' judgment. The percentage of patients receiving subsequent therapy for AML was similar in the two treatment groups. Changing the primary end point from overall survival to event-free survival allowed for direct assessment of the activity of protocol therapy while adjusting the sample size to a feasible range, given the rarity of *IDH1*-mutated AML and in consideration of the emerging treatment landscape. The results for overall survival and all other key secondary end points of clinical response were robustly positive. The change in the primary end point was discussed with regulatory agencies. The decision by the sponsor to discontinue further recruitment followed the recommendation of the independent data monitoring committee. To account for the unplanned interim analysis by the data monitoring committee, an individual set of group-sequential boundaries was applied to the primary and key secondary end points, which maintained the stringency for statistical significance.

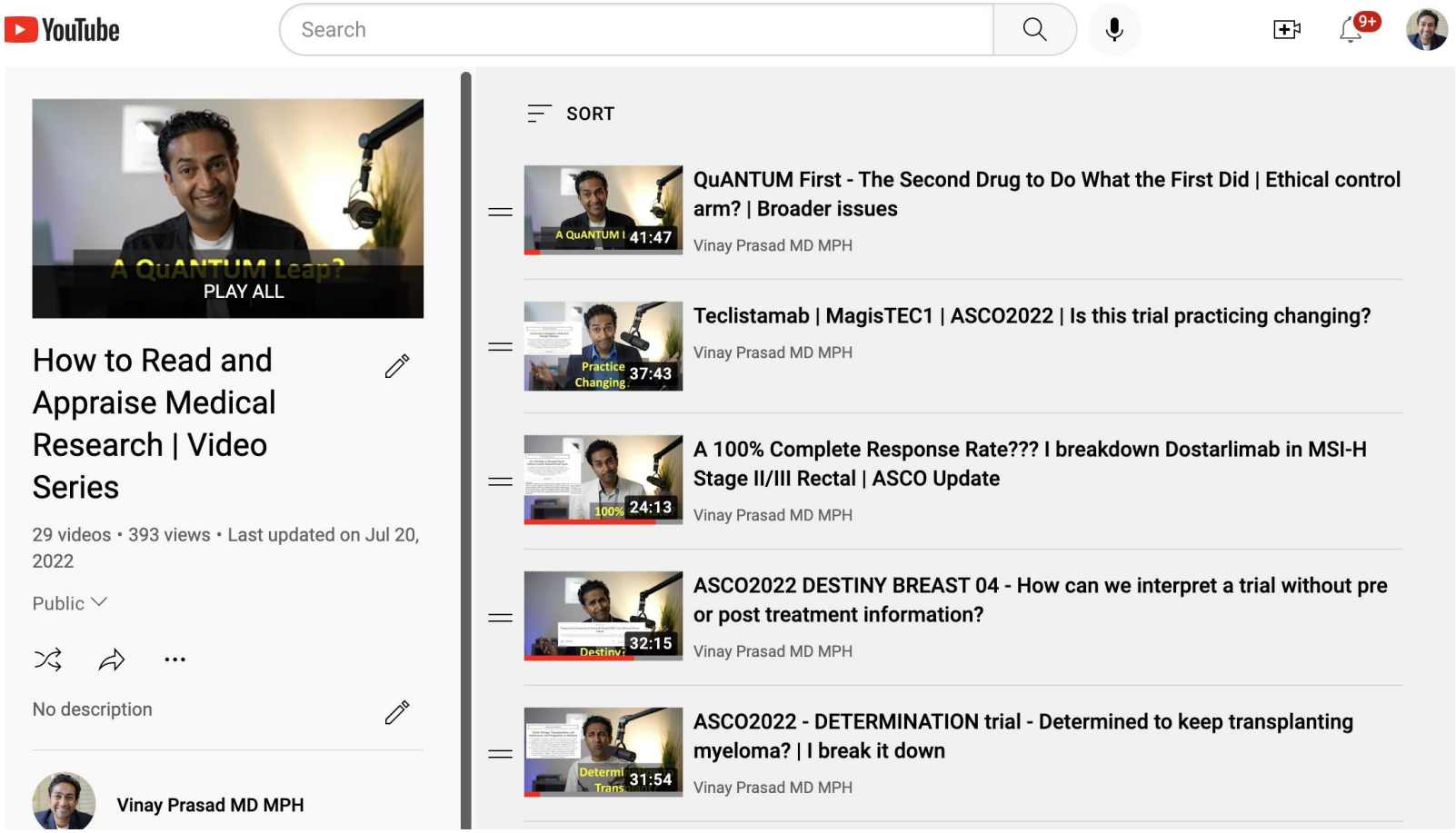
Tibsovo (ivosidenib) in combination with azacitidine for newly diagnosed acute myeloid leukemia with a susceptible IDH1 mutation, as detected by an FDA-approved test in adults 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy

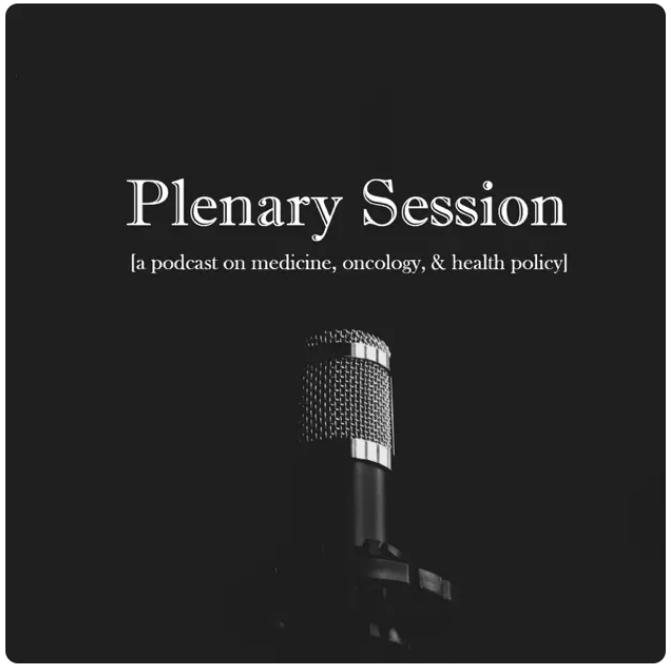
Podcast

Content curr
06/17/2022

Welcome back to the D.I.S.C.O., FDA's Drug Information Soundcast in Clinical Oncology, Burst Edition, brought to you by FDA's Division of Drug Information in partnership with FDA's Oncology Center of Excellence. Today we'll provide another quick update on a recent FDA cancer drug approval. On May 25, 2022, the FDA approved ivosidenib (brand name Tibsovo) in combination with azacitidine for newly diagnosed acute myeloid leukemia with a susceptible IDH1 mutation, as detected by an FDA-approved test in adults 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.

Future things to explore if you liked this talk





303 episodes

A podcast on medicine, oncology, & health policy.
Host: Vinay Prasad, MD MPH from University of California, San Francisco.
Tweet your feedback to @Plenary_Session or e-mail plenarysessionpodcast@gmail.com.

Plenary Session

Vinay Prasad, MD MPH

Science

★★★★★ 4.8 • 611 Ratings

Listen on Apple Podcasts ↗

SEP 2, 2022

5.12 - Academics Vs Industry - A.Goodman S.Loghavi D.Steensma V.P. E

How do careers vary between the academy and industry? We have a panel of the best: Sanam Loghavi from MD Anderson, Aaron Goodman UCSD, and David Steensma Novartis (formerly Farber/ Mayo) and VP #Real talk

PLAY 1 hr 29 min

AUG 25, 2022

5.11 - Malignant Book Club - Part 5 E

Timothee Olivier joinrs me as we explore part 3 of the book Crossover, sample size, observational vs RCTs

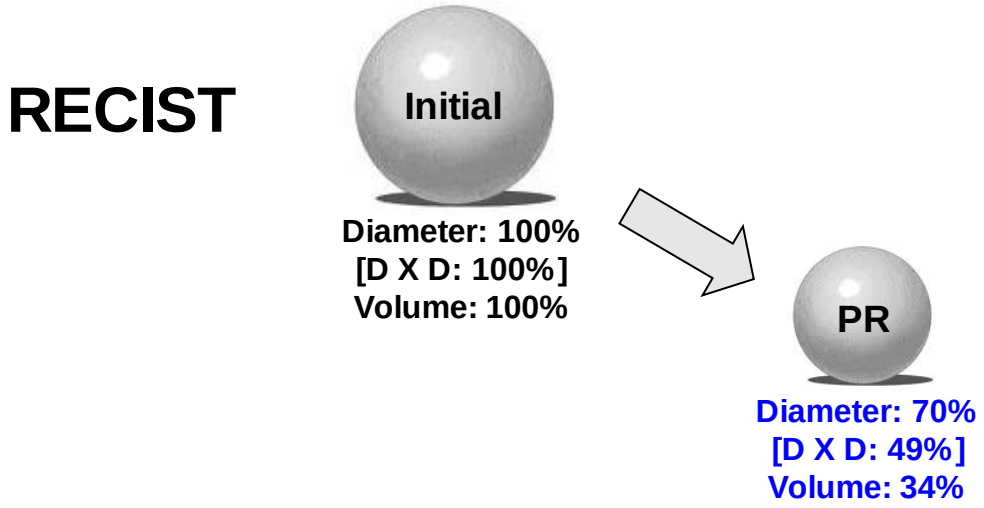
PLAY 52 min

Questions

- Vinayak.prasad@ucsf.edu

“A response is 30% tumor shrinkage!”

- That sounds arbitrary
- Where did these numbers come from?



Where did the definition of partial response [PR] come from?

1976
16 oncologists
12 spheres
1920 measurements

Charles G. Moertel, MD
[1927 – 1994]

Where did the definition of PR come from?

Twelve solid spheres were selected, measuring from 1.8 to 14.5 cm in diameter. It was assumed that this size range would cover the sizes usually encountered in measurable clinical masses such as subcutaneous, lymph node, and intra-abdominal tumors. These masses were then arranged in random size order on a soft mattress and covered with a layer of foam rubber. This layer measured 0.5 in. in thickness for the six smaller masses to approximate skin and subcutaneous tissue and 1.5 in. for the six larger masses to approximate abdominal wall. Each of 16 experienced physicians practicing in oncology was then asked to measure the diameter of each sphere using the usual technique and equipment (ruler or caliper) he employed in clinical practice.

Where did the definition of PR come from?

The actual "tumor" diameters are shown in Table 1. The participants were unaware that "tumors" 5 and 6 were designed to have the same diameter and so to provide an estimate of the reproducibility of each physician's measurements of tumor size. Tumors 7 and 8 were also designed for this purpose (the slight difference in true diameters 5 and 6 and in 7 and 8 reflect variations in the manufacturing process).

Where did the definitions of response come from?

How often did two different investigators think the same tumor was actually different?

No. of pairings who report objective responses	
≥ 25% shrinkage	≥ 50% shrinkage
29	6
70	26
60	8
83	39
57	7
64	18
51	7
65	19
479 (24.9%)	130 (6.8%)

How often did the same investigators think the same tumor was actually different?

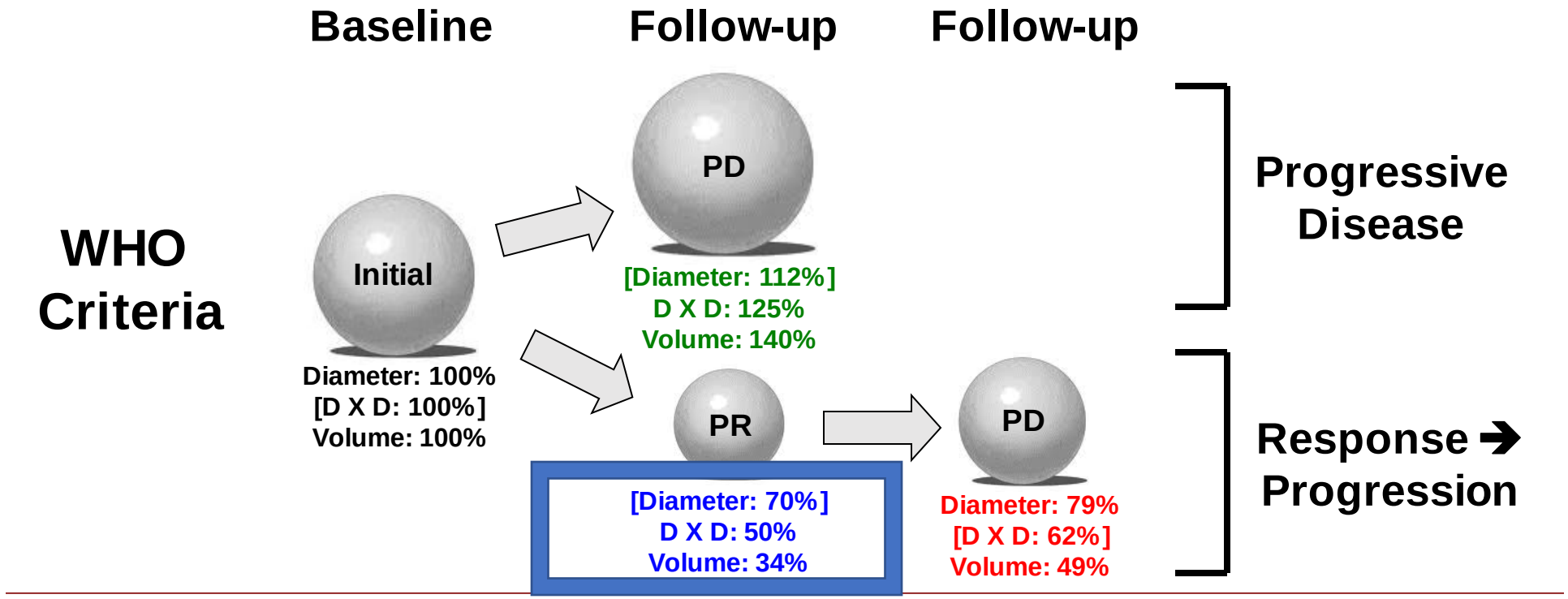
No. of investigators who reported objective responses	
≥ 25% shrinkage	≥ 50% shrinkage
4	4
2	0
3	1
3	0
12 (18.8%)	5 (7.8%)

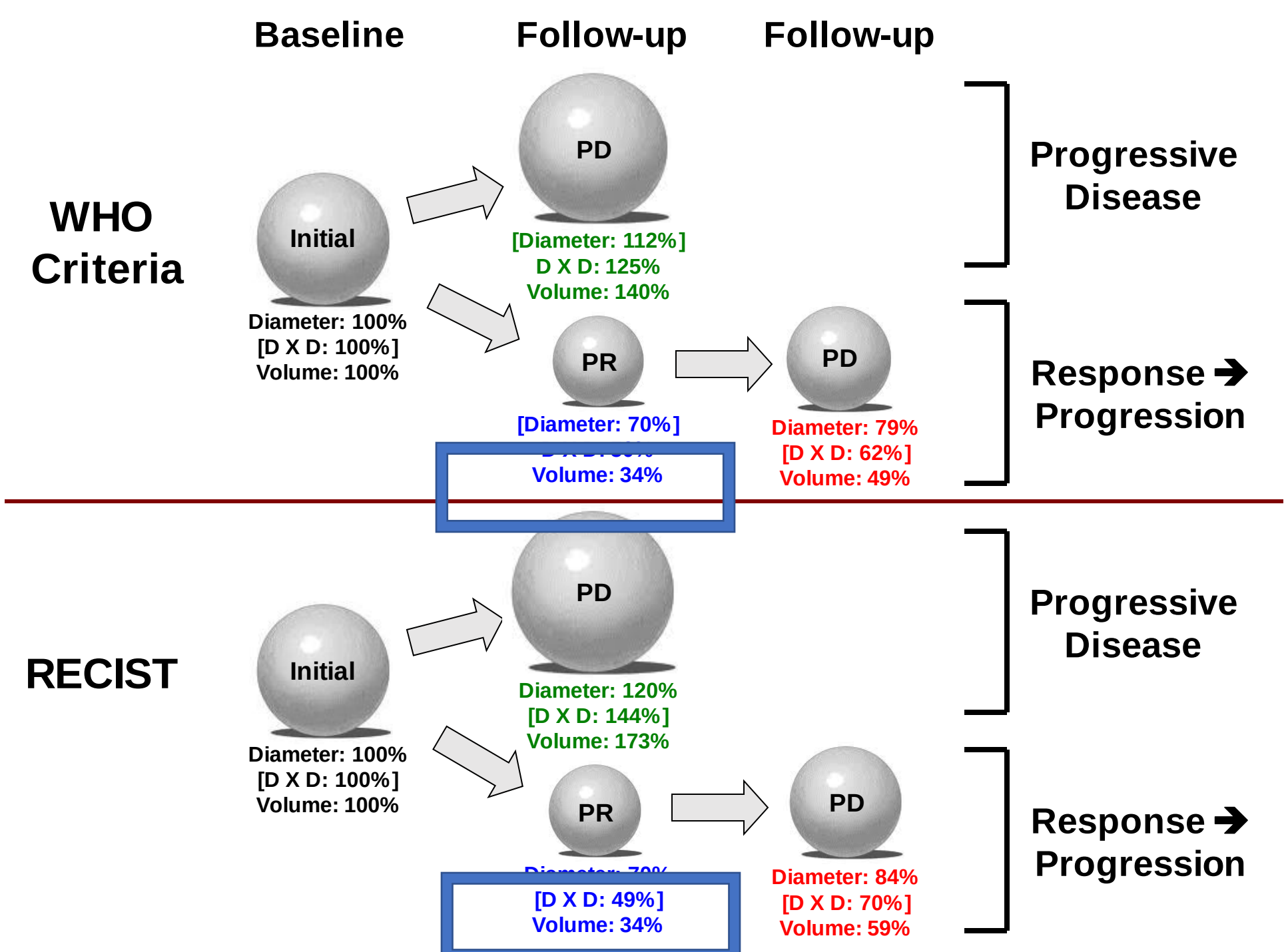
THE EFFECT OF MEASURING ERROR ON THE RESULTS OF THERAPEUTIC TRIALS IN ADVANCED CANCER

CHARLES G. MOERTEL, MD,* AND JAMES A. HANLEY, PHD†

Cutoffs chosen for "operational reasons" not for "efficacy"….become measures of efficacy

“But Moertel used 50% not 30%?”


Baseline
Follow-up
Follow-up
WHO Criteria
Initial
Diameter: 100%
[D X D: 100%]
Volume: 100%
PD
[Diameter: 112%]
D X D: 125%
Volume: 140%
PR
[Diameter: 70%]
D X D: 50%
Volume: 34%
PD
Diameter: 79%
[D X D: 62%]
Volume: 49%
Progressive Disease
Response ➔ Progression


Baseline
Follow-up
Follow-up
WHO Criteria
Initial
Diameter: 100%
[D X D: 100%]
Volume: 100%
PD
[Diameter: 112%]
D X D: 125%
Volume: 140%
PR
[Diameter: 70%]
Volume: 34%
PD
Diameter: 79%
[D X D: 62%]
Volume: 49%
Progressive Disease
Response ➔ Progression
RECIST
Initial
Diameter: 100%
[D X D: 100%]
Volume: 100%
PD
Diameter: 120%
[D X D: 144%]
Volume: 173%
PR
[D X D: 49%]
Volume: 34%
PD
Diameter: 84%
[D X D: 70%]
Volume: 59%
Progressive Disease
Response ➔ Progression