2° Convegno Nazionale

IL TEAM INTERDISCIPLINARE NEL CARCINOMA DELLA PROSTATA

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Sala Perez - IRCCS Ospedale Sacro Cuore Don Calabria

Carcinoma della prostata localmente avanzato: quali strategie di trattamento?

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Disclosure

No conflict of interest related to the following presentation

Who are locally advanced prostate cancer patients?

Table 1 – EAU risk groups for biochemical recurrence of localised and locally advanced prostate Cancer

Low-risk	Intermediate-risk	High-risk	
	Definition		
PSA < 10 ng/mL	PSA 10–20 ng/mL	PSA > 20 ng/mL	any PSA
and GS < 7	or GS 7	or GS >7	any GS
and cT1-2a	or cT2b	or cT2c	cT3–4 or cN+
Localised	Localised	Localised	Locally advanced

GS = Gleason score; PSA = prostate-specific antigen.

EAU – ESTRO – SIOG Guidelines 2018

Agenda

- Surgery
- Radiotherapy
- Systemic treatments

Agenda

- **Surgery**
- Radiotherapy
- Systemic treatments

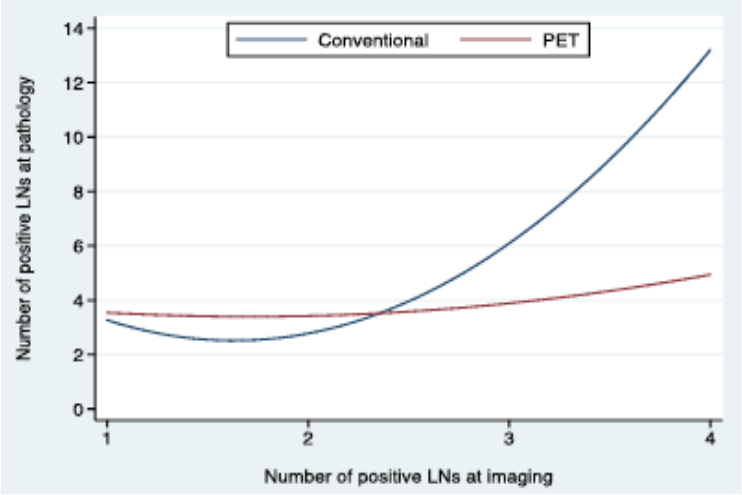
Is there a role for surgery in locally advanced prostate cancer ?

- ✓ Only retrospective evidence
- ✓ High risk of patient selection bias
- ✓ No standardized extent of PLND/use of multimodal approaches
- ✓ (Mainly) use of conventional imaging

Conventional and molecular imaging in cN+

- ✓ **Conventional imaging:** low sensitivity for detecting small volume lesions and poorly quantifies the burden and the site of oligometastatic disease
- ✓ **Molecular and conventional imaging** were characterized by the **risk of underestimating nodal burden in patients ≤ 2 positive spots**

	Sensitivity	Specificity
CT/MRI	13%	82%
DW-MRI	20%	79-81%
[^{11}C]/[^{18}F] Choline PET-CT	20-49%	89-95%
^{68}Ga-PSMA PET/CT	66%	85-99%



Gandaglia et al EAU 2019

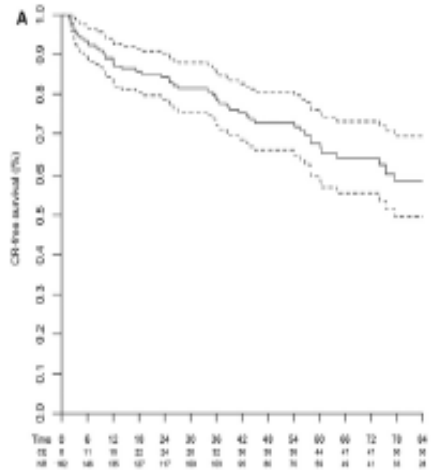
Potential implications of surgery

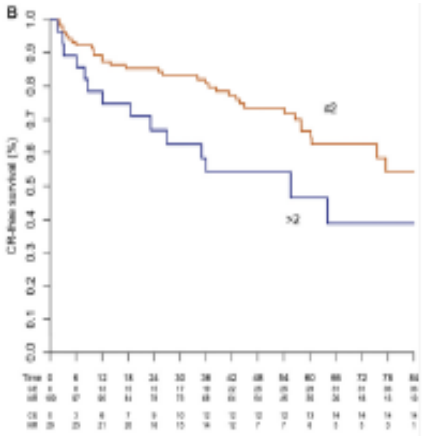
Pros	Cons
Accurate assessment of the real extent of nodal invasion	Short- and long-term side effects (multi-modal approahces)
Maximize local control in bulky disease	Some patients would not benefit from surgery
Multimodal approach with accurate tumor debulking	No abscopal effect
Tailored approach (pathological report available – post op PSA)	

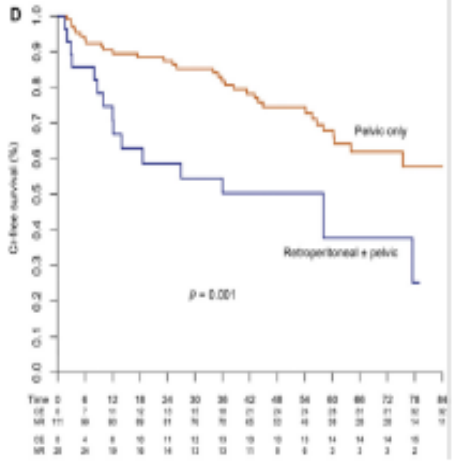
Briganti A. ESMO 2019

Outcomes in cN+ patients treated with surgery

- ✓ 162 patients with cN1 PCa treated with RP + ePLND at three tertiary referral centers
- ✓ 80% pN1





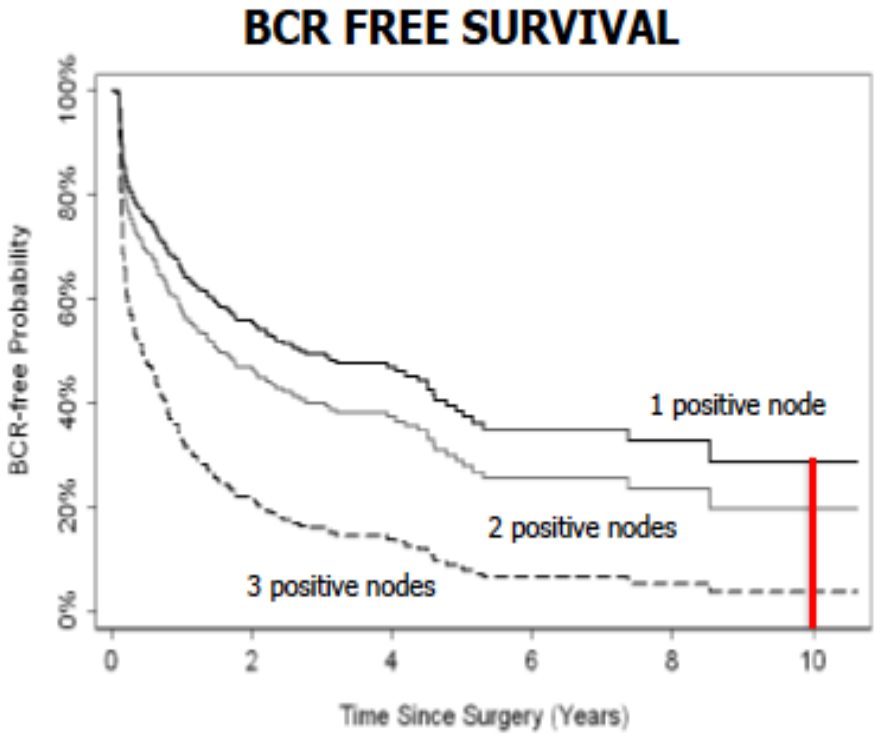


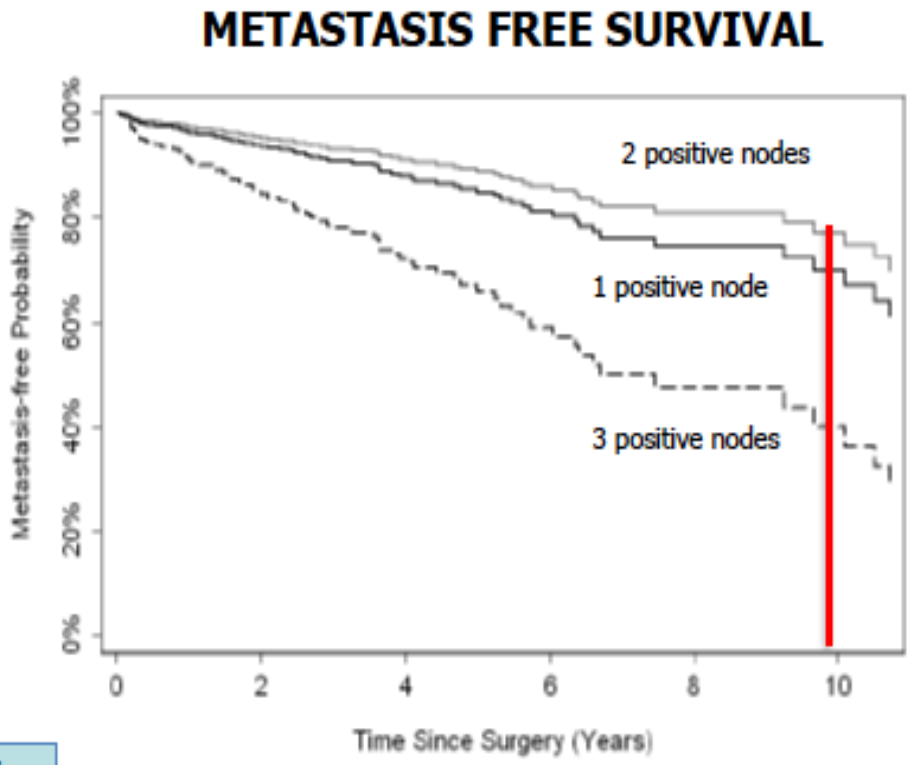
5-yr CSS: 85%
Median follow-up: 64 months

Gandaglia et al. Eur Urol 2019;75:817-25

Should ePLND be performed in cN1+ patients?

369 patients treated with ePLND (median n. of nodes removed: 15) without adjuvant therapies

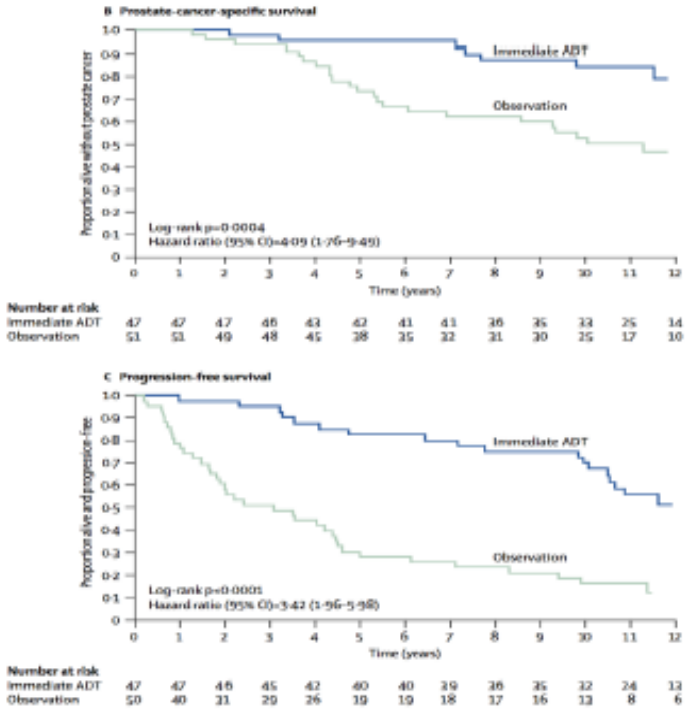




Roughly 30% of patients with <=2 positive nodes would not experience recurrence at 10-year follow-up

Toujer et al, Eur Urol 2014, 65;20-5

Should we always consider adjuvant ADT in cN1+ patients?

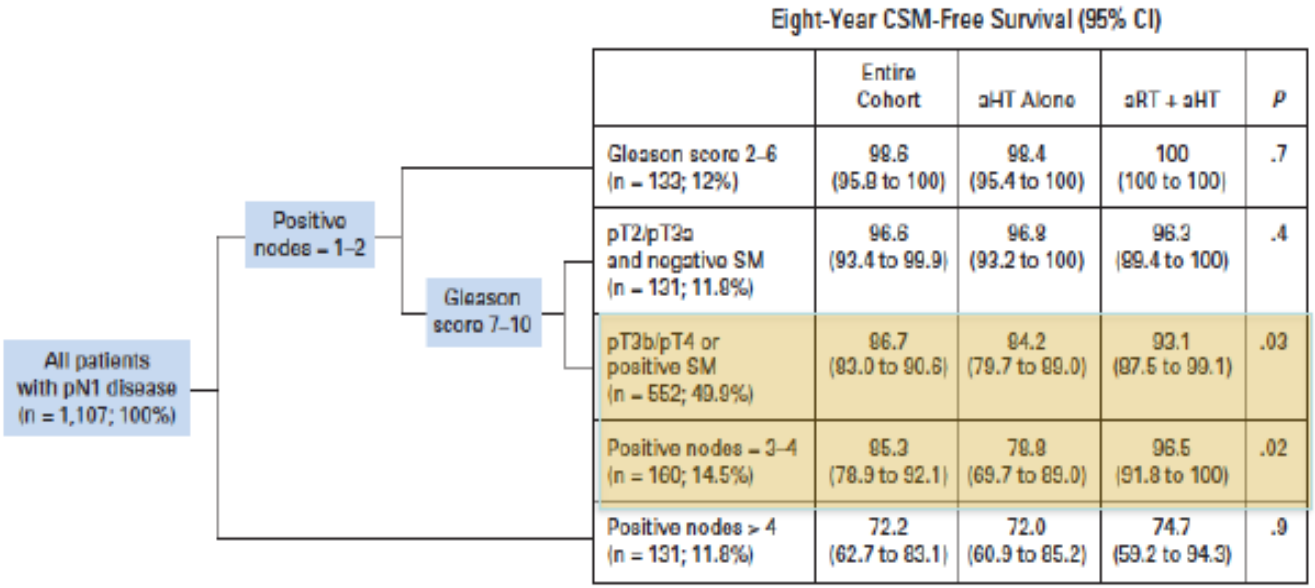


Recommendations	Strength ra
Discuss three management options with patients with pN+ disease after an extended lymph node dissection, based on nodal involvement characteristics: 1. Offer adjuvant ADT for node-positive (pN+). 2. Offer adjuvant ADT with additional radiotherapy. 3. Offer observation (expectant management) to a patient after eLND and ≤ 2 nodes with microscopic involvement, and a PSA < 0.1 ng/mL and absence of extranodal extension.	Weak

Messing et al. Lancet Oncol 2006;7:472-79

Should we always consider adjuvant RT in cN1+ patients?

N= 1,173 LNI patients treated 1988 and 2012, at Mayo Clinic and San-Raffaele Hospital. All patients received adjuvant HT with or without aRT.



Eight-Year CSM-Free Survival (95% CI)

	Entire Cohort	aHT Alone	aRT + aHT	*P*
Gleason score 2–6 (n = 133; 12%)	98.6 (95.8 to 100)	98.4 (95.4 to 100)	100 (100 to 100)	.7
pT2/pT3a and negative SM (n = 131; 11.8%)	96.6 (93.4 to 99.9)	96.8 (93.2 to 100)	96.3 (89.4 to 100)	.4
pT3b/pT4 or positive SM (n = 552; 49.9%)	86.7 (83.0 to 90.6)	84.2 (79.7 to 89.0)	93.1 (87.5 to 99.1)	.03
Positive nodes = 3–4 (n = 160; 14.5%)	85.3 (78.9 to 92.1)	78.8 (69.7 to 89.0)	96.5 (91.8 to 100)	.02
Positive nodes > 4 (n = 131; 11.8%)	72.2 (62.7 to 83.1)	72.0 (60.9 to 85.2)	74.7 (59.2 to 94.3)	.9

Intermediate risk

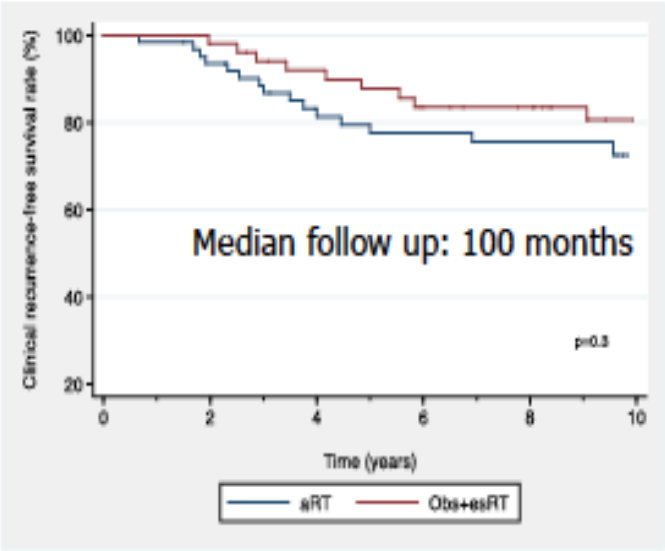
High risk

Abdollah et al. JCO 2014

Adjuvant vs early salvage RT in cN1+ patients?

....Unknown since in RADICALS. RAVES, GETUG-17 node positive patients were virtually all excluded....

- ✓ Multi-institutional cohort from 6tertiary referral centres, 171 pN1 patients (RP+ PLND)
- ✓ Patients were stratified into two groups: aRT (Group 1) versus initial observation followed by esRT in case of PSA relapse (Group 2)



Fossati et al., EAU 2017

What do the guidelines say?

Recommendations	Strength rating
Radical Prostatectomy (RP)	
Offer RP to highly selected patients with (cT3b-T4 N0 or any T N1) only as part of multimodal therapy.	Strong
Extended pelvic lymph node dissection (ePLND)	
Perform an ePLND in high-risk PCa.	Strong
Do not perform a frozen section of nodes during RP to decide whether to proceed with, or abandon, the procedure.	Strong

involvement (cN0). In case of suspected positive LNs during RP (initially considered cN0), the procedure should not be abandoned since RP may have a survival benefit in these patients. Intra-operative frozen section analysis is not justified in this case [401]. Only limited evidence exists supporting RP for cN+ patients. Moschini *et al.* compared the outcomes of 50 patients with cN+ with those of 252 patients with pN1, but cN0 at pre-operative staging. cN+ was not a significant predictor of CSS [606]. An ePLND is considered standard if a RP is planned.

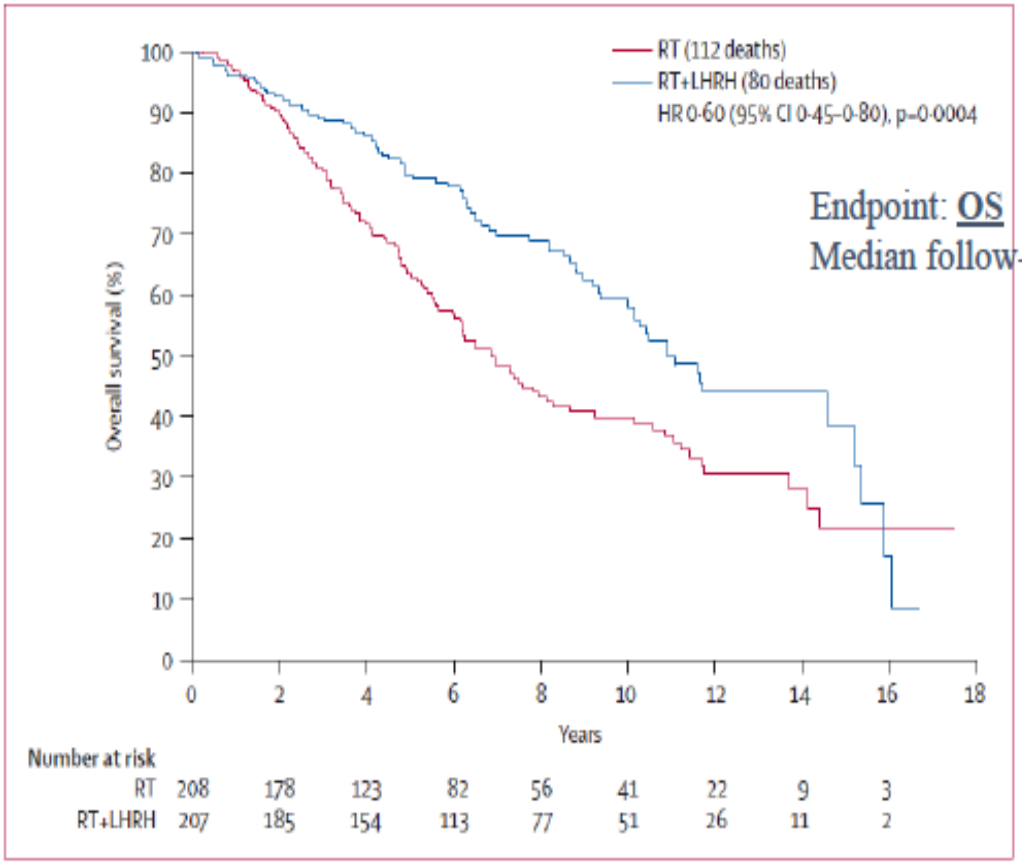
Agenda

- Surgery
- **Radiotherapy**
- Systemic treatments

Do we have evidence to treat locally advanced prostate cancer with radical RT?

Study	Number of patients	Therapy	Survival HR (95% CI)
Bryant, 2018	648	RT+ADT vs ADT	0.38 (0.25-0.57)
Seisen, 2017	1987	LT+ADT vs ADT	0.31 (0.13-0.74)
James, 2016	177	RT+ADT vs ADT	0.35 (0.19-0.65)
Rusthoven, 2014	796	RT vs no RT	0.58 (0.47-0.71)
Tward, 2013	1100	RT vs no RT	CSS (78% vs 71%)
Lin, 2005	636	RT+ADT vs ADT	0.5 (0.37-0.67)

Is RT+ ADT better than RT alone?



RT+ADT>RT

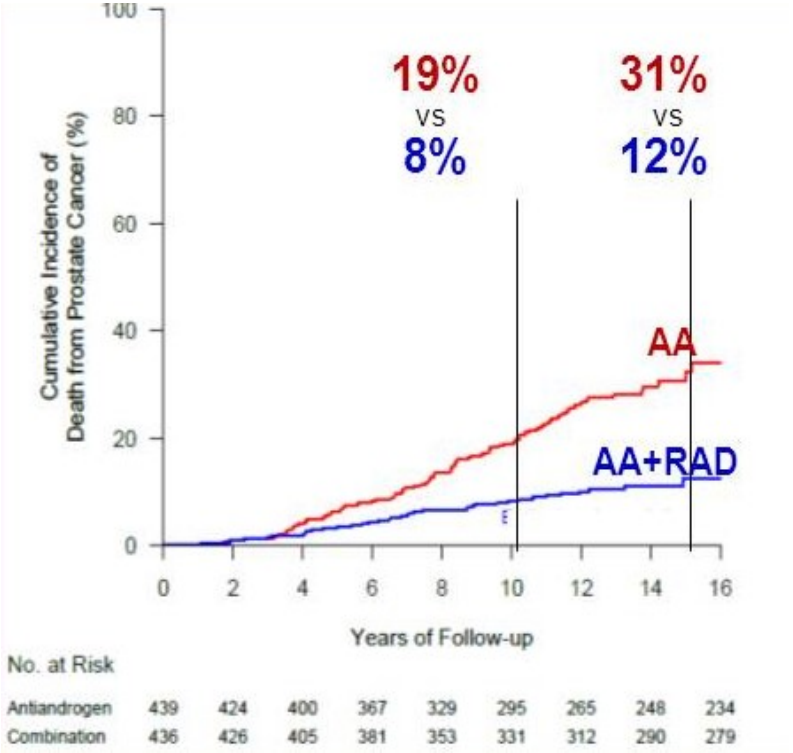
Bolla M. et al Lancet Oncol 2010

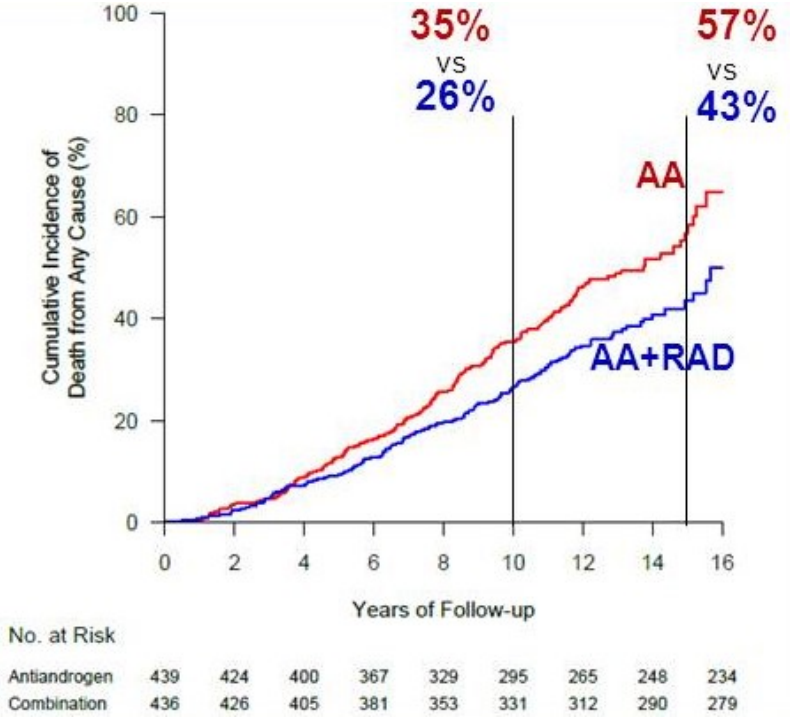
Is RT+ ADT better than ADT upfront?

PCa specific mortality

Overall mortality

RT+ADT>ADT





Widmark A et al, Lancet 2009

Which is the optimal duration of neo-adj ADT in patients treated with radical RT?

Study	N° patients	treatment	OS
TROG 96-01[1]	818	3mo ADT + RT vs 6mo ADT + RT vs RT	HR 0.63 (0.48–0.83)
RTOG 8610[2]	456	4 mo ADT + RT vs RT	CSS 23% vs 36% (p = 0.01)

[1] Denham JW Lancet Oncol 2011; [2] Roach M JCO 2008

Which is the optimal duration of adj ADT in patients treated with radical RT?

Study	N° patients	treatment	OS
RTOG 92-02[1]	1514	4mo ADT + RT vs 24mo ADT + RT vs RT	81% vs70.7% p=0.044
EORTC 22961[2]	970	6mo ADT + RT vs 32mo ADT + RT vs RT	19 % vs 15.2% HR 1.42; 95% CI 1.09–1.85

[1]Hanks GE JCO 2003; [2]Bolla M NEJM 2009

What do the guidelines say?

Neoadjuvant and adjuvant hormone treatment

- Neoadjuvant and concurrent ADT for 4–6 months are recommended for men receiving radical RT for high-risk disease, and should be considered for men with intermediate-risk disease [I, A].
- Adjuvant ADT, for 2–3 years, is recommended for men receiving neoadjuvant hormonal therapy and radical RT, who are at high risk of prostate cancer mortality [I, A].

ESMO

[1] ESMO Guidelines updated 2019

Agenda

- Surgery
- Radiotherapy
- **Systemic treatments**

Why ld we anticipate systemic treatment?

Effect on Survival

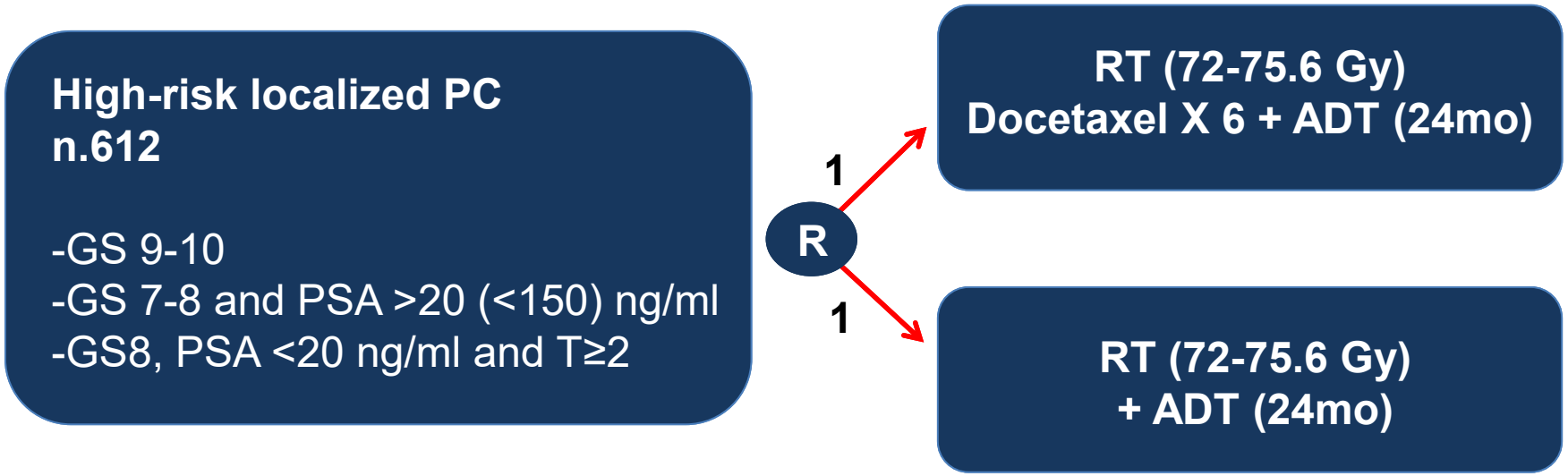
- **Increase Cure Rate** *(locally advanced disease)*
- **Prolong Survival** *(advanced disease)*

Symptoms delay/control

Maintain QoL

- Disease *(symptoms)*
- Drug *(toxicities)*

Effect of Chemotherapy With Docetaxel With Androgen Suppression and Radiotherapy for Localized High-Risk Prostate Cancer: The Randomized Phase III NRG Oncology RTOG 0521 Trial



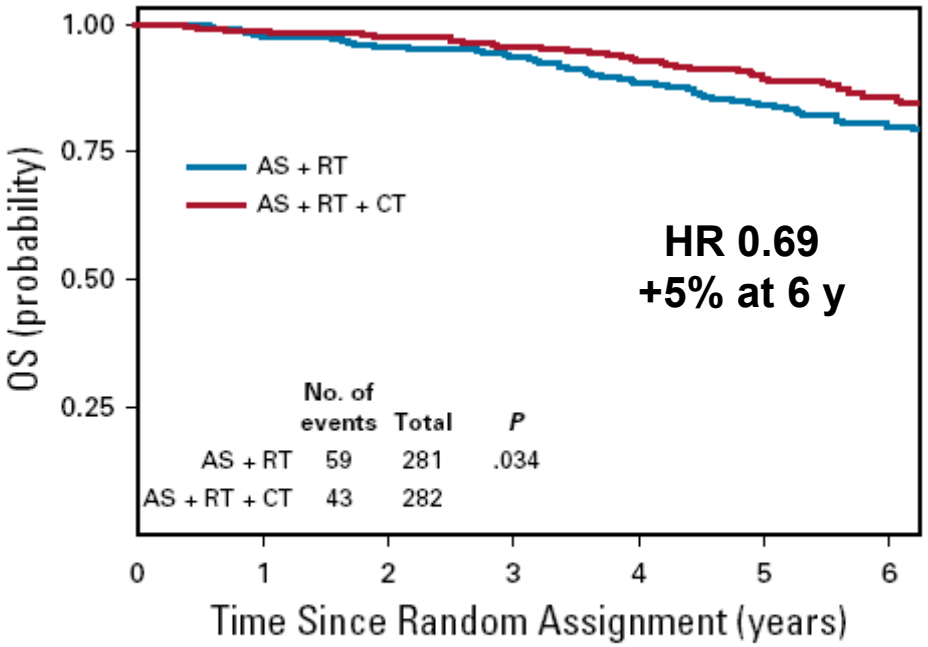
Primary end point: Overall Survival

Secondary end point:
-freedom from biochemical failure (PSA)
-freedom from distant metastasis
-disease-free survival

Rosenthal, JCO 2019

Effect of Chemotherapy With Docetaxel With Androgen Suppression and Radiotherapy for Localized High-Risk Prostate Cancer: The Randomized Phase III NRG Oncology RTOG 0521 Trial

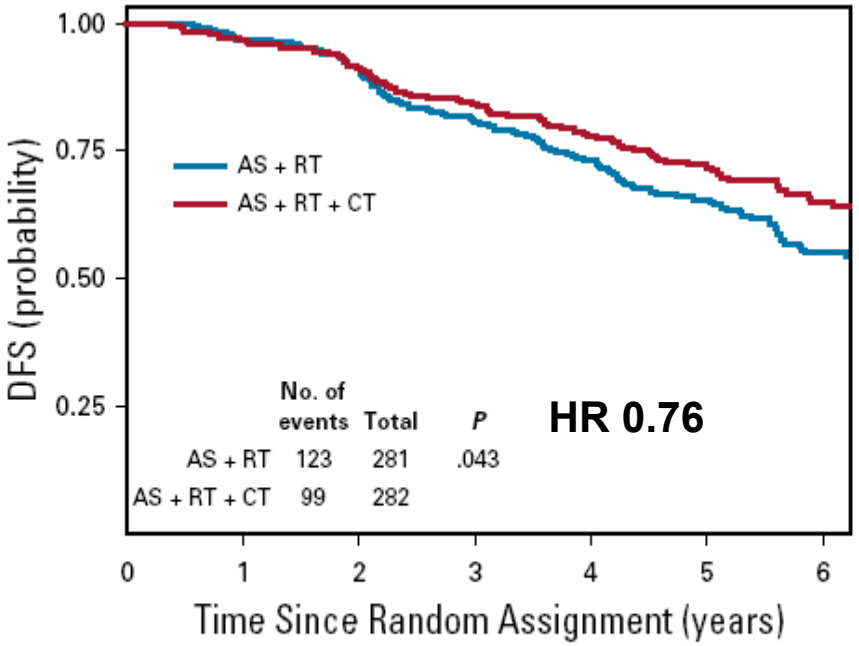
Overall Survival



No. at risk:

AS + RT	281	274	263	255	240	204	128
AS + RT + CT	282	273	267	254	241	218	121

Disease free Survival



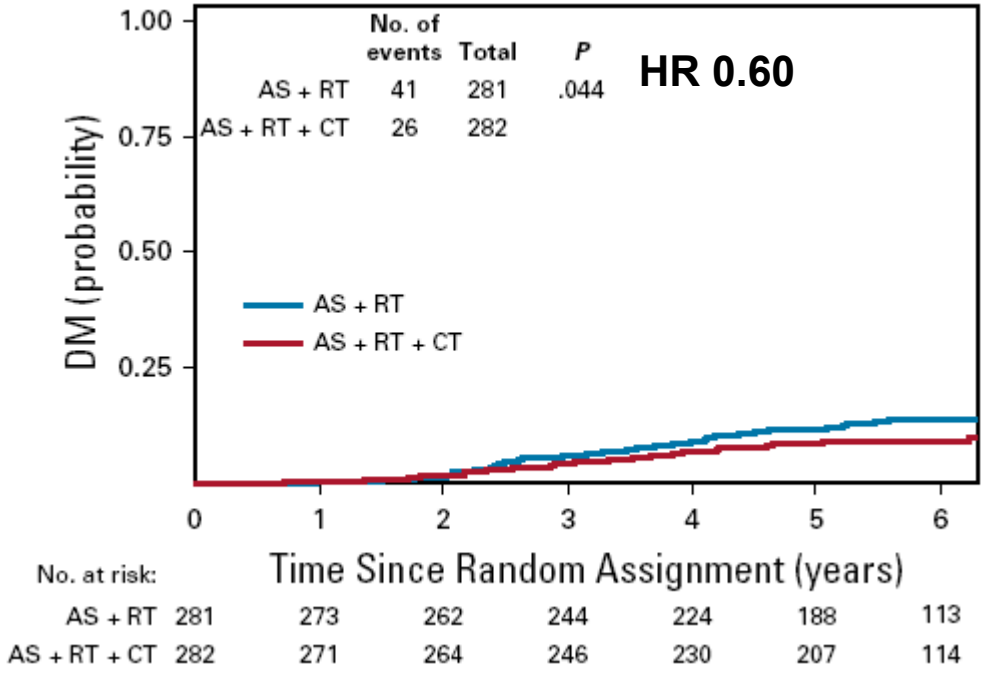
No. at risk:

AS + RT	281	271	252	222	197	156	84
AS + RT + CT	282	268	251	224	202	173	88

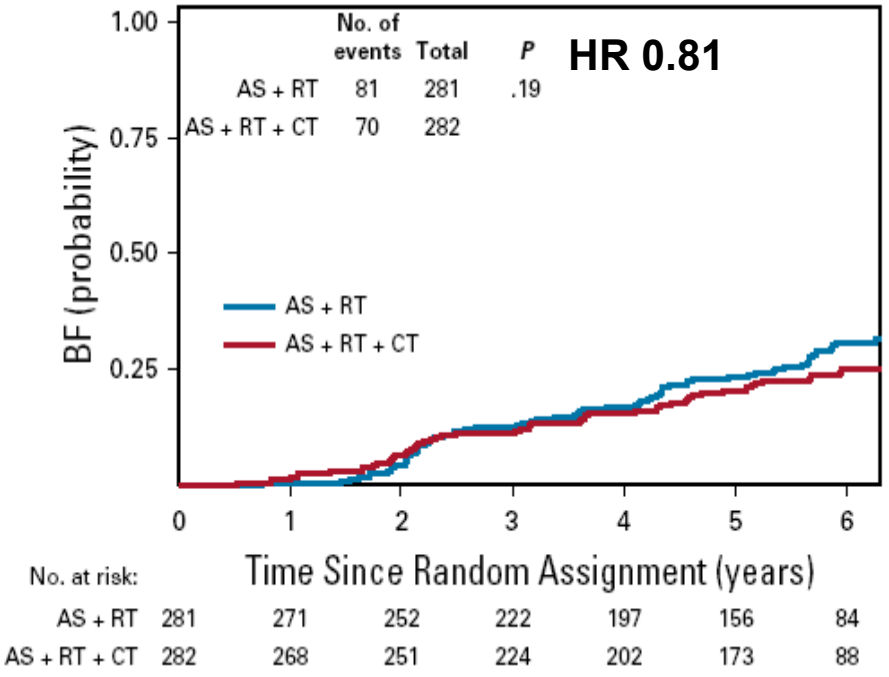
Rosenthal, JCO 2019

Effect of Chemotherapy With Docetaxel With Androgen Suppression and Radiotherapy for Localized High-Risk Prostate Cancer: The Randomized Phase III NRG Oncology RTOG 0521 Trial

Distant Metastases



Biochemical failure



Rosenthal, JCO 2019

Benefit of Adjuvant treatment in solid tumors

Disease	Absolute Survival Benefit, %	Relative Risk Reduction, %	NNT
Lung cancer[4]	5.4 at 5 years (HR, 0.89)	10	18.5
Colon cancer stage III (MOSAIC)[5]	4 at 6 years (73 *v* 69; HR, 0.80)	13	25
Breast cancer EBCTCG meta-analysis (anthracycline *v* no treatment)[6]	5 (40 *v* 35; HR, 0.84)	12.5	20
Prostate cancer RTOG 0521[14]	5.4 at 6 years (86 *v* 80.6)	6.3	18.5

Abbreviations: EBCTCG, Early Breast Cancer Trialists' Collaborative Group; HR, hazard ratio; MOSAIC, Adjuvant Treatment of Colon Cancer; NNT, number needed to treat.

Ready for clinical practice?

Parikh, JCO 2019

Randomized trials of Adjuvant Docetaxel

Study	Intervention	Primary therapy	Patients characteristics	I outcome results
GETUG-12[1] (n. 413)	ADT+Doce+EstrX4 Vs **ADT**		..., GS ≥ 8, ...20 ng/mL, ...1	12y RFS pos OS **Neg**
SPCG-12[2] (n. 459)	DoceX6 V...		High-risk pT2 R1; pT3a GS ≥ 4+3; pT3b or pN1+	PFS **Neg**
SPCG-13[3] (n. 376)	L... Obse...	RT	Intermediate- or high-risk patients	BDFS **Neg**
VA CSP 553[4] (n. 297)	DoceX6 Vs Observ	RP	High-risk pathologic features on RP	PFS **Neg**

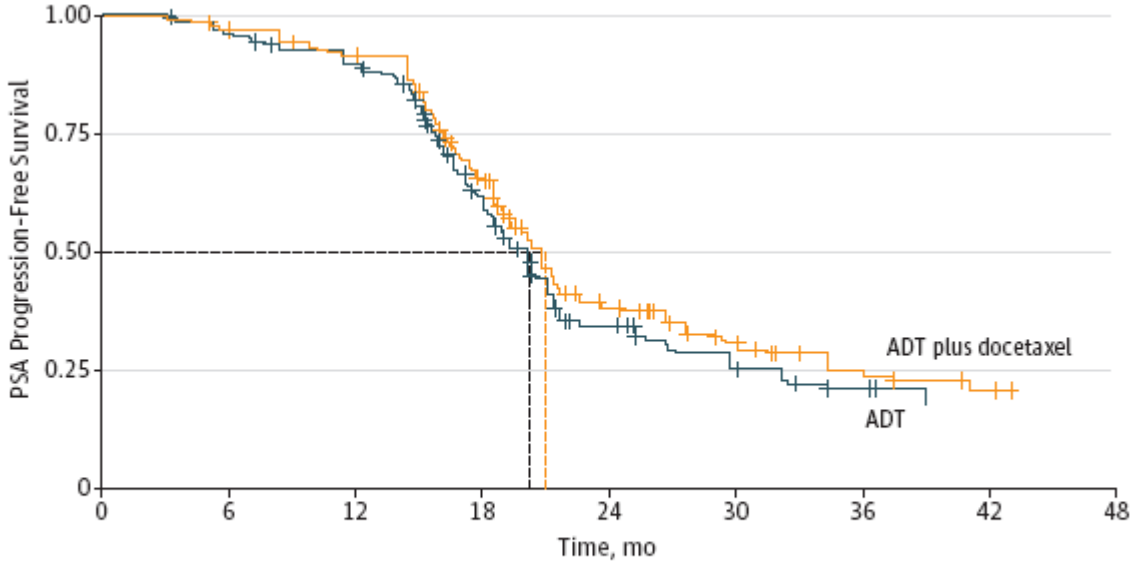
FAILED

1. Fizazi, Lancet Onc 2015; 2. Ahlgren, Eur Urol 2018; 3. Lehtinen, JCO 2018; 4. Lin, J Urol 2016

Effect of Adding Docetaxel to Androgen-Deprivation Therapy in Patients With High-Risk Prostate Cancer With Rising Prostate-Specific Antigen Levels After Primary Local Therapy

A Randomized Clinical Trial

PSA Progression-Free Survival



No. of patients at risk

ADT	125	120	110	62	28	18	12	9
ADT plus docetaxel	125	116	108	74	33	19	11	6

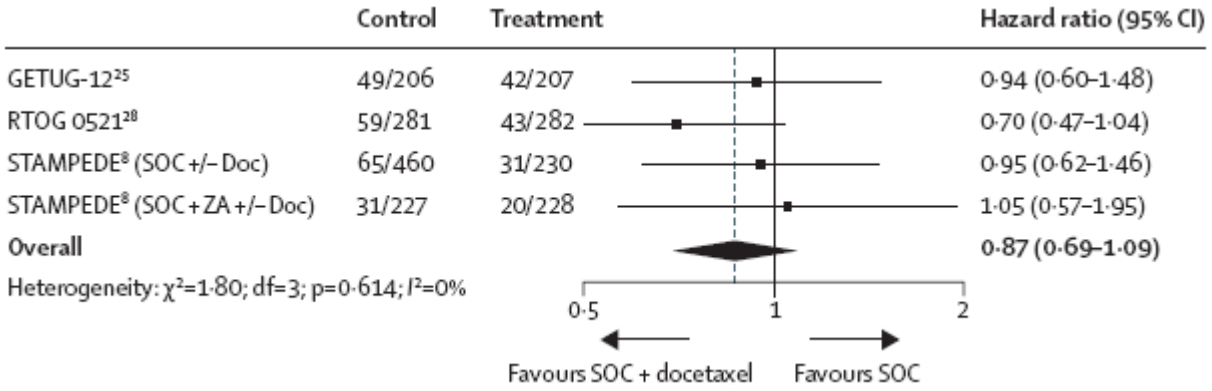
Radiologic PFS
HR 1.03, p 0.88

Overall Survival
HR 0.86, p 0.49

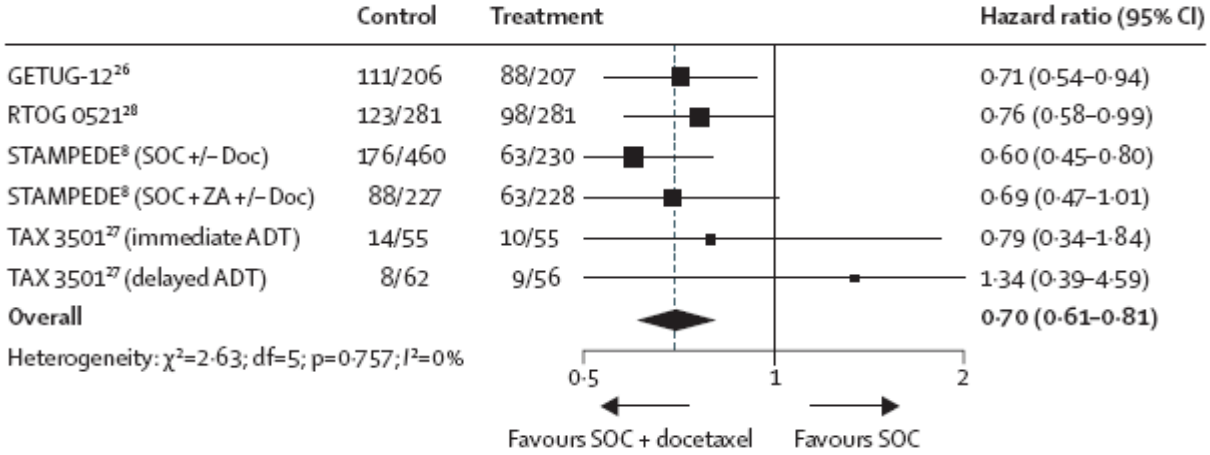
Oudard , JAMA 2019

Addition of docetaxel or bisphosphonates to standard of care in men with localised or metastatic, hormone-sensitive prostate cancer: a systematic review and meta-analyses of aggregate data

Overall Survival in M0

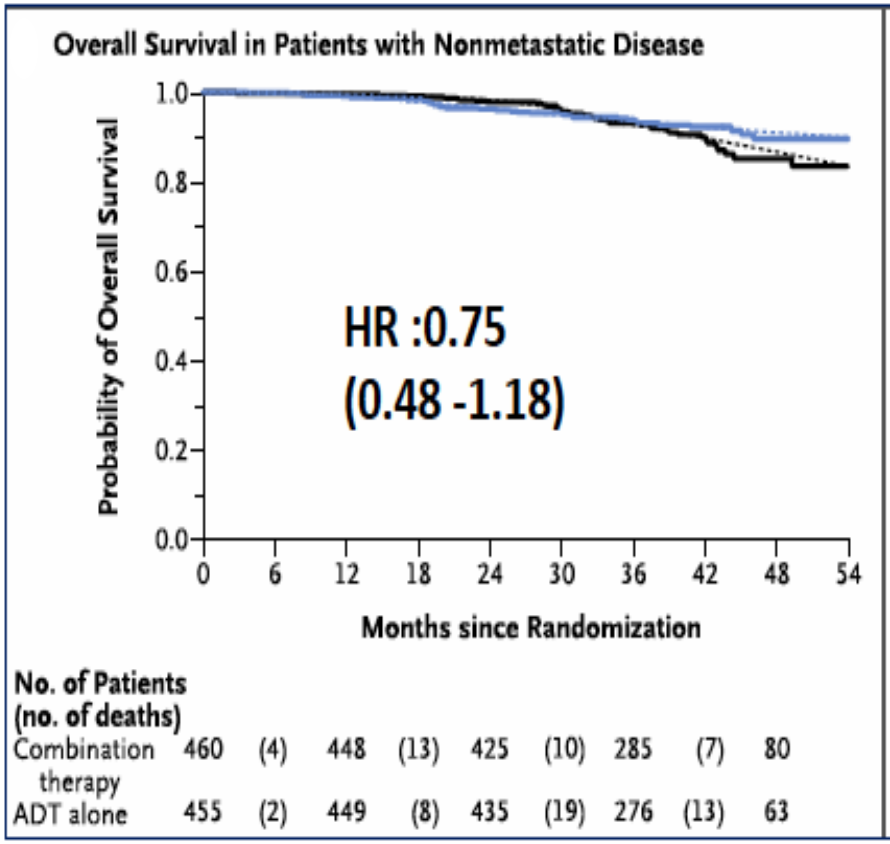


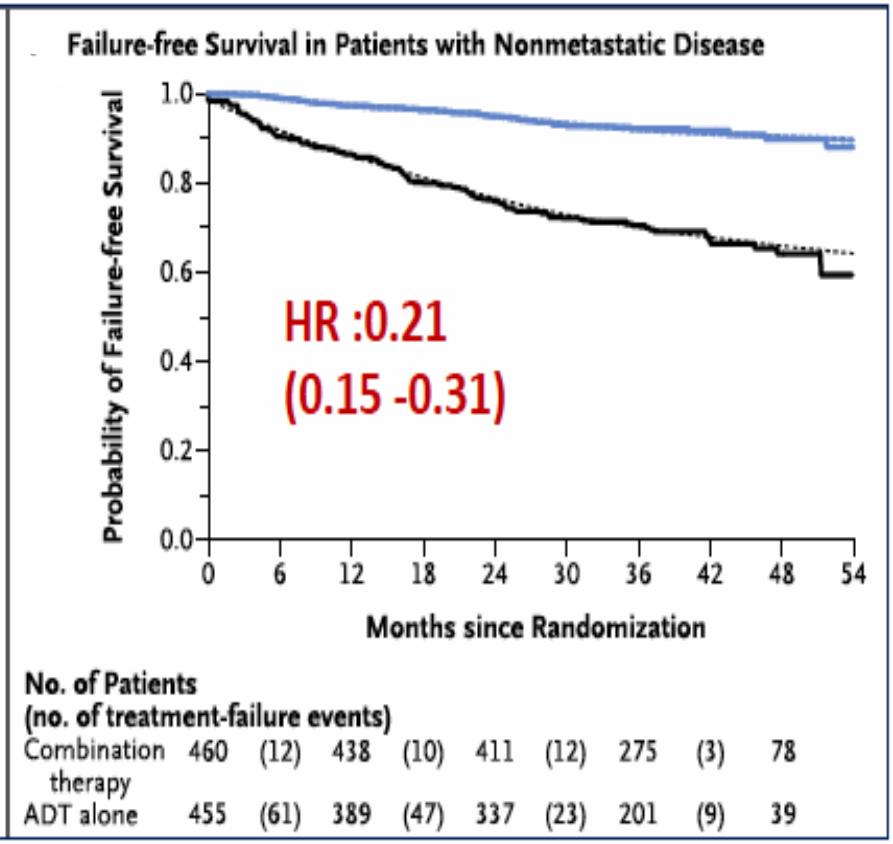
Failure-free Survival in M0



Vale et Al. Lancet Oncol 2016

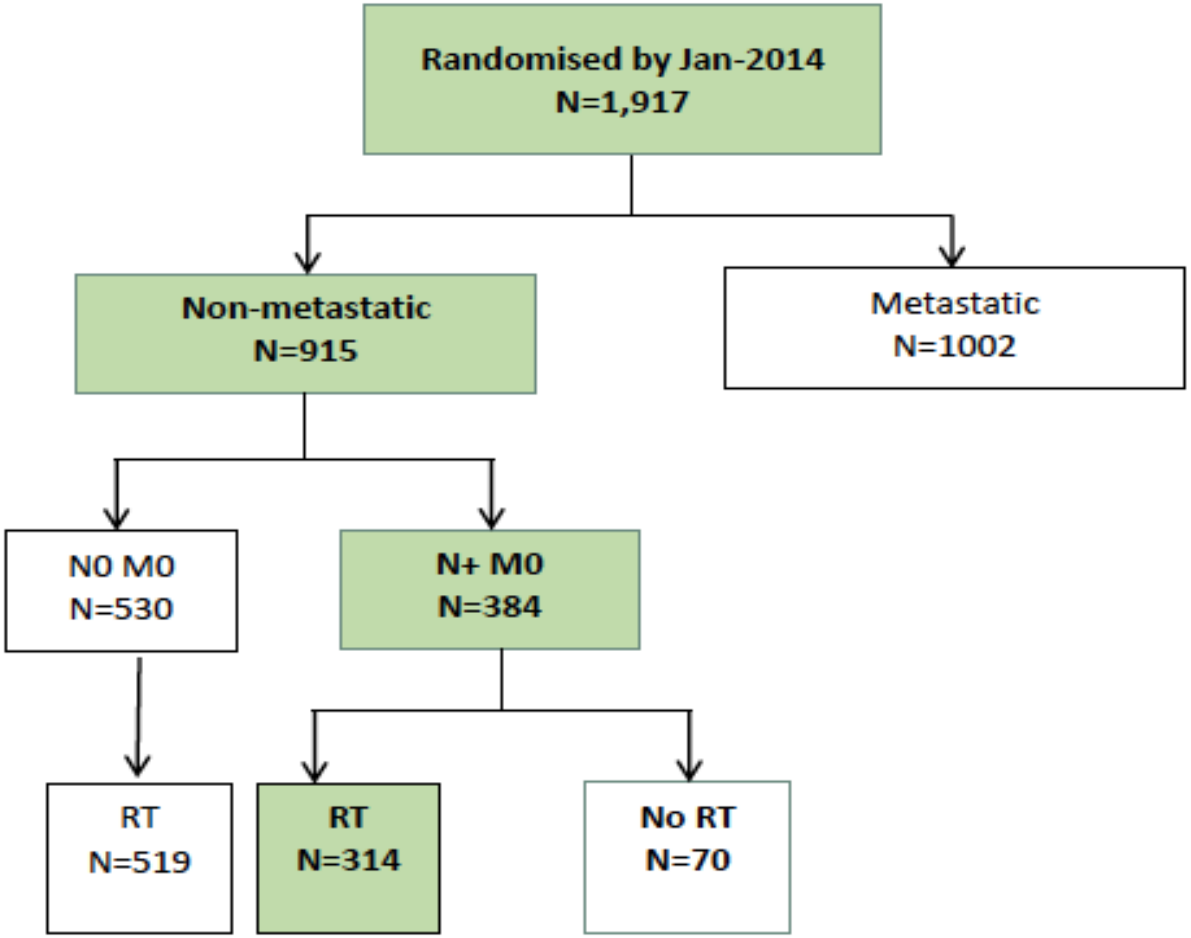
STAMPEDE: Abiraterone/P in M0 HSPCa





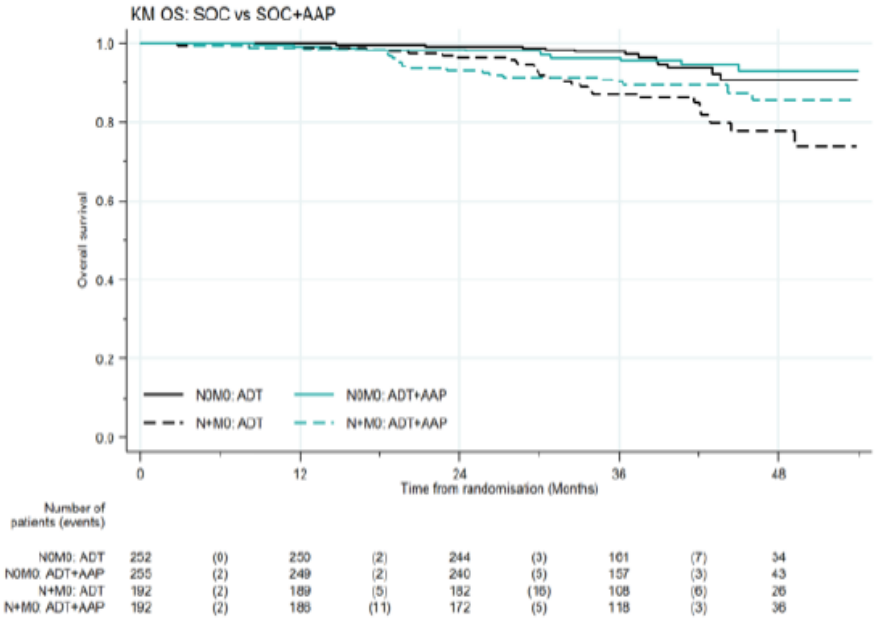
James N NEJM 2017

STAMPEDE: Abiraterone/P in M0 HSPCa



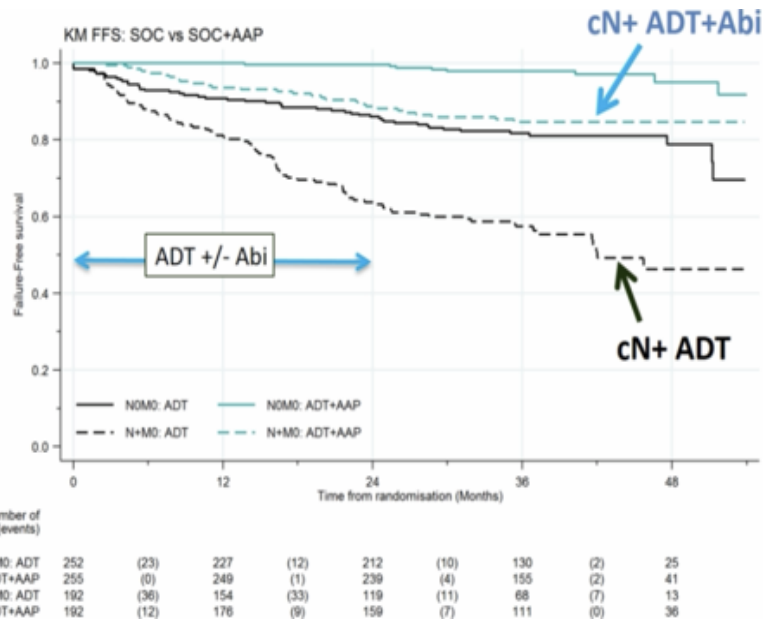
Courtesy of MRC

STAMPEDE: Abiraterone/P in M0 HSPCa



Number of patients (events)

N0M0: ADT	252	(0)	250	(2)	244	(3)	161	(7)	34
N0M0: ADT+AAP	255	(2)	249	(2)	240	(5)	157	(3)	43
N+M0: ADT	192	(2)	189	(5)	182	(16)	108	(6)	26
N+M0: ADT+AAP	192	(2)	188	(11)	172	(5)	118	(3)	36

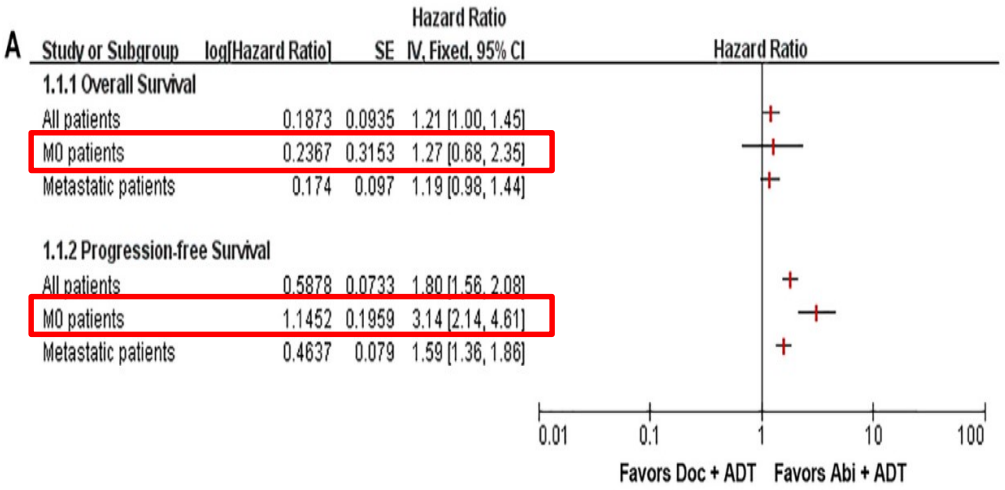


Number of patients (events)

N0M0: ADT	252	(23)	227	(12)	212	(10)	130	(2)	25
N0M0: ADT+AAP	255	(0)	249	(1)	239	(4)	155	(2)	41
N+M0: ADT	192	(36)	154	(33)	119	(11)	68	(7)	13
N+M0: ADT+AAP	192	(12)	176	(9)	159	(7)	111	(0)	36

James N., NEJM 2017

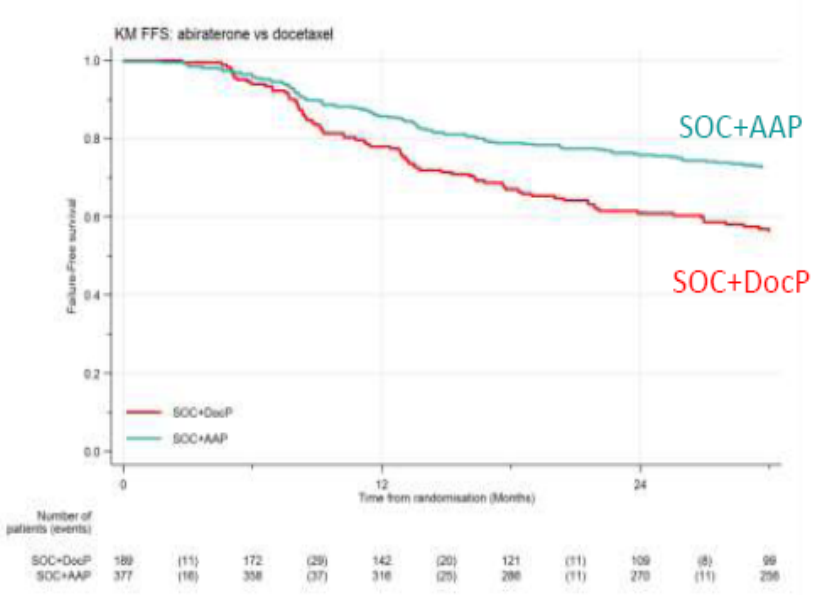
Abiraterone or Docetaxel in M0 HSPCa….
This is the question....



Sun G., Urol Oncol 2018

Adding abiraterone or docetaxel to long-term hormone therapy for prostate cancer: directly randomised data from the STAMPEDE multi-arm, multi-stage platform protocol

Failure-free survival [driven by PSA failure]



	HR (95%CI)	P-val	*Interact^{n} test*
All	**0.51** (0.39 to 0.67)	<0.001	
M0	**0.34** (0.16 to 0.69)	0.003	*0.17*
M1	**0.56** (0.42 to 0.75)	<0.001	

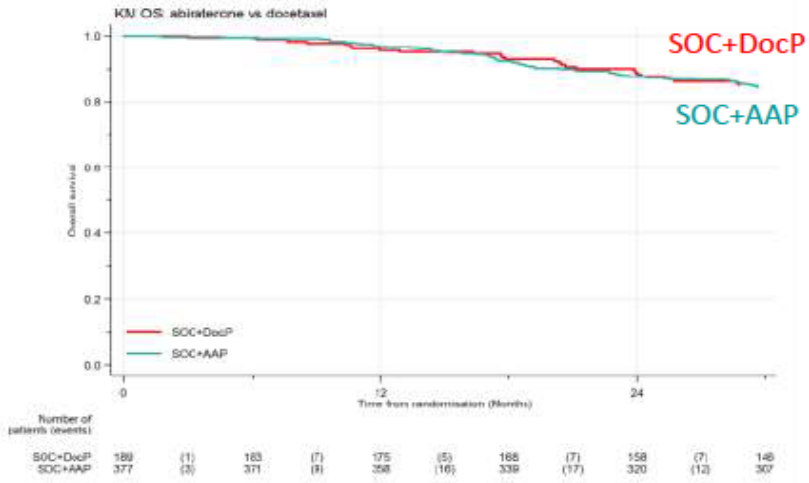
	SOC+DocP		SOC+AAP	
	Events	Pts	Events	Pts
All	**97**	189	**122**	377
M0	**18**	74	**13**	150
M1	**79**	115	**109**	227

Key:
HR<1 favours SOC+AAP
HR>1 favours SOC+DocP

Sydes et Al. Ann Oncol 2018

Adding abiraterone or docetaxel to long-term hormone therapy for prostate cancer: directly randomised data from the STAMPEDE multi-arm, multi-stage platform protocol

Overall survival [primary outcome measure]



	HR (95%CI)	P-val	*Interact^n test*
All	**1.16** (0.82 to 1.65)	0.40	
M0	**1.51** (0.58 to 3.93)	0.40	*0.69*
M1	**1.13** (0.77 to 1.66)	0.53	

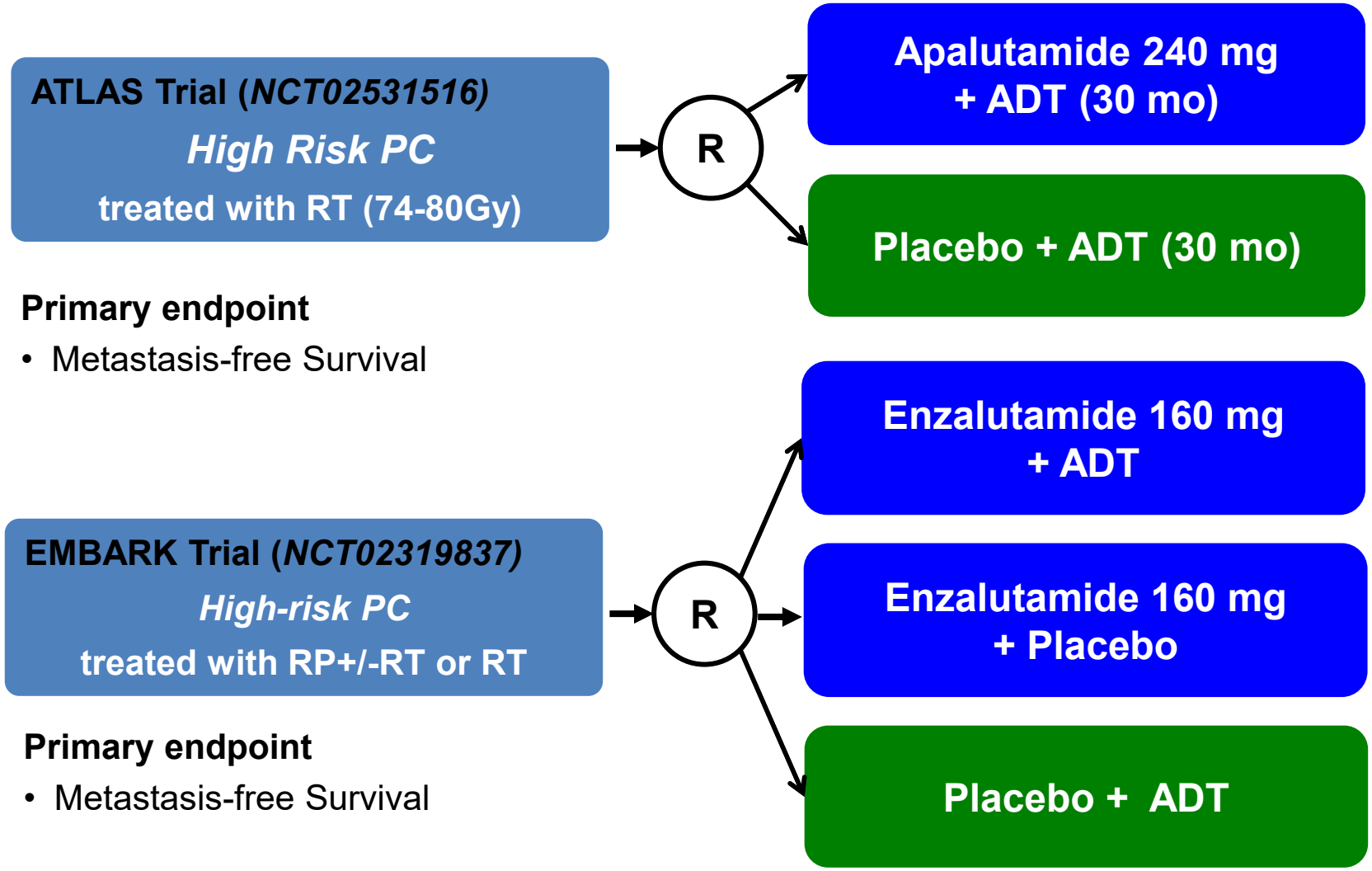
	SOC+DocP		SOC+AAP	
	Events	Pts	Events	Pts
All	44	189	105	377
M0	6	74	16	150
M1	38	115	89	227

Key:
HR<1 favours SOC+AAP
HR>1 favours SOC+DocP

Interact^n = test for interaction (heterogeneity of treatment effect)

Sydes et Al. Ann Oncol 2018

Ongoing phase III trials in locally advanced/High-risk PC



Conclusions

- Multimodality treatment play a key role for the management of locally advanced PCa

- Limited evidence support RP. It might be offered to highly selected patients. If RP is planned ePLND should be considered standard.

- RT + ADT (24-36 mo) is an option for locally advanced prostate cancer (evidence IB)

- Suggestion for greater effect of Abiraterone on FFS (No Rand. Trials) but no impact on OS

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