

Radium-223 and Bone Health Agents: Lessons Learned

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Disclosures

- Consultant: AAA, Astellas, Bavarian-Nordic, Bayer, Constellation, Dendreon, Endocyte, Janssen, Medivation, Novartis, Oncogenex, Pfizer, Sanofi, Noria
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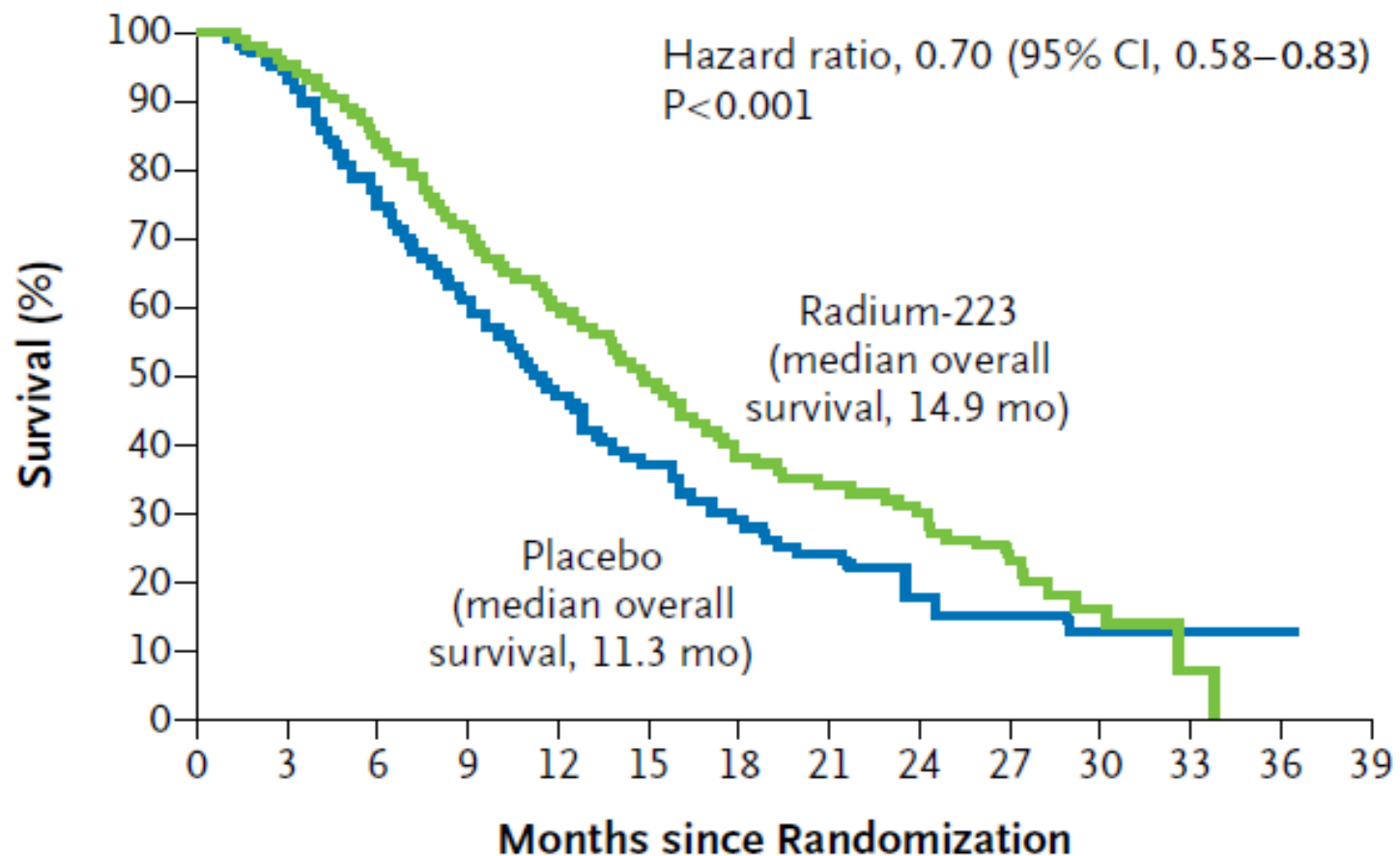
Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer

C. Parker, S. Nilsson, D. Heinrich, S.I. Helle, J.M. O'Sullivan, S.D. Fosså, A. Chodacki, P. Wiechno, J. Logue, M. Seke, A. Widmark, D.C. Johannessen, P. Hoskin, D. Bottomley, N.D. James, A. Solberg, I. Syndikus, J. Kliment, S. Wedel, S. Boehmer, M. Dall'Oglio, L. Franzén, R. Coleman, N.J. Vogelzang, C.G. O'Bryan-Tear, K. Staudacher, J. Garcia-Vargas, M. Shan, Ø.S. Bruland, and O. Sartor, for the ALSYMPCA Investigators*

Overall Survival ALSYMPCA

Parker et al. NEJM 369: 213-23, 2013

A Overall Survival

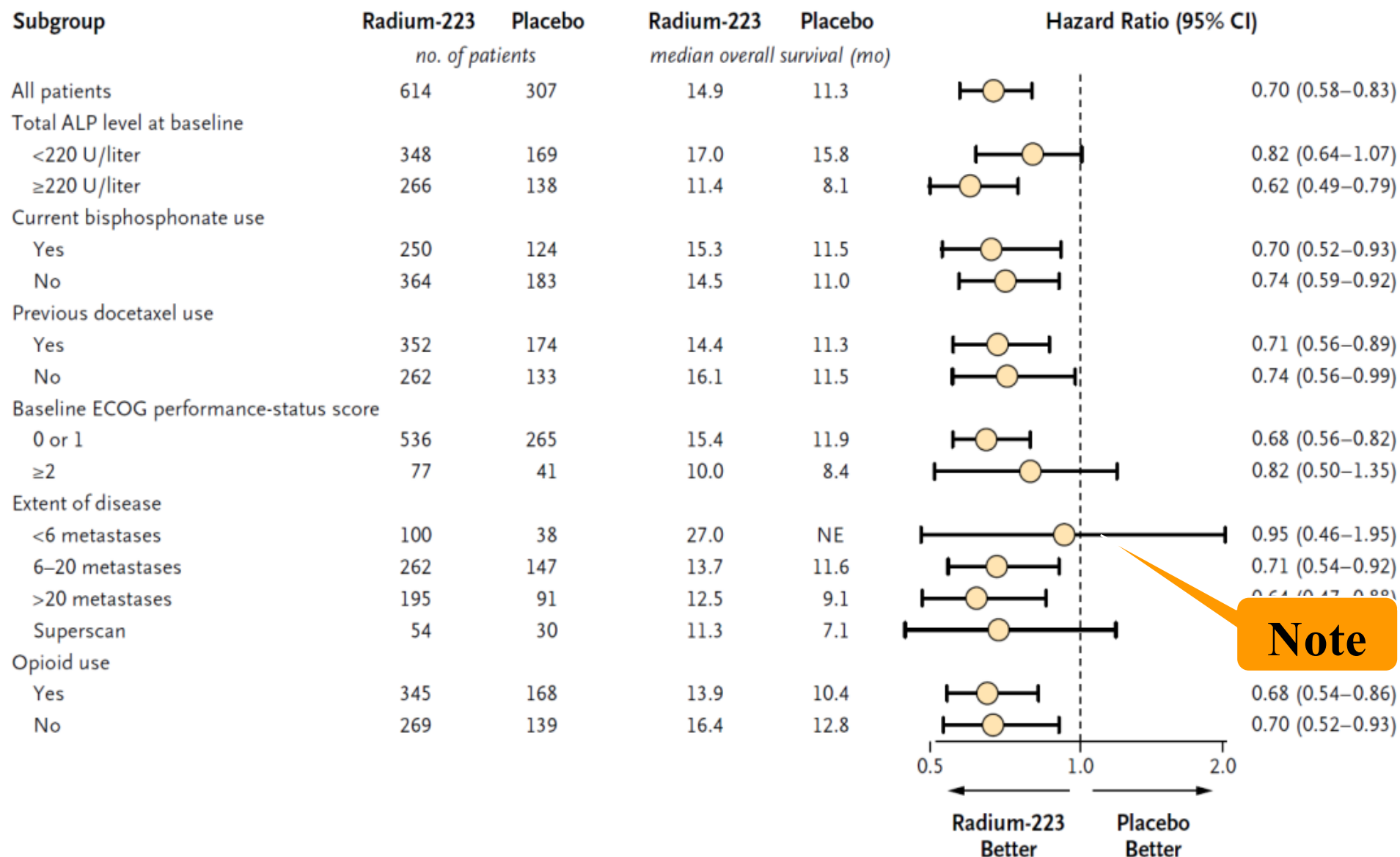


No. at Risk

Radium-223	614	578	504	369	274	178	105	60	41	18	7	1	0	0
Placebo	307	288	228	157	103	67	39	24	14	7	4	2	1	0

Overall Survival ALSYMPCA

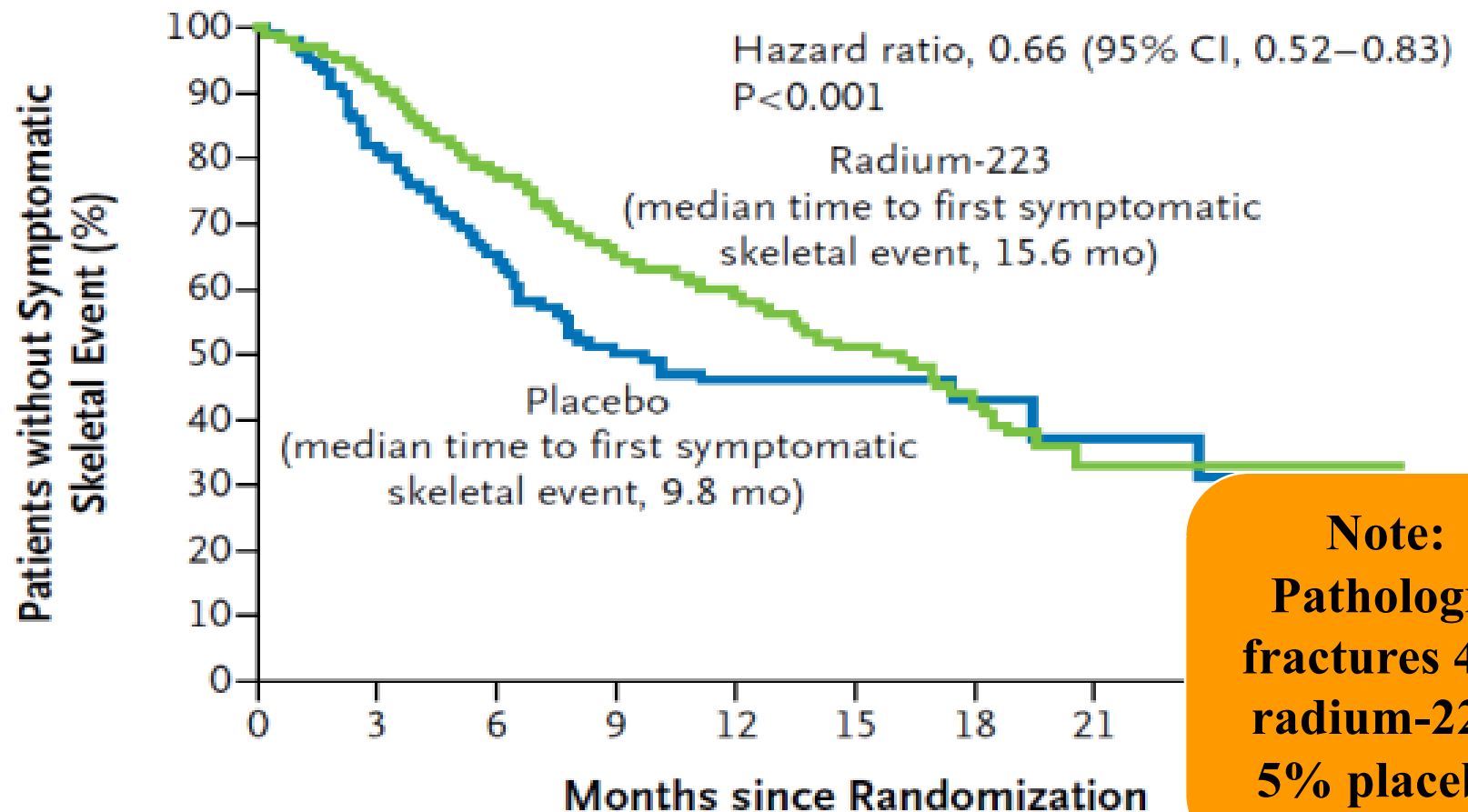
Parker et al. NEJM 369: 213-23, 2013



Time to SSE in ALSYMPCA

Parker et al. NEJM 369: 213-23, 2013

B Time to First Symptomatic Skeletal Event



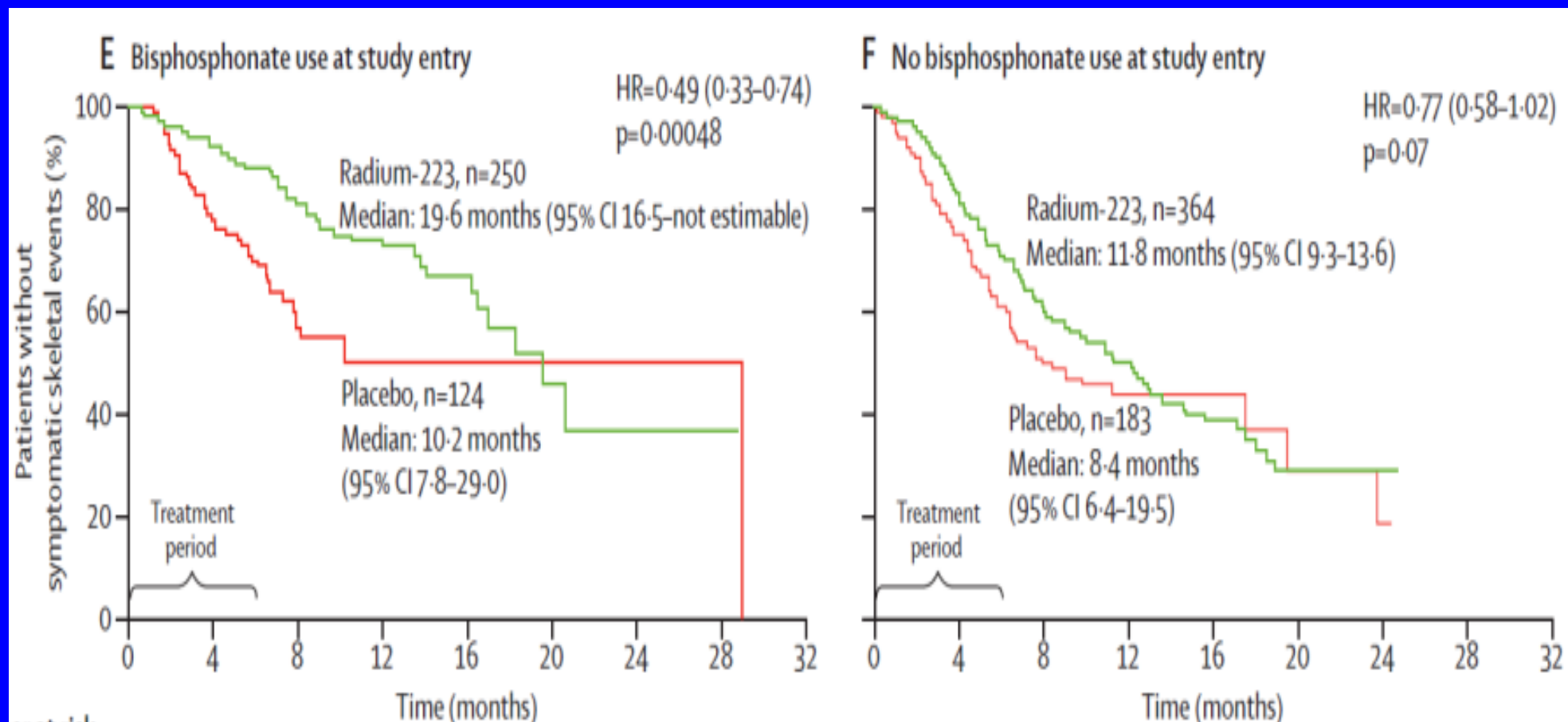
Note:
Pathologic fractures 4%
radium-223,
5% placebo

No. at Risk

Radium-223	614	496	342	199	129	63	31	8	8	1	0
Placebo	307	211	117	56	36	20	9	7	4	1	0

SSE rate as a function of bisphosphonate use in ALSYMPCA (pre-specified analysis)

Sartor et al. Lancet Oncology 15:738-46, 2015

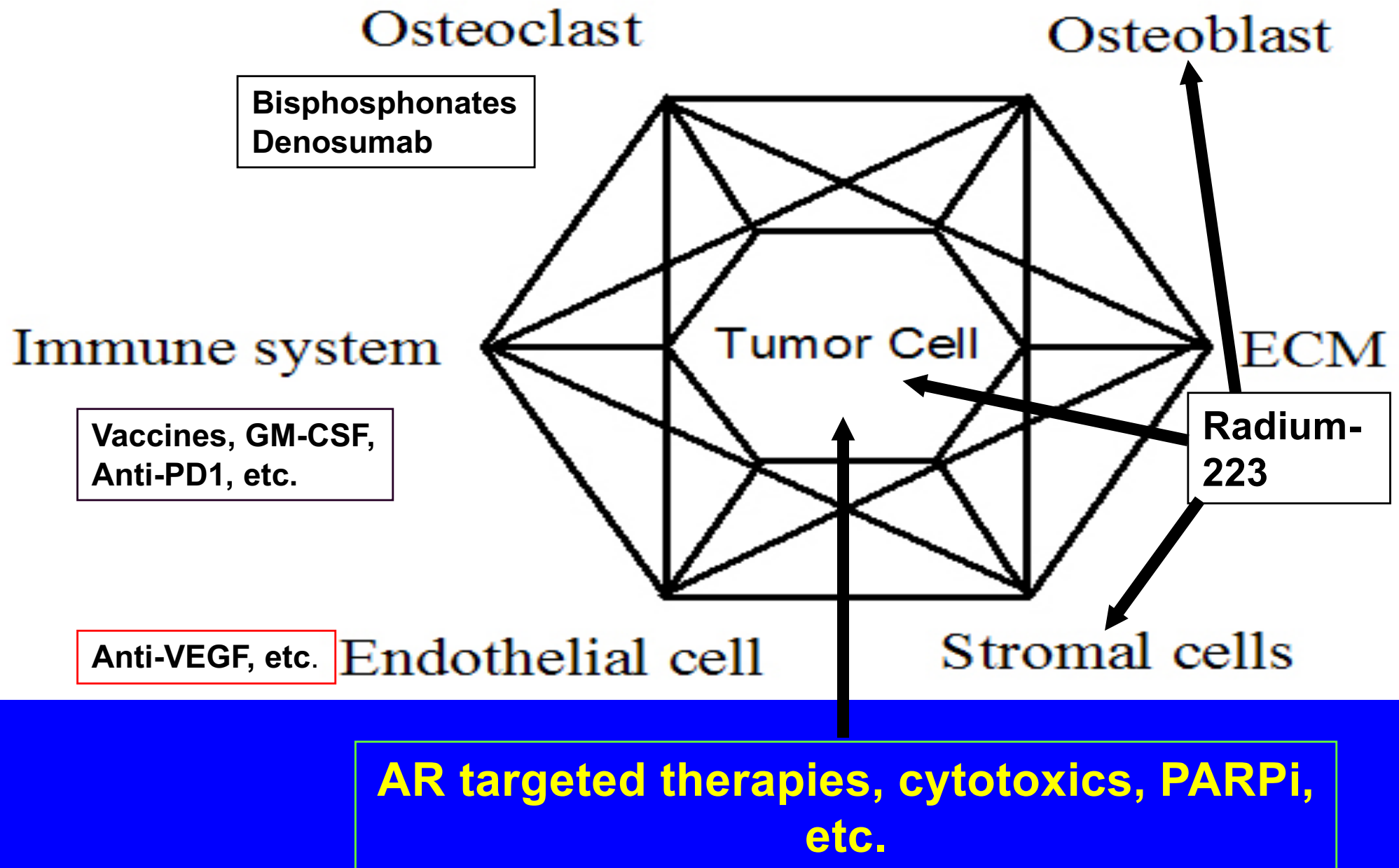


What we learned and did not learn with ALSYMPCA

- Radium-223 was safe and associated with better survival and symptomatic skeletal event (SSE) rates
- Concomitant therapies were fine
 - External beam radiation or bisphosphonates
 - Any “old” hormonal agent can be combined
 - Bicalutamide, dexamethasone, DES, etc.
- However...no abi, no enza, no imaging, etc.
- So.....we had much more to learn

Multi-Targeted Therapy in Bone Metastases

Modified from K. Pienta: U Michigan



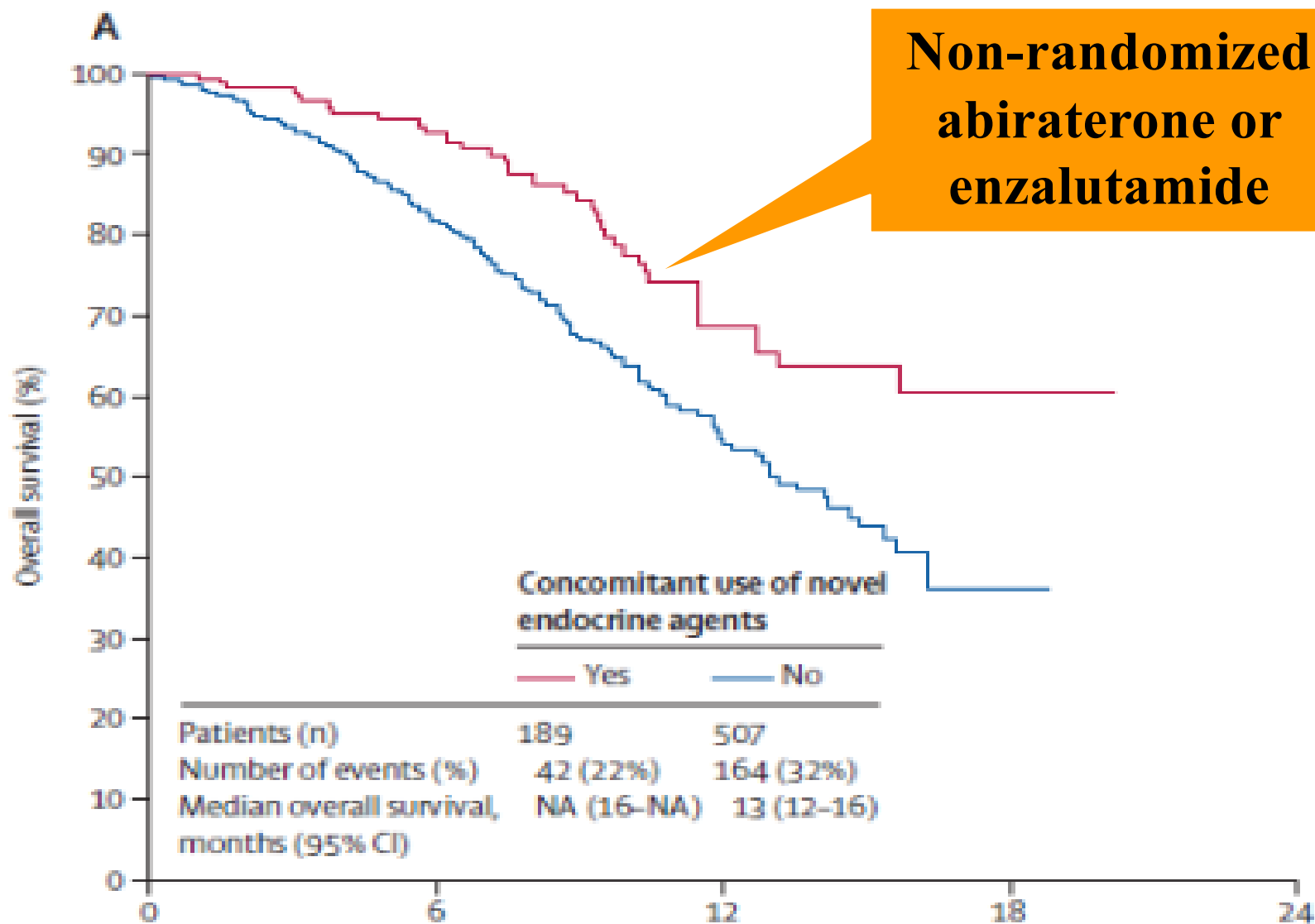
Can Radium add value to Abiraterone or Enzalutamide in Bone-Metastatic CRPC?

Two large trials in chemo-naïve pts

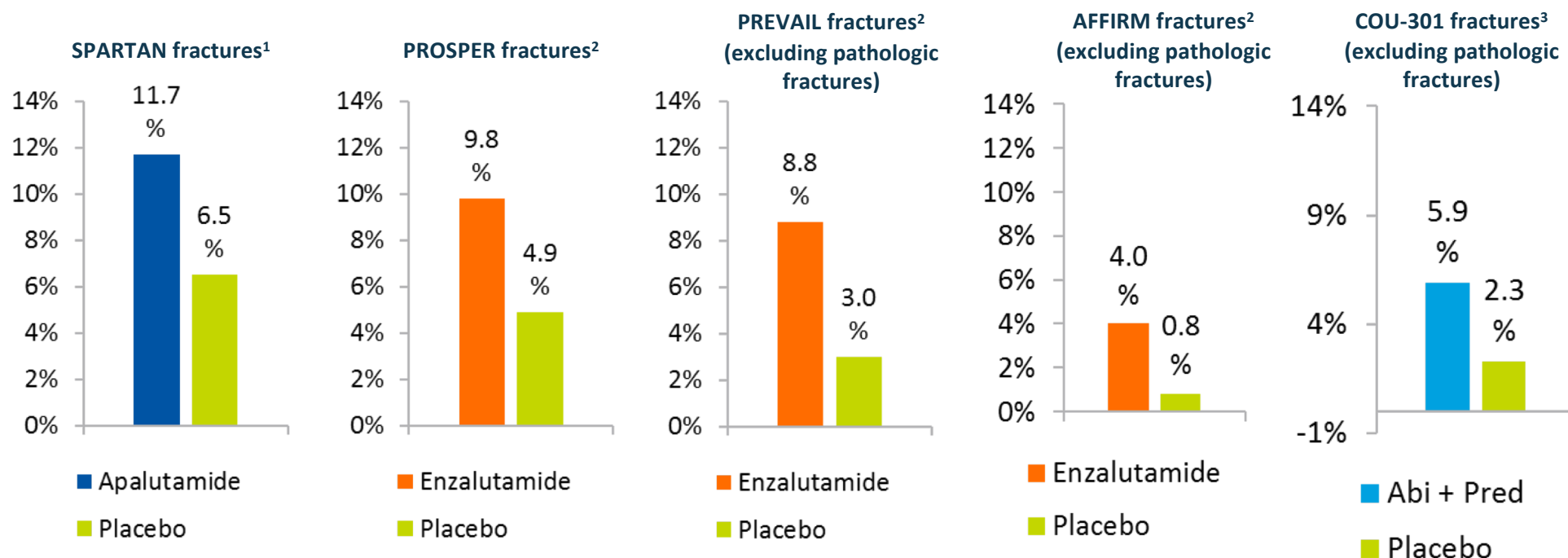
- Abiraterone +/- radium phase III (ERA-223)
- Enzalutamide +/-radium phase III (PEACE III) trial underway

Radium-223 and concomitant therapies in patients with metastatic castration-resistant prostate cancer: an international, early access, open-label, single-arm phase 3b trial

Fred Saad, Joan Carles, Silke Gilleisen, Axel Heidenreich, Daniel Heinrich, Jeremy Gratt, J  r  my L  vy, Kurt Miller, Sten Nilsson, Oana Petrenciuc, Marcello Tucci, Manfred Wirth, Judith Federhofer, Joe M O'Sullivan, for the Radium-223 International Early Access Program Investigators*



Fractures are commonly reported in the investigational arm of phase III studies with new AR pathways inhibitors



Note: ALSYMPCA phase 3 had pathologic fractures 5% in placebo and 4% in radium

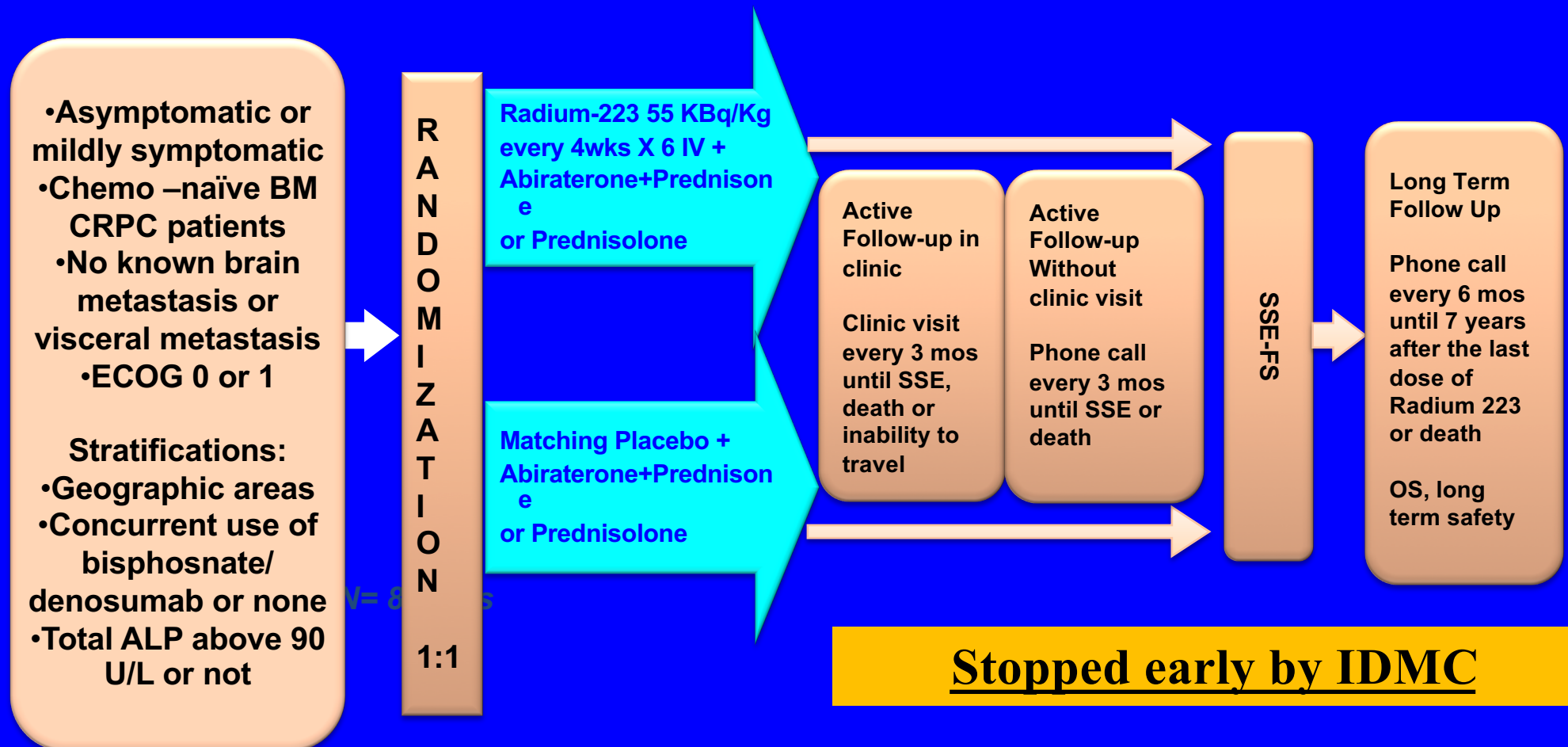
USPI, U.S. prescribing information.

1. Smith MR *et al.* *N Engl J Med* 2018; doi:10.1056/NEJMoa1715546 [Epub ahead of print]. 2. Xtandi (enzalutamide) [prescribing information]. Astellas Pharma US, Inc., Northbrook, IL. July 2018. 3. Zytiga (abiraterone acetate) [prescribing information]. Janssen Biotech, Inc., Horsham, PA. February 2018. 4. Erleada (apalutamide) [prescribing information]. Janssen Products, LP, Horsham, PA. February 2018.

From Bertrand Tombal at ASCO 2019

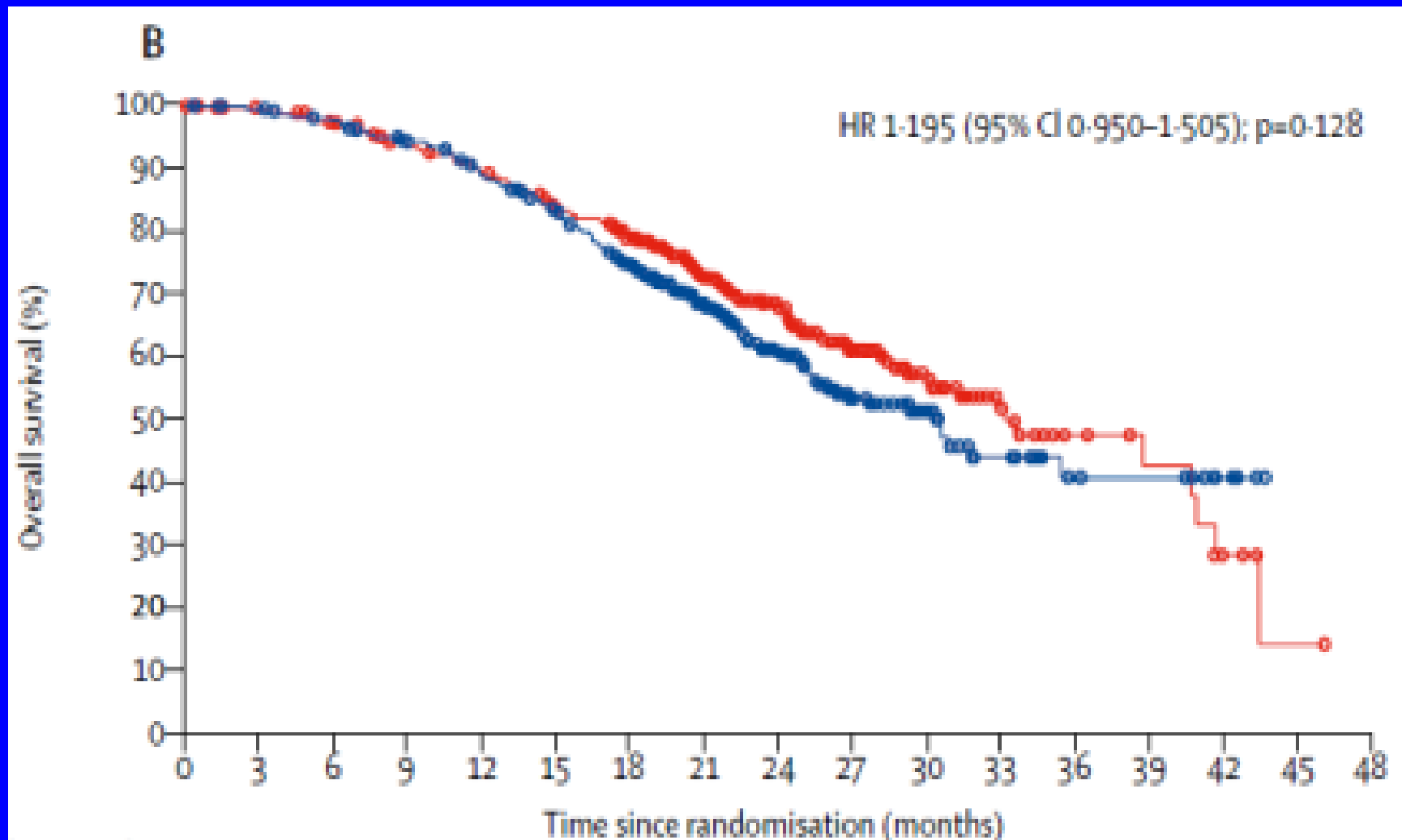
ERA-223: Abiraterone+Prednisone or Prednisolone +/- Radium-223

Patient population different from ALSYMPCA:
Asymptomatic, chemotherapy-naïve plus ongoing imaging



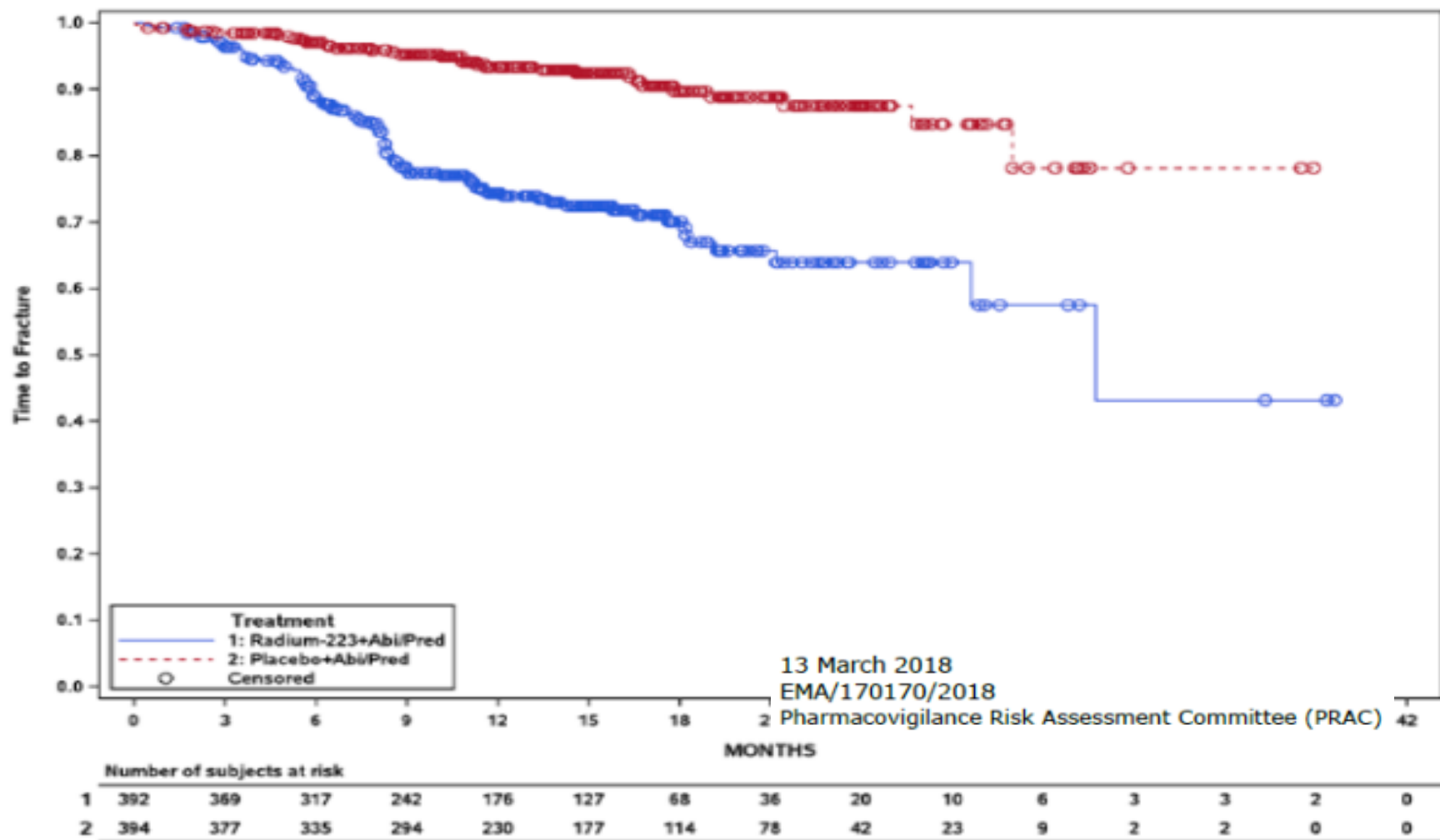
Addition of radium-223 to abiraterone acetate and prednisone or prednisolone in patients with castration-resistant prostate cancer and bone metastases (ERA 223): a randomised, double-blind, placebo-controlled, phase 3 trial

MR Smith et al. Lancet Oncology 20:408-19, 2019



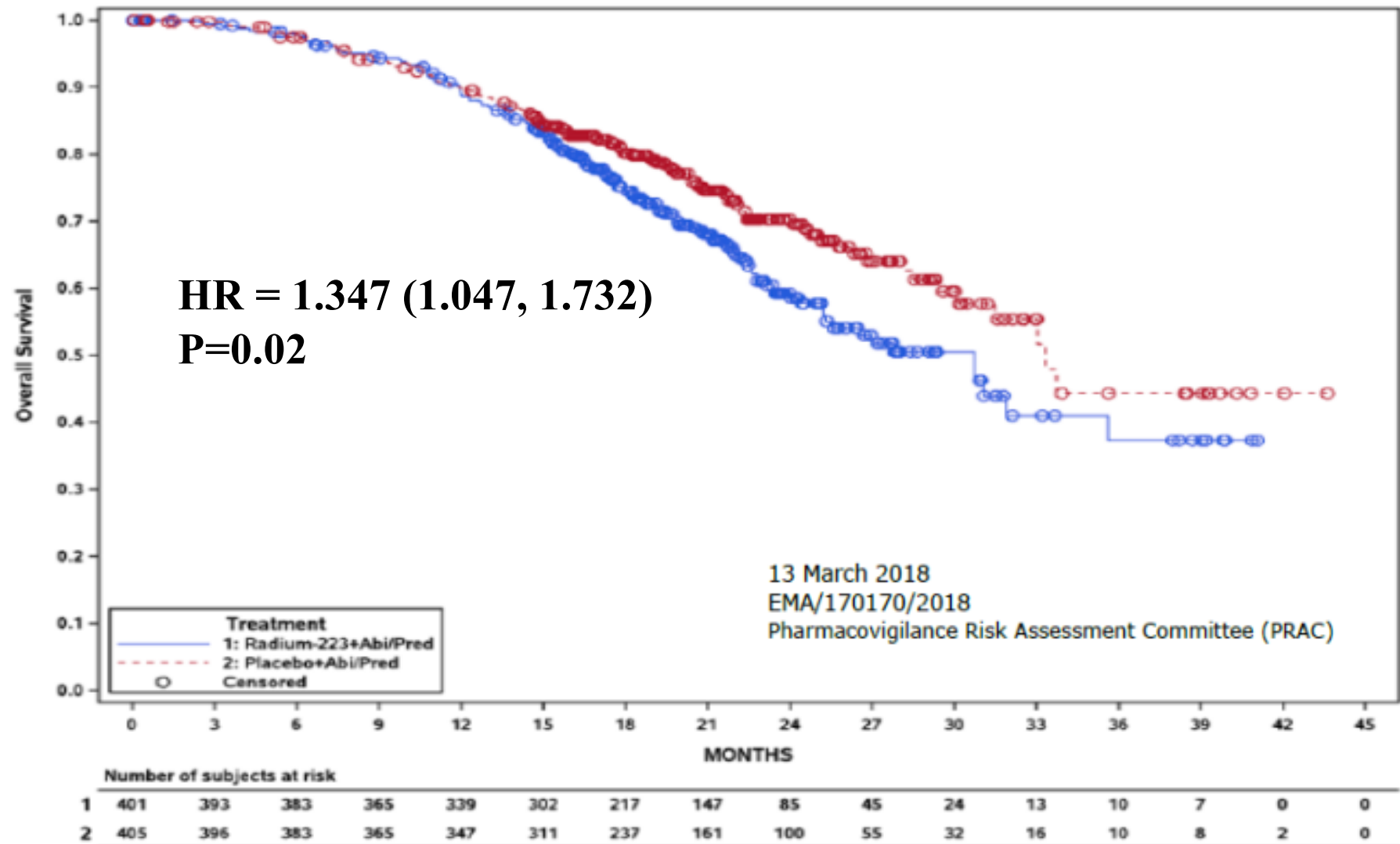
ERA-223 Stopped Early by IDMC for Adverse Findings: Fracture

Figure 2. Kaplan-Meier figure of time to first fracture



ERA-223 Stopped Early by IDMC for Adverse Findings: Survival

Figure 1. Kaplan-Meier curve for overall survival (ITT analysis)



IDMC Review

Increased Fractures and Decreased Survival Were Observed in ERAS-223 Combination Arm

	Radium-223 + abiraterone + prednisone	Placebo + abiraterone + prednisone
Survival analysis		
Deaths	34.7% (139/401)	27.4% (111/405)
P-value	0.02	
HR (95% CIs)	1.347 (1.047, 1.732)	
Median OS (95% CIs), months	30.7 (25.2, 35.6)	33.3 (30.2, A)
Fractures		
≥1 fracture	26.0% (102/392)	8.1% (32/394)

Available at: https://www.ema.europa.eu/documents/referral/xofigo-article-20-procedure-assessment-report-provisional-measures_en.pdf;
last accessed on 10/04/18

Fractures were correlated with death

Table 3. Relationship between all fractures, SSE fractures and deaths (safety analysis set)

	Ra223+Abi/Pred (n = 392) (=100%)	Placebo+Abi/Pred (n = 394) (=100%)	Relative Risk (RR)/ Risk difference (RD) (Ra223 vs. Plc)
Number of deaths	136 (34.7%)	111 (28.2%)	RD 6.5% RR 1.23
Death without any prior fractures	97 (24.7%)	99 (25.1%)	RD -0,4% RR 0.98
Death with prior fractures	39 (9.9%)	12 (3.0%)	RD 6.9% RR 3.27
Death with prior SSE fractures	20 (5.1%)	8 (2.0%)	RD 3.1% RR 2.51
Death with prior non-SSE fractures	23 (5.9%)	4 (1.0%)	RD 4.9% RR 5.78

https://www.ema.europa.eu/documents/referral/xofigo-article-20-procedure-assessment-report-provisional-measures_en.pdf

Almost half of fractures were in pts with <6 mets

Table 4. Baseline characteristics of patients with and without fractures, Study 15396 (safety analysis set)

	Radium-223+Abl/Pred N=392 (100%)		Placebo+Abl/Pred N=394 (100%)	
	With fractures N = 102	Without fractures N = 290	With fractures N = 32	Without fractures N = 362
Extent of bone disease at baseline				
<6 metastases	50(49.0%)	83(28.6%)	10(31.3%)	126(34.8%)
6-20 metastases	27(26.5%)	143(49.3%)	16(50.0%)	158(43.6%)
>20 lesions but not a superscan	19(18.6%)	51(17.6%)	5(15.6%)	64(17.7%)
Superscan	6(5.9%)	13(4.5%)	1(3.1%)	13(3.6%)
Missing	0	0	0	1(0.3%)
ECOG performance status at baseline				

Available at: https://www.ema.europa.eu/documents/referral/xofigo-article-20-procedure-assessment-report-provisional-measures_en.pdf; last accessed on 10/04/18

Miccini

1/1 (0%)

0

0

0

Most ERA-223 fractures occurred in sites with no bone metastases

MR Smith et al. Lancet Oncology 20:408-19, 2019

- “Among 76 patients with one or more independently assessed fractures in the radium-223 group, 60 (79%) occurred at a skeletal site with no bone metastasis....”

Bone Health Agents Dramatically Reduce the Risk of Fractures and Other SSEs in ERA 223 (Unplanned)

	Radium-223 + Abi/Pred n=155	Radium-223 + Abi/Pred n=246	Placebo + Abi/Pred n=169	Placebo + Abi/Pred n=236
	With BHA	Without BHA	With BHA	Without BHA
Number of all events* (%)	62 (40.0%)	122 (49.6%)	71 (42.0%)	98 (41.5%)
EBRT	25 (16.1%)	65 (26.4%)	32 (18.9%)	52 (22.0%)
Symptomatic bone fracture	2 (1.3%)	37 (15.0%)	4 (2.4%)	11 (4.7%)
Orthopedic surgery	1 (0.6%)	9 (3.7%)	2 (1.2%)	4 (1.7%)
Spinal cord compression	6 (3.9%)	5 (2.0%)	5 (3.0%)	14 (5.9%)
Death	53 (34.2%)	86 (35.0%)	48 (28.4%)	63 (26.7%)

ERA-223 Insights

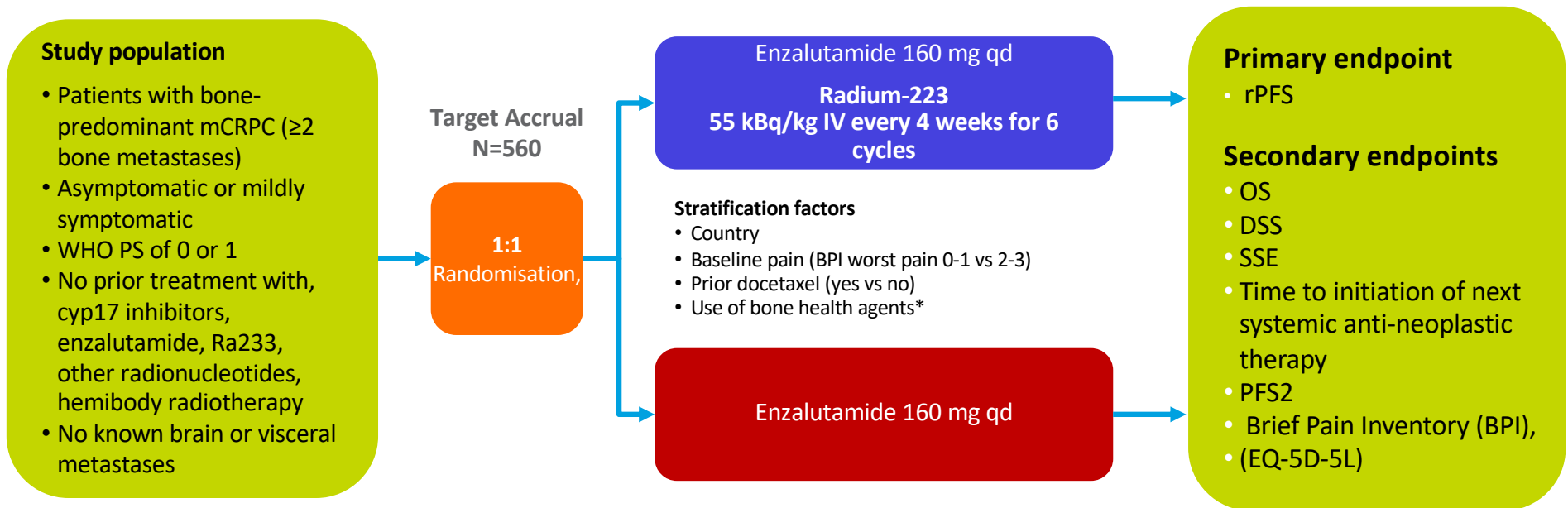
- Abiraterone and radium-223, started concomitantly, increases fractures and possibly deaths in men with asymptomatic bone-metastatic chemotherapy naïve CRPC
- Fractures occurred across all subsets but especially those with low volume metastatic disease
 - Most fractures were not at sites of metastases
- Bone-health agents (zoledronate or denosumab) substantially decreased risk of fractures

Decreased fracture rate by mandating bone protecting agents in the EORTC 1333/PEACEIII trial combining Ra223 with enzalutamide versus enzalutamide alone Early results

Bertrand TOMBAL, Yohann LORIOT, Fred SAAD, Ray McDERMOTT, Tony ELLIOTT, Alejo RODRIGUEZ-VIDA, Franco NOLE, Beatrice FOURNIER, Laurence COLLETTE, Silke GILLESSEN
For EORTC GUCG, CUOG, UNICANCER and Cancer Trials Ireland.

From Bertrand Tombal at ASCO 2019

EORTC GUCG 1333 (PEACE III) original design



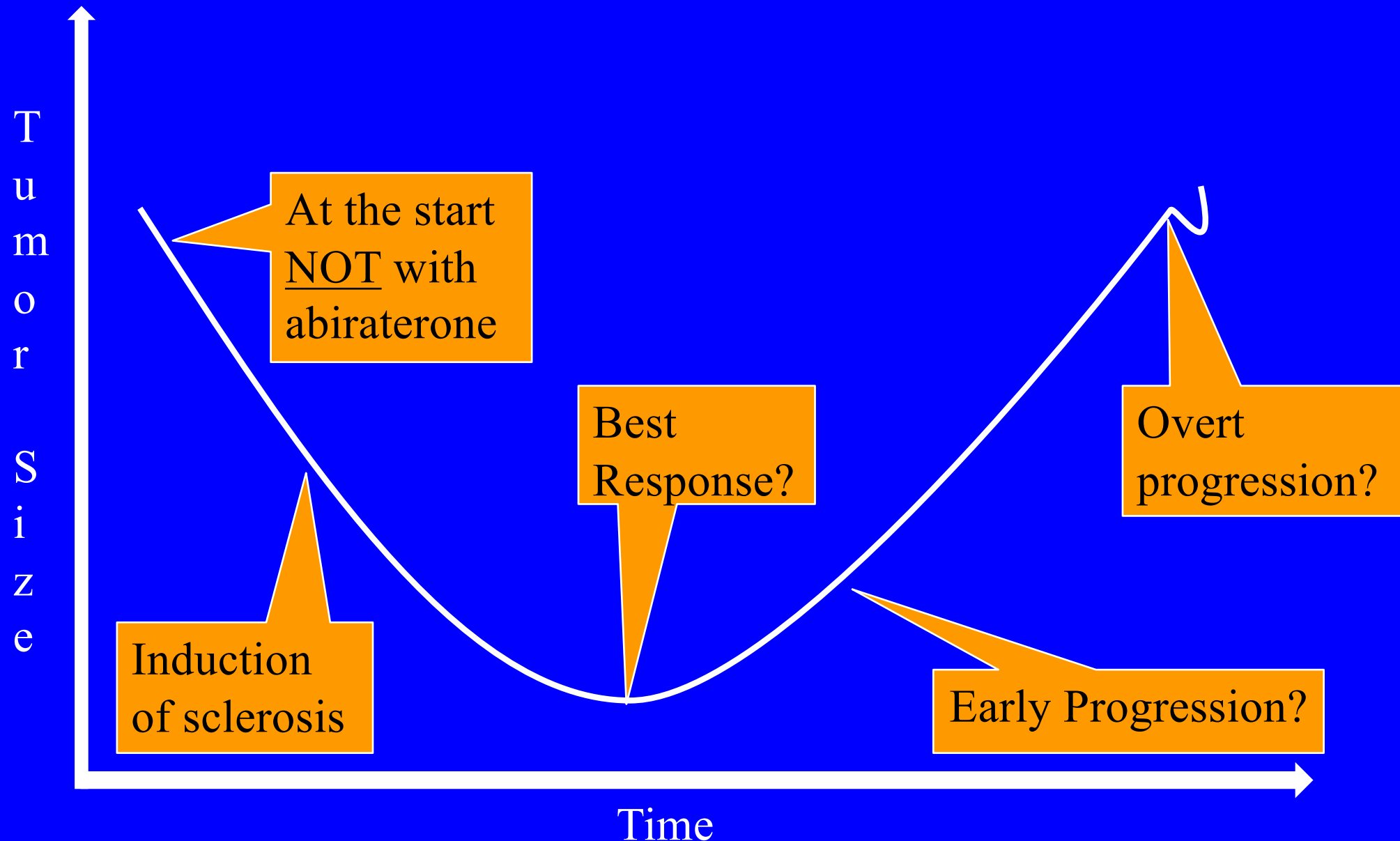
From Betrand Tombal at ASCO 2019

Note IDMC for PEACE III modified trial early on given ERA223 data and early fractures noted in this trial

Bone fractures and cumulative incidence safety population.....after IDMC changes

Time point	Treatment and use of bone protecting agents			
	With exposure to BPA		Without exposure to BPA	
	Enza+Rad (N=39)	Enza (N=49)	Enza+Rad (N=37)	Enza (N=35)
	Cum Incidence (95% CI)*	Cum Incidence (95% CI)	Cum Incidence (95% CI)	Cum Incidence (95% CI)
3 months	0 (-)	0 (-)	0 (-)	5.7 (1.0-16.7)
6 months	0 (-)	0 (-)	5.6 (1.0-16.3)	8.8 (2.2-21.0)
9 months	0 (-)	0 (-)	22.6 (10.6-37.3)	8.8 (2.2-21.0)
12 months	0 (-)	0 (-)	37.4 (21.8-53.1)	12.4 (3.9-26.2)
15 months	0 (-)	0 (-)	43.6 (26.8-59.3)	16.6 (5.9-32.0)
18 months	0 (-)	0 (-)	43.6 (26.8-59.3)	16.6 (5.9-32.0)

If novel hormonal agents are used, when should radium-223 be added?



Conclusions

- Combinations of radium-223 + abiraterone or enzalutamide, used concomitantly, dramatically increase fractures risk in chemotherapy naïve mCRPC
 - Most fractures in ERA-223 occur at sites without metastases
- Bone health agents (zoledronic acid or denosumab) dramatically decrease fracture risk in this population
- When using radium, consider the use of concomitant bone health agents