Biochemical failure post-local treatment for prostate cancer

Karim Fizazi, MD, PhD

Institut Gustave Roussy

Villejuif, France

Disclosure

Participation to advisory boards/honorarium for:

Amgen, Astellas, Astrazeneca, Bayer, Clovis, Curevac, Essa, Genentech, Janssen, MSD, Orion, Sanofi

Biochemical relapses

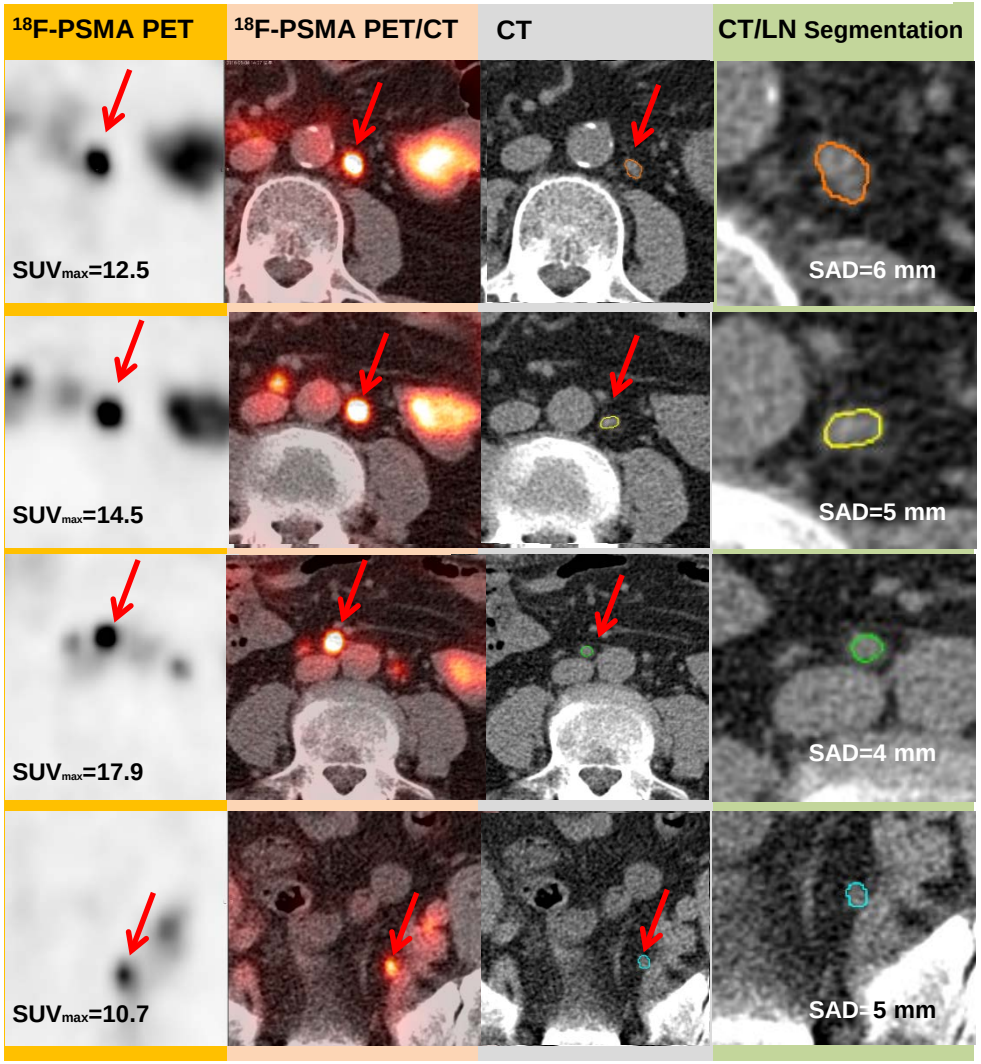
- Définition:
  - PSA>0,2 ng/mL after prostatectomy
  - PSA rise > 2 ng/mL beyond the nadir after radiotherapy

- Frequent, associated with anxiety

- Bone scan and CT scan not recommended
- Role of next generation imaging? (WB MRI, PET-choline, PET-PSMA) PSA> 0.5-2 ng/mL

PSMA-Pet: detection of 17 lymph nodes with diameter below the morphological detection limit; Median 0.46mm; Max 0.66; Min 0.32

a



Little radioactivity in the bladder
Cleavage of the tracer in the kidneys
Renal storage of the chelator

Giesel et al., Clinical Genitourinary Cancer 2017

EAU - ESTRO - ESUR - SIOG Guidelines on

Prostate Cancer

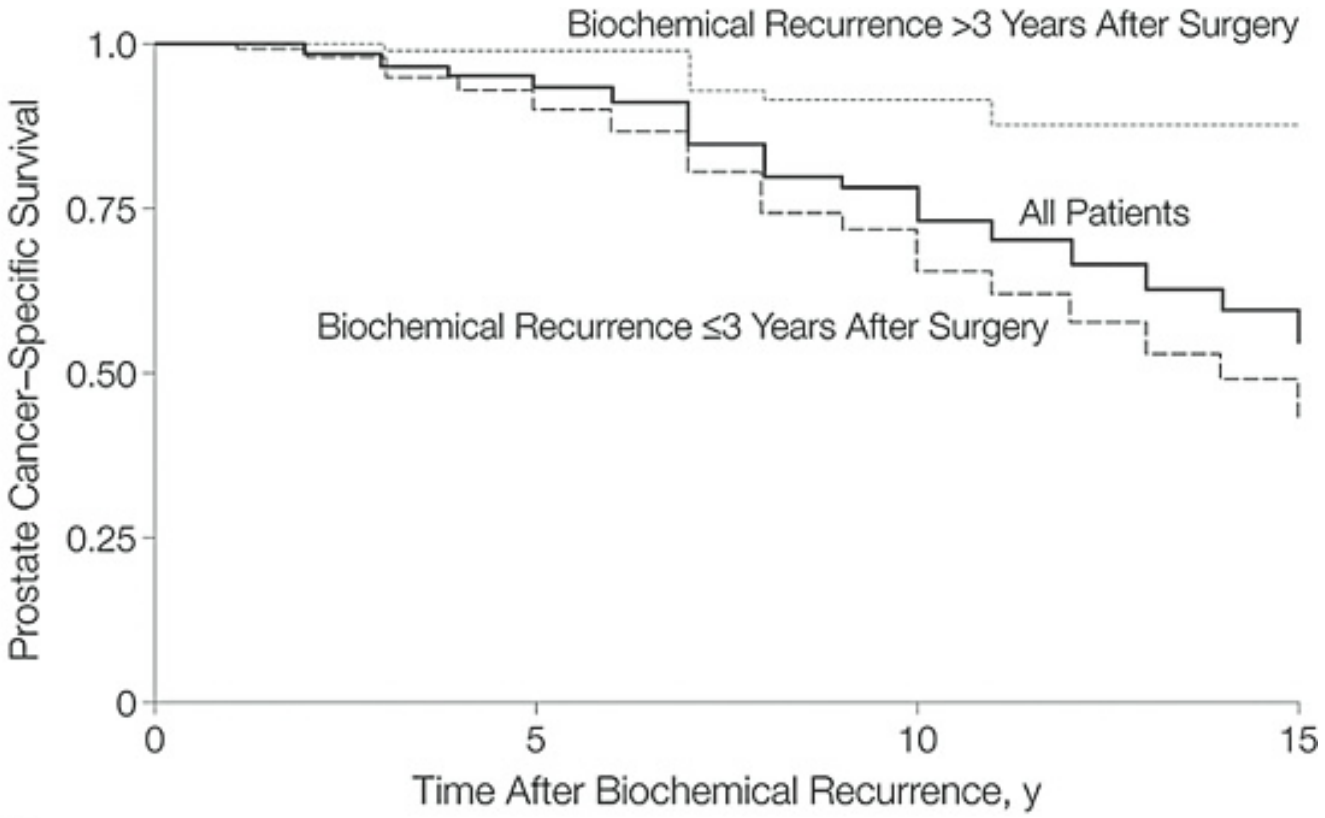
Prostate-specific antigen (PSA) recurrence after radical prostatectomy	LE	Strength rating
Perform imaging only if the outcome will influence subsequent treatment decisions.		Strong
If the PSA level is ≥ 1 ng/mL, perform a prostate-specific membrane antigen positron emission tomography computed tomography (PSMA PET/CT), if available, or a choline PET/CT imaging otherwise.	2b	Weak

What Is the Natural History of Patients Who Relapse After Local Therapy?

- 304 men relapsed after surgery
- No hormones until (+) bone scan
- Time to PSA rise, Gleason, PSADT were predictors of survival

Pound *JAMA*.1999.

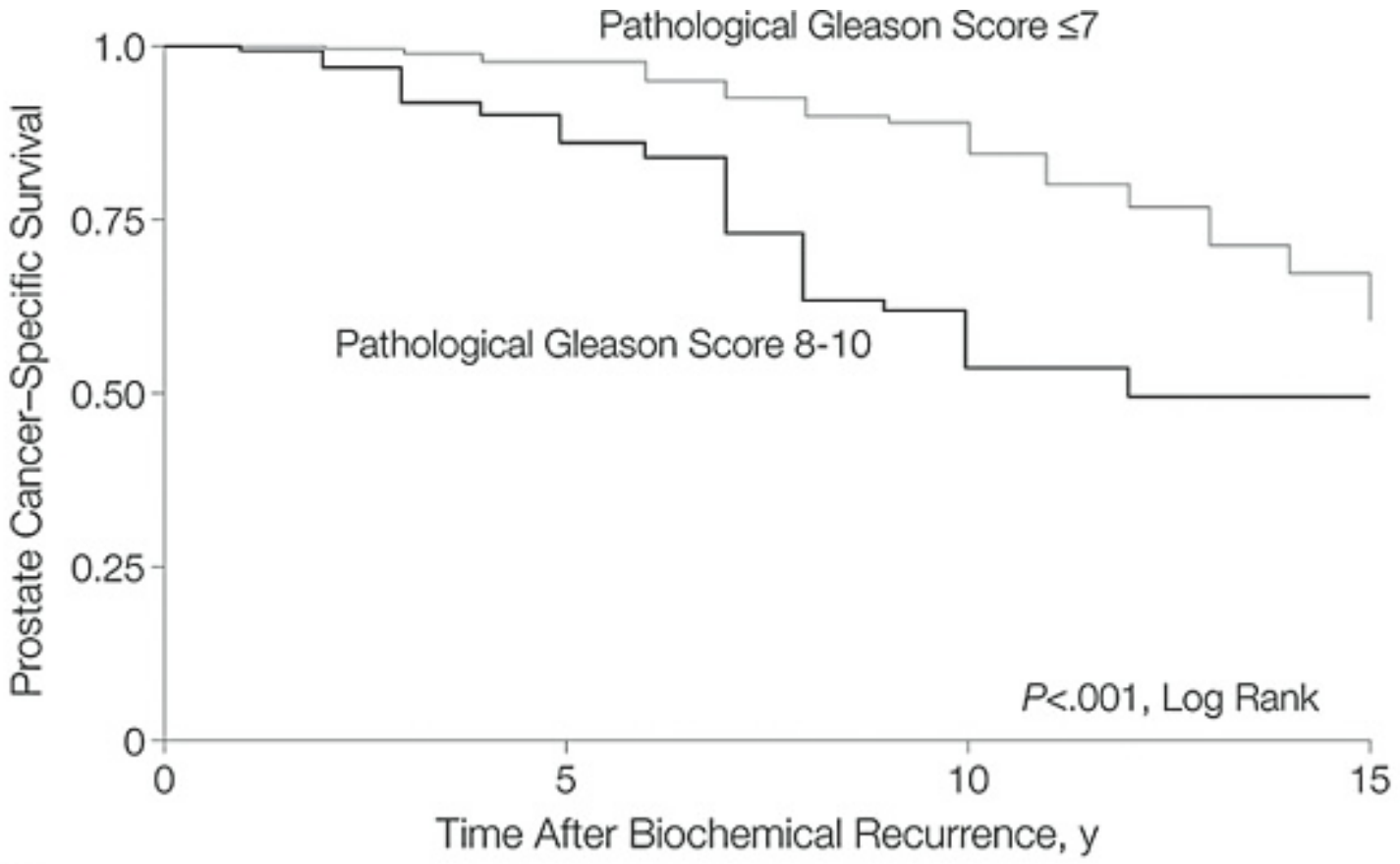
Specific Survival by time from RP to PSA relapse



No. at Risk				
All Patients	379	259	92	12
Time From Surgery to Biochemical Recurrence, y				
>3	135	96	30	3
≤3	244	163	62	9

Freedland SJ, et al. *JAMA* 2005; 294: 433-439

Specific Survival by Gleason score

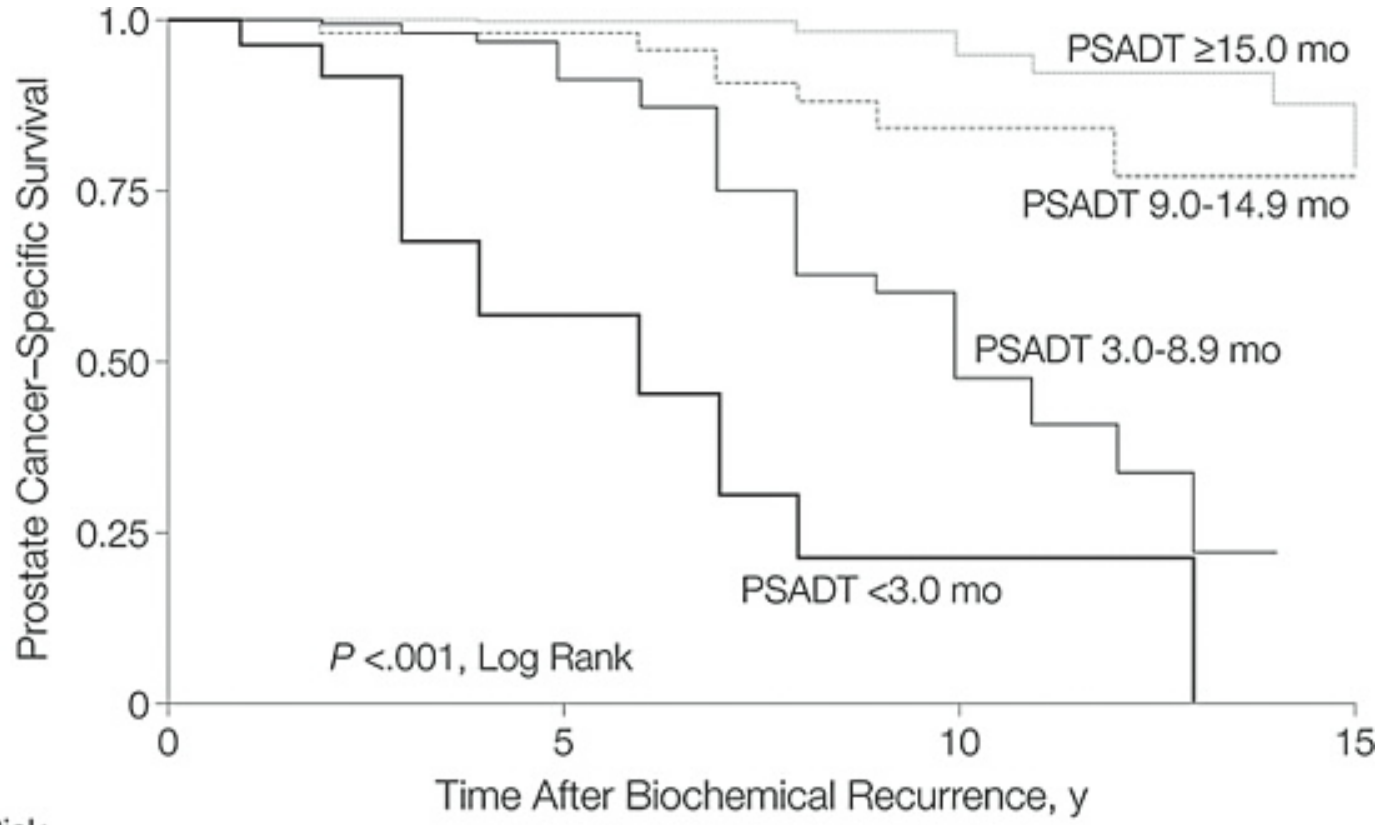


No. at Risk

Pathological Gleason Score				
≤7	252	166	68	10
≥8	127	93	24	2

Freedland SJ, et al. *JAMA* 2005; 294: 433-439

Specific Survival by PSA doubling time (PSADT)



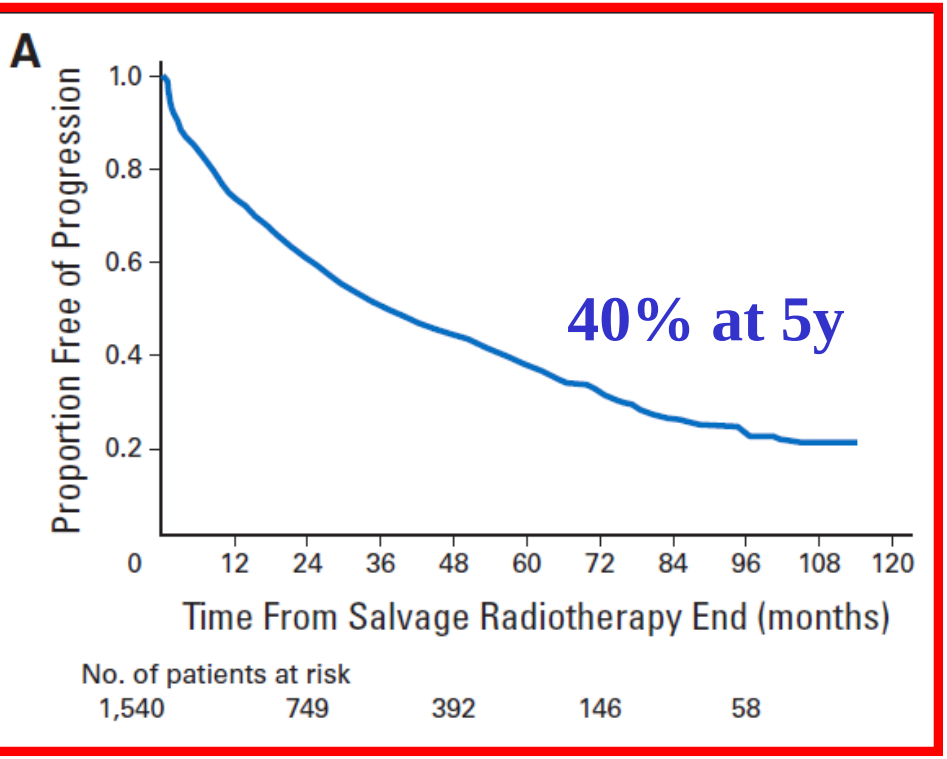
No. at Risk PSADT, mo				
<3.0	23	10	2	0
3.0-8.9	119	85	19	0
9.0-14.9	79	51	19	3
≤15	158	113	52	9

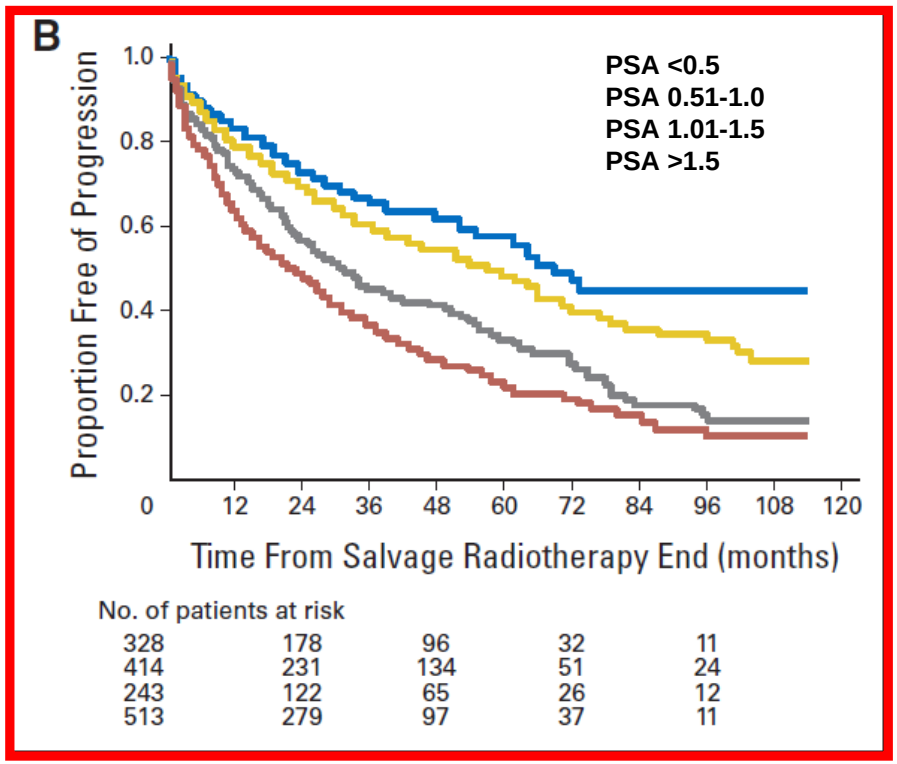
Freedland SJ, et al. *JAMA* 2005; 294: 433-439

Should a second local treatment be used in case of PSA relapse?

Predicting the Outcome of Salvage Radiation Therapy for Recurrent Prostate Cancer After Radical Prostatectomy

Andrew J. Stephenson, Peter T. Scardino, Michael W. Kattan, Thomas M. Pisansky, Kevin M. Slawin, Eric A. Klein, Mitchell S. Anscher, Jeff M. Michalski, Howard M. Sandler, Daniel W. Lin, Jeffrey D. Forman, Michael J. Zelefsky, Larry L. Kestin, Claus G. Roehrborn, Charles N. Catton, Theodore L. DeWeese, Stanley L. Liauw, Richard K. Valicenti, Deborah A. Kuban, and Alan Pollack





J Clin Oncol 35:2035-2041, 2007

Amsterdam UMC
Universitair Medische Centra

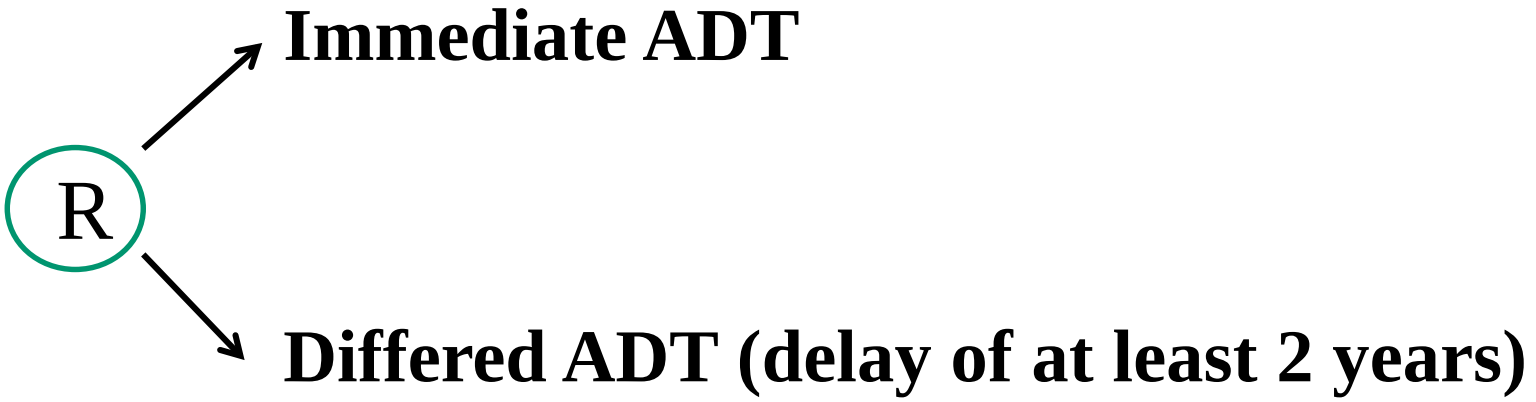
ESMO

Should we used salvage ADT in men with PSA relapses?

Timing of androgen-deprivation therapy in patients with prostate cancer with a rising PSA (TROG 03.06 and VCOG PR 01-03 [TOAD]): a randomised, multicentre, non-blinded, phase 3 trial

Gillian M Duchesne, Henry H Woo, Julie K Bassett, Steven J Bowe, Catherine D'Este, Mark Frydenberg, Madeleine King, Leo Ledwich, Andrew Loblaw, Shawn Malone, Jeremy Millar, Roger Milne, Rosemary G Smith, Nigel Spry, Martin Stockler, Rodney A Syme, Keen Hun Tai, Sandra Turner*

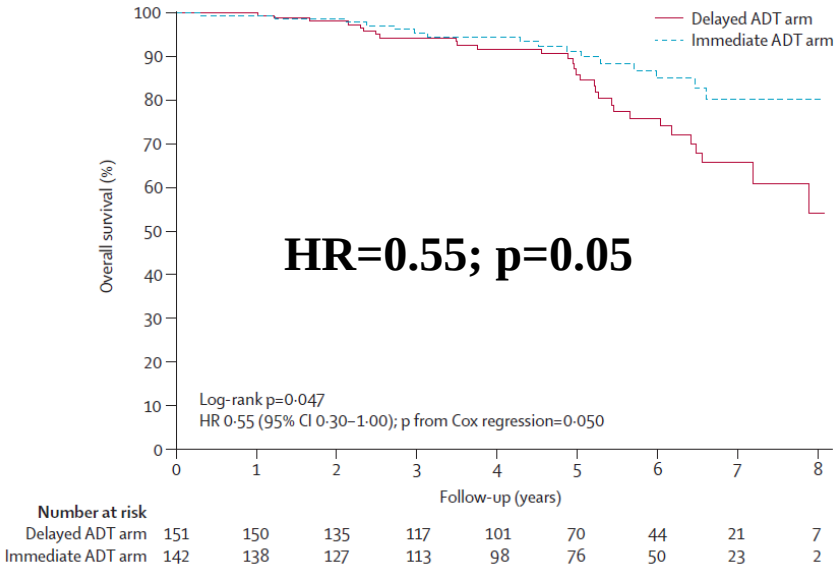
- 293 men:
  - 261 with a rising PSA post-local treatment
  - 32 not candidate for local treatment
- **Superiority trial** (hypothesis=immediate is better)



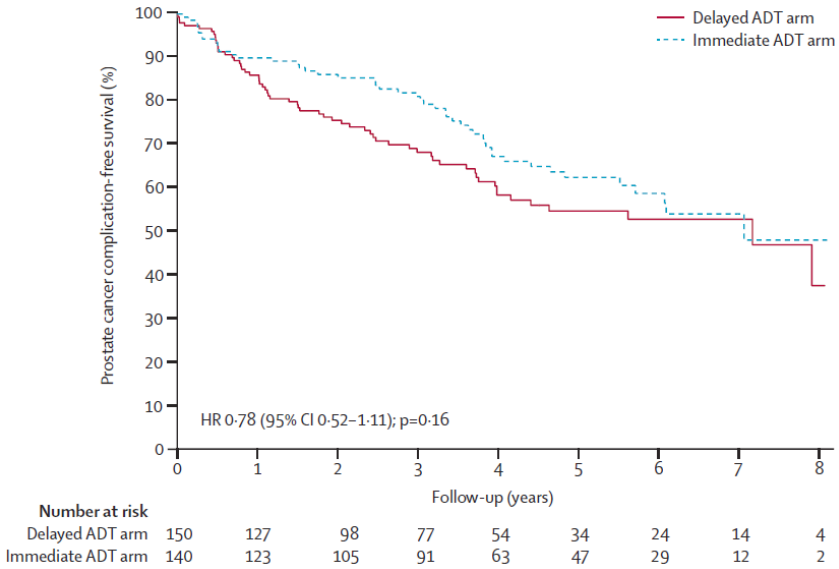
Early vs differed ADT

Median follow-up: 5 years

Overall Survival (Primary)



Time to prostate cancer complication

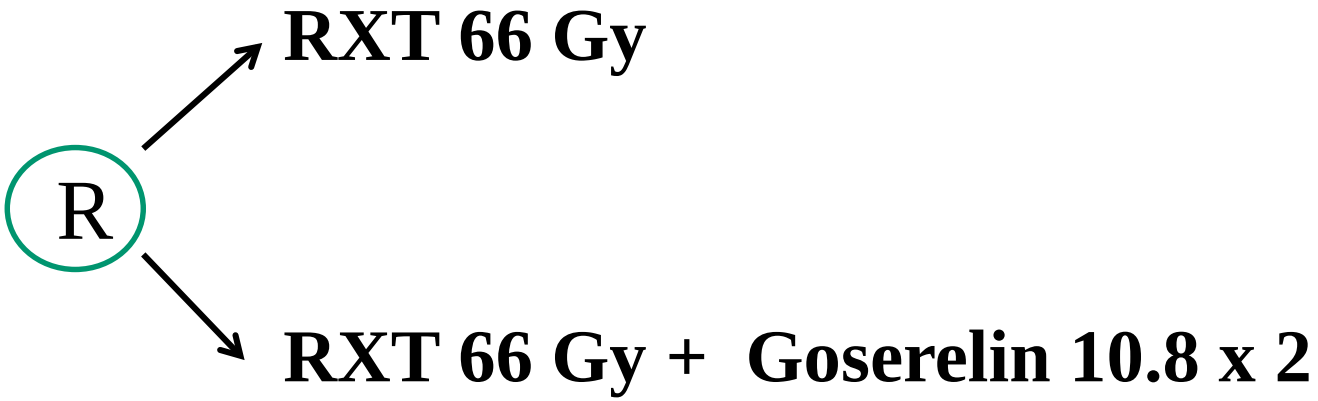


Duchesne GM, Lancet Oncol 2016

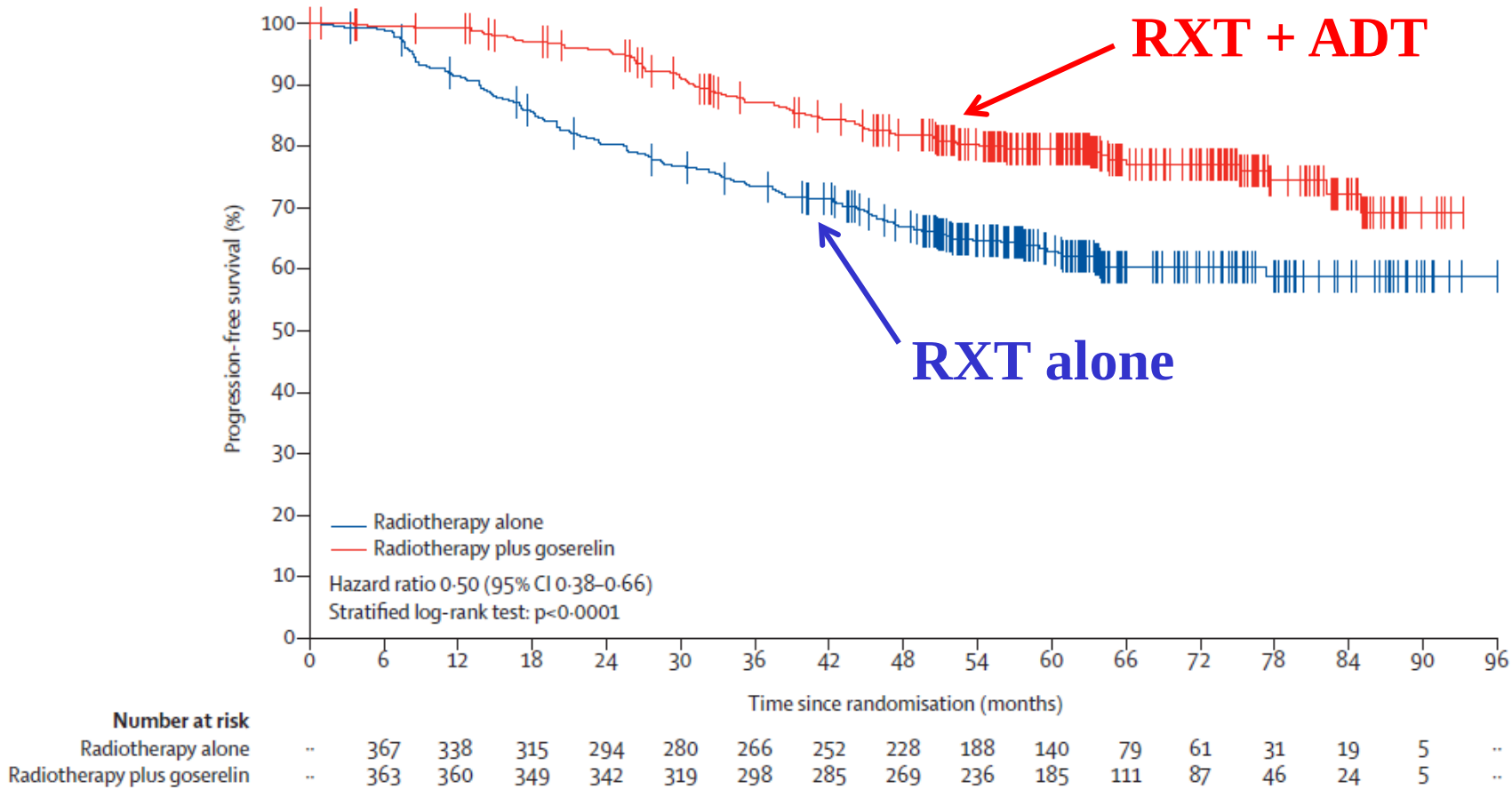
Salvage radiotherapy with or without short-term hormone therapy for rising prostate-specific antigen concentration after radical prostatectomy (GETUG-AFU 16): a randomised, multicentre, open-label phase 3 trial

Christian Carrie, Ali Hasbini, Guy de Laroche, Pierre Richaud, Stéphane Guerif, Igor Latorzeff, Stéphane Supiot, Mathieu Bosset, Jean-Léon Lagrange, Véronique Beckendorf, François Lesaunier, Bernard Dubray, Jean-Philippe Wagner, Tan Dat N'Guyen, Jean-Philippe Suchaud, Gilles Créhange, Nicolas Barbier, Muriel Habibian, Céline Ferlay, Philippe Fourneret, Alain Ruffion, Sophie Dussart

- 743 men with pT2-4 post-RP, PSA 0.2-2 ng/mL
- **Superiority trial**



Relapse-free survival



Carrie C, Lancet Oncol 2016; 17: 747-56

RXT +/- Bicalutamide for rising PSA post-Prostatectomy: OS

3 trials supporting earlier use of ADT in biochemical failures post-local treatment.

PSA doubling time to help decision making?

Patients at Risk															
Placebo+RT	376	372	368	359	350	332	319	307	294	280	262	240	203	130	71	25
AAT+RT	384	382	376	368	362	347	337	326	308	294	280	259	223	151	78	32

NRG ONCOLOGY™

Shipley W, NEJM 2017

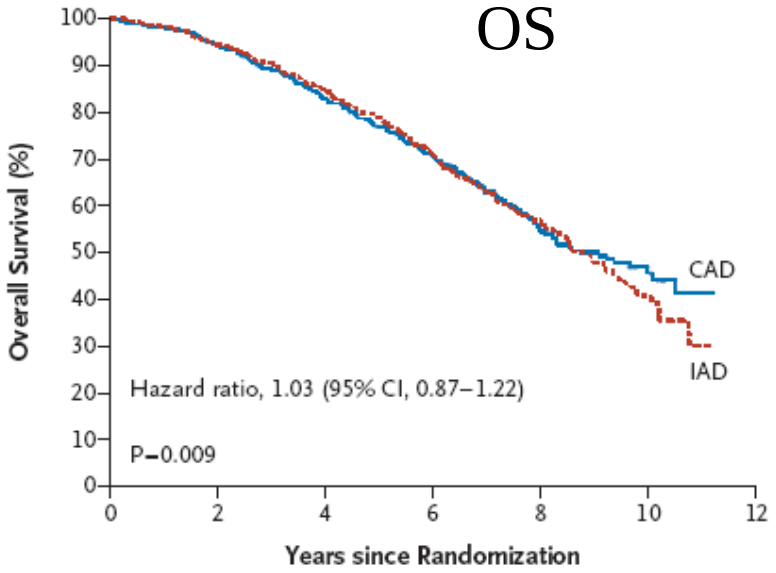
Intermittent vs Continuous ADT for PSA relapses: The NCIC trial

n= 1386 with PSA progression after RXT (primary or salvage)
PSA> 3

R → Continuous ADT
R → Intermittent ADT

Intermittent ADT:
- 8 months ADT
- Stopped if PSA<4
- Recycled when PSA > 10

OS



I-ADT better for physical function, fatigue, urinary problems, hot flashes, libido, and erectile function

Crook J, N Engl J Med 2012; 367

Should we used:

- pelvic radiation
- salvage ADT

in men with PSA relapses?

NRG Oncology/RTOG 0534/SPPORT Trial Design

STRATIFY	**SV Involvement** 1. No 2. Yes **Prostatectomy Gleason Score** 1. Gleason ≤ 7 2. Gleason 8-9 **Pre-Radiotherapy PSA** 1. PSA ≥ 0.1 and ≤ 1.0 ng/mL 2. PSA > 1.0 and < 2.0 ng/mL **Pathology Stage** 1. pT2 and margin negative 2. All others	**RANDOMIZE**	**Arm 1: PBRT Alone** PBRT 64.8-70.2 Gy **Arm 2: PBRT + STAD** PBRT 64.8-70.2 Gy + STAD for 4-6 months beginning 2 months before RT **Arm 3: PLNRT + PBRT + STAD** PLNRT to 45 Gy and PBRT to 64.8-70.2 Gy,+ STAD for 4-6 months beginning 2 months before RT

SV = seminal vesicle; RT = radiation therapy; PBRT = prostate bed RT; PLNRT = pelvic lymph node RT; STAD = neoadjuvant and concurrent short-term androgen deprivation

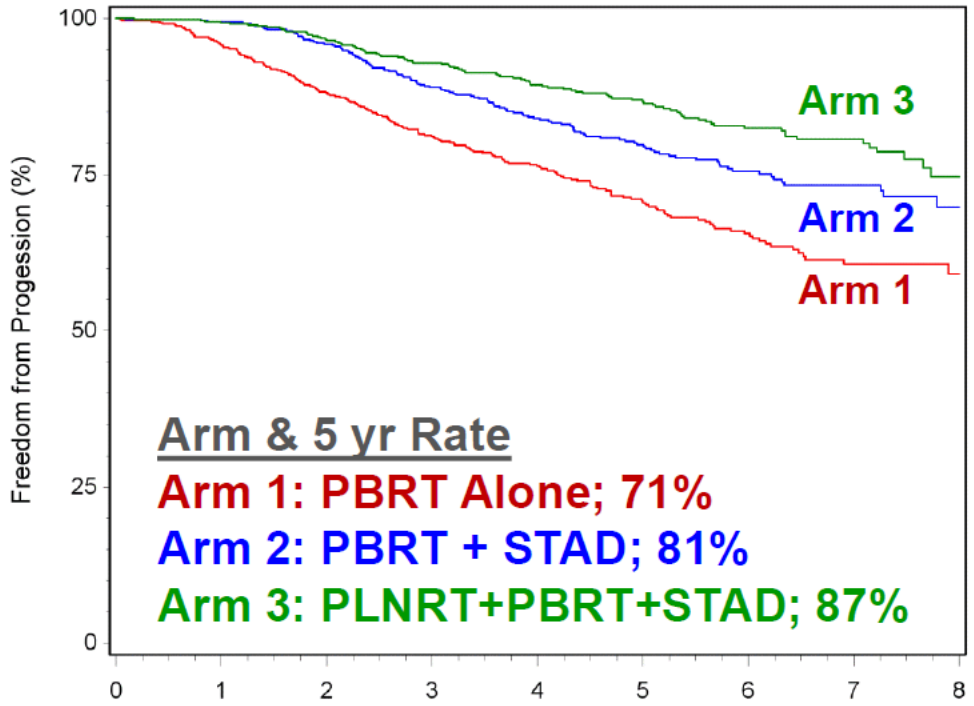
Primary endpoint: FFP at 5 years

Failure defined as first occurrence of:

- PSA ≥ Nadir+2 ng/mL
- Clinical progression (local, regional or distant)
- Death due to any cause

Pollack I, ASTRO 2018

FFP: All eligible patients (1,792)



No. at Risk									
PBRT Alone	573	529	480	417	334	243	165	89	37
PBRT+NC-STAD	585	559	532	467	366	275	179	94	39
PLNRT+PBRT+NC-STAD	576	563	540	488	399	315	209	126	52

5 yr Rate Comparison

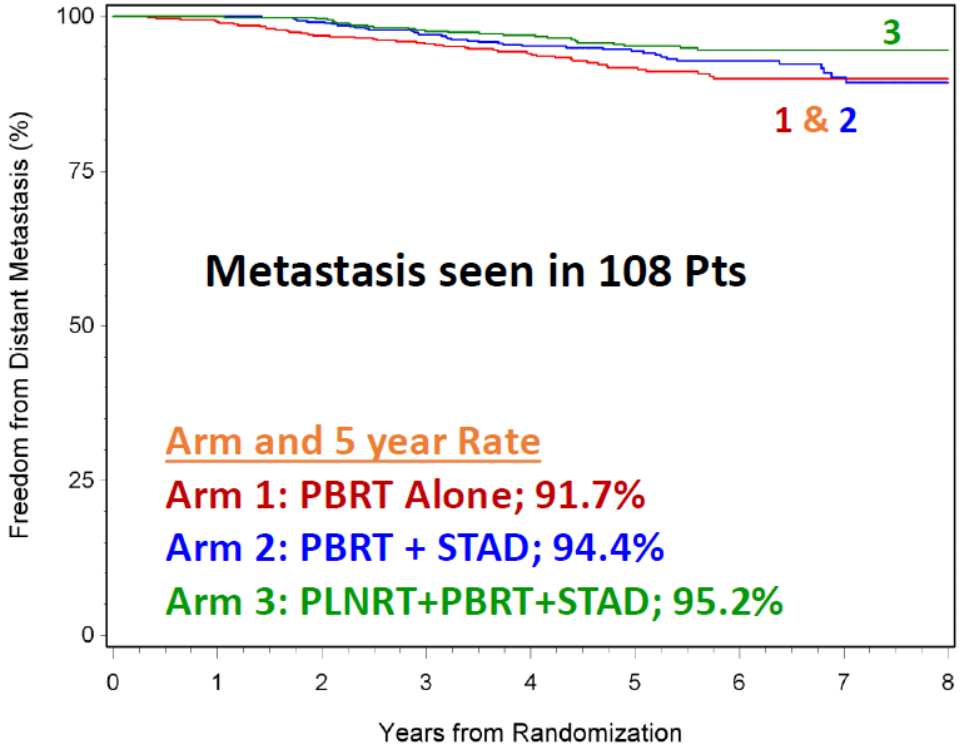
Arm 3 vs Arm 1: p<0.0001
Arm 2 vs Arm 1: p<0.0001
Arm 3 vs Arm 2: p=0.0039

HRs and 97.5% CIs

3 vs 1: 0.45 (0.34-0.61)
2 vs 1: 0.62 (0.47-0.82)
3 vs 2: 0.71 (0.52-0.98)

Pollack I, ASTRO 2018

Freedom from distant metastasis: All eligible patients



No. at Risk									
PBRT Alone	573	546	522	482	398	302	214	123	54
PBRT+NC-STAD	585	562	547	499	405	315	213	111	48
PLNRT+PBRT+NC-STAD	576	565	551	502	417	330	220	134	56

5 yr Rate Comparison

Arm 3 vs Arm 1: p=0.014

Arm 2 vs Arm 1: p=0.05

Arm 3 vs Arm 2: p=0.28

HRs and 97.5% CIs

3 vs 1: 0.52 (0.30-0.92)

2 vs 1: 0.81 (0.49-1.33)

3 vs 2: 0.64 (0.36-1.14)

No statistically significant differences in OS

Pollack I, ASTRO 2018

Conclusion: Biochemical failures

- Long delay between PSA relapse and clinical symptoms
- Prognostic factors, mostly:
  - Gleason ≥ 8
  - PSA doubling time < 9 mo

- Conventional imaging useless
- Pet-PSMA likely to change the game (local relapses, oligo-mets)

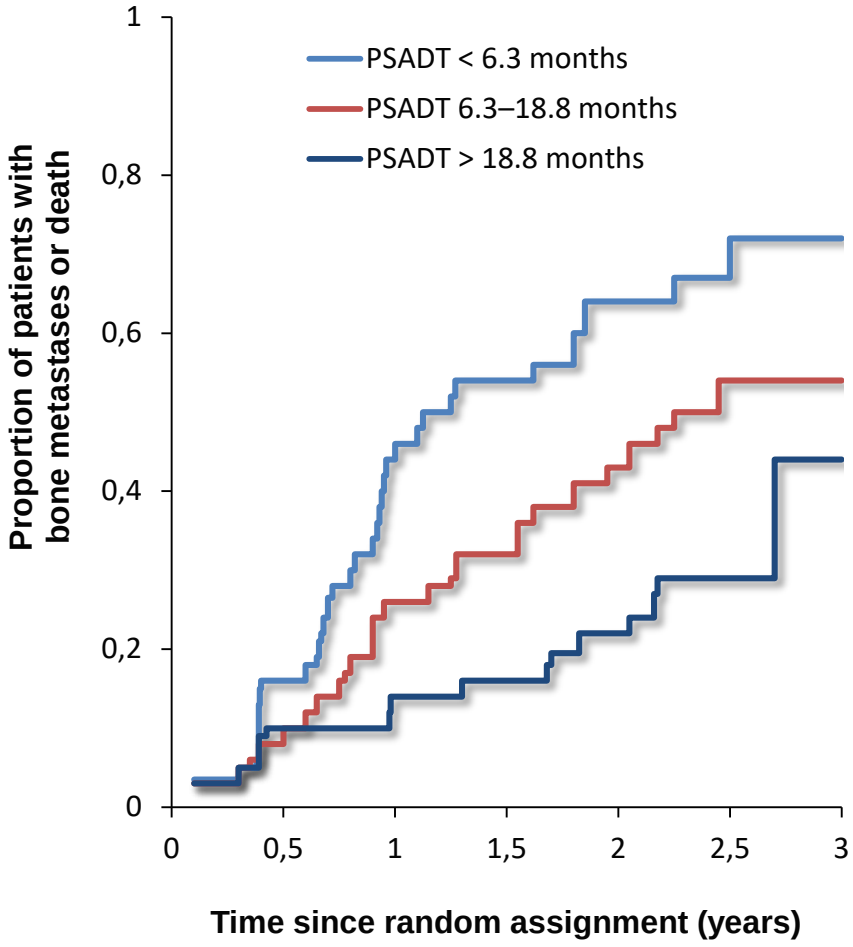
Conclusion:
Treatment of Biochemical failure

- Radiotherapy (prostate bed + pelvis) and short-term ADT likely to become standard of care post-RP
- If relapse post-RXT, intermittent ADT as standard treatment if short PSA DT ?
- All indications to be balanced with co-morbidities and life expectancy

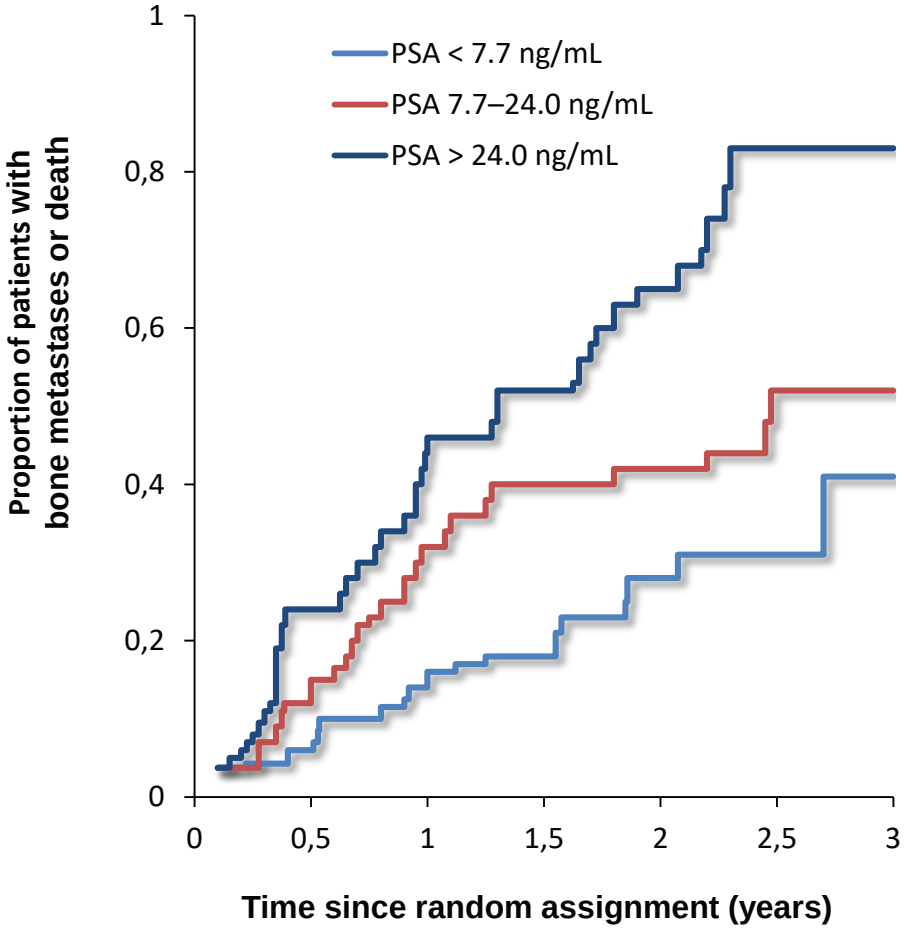
CRPC M0: Definition

- A man with prostate cancer:
  - Who often had a previous local treatment
  - PSA relapse and then received ADT (or ADT together with primary local Tx)
  - Who is now **progressing by PSA while on ADT**
- **No detectable metastases** on conventional imaging (bone scan, CT scan)
- **Testosterone at castrated levels**

High-risk nmCRPC patients, at risk of metastases or death, can be readily identified



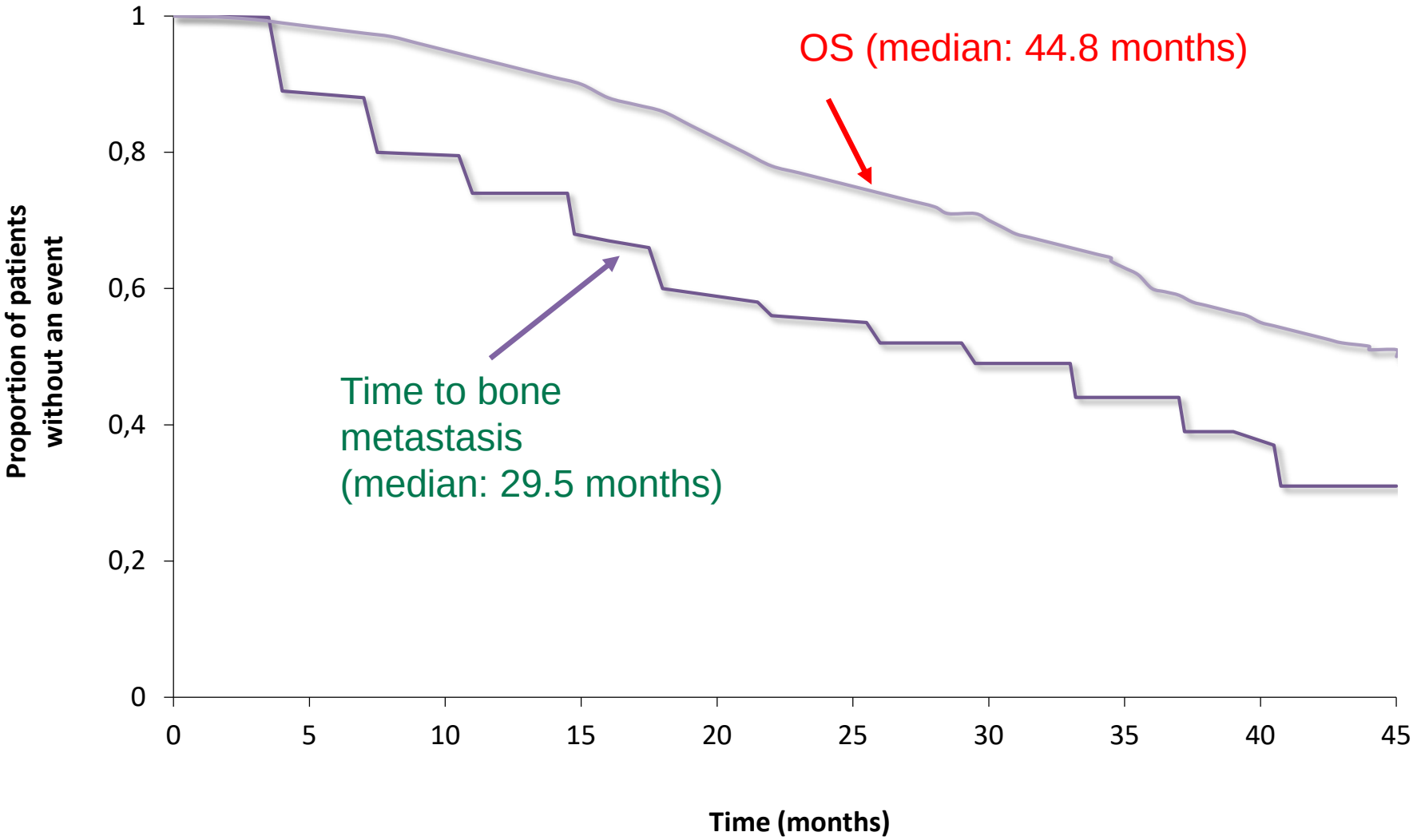
Time to bone metastases or death by PSA doubling time (PSADT)



Time to bone metastases or death by PSA level

Smith MR, et al. J Clin Oncol. 2005;23:2918-25.

High-risk nmCRPC is a deadly cancer

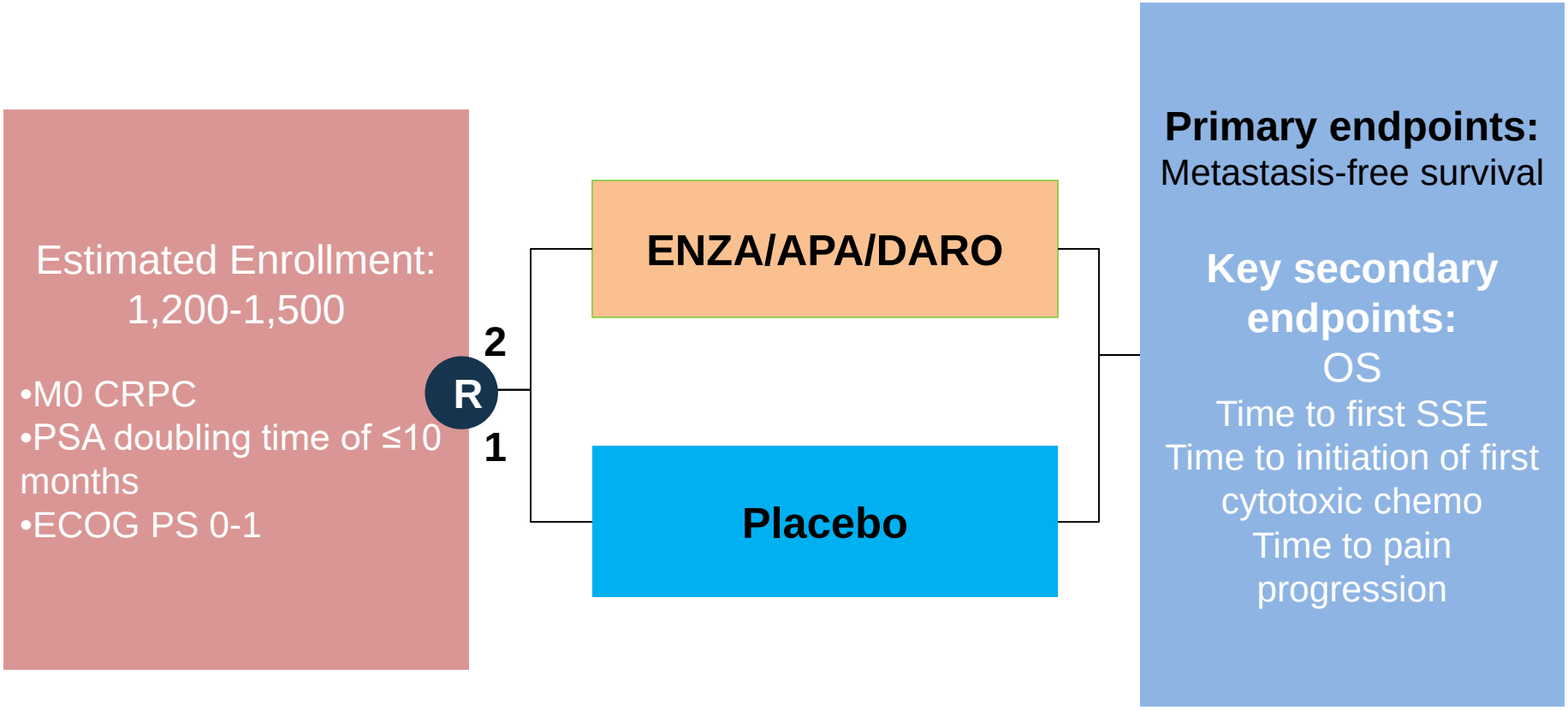


All patients had PSA ≥ 8 and/or PSADT ≤ 10 months at baseline.
OS, overall survival

Smith MR, et al. Lancet. 2012;379:39-46

PROSPER/SPARTAN/ARAMIS Study Design:
in High-Risk M0 CRPC

Similar trials with Enzalutamide (Prosper), Apalutamide (Spartan) and Darolutamide (Aramis)

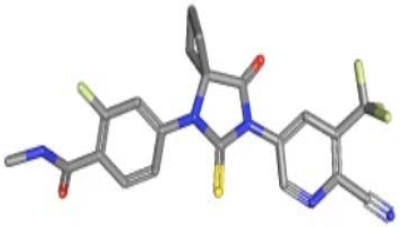


K Fizazi, personal slide

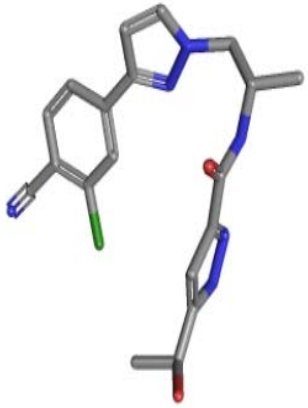
Background: next-generation androgen receptor inhibitors

Enzalutamide

Apalutamide



Darolutamide

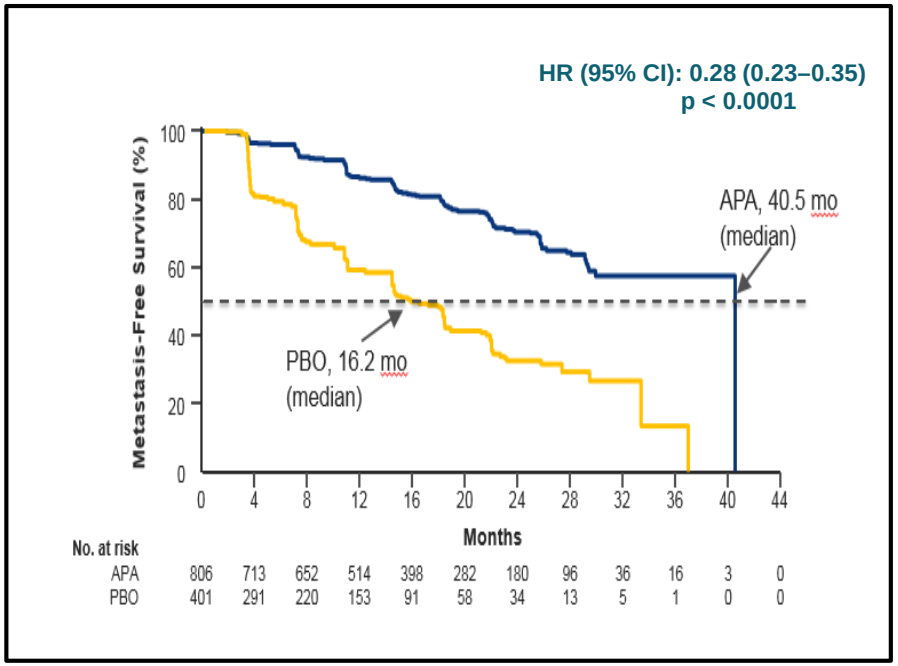


- Darolutamide is structurally distinct from apalutamide and enzalutamide
- Low blood–brain barrier penetration[1,2]
- This could result in less CNS toxicity and improved tolerability

1. Zurth C et al. J Clin Oncol 2018;36:abstr 345. 2. Sandmann S et al. ASCO GU 2019; Poster abstr 156.
Images from PubChem database: https://pubchem.ncbi.nlm.nih.gov/

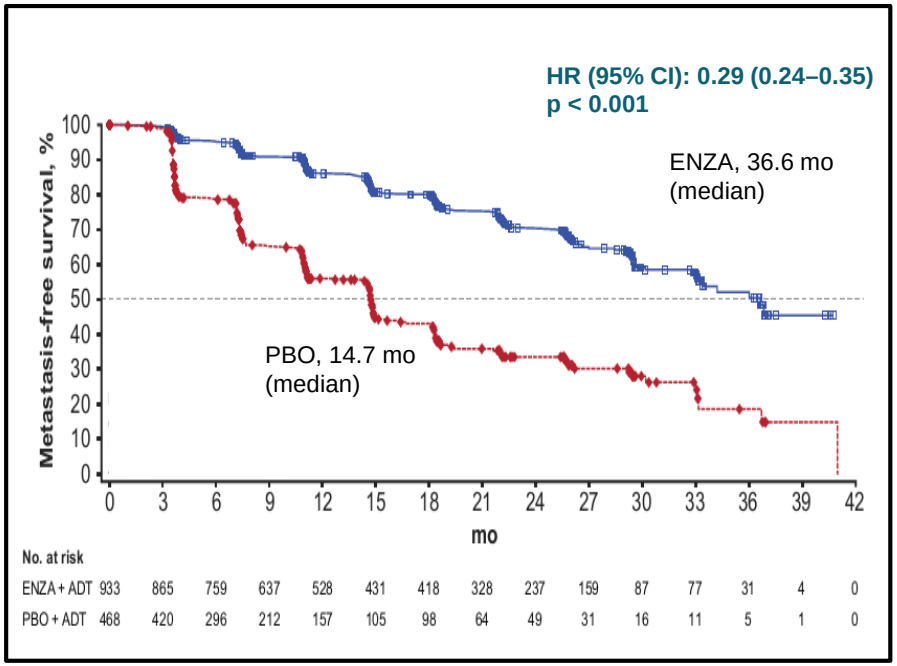
SPARTAN and PROSPER: primary endpoint – MFS

SPARTAN



- 72% reduction of distant progression or death
- Median MFS: APA 40.5 vs PBO 16.2 months
- 24-month additional MFS benefit

PROSPER



- 71% reduction of distant progression or death
- Median MFS: ENZA 36.6 vs PBO 14.7 months
- 22-month additional MFS benefit

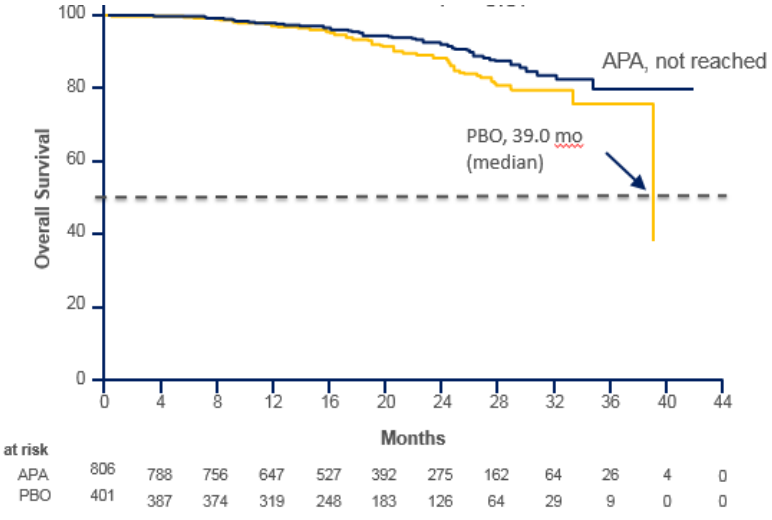
CI, confidence interval; HR, hazard ratio; mo, months.

1. Smith MR, et al. N Engl J Med. 2018;378:1408-18.
2. Hussain M, et al. N Engl J Med. 2018;378:2465-74.

SPARTAN and PROSPER secondary endpoint: OS

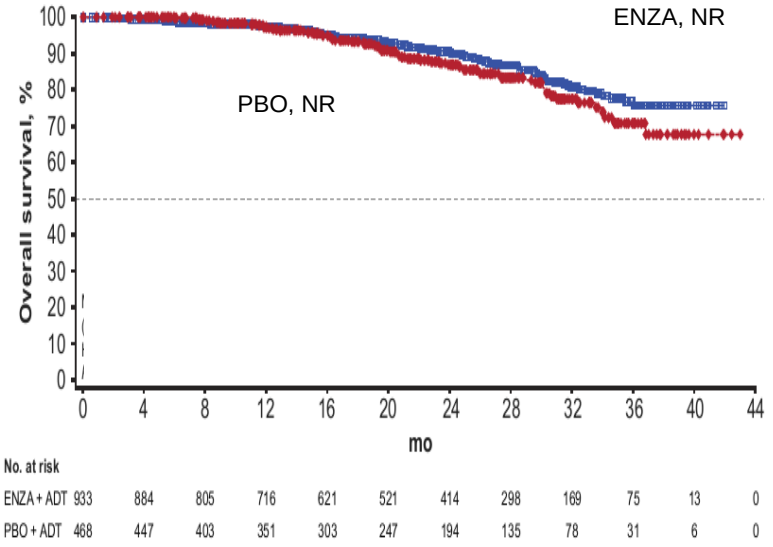
SPARTAN[1] **(Median follow-up: 2 years)** **PROSPER[2]**

HR (95% CI): 0.70 (0.47–1.04)
p = 0.07



- 30% risk reduction of death (HR 0.70; p = 0.07)
- Median OS: APA NR vs PBO 39 months

HR (95% CI): 0.80 (0.58–1.09)
p = 0.1519



- 20% risk reduction of death (HR 0.80; p = 0.15)
- Median OS: ENZA NR vs PBO NR

1. Smith MR, et al. N Engl J Med. 2018;378:1408-18.
2. Hussain M, et al. Oral presentation at ASCO-GU 2018; abstract 3.

SPARTAN and PROSPER: AEs of interest

	SPARTAN[1]		PROSPER[2]	
	APA (n = 803)	**PBO (n = 398)**	**ENZA (n = 930)**	**PBO (n = 465)**
Safety	AE reporting every 4 weeks		AE reporting every 4 months	
AEs (all grades), %				
Fatigue	30.4	21.1	33.0	14.0
Hypertension	24.8	19.8	12.0	5.0
Rash	23.8	5.5		
Falls	15.6	9.0	11.0	4.0
Mental impairment disorders	5.1	3.0	5.0	2.0
Fractures	11.7	6.5		
AEs (grade 3 and 4 only), %				
Fatigue	0.9	0.3	3.0	1.0
Hypertension	14.3	11.8	5.0	2.0
Rash	5.2	0.3		
Falls	1.7	0.8	1.0	1.0
Mental impairment disorders	0	0	<1	0
Seizures	0.2	0	0.3	0
Major CV event	1[a]	1[a]	5.0	3.0
AEs leading to discontinuation, %	11.0	7.0	9.0	6.0
AEs leading to death, n (%)	10 (1.2)	1 (0.3)	32 (3.4)	3 (0.7)

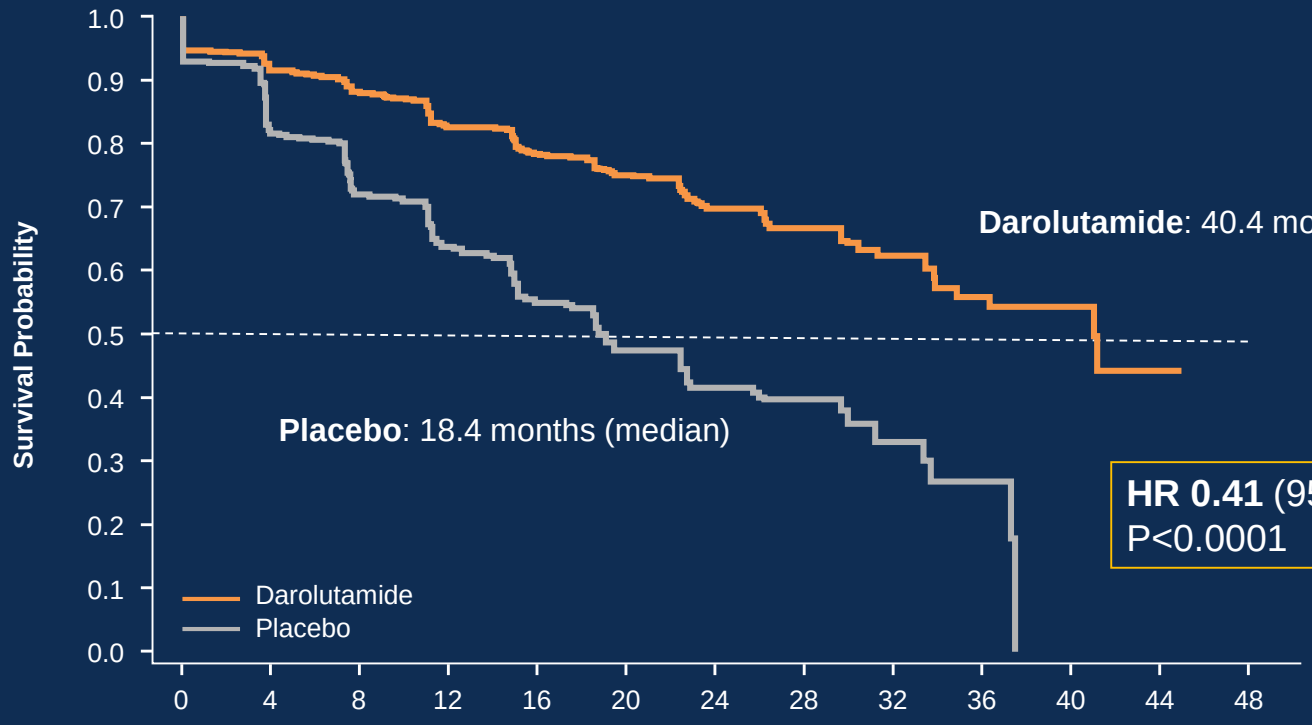
[a]Ischaemic event. AEs in SPARTAN were measured to 28 days after the end of regimen.

AE, adverse event; CV cardiovascular.

1. Smith MR, et al. N Engl J Med. 2018;378:1408-18.
2. Hussain M, et al. N Engl J Med. 2018;378:2465-74.

Primary endpoint: Metastasis-free survival

59% risk reduction of distant metastases or death



Darolutamide: 40.4 months (median)

Placebo: 18.4 months (median)

HR 0.41 (95% CI 0.34–0.50)
P<0.0001

Number of subjects at risk

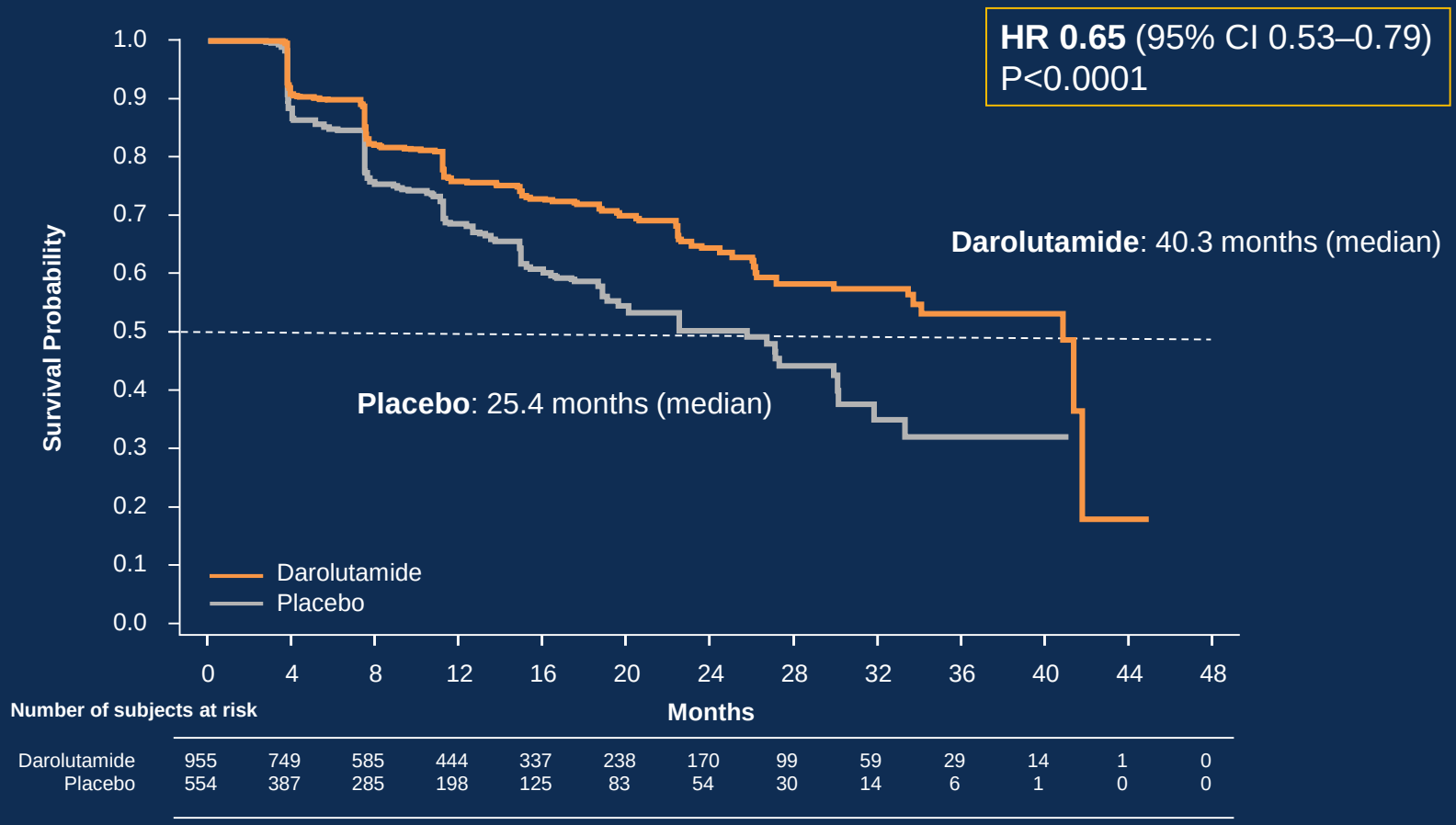
Darolutamide	955	817	675	506	377	262	189	116	68	37	18	2	0
Placebo	554	368	275	180	117	75	50	29	12	4	0	0	0

Median follow-up time at primary analysis was 17.9 months

CI, confidence interval; HR, hazard ratio.

Secondary endpoint: Time to pain progression (BPI-SF)

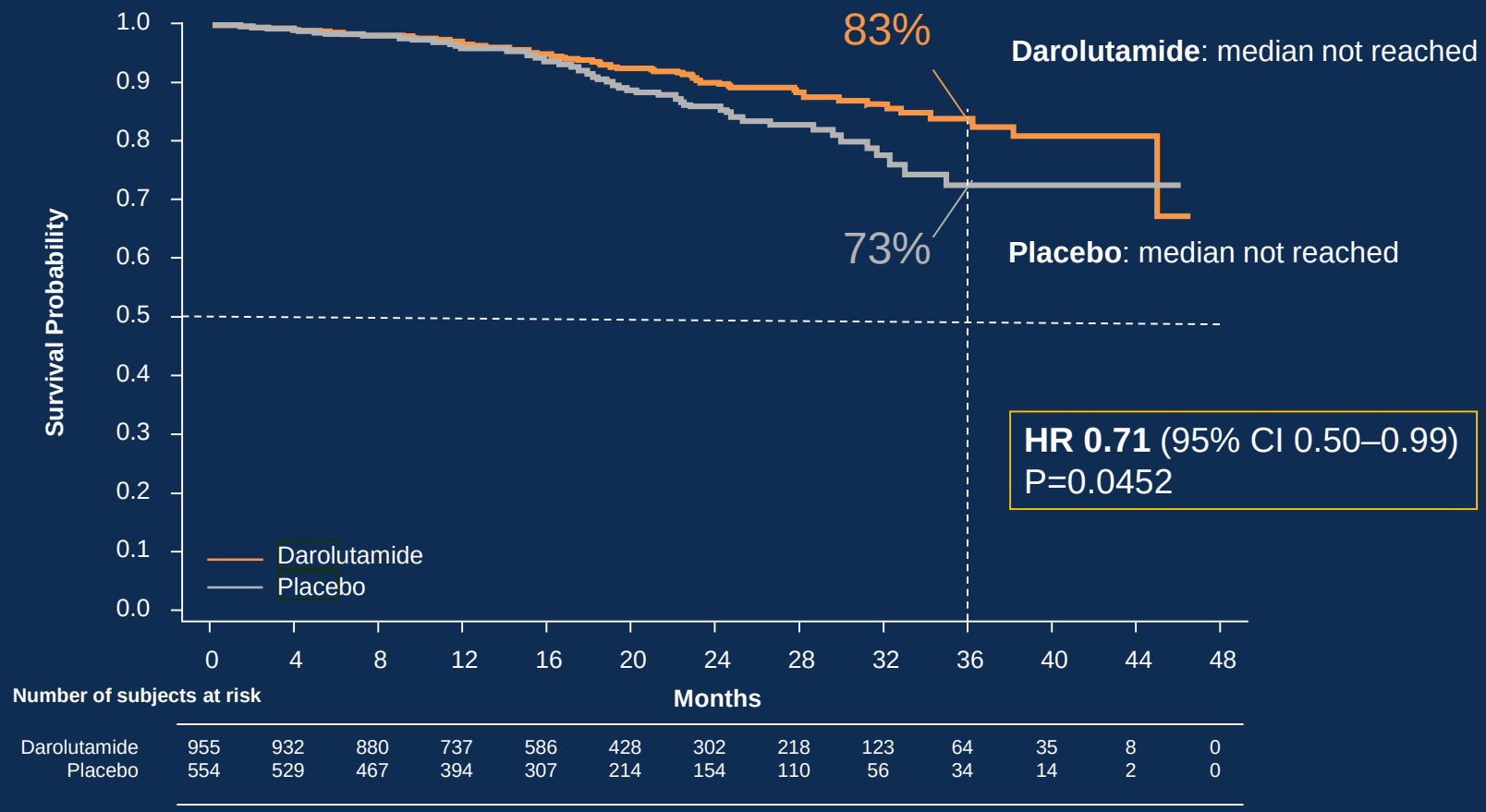
35% risk reduction of increase in pain



BPI-SF, Brief Pain Inventory – Short Form; CI, confidence interval; HR, hazard ratio.

Secondary endpoint: Overall survival

29% risk reduction of death



CI, confidence interval; HR, hazard ratio.

Presented by: Karim Fizazi

TEAEs of interest

Adverse event, all grades, n (%)	Darolutamide (N = 954)	Placebo (N = 554)
Fatigue/asthenic conditions	151 (15.8)	63 (11.4)
Dizziness (including vertigo)	43 (4.5)	22 (4.0)
Cognitive disorder	4 (0.4)	1 (0.2)
Memory impairment	5 (0.5)	7 (1.3)
Seizure (any event)	2 (0.2)	1 (0.2)
Bone fracture	40 (4.2)	20 (3.6)
Falls (including accident)	40 (4.2)	26 (4.7)
Hypertension	63 (6.6)	29 (5.2)
Coronary artery disorders	31 (3.2)	14 (2.5)
Heart failure	18 (1.9)	5 (0.9)
Rash	28 (2.9)	5 (0.9)
Weight decreased (any event)	34 (3.6)	12 (2.2)
Hypothyroidism	2 (0.2)	1 (0.2)

TEAE, treatment-emergent adverse event.

Conclusion: M0 CRPC

- Quite rare situation, unmet need
- Even rarer if next generation imaging is used
- 3 agents (Darolutamide, Enzalutamide, Apalutamide):
  - Clear and meaningful improvement of MFS
  - Remarkable safety profile with Darolutamide
  - Clear suggestion that clinical endpoints are improved (Pain progression, OS)
  - Cost-effectiveness?