Metastatic Castration Sensitive Prostate Cancer: Contemporary Clinical Management

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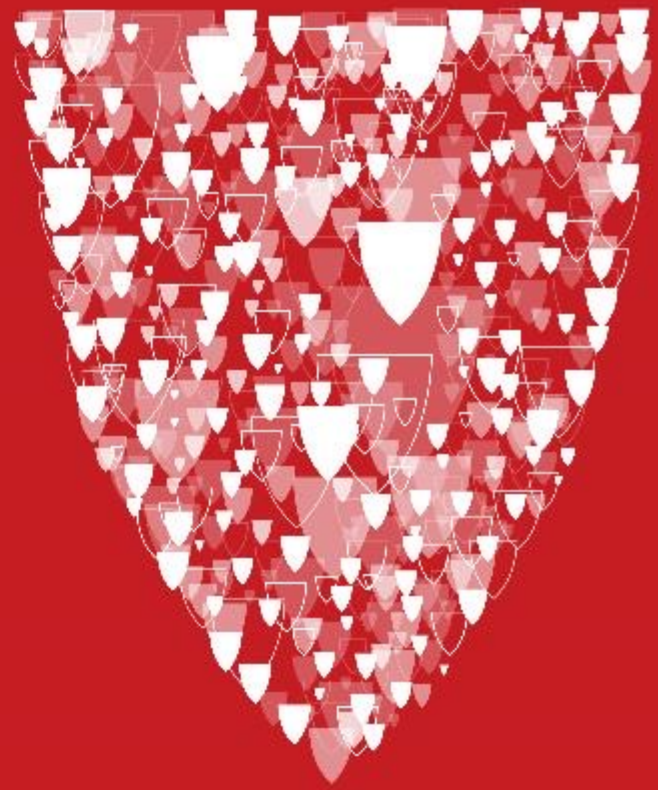
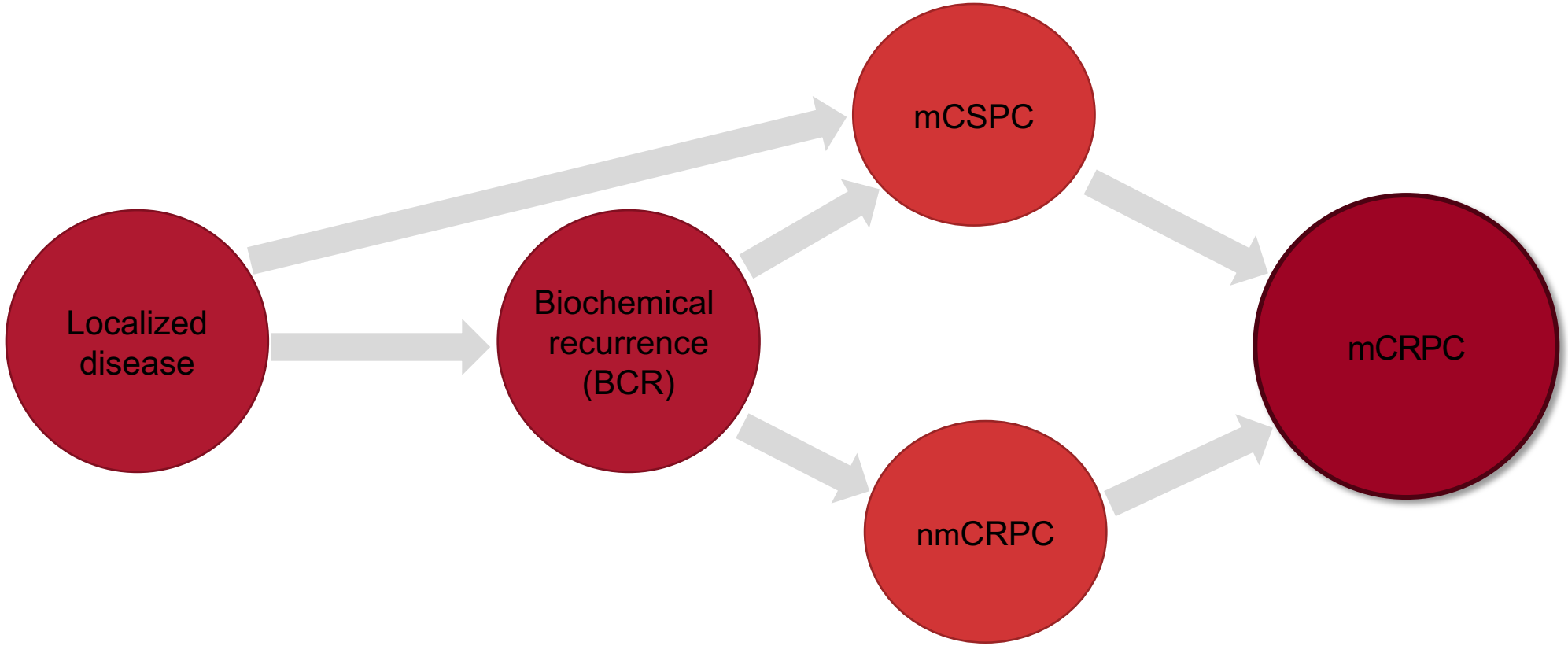


Who dies of prostate cancer?

- Even in a screened population such as the USA ~ 5-10% present with De-novo metastatic prostate cancer
  - 5-10% of ~160,000 = 8-16,000 pts
  - This is ≥ 1/3rd of the 24,000 deaths in USA
  - Since 2012 USTPF has increased incidence of locally advanced and Met disease – COVID didn't help us either….

- Remaining of Pts relapse from prior localized therapy
  - Biochemical relapses – slow and never need treatment or fast and do need intervention
  - PSADT vs. timing to imaging
  - Early ADT in M0 will lead to early M0CRPC > M1CRPC > Death

Natural History of Prostate Cancer: A disease continuum



Adapted from 1. Scher, HI, et al: *J Clin Oncol* 34. (12), 2016: 1402-1418. 2. Pound CR, et al. *JAMA*. 1999;281(17):1591-1597. 3. Morris MJ, et al. *J Clin Oncol.* 2018; 36(15):1521-1539.

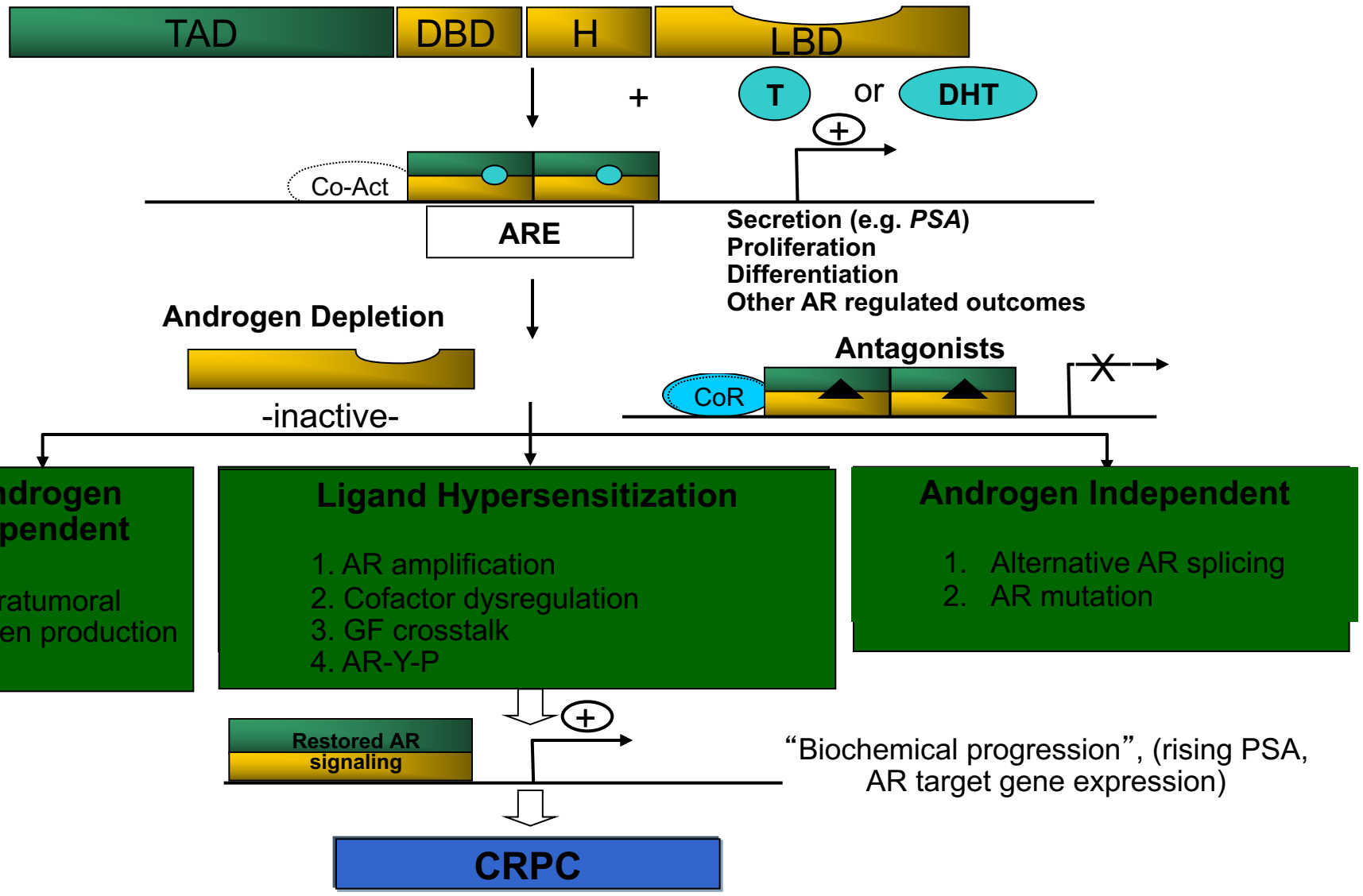
Androgen Receptor Reactivation in Prostate Cancer Progression

AR Structure

AR Regulation

Targeted AR Therapies

AR Reactivation



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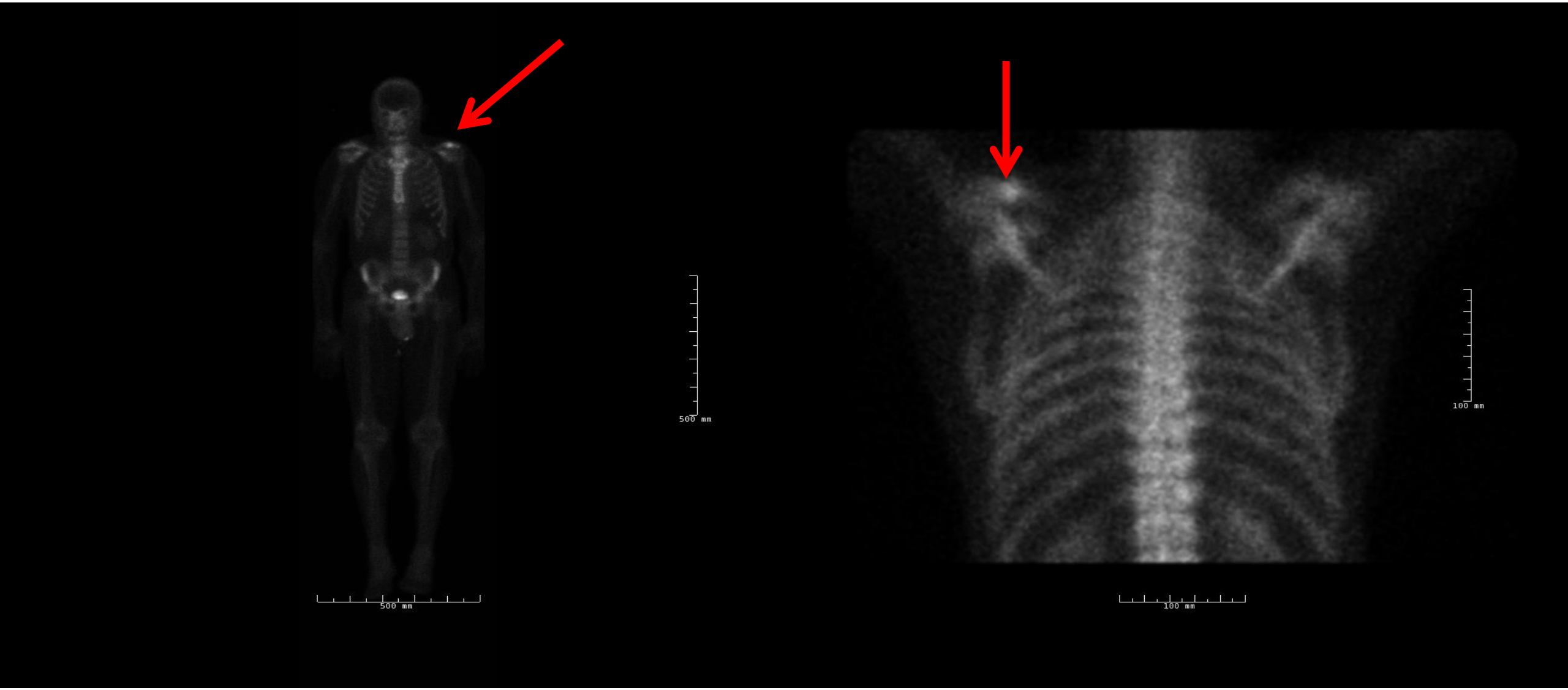
Adapted from Knudsen and Scher. Clin Cancer Res 2009:15;4792-4798.

Prostate Cancer Case (1)

- 54 years-old Caucasian male with some vague atypical LTUs presents to his Urologist

  - DRE: Large prostate, no nodules
  - TRUS/Bx showed GS 5+4 (9) in 8/12 cores. All positive cores with more than 25% of involvement
  - Discussions surrounding RP vs. RT +/- ADT +/- AA/P are held
  - Pt undergoes baseline imaging
  - CT A/P showed No LN disease and no visceral disease


500 mm
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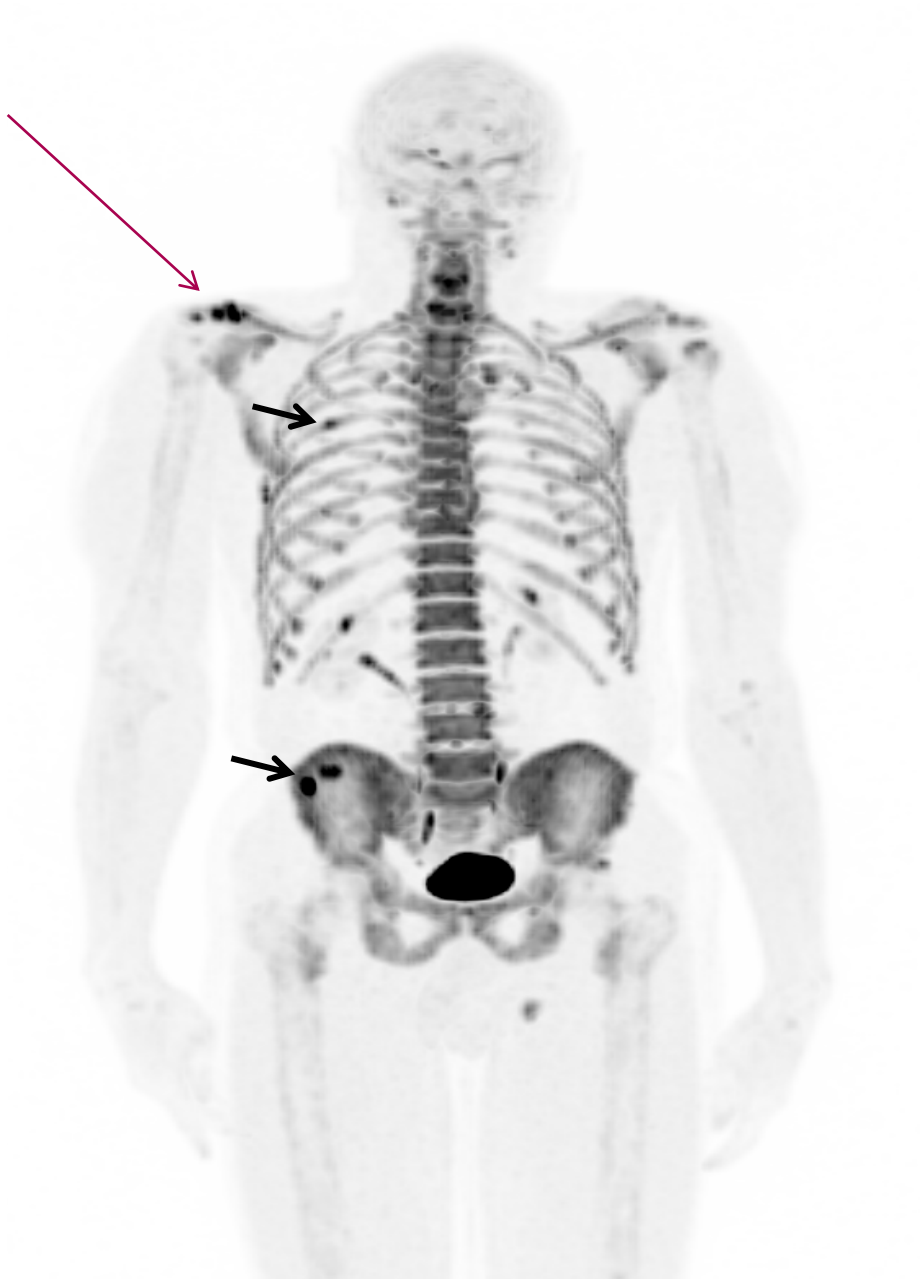
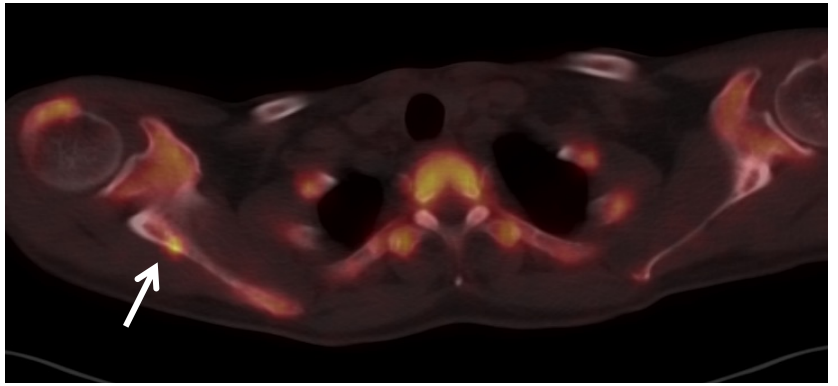
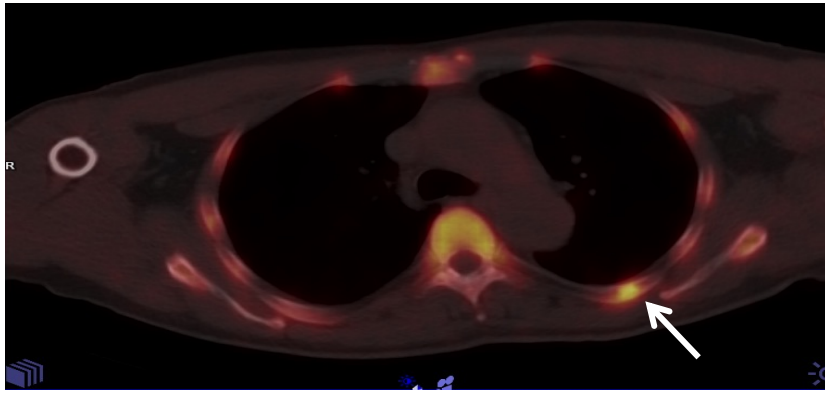
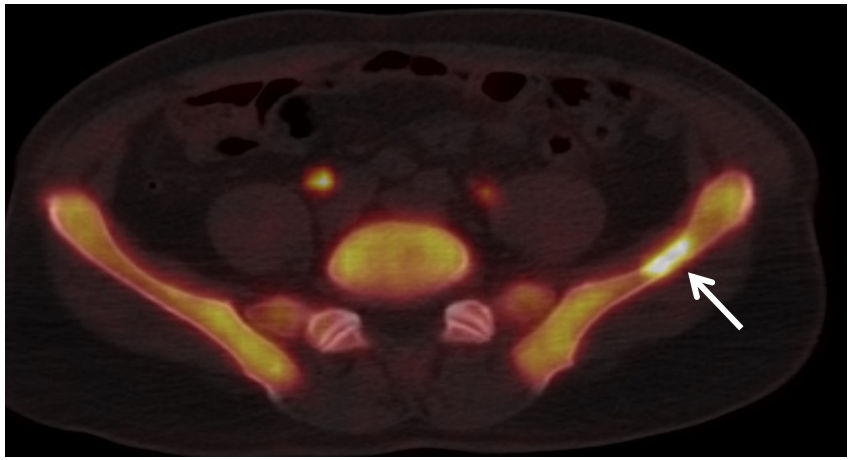




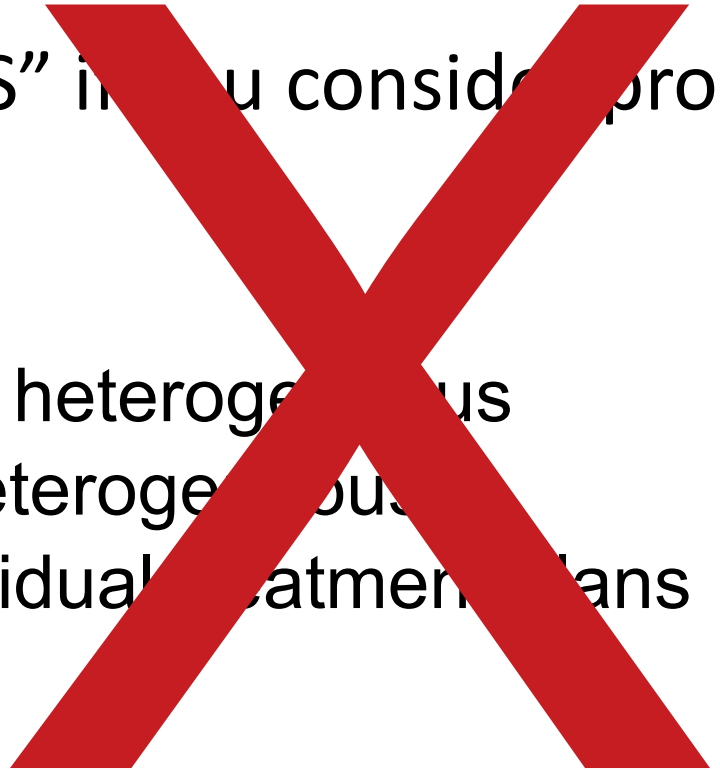




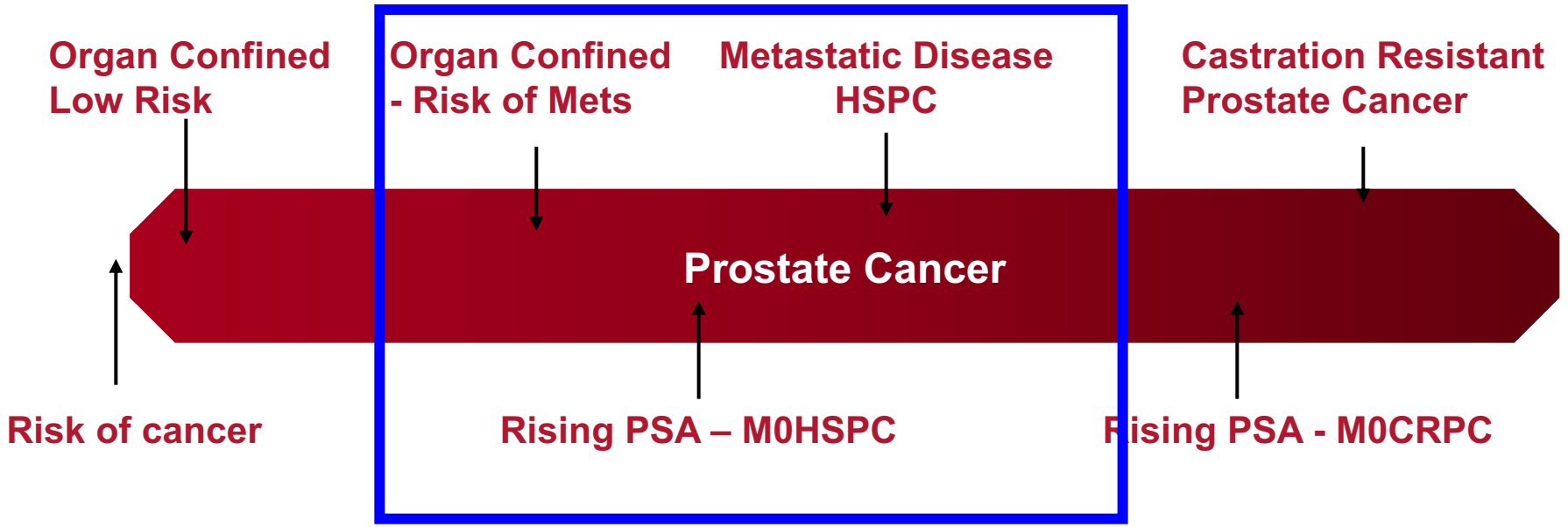
Does volume matter for upfront chemotherapy for castration-naïve metastatic prostate cancer?

The answer is “YES” if you consider prostate cancer is a disease that

1) is biologically heterogeneous
2) is clinically heterogeneous
3) requires individualized treatment plans



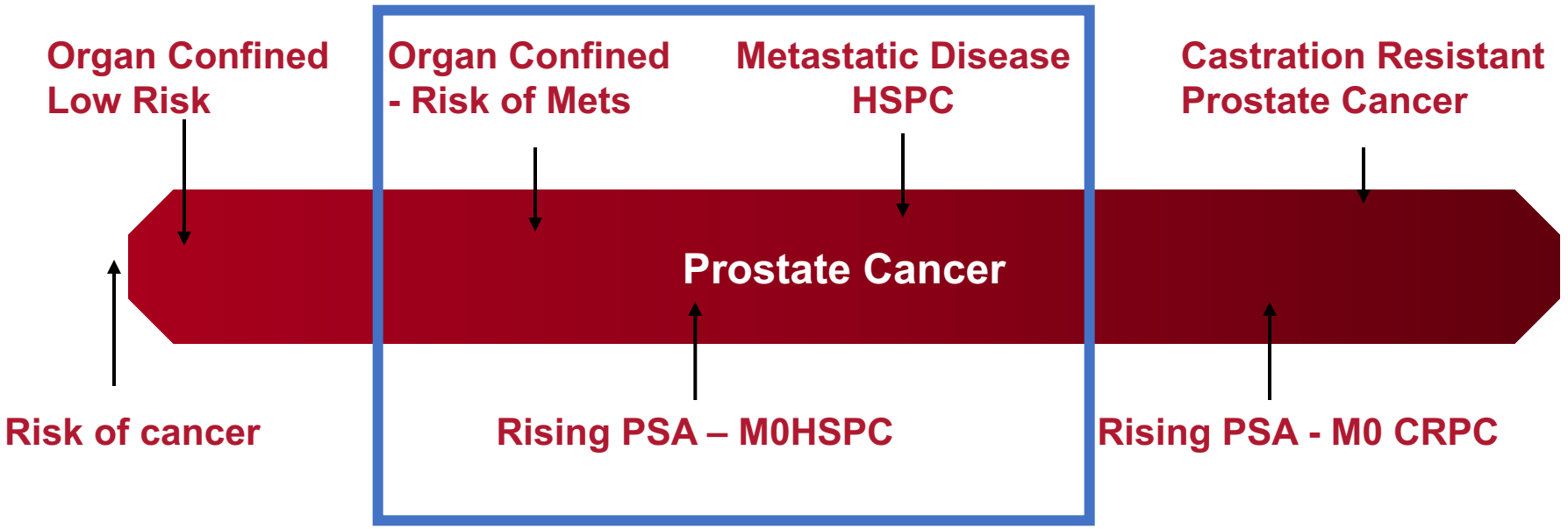
The “All-in-One” Approach



Within the blue box, **STAMPEDE** investigators report no evidence of heterogeneity and infer docetaxel for all pts where give long course ADT.

This box covers: High risk localized; Rising PSA post localized therapy; Low volume mHSPC; High volume mHSPC

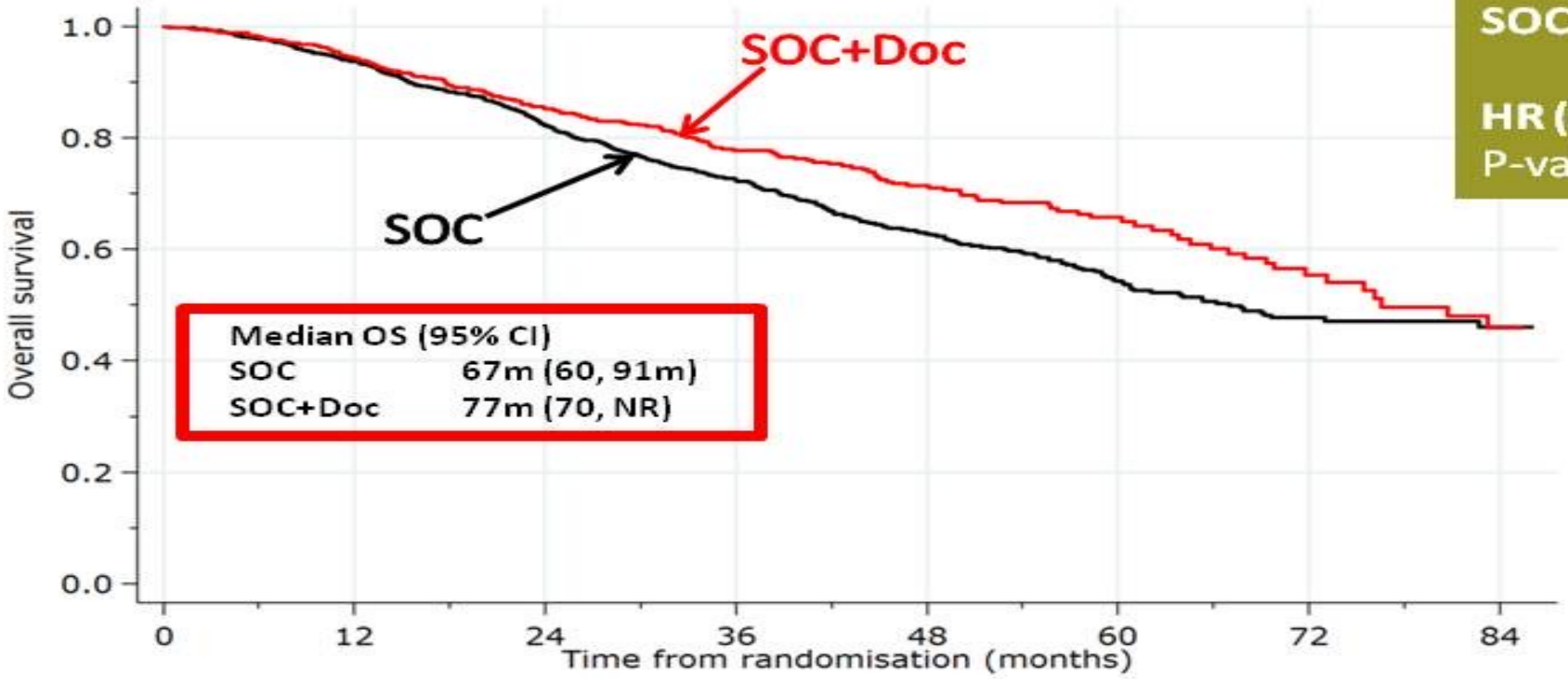
The “Selective” Approach



Treat early and ONLY those who present with De-novo Metastatic disease: uncommon now days but a significant issue in practice sec aggressive nature of disease

- **GETUG and CHAARTED, Latitude, TITAN, ENZAMET and ARASENS**

Docetaxel: Survival



SOC	405 deaths
SOC+Doc	165 deaths
HR (95%CI)	0.76 (0.63, 0.91)
P-value	0.003

Non-PH p-value 0.51

Restricted mean OS time

SOC	58.8m
SOC+Doc	63.4m
Diff (95%CI)	4.6m (1.8, 7.3m)

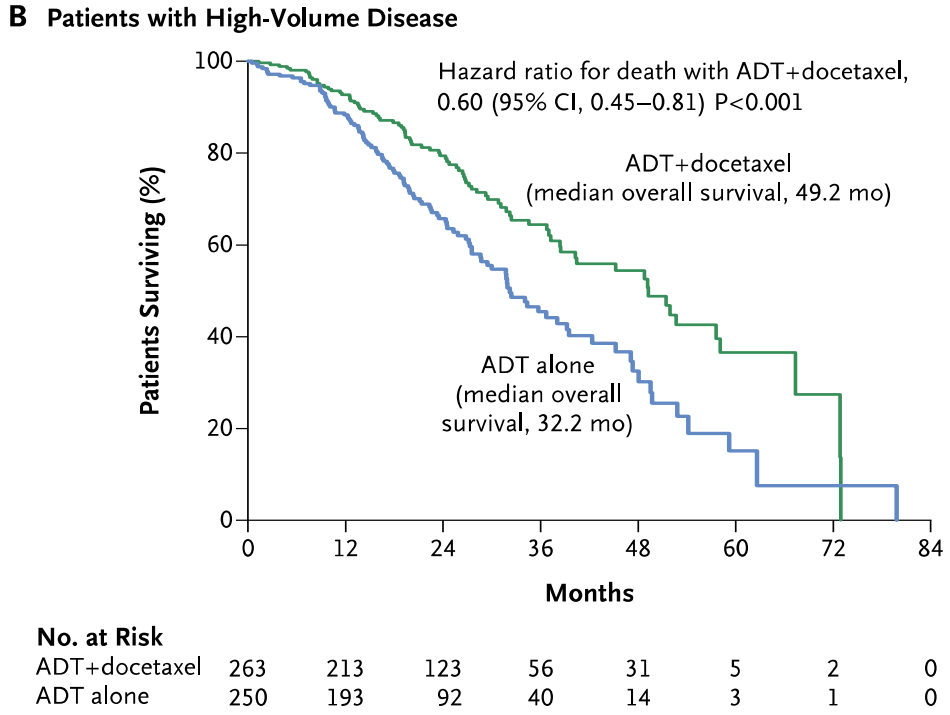
Group
At risk (events)

SOC	1184	(73)	1092	(130)	860	(89)	521	(59)	310	(33)	156	(17)	81	(2)	36
SOC+Doc	592	(33)	545	(51)	437	(32)	283	(19)	180	(12)	91	(12)	48	(6)	18

James ND, et al. Lancet. 2016 Mar 19;387(10024):1163-77.

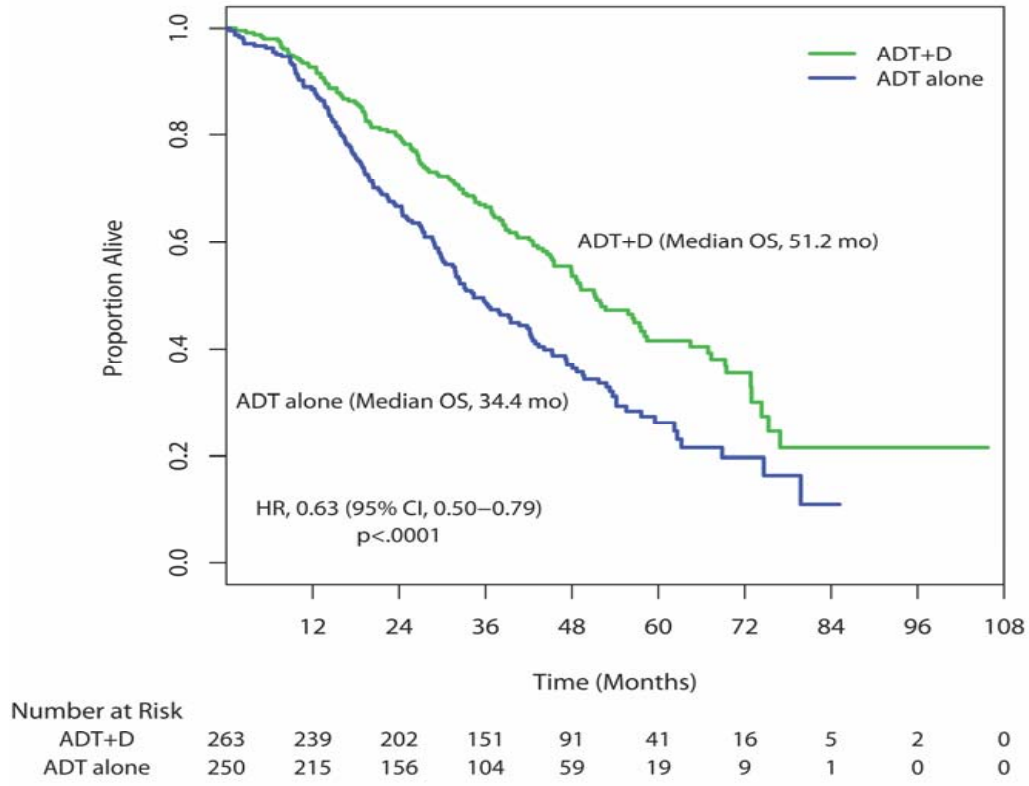
What are we learning from long term follow-up of CHAARTED: *High volume*

Median Follow-up 28.9 months



17 months / HR 0.6

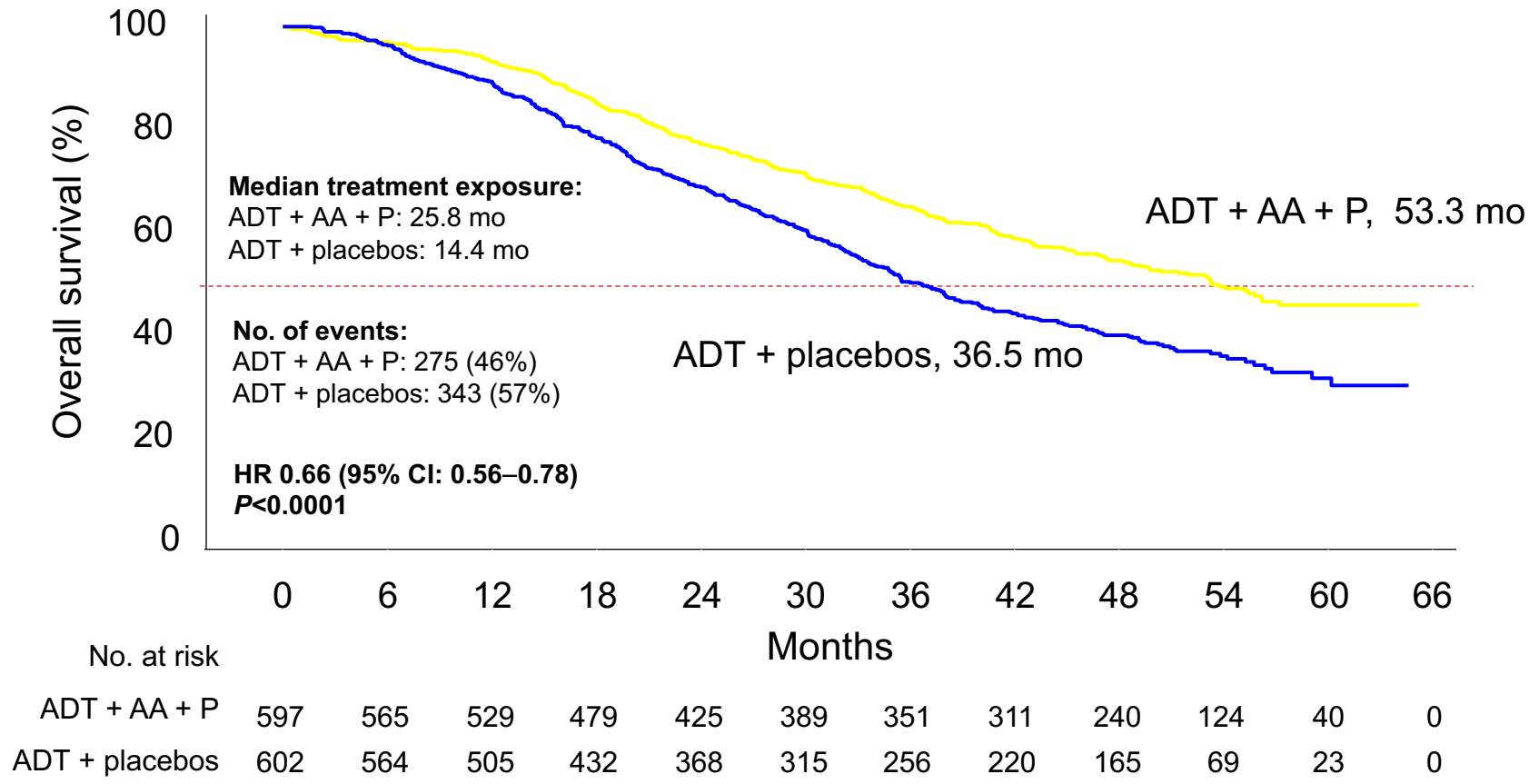
Median Follow-up: 53.7 months



17 months / HR 0.6

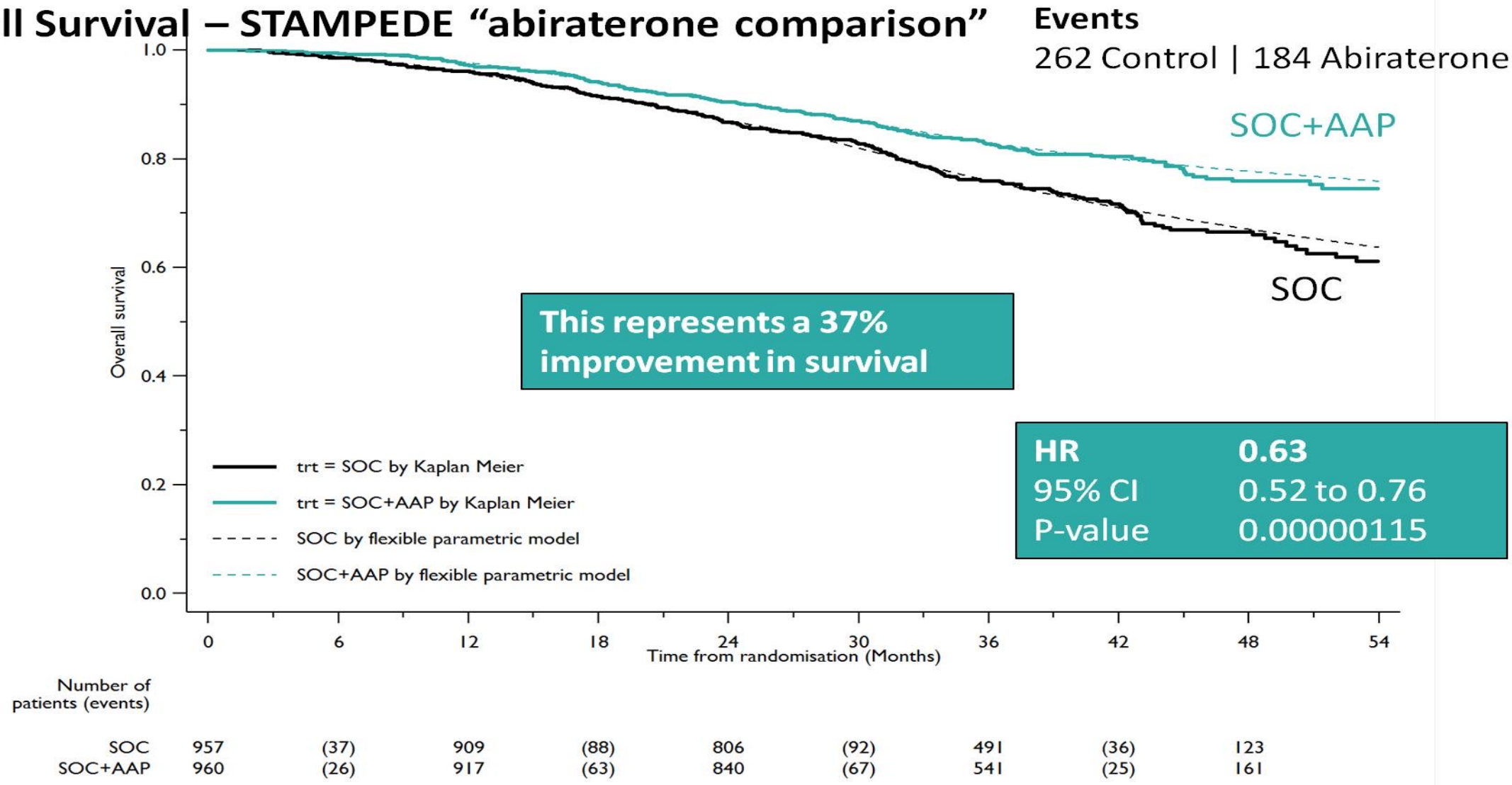
Kyriakopolus C, et al. JCO 2018

Final Analysis: Overall Survival - Latitude



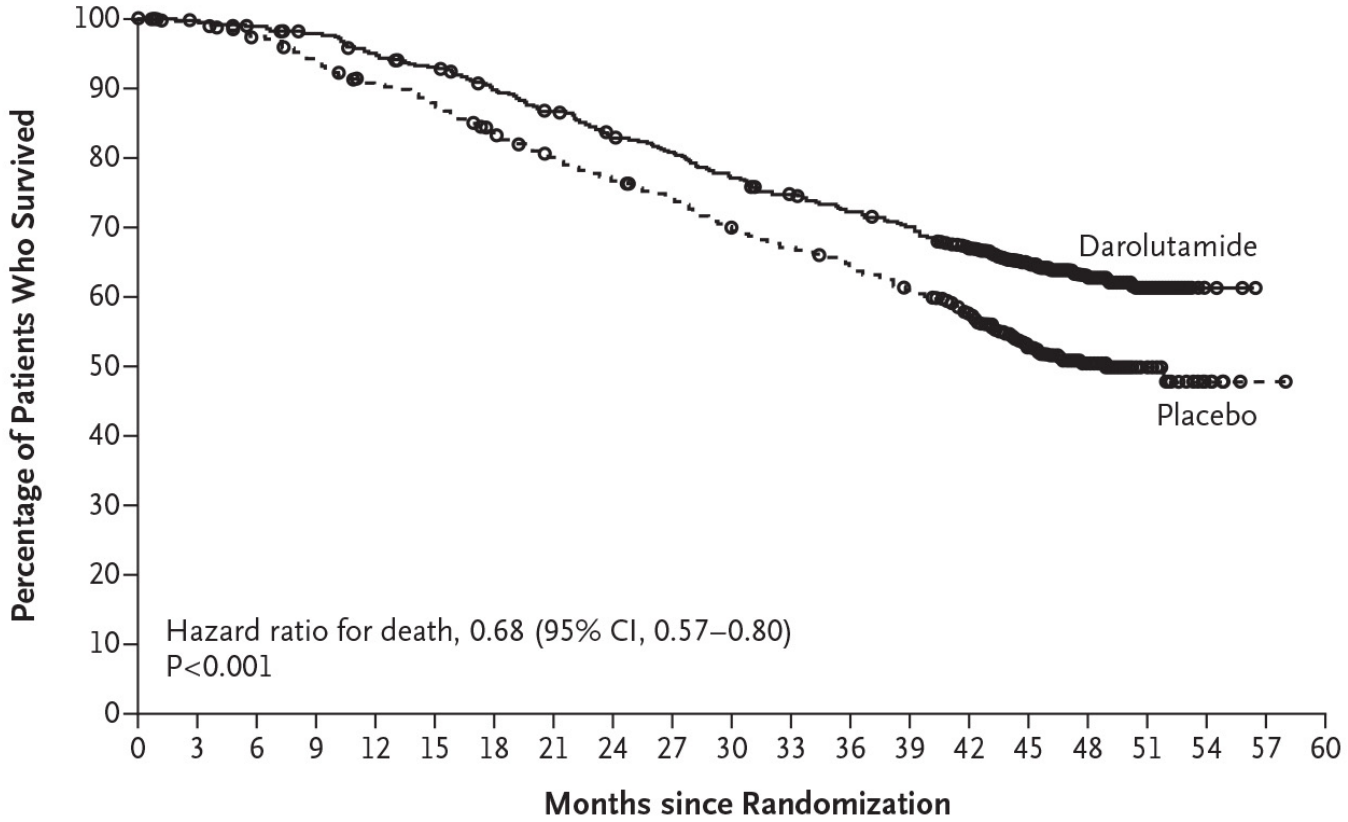
Fizazi K, et al. Lancet Oncol. 2019 May;20(5):686-700.

Overall Survival – STAMPEDE "abiraterone comparison"



James ND, et al. N Engl J Med. 2017 Jul 27;377(4):338-351

Darolutamide and Survival in Metastatic, Hormone-Sensitive Prostate Cancer



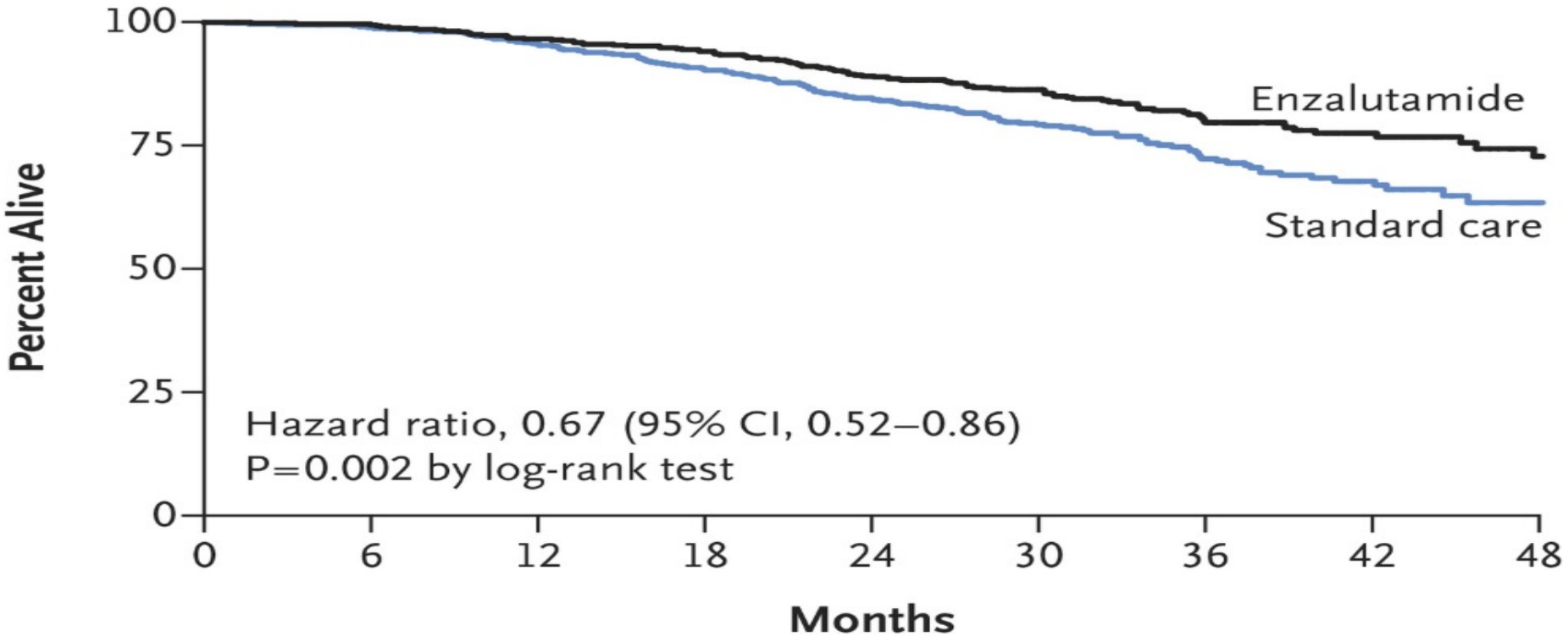
	Median Survival (95% CI)
	mo
Darolutamide	NE
Placebo	48.9 (44.4–NE)

No. at Risk

Darolutamide	651	645	637	627	608	593	570	548	525	509	486	468	452	436	402	267	139	56	9	0	0
Placebo	654	646	630	607	580	565	535	510	488	470	441	424	402	383	340	218	107	37	6	1	0

Smith MR, et al. N Engl J Med 2022;386:1132-42.

Phase III ENZAMET: OS

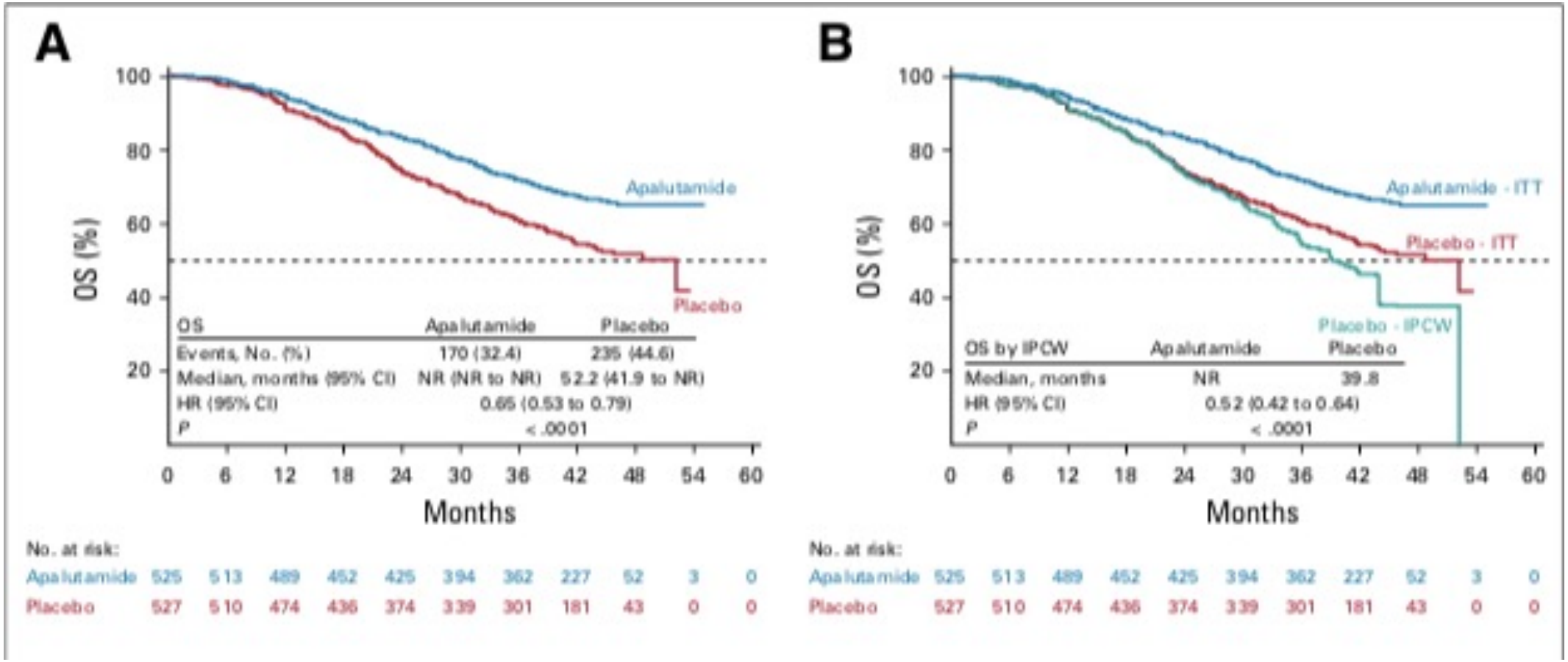


No. at Risk

Enzalutamide	563	558	541	527	480	340	189	106	45
Standard care	562	551	531	501	452	311	174	86	32

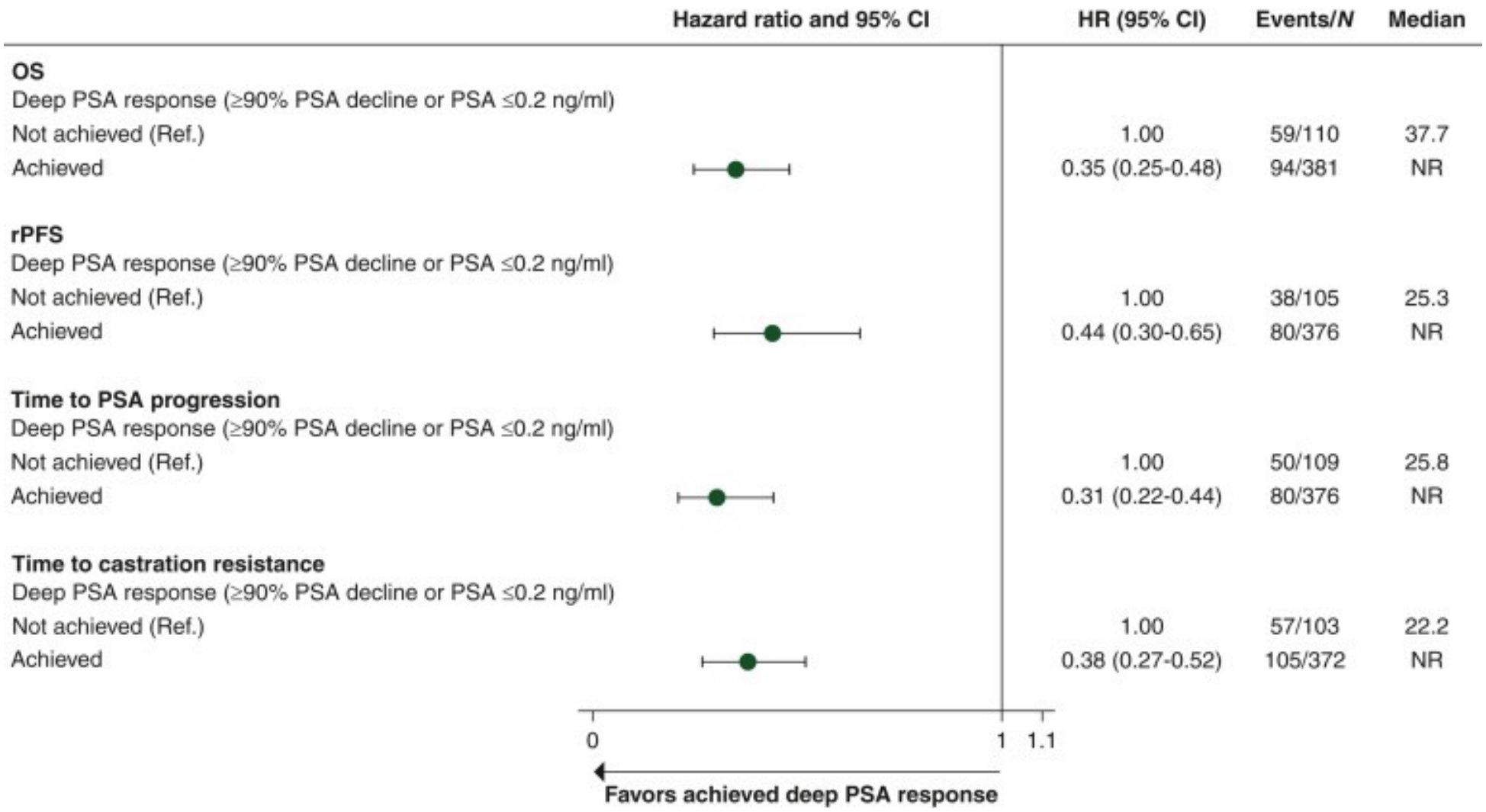
Davis ID, et al. N Engl J Med. 2019;381:121-131.

Final Survival Analysis of the Randomized, Double-Blind, Phase III TITAN Study



Chi KN, et al. J Clin Oncol 39:2294-2303

PSA reductions are imperfect but quite telling…



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S. Chowdhury, et al. Annals of Oncology Volume 34, Issue 5, May 2023, Pages 477-485

Impact of Radiation Therapy to Prostate

HORRAD

- 432 patients with mHSPC randomized to EBRT of prostate and ADT versus ADT alone
- 63% had > 5 osseous metastasis, median followup 47 months
- No difference in OS (45 months vs 43 months)
- No difference in PSA recurrence-free survival (15 months versus 12 months)

STAMPEDE-arm H

- 2061 patients with mHSPC randomized to EBRT plus ADT +/-docetaxel versus ADT +/-docetaxel
- Low volume=40%, high volume=54%
- No difference in OS at 37 months
- Low metastatic burden, improvement in OS with Hazard Ratio 0.68

PEACE-1

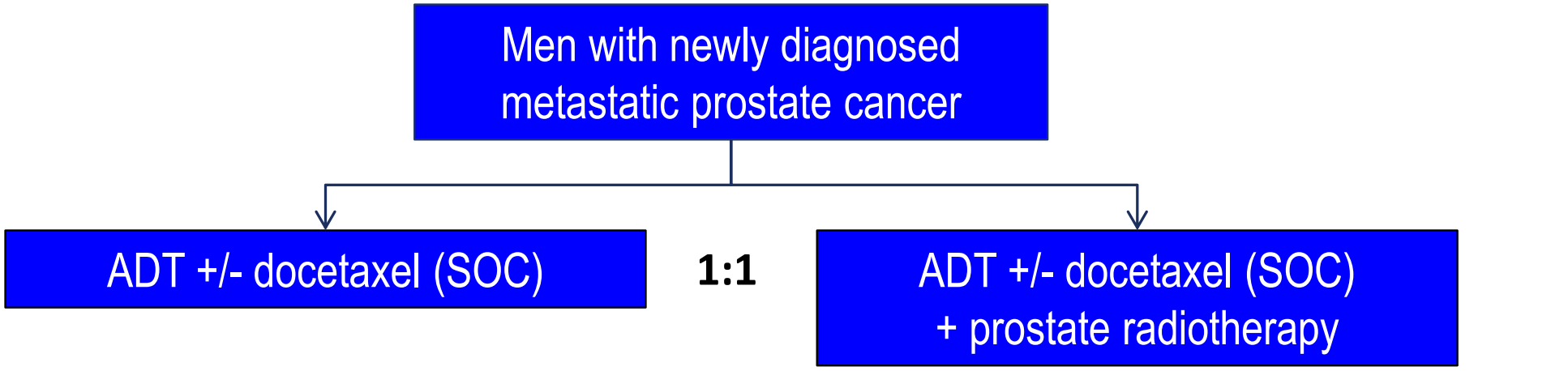
- 1173 patients with mHSPC randomized to ADT, docetaxel, abiraterone, XRT versus ADT, docetaxel, XRT
- Analyzing role of abiraterone and radiation therapy separately
- rPFS: median 4.5 y (ADT, docetaxel, abiraterone) vs 2.2 y (ADT, docetaxel)
- Impact of XRT pending

SWOG1802

- Anticipated 1273 patients with mHSPC randomized to definitive treatment with EBRTor Surgery versus Standard SystemicTherapy

Boeve LMS et al. Eur Urol 2019/75(3):410-418. Parker CC et al. Lancet 2018;392(10162):2353-2366. Fizazi K et al. J Clin Oncol 39, 2021(suppl15; abstr 5000). NCT03678025.

Study design

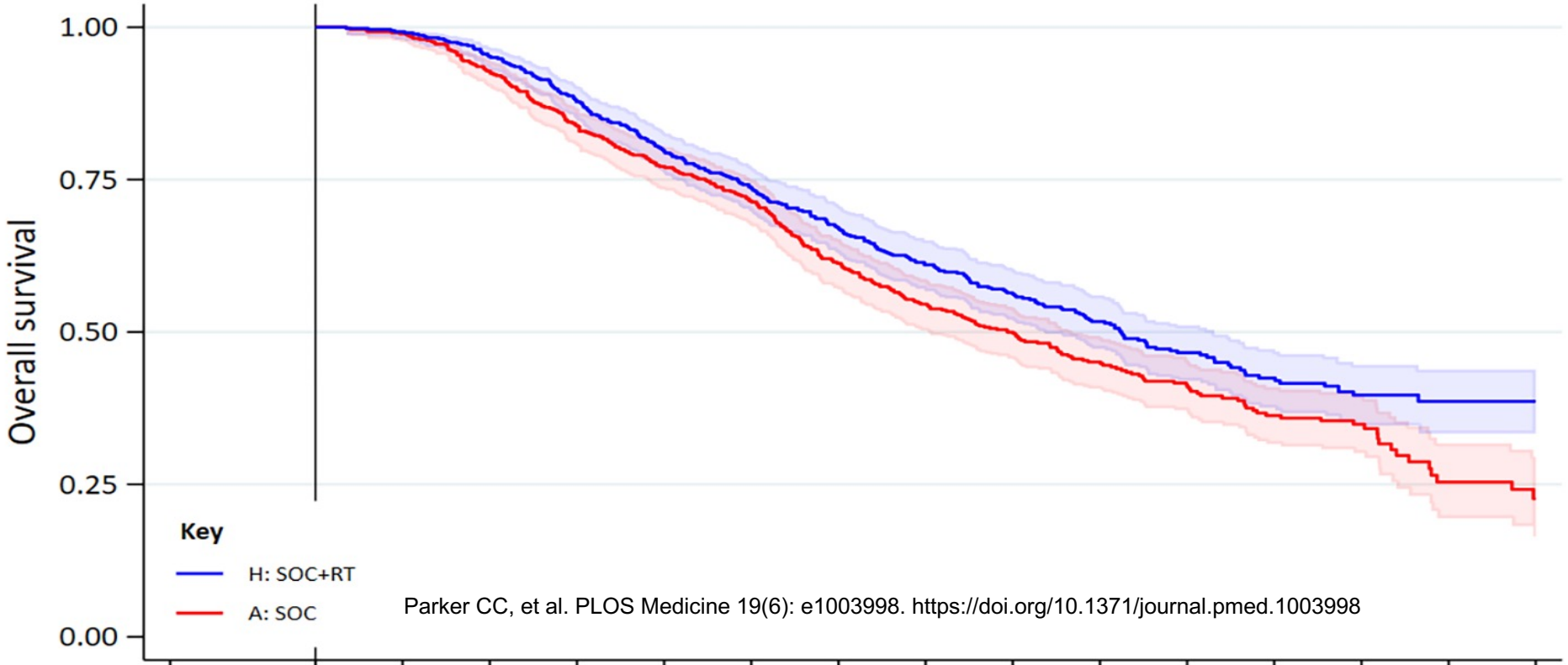


Stratification variables

Age (<70 vs ≥70 years), nodal involvement (N0 vs N1 vs Nx), randomising site,
WHO performance status (0 vs 1 or 2), type of ADT, aspirin or NSAID use, docetaxel use

MRC CTU at UCL

Parker CC, et al. Lancet. 2018 Dec 1;392(10162):2353-2366.



Parker CC, et al. PLOS Medicine 19(6): e1003998. https://doi.org/10.1371/journal.pmed.1003998

A: SOC															
At-risk now	547	535	500	451	412	377	322	278	231	167	121	87	54	23	8
Censored now	0	6	8	9	12	17	18	27	51	94	127	148	178	199	212
Event by now	0	6	39	87	123	153	207	242	265	286	299	312	315	325	327
H: SOC+RT															
At-risk now	534	520	498	459	416	383	346	308	255	196	140	98	62	34	18
Censored now	0	10	11	11	12	13	16	23	52	92	130	162	192	219	235
Event by now	0	4	25	64	106	138	172	203	227	246	264	274	280	281	281

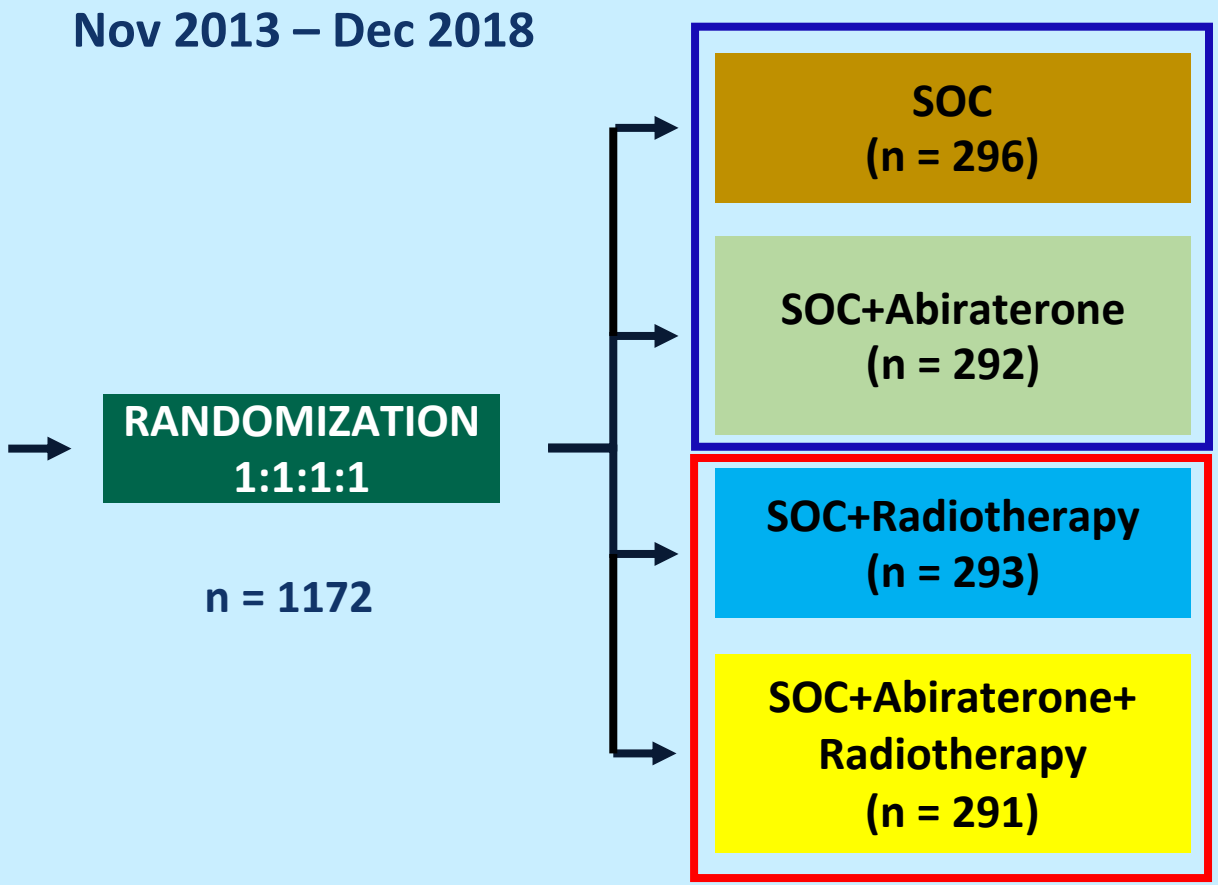
Design of PEACE-1

Key Eligibility Criteria
De novo mCSPC
Distant metastatic disease by ≥ 1 lesion on bone scan and/or CT scan
ECOG PS 0 -2

On-Study Requirement
Continuous ADT

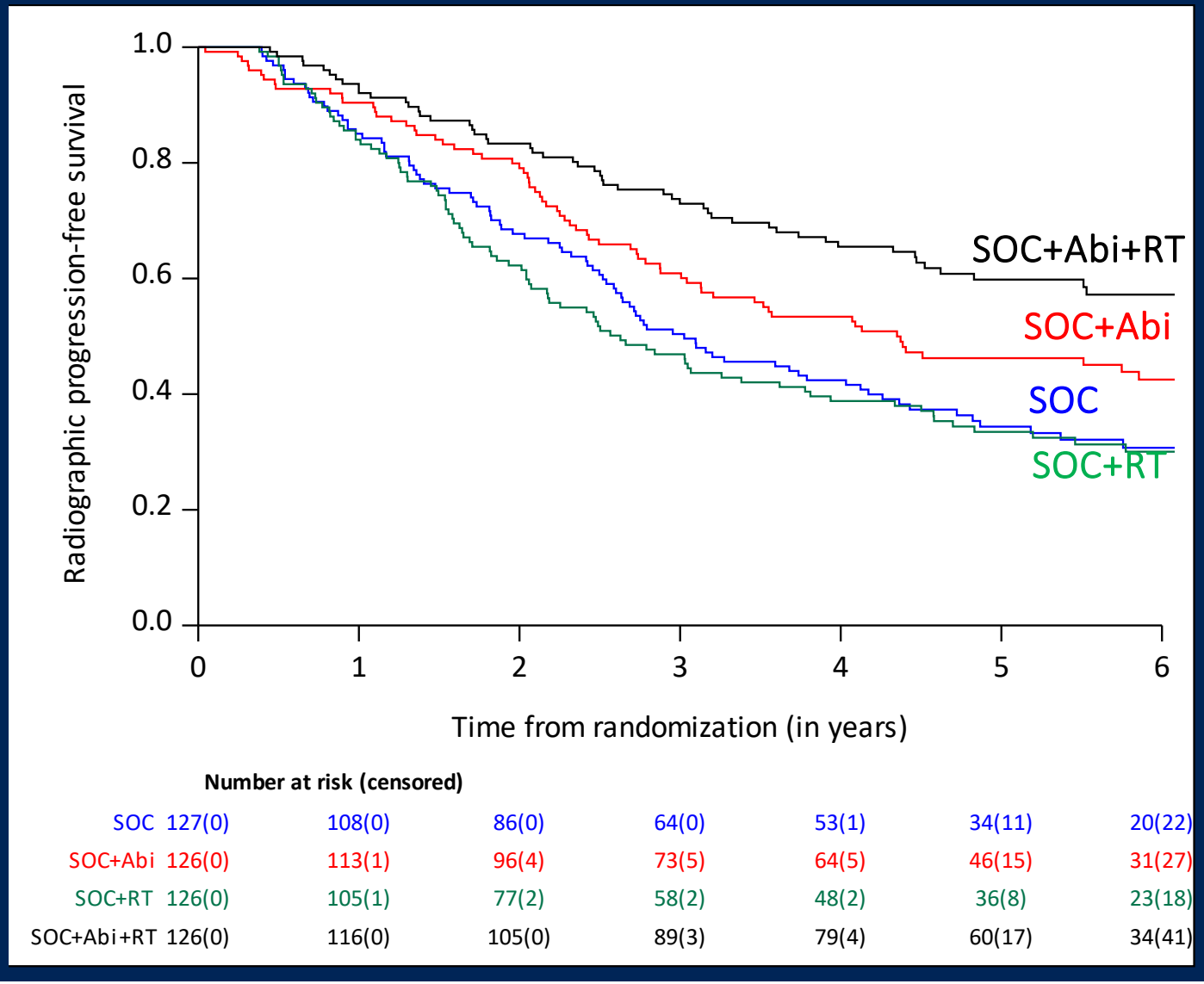
Permitted
ADT ≤ 3 months

Stratification
ECOG PS (0 vs 1-2)
Metastatic sites (LN vs bone vs visceral)
Type of castration (orchidectomy vs LHRH agonist vs LHRH antagonist)
Docetaxel (yes vs no)



ECOG PS, Eastern Cooperative Oncology Group performance status

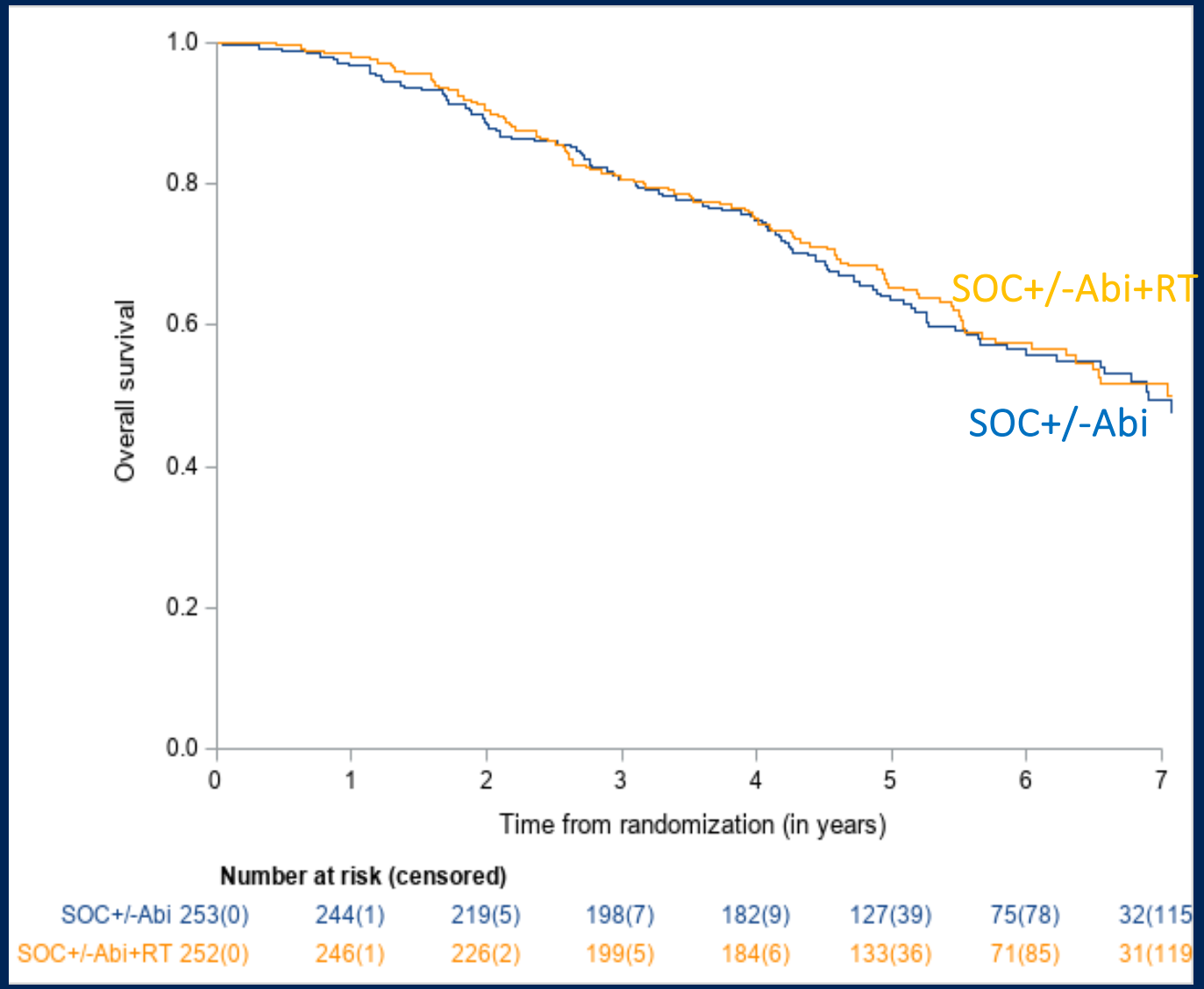
rPFS (low volume population)



	SOC (n=127)	SOC+RT (n=126)	SOC+Abi (n=126)	SOC+Abi+RT (n=126)
Median, ys. (99.9% CI)	3.0 (2.3-4.8)	2.6 (1.7-4.6)	4.4 (2.5-7.3)	7.5 (4,0-NE)
Events, n.	87	89	74	55
HR (99.9% CI)*	Ref	1.11 (0.67-1.84)	0.76 (0.45-1,28)	0.50 (0.28-0.88)
Global p-value	<0.0001			
HR (99.9% CI)*	Ref	1.08 (0.65-1.80)	Ref	0.65 (0.36-1.19)
P-values in arms w/wo Abi	0.61		0.02	

*Adjusted on stratification factors (PS, type of castration, docetaxel)

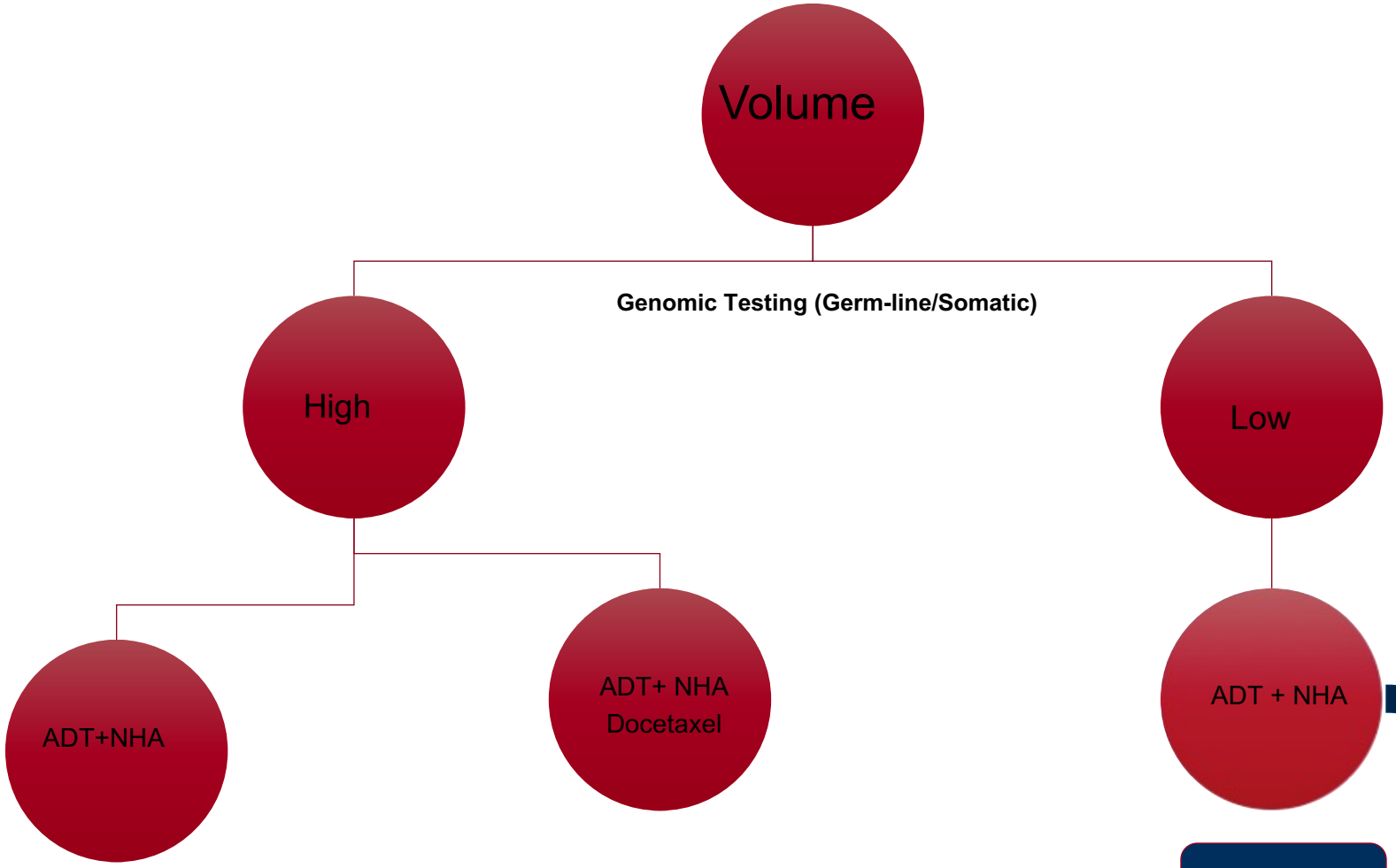
OS (low volume population)



	SOC+/Abi (n=253)	SOC+/- Abi++RT (n=252)
Median, ys. (95.1% CI)	6.9 (5,9-7,5)	7,5 (6-NE)
Events, n	111	104
HR	Ref	0,98 (0.74-1.28)
p-value	0.86	

*Adjusted on Abitaerone and stratification factors (PS, type of castration, docetaxel)

JG's Simple Approach



- Timing for RT to primary?
- Definition of Oligo
- Who in the Oligo Met setting?
- Length of Rx for those who go off?

ADT-Free Survival Longer with Metastasis-Directed Therapy than with Surveillance Alone for Oligorecurrent Prostate Cancer

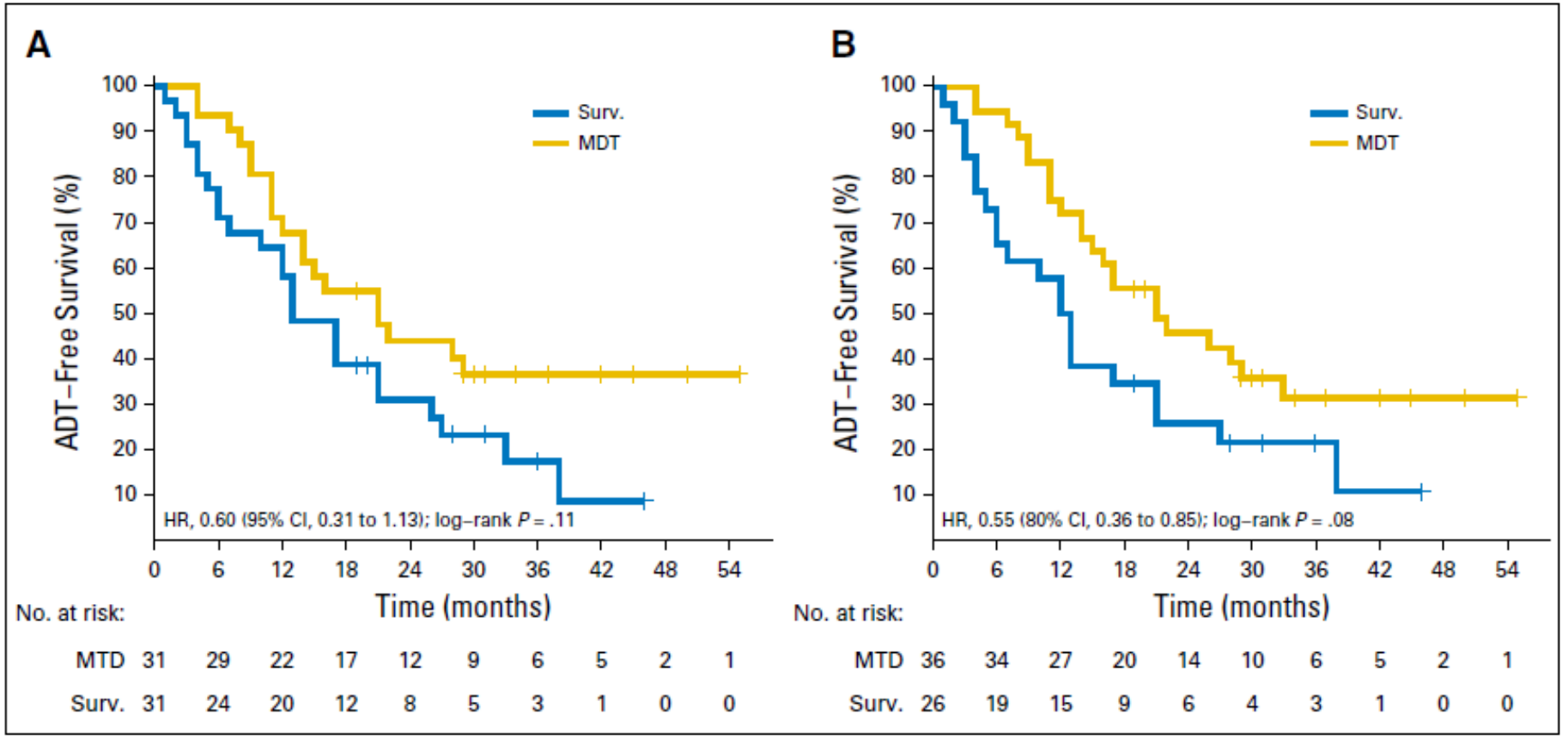


Fig 2. Kaplan-Meier plot comparing androgen deprivation therapy (ADT)–free survival of surveillance versus metastasis-directed therapy (MDT) for (A) the intention-to-treat analysis and (B) the per-protocol analysis. HR, hazard ratio; Surv., surveillance.

- Median ADT-free survival: 21 months with SABR vs 13 months

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SCHOOL OF MEDICINE CASE WESTERN RESERVE UNIVERSITY

Ost P et al. J Clin Oncol 36:446-453.

Summary Statements

Defining Volume of Disease is a MUST

- Independent of what definition one uses
- Emerging imaging techniques are an issue since existing trials did not use them
- I still would treat when I see objective disease – despite of imaging used
- Biology/Biology – *DNA Def/HRR/PTEN/RB loss/SPOP*

Low-volume: ADT + any of the oral NHAs

- If primary in place and untreated – RT to prostate
- Main question is management of Oligometastatic sites (definition/timing/length/SBRT?)

High-volume: ADT + NHA vs. ADT + NHA + Docetaxel

- When chemo is selected – Docetaxel alone is not the SOC!
- No role for RT to primary tumor, though predict a significant proportion of them would need palliative local therapy over time

Summary Statements

P = Prolong

Prolong survival

P = Prevent

Prevent Progression – Serologic/Radiographic Symptomatic

P & M = Protect and Maintain

Quality of Life (PROs)

THANK YOU