State of the Art:
Hormone Sensitive Prostate Cancer

19th California Cancer Consortium Conference

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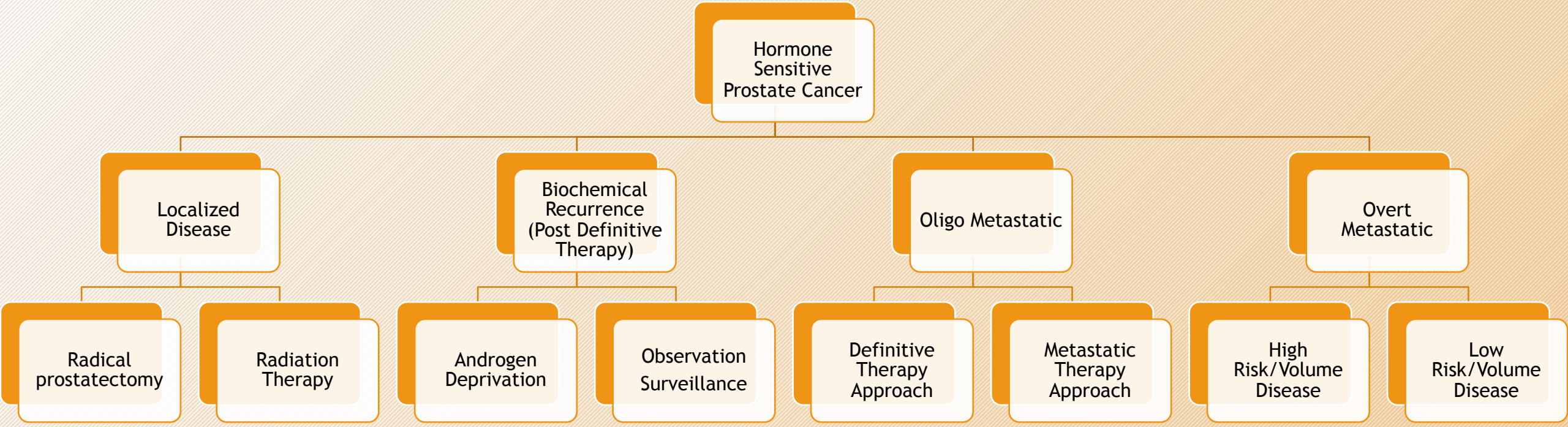
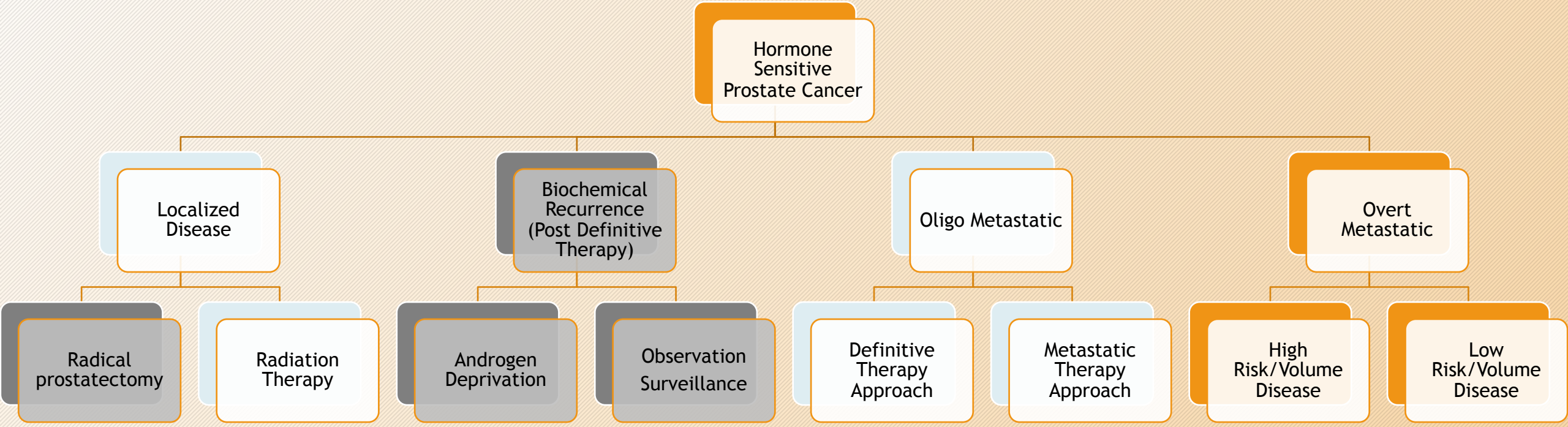
August 26, 2023


Hormone Sensitive Prostate Cancer
Localized Disease
Biochemical Recurrence (Post Definitive Therapy)
Oligo Metastatic
Overt Metastatic
Radical prostatectomy
Radiation Therapy
Androgen Deprivation
Observation Surveillance
Definitive Therapy Approach
Metastatic Therapy Approach
High Risk/Volume Disease
Low Risk/Volume Disease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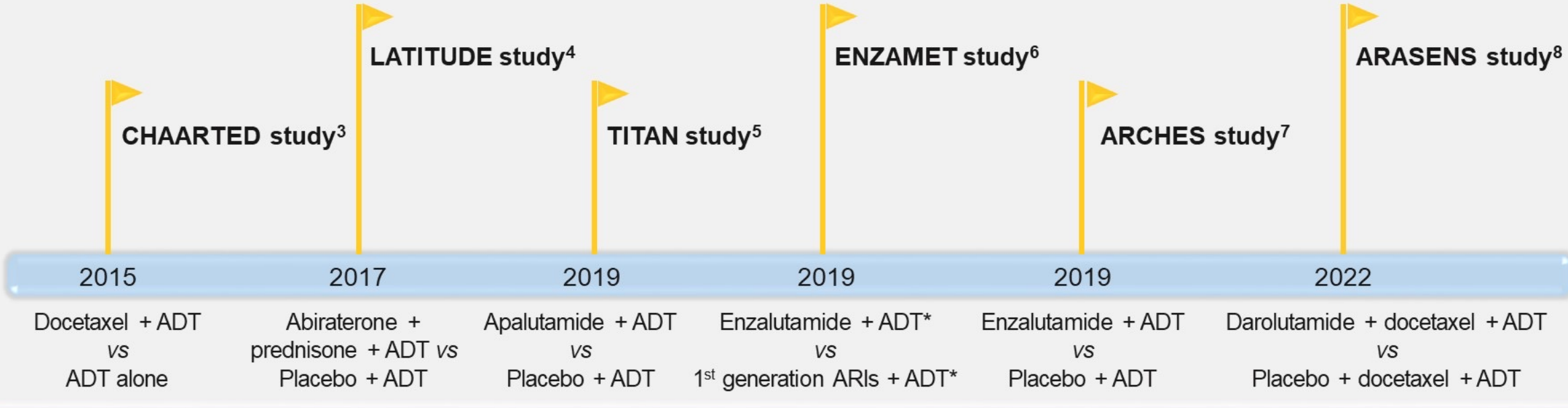
Key Clinical Trials for mHSPC



- Both TITAN and ARCHES studies have demonstrated significant clinical benefits of second-generation androgen receptor inhibitors (ARIs) plus ADT versus placebo plus ADT in the treatment of mHSPC.
- However, first-generation ARIs plus ADT is also widely used in clinical practice and the advantage of the second-generation ARIs over the first-generation remains to be determined.
- This **CHART** study evaluated the efficacy and safety of SHR3680, a novel oral ARI, versus bicalutamide in high-volume mHSPC.

3. C. J. Sweeney, et al. N Engl J Med 2015;373:737-746. 4. K. Fizazi, et al. N Engl J Med 2017;377:352-360. 5. K. N. Chi, et al. N Engl J Med 2019;381:13-24. 6. I. D. Davis, et al. N Engl J Med 2019;381:121-31. 7. A. J. Armstrong, et al. J Clin Oncol 2019;37:2974-2986. 8. M. R. Smith, et al. N Engl J Med 2022;386:1132-1142. *With or without early docetaxel.

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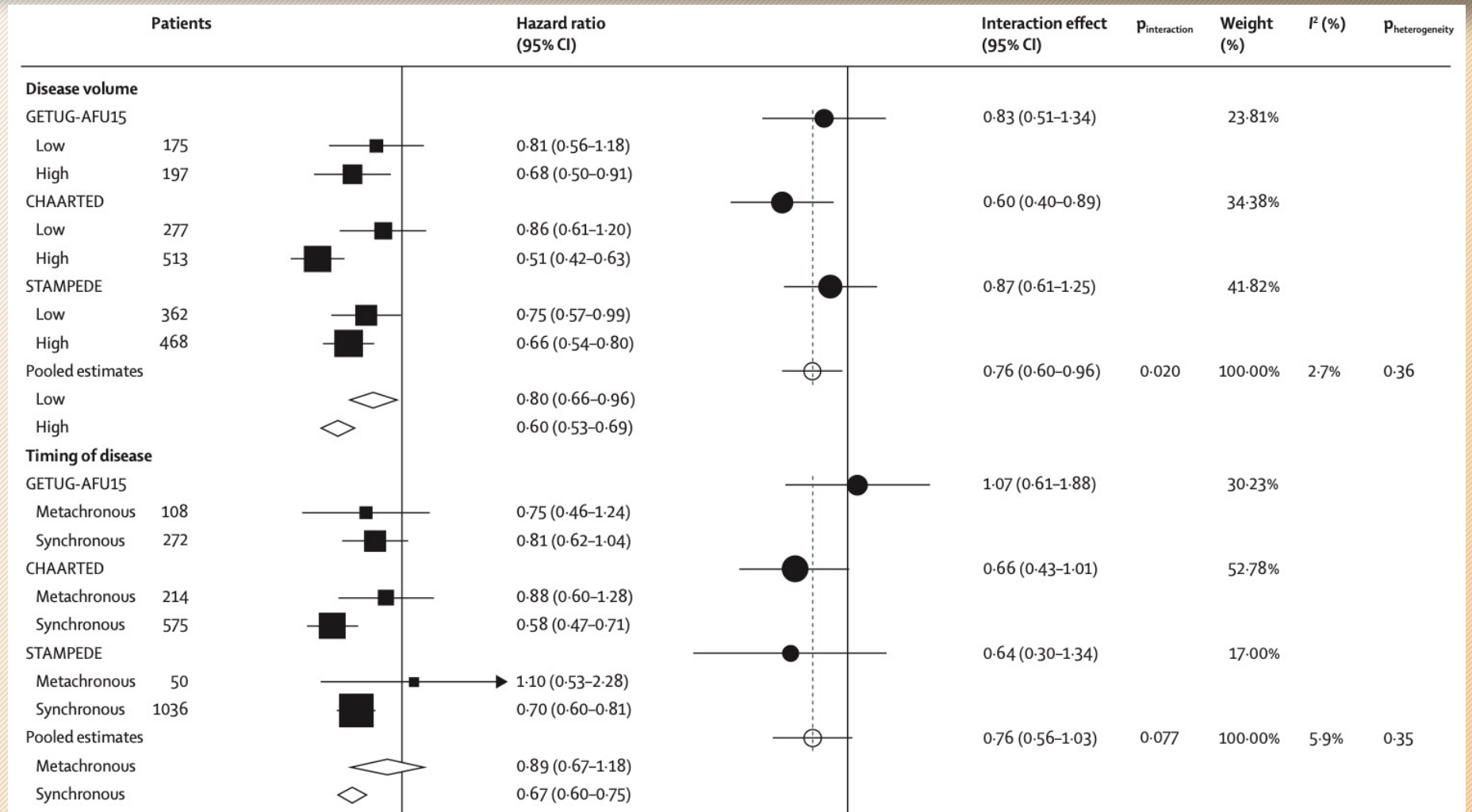
ADT combinations for metastatic HSPC

	CHAARTED	STAMPEDE Arm C	STAMPEDE Arm G	LATITUDE	ENZAMET	ARCHES	TITAN
Control vs. Experimental	ADT vs. ADT+Docetaxel	ADT vs. ADT+Docetaxel	ADT vs. ADT+Abiraterone	ADT vs. ADT+Abiraterone	ADT+1st G ARI vs. ADT+Enzalutamide	ADT vs. ADT+Enzalutamide	ADT vs. ADT+Apalutamide
N	393/397	724/362	452/449	597/602	562/563	576/574	527/525
Metastatic Presentation	Synchronus + Metachronus	Synchronus	Synchronus + Metachronus	Sunchronus	Synchronus + Metachronus	Synchronus + Metachronus	Synchronus + Metachronus
High Volume (HV) %	64/66	44/41	57/54	78/82	52/53	64.8/61.7	64/62
OS ALL HR (95% CI)	0.72 (0.59-0.89)	0.81 (0.69-0.95)	0.61 (0.49-0.79)	0.66 (0.56-0.78)	0.67 (0.52-0.86)	0.66 (0.53-0.81)	0.65 (0.53-0.79)
OS HV HR (95% CI)	0.63 (0.5-0.79)	0.81 (0.64-1.02)	0.60 (0.46-0.78)	0.62 (0.52-0.74)	0.43 (0.26-0.72)	0.66 (0.52-0.83)	0.7 (0.56-0.88)
OS LV HR (95% CI)	1.04 (0.7-1.55)	0.76 (0.54-1.07)	0.64 (0.42-0.97)	0.72 (0.47-1.10)	0.8 (0.59-1.07)	0.66 (0.43-1.03)	0.52 (0.35-0.79)

Docetaxel and High vs Low Volume HSPC

Vale et al, Lancet Oncol 2023; 783-797



Takeaway

- ADT alone is obsolete and should rarely be used
- Docetaxel benefit is for high volume disease

Triple Therapy

Docetaxel + Darolutamide

Docetaxel + Abiraterone

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Darolutamide and Survival in Metastatic, Hormone-Sensitive Prostate Cancer

Matthew R. Smith, M.D., Ph.D., Maha Hussain, M.D., Fred Saad, M.D., Karim Fizazi, M.D., Ph.D., Cora N. Sternberg, M.D., E. David Crawford, M.D., Evgeny Kopyltsov, M.D., Chandler H. Park, M.D., Boris Alekseev, M.D., Álvaro Montesa-Pino, M.D., Dingwei Ye, M.D., Francis Parnis, M.B., B.S., Felipe Cruz, M.D., Teuvo L.J. Tammela, M.D., Ph.D., Hiroyoshi Suzuki, M.D., Ph.D., Tapio Utriainen, M.D., Cheng Fu, M.D., Motohide Uemura, M.D., Ph.D., María J. Méndez-Vidal, M.D., Benjamin L. Maughan, M.D., Pharm.D., Heikki Joensuu, M.D., Silke Thiele, M.D., Rui Li, M.S., Iris Kuss, M.D., and Bertrand Tombal, M.D., Ph.D., for the ARASENS Trial Investigators*

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ARASENS Study Design

Global, randomized, double-blind, placebo-controlled phase III study (NCT02799602)

Patients (N=1306)
- mHSPC
- ECOG PS 0 or 1
- Candidates for ADT and docetaxel

Stratification
- Extent of disease: M1a vs M1b vs M1c
- ALP < vs ≥ ULN

1:1 randomization (N=1305*)

- Darolutamide 600 mg twice daily + ADT + Docetaxel × 6
- Placebo twice daily + ADT + Docetaxel × 6

FPFV: Nov 2016
LPFV: June 2018

Primary analysis

Data cut-off Oct 25, 2021

Endpoints

Primary: OS

Secondary
- Time to CRPC
- Time to pain progression
- SSE-free survival
- Time to first SSE
- Time to initiation of subsequent systemic antineoplastic therapy
- Time to worsening of disease-related physical symptoms
- Time to initiation of opioid use for ≥7 consecutive days
- Safety

- The primary analysis was planned to occur after ~509 deaths
- Secondary efficacy endpoints were tested hierarchically

*One enrolled patient was excluded from all analysis sets because of Good Clinical Practice violations. ALP, alkaline phosphatase; CRPC, castration-resistant prostate cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; FPFV, first patient first visit; LPFV, last patient first visit; M1a, nonregional lymph node metastases only; M1b, bone metastases ± lymph node metastases; M1c, visceral metastases ± lymph node or bone metastases; Q3W, every 3 weeks; SSE, symptomatic skeletal event; ULN, upper limit of normal.

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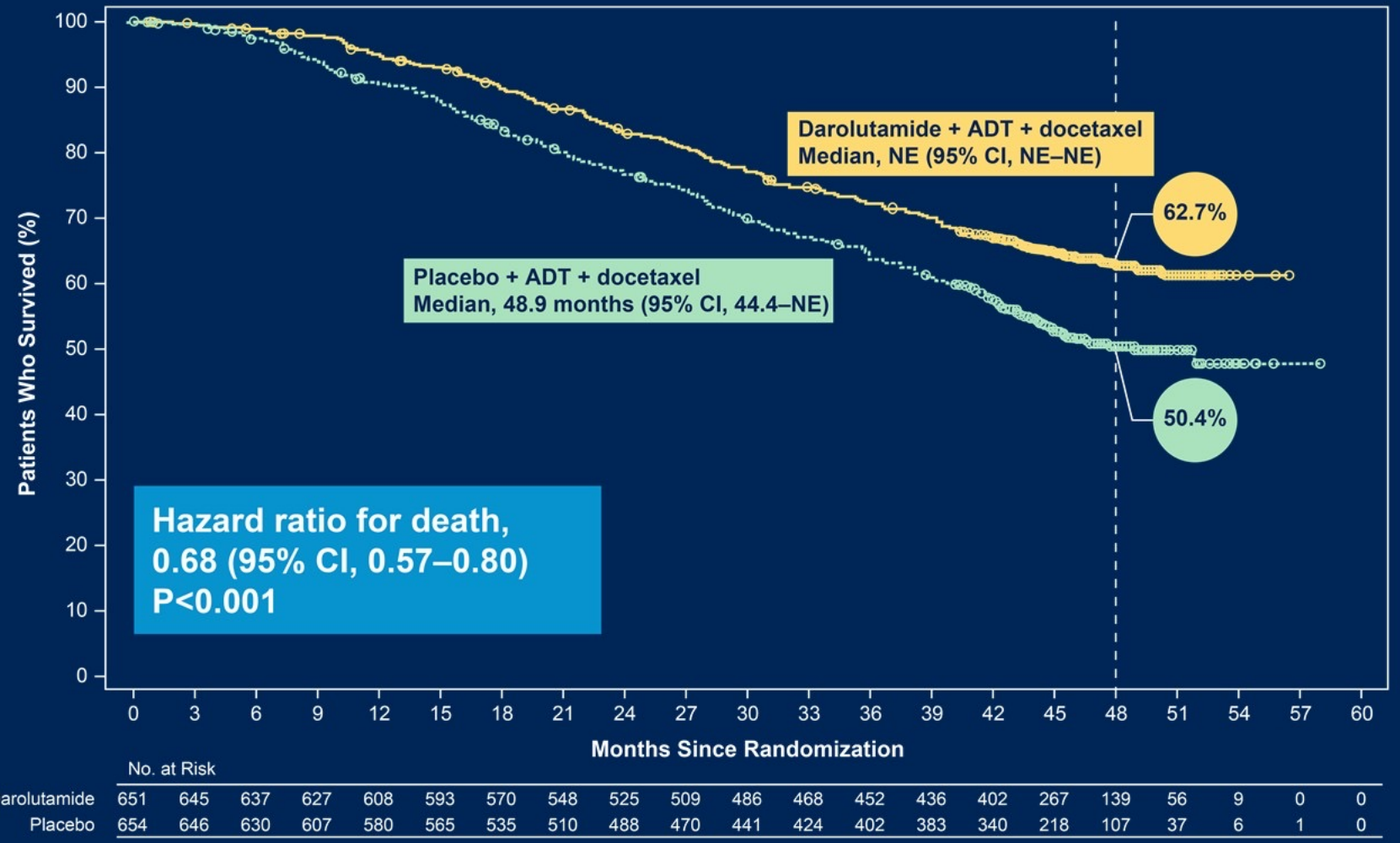
ARASENS Primary Endpoint*: Overall Survival

Darolutamide significantly reduced the risk of death by 32.5%



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

*Primary analysis occurred after 533 deaths (darolutamide, 229; placebo, 304). CI, confidence interval; NE, not estimable.

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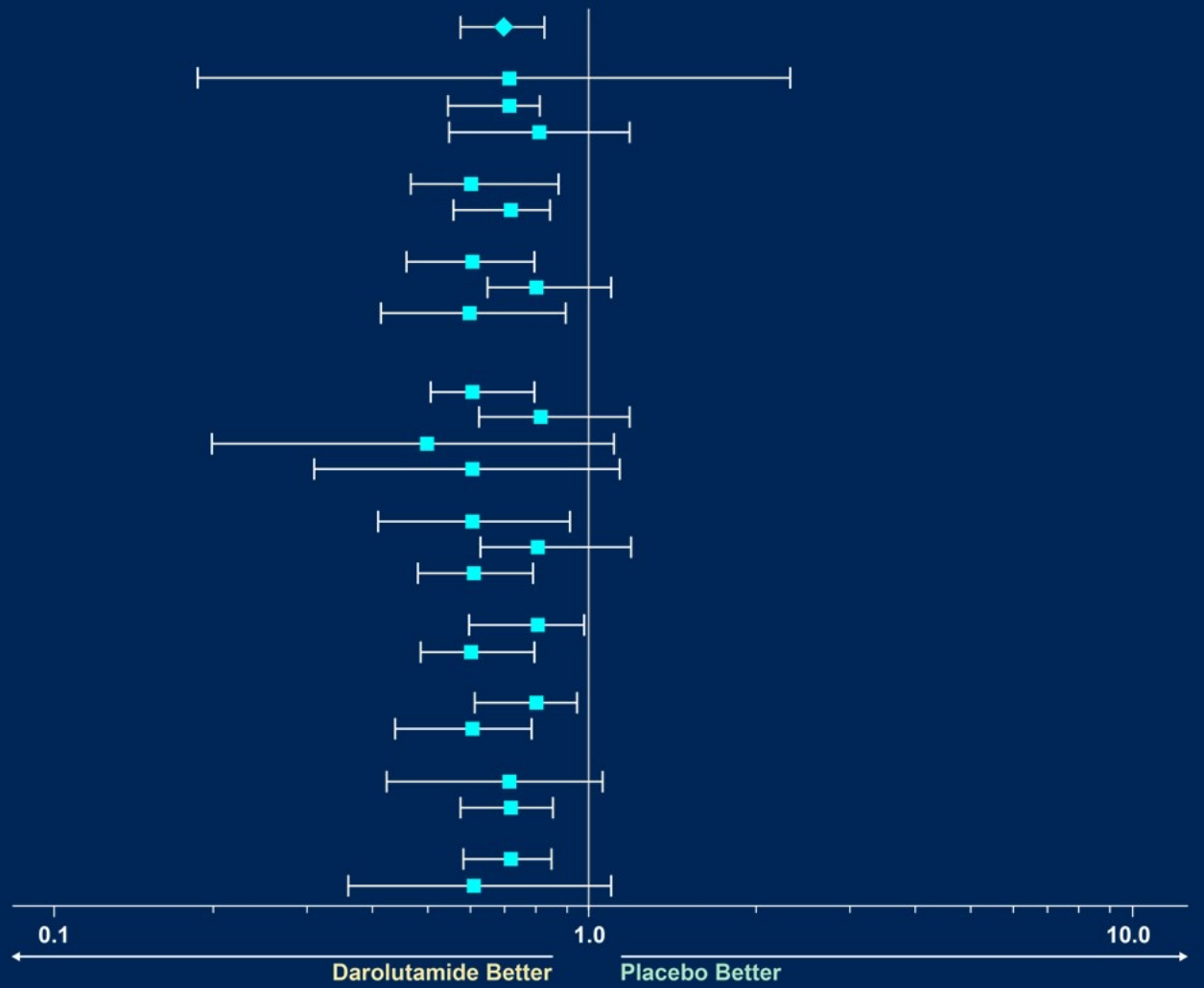
ARASENS Overall Survival: Subgroup Analyses

	Darolutamide + ADT + Docetaxel	Placebo + ADT + Docetaxel	Hazard Ratio (95% CI)
	No. of Events/No. of Patients		
Overall	229/651	304/654	0.69 (0.58–0.82)
Extent of disease (eCRF)			
Nonregional lymph node metastasis	5/23	5/16	0.65 (0.19–2.25)
Bone metastasis	171/517	237/520	0.67 (0.55–0.81)
Visceral metastasis	53/111	62/118	0.79 (0.55–1.14)
ALP stratification factor (eCRF)			
Below upper limit of normal	62/290	93/291	0.64 (0.46–0.88)
At or above upper limit of normal	167/361	211/363	0.69 (0.56–0.85)
Age (years)			
<65 yr	80/243	117/234	0.59 (0.45–0.79)
65–74 yr	107/303	124/306	0.82 (0.63–1.06)
75–84 yr	40/102	60/110	0.61 (0.41–0.90)
≥85 yr	2/3	3/4	
Race			
White	131/345	173/333	0.63 (0.50–0.79)
Asian	74/230	93/245	0.84 (0.62–1.14)
Black or African American	8/26	16/28	0.46 (0.20–1.08)
Other or not reported	16/50	22/48	0.58 (0.30–1.11)
Geographical region			
North America	42/125	56/119	0.61 (0.41–0.91)
Asia Pacific	74/229	92/244	0.85 (0.63–1.15)
Rest of the world	113/297	156/291	0.61 (0.48–0.78)
PSA at baseline			
Below median	110/315	142/337	0.77 (0.60–0.98)
At or above median	119/336	162/316	0.62 (0.49–0.78)
ECOG at baseline			
0	150/466	188/462	0.75 (0.61–0.93)
1	79/185	115/190	0.58 (0.43–0.77)
Gleason score			
<8	33/122	44/118	0.65 (0.42–1.03)
≥8	187/505	248/516	0.71 (0.59–0.86)
Metastatic stage at initial diagnosis			
M1 (*de novo*)	206/558	271/566	0.71 (0.59–0.85)
M0 (recurrent)	22/86	30/82	0.61 (0.35–1.05)



eCRF, electronic case report form.

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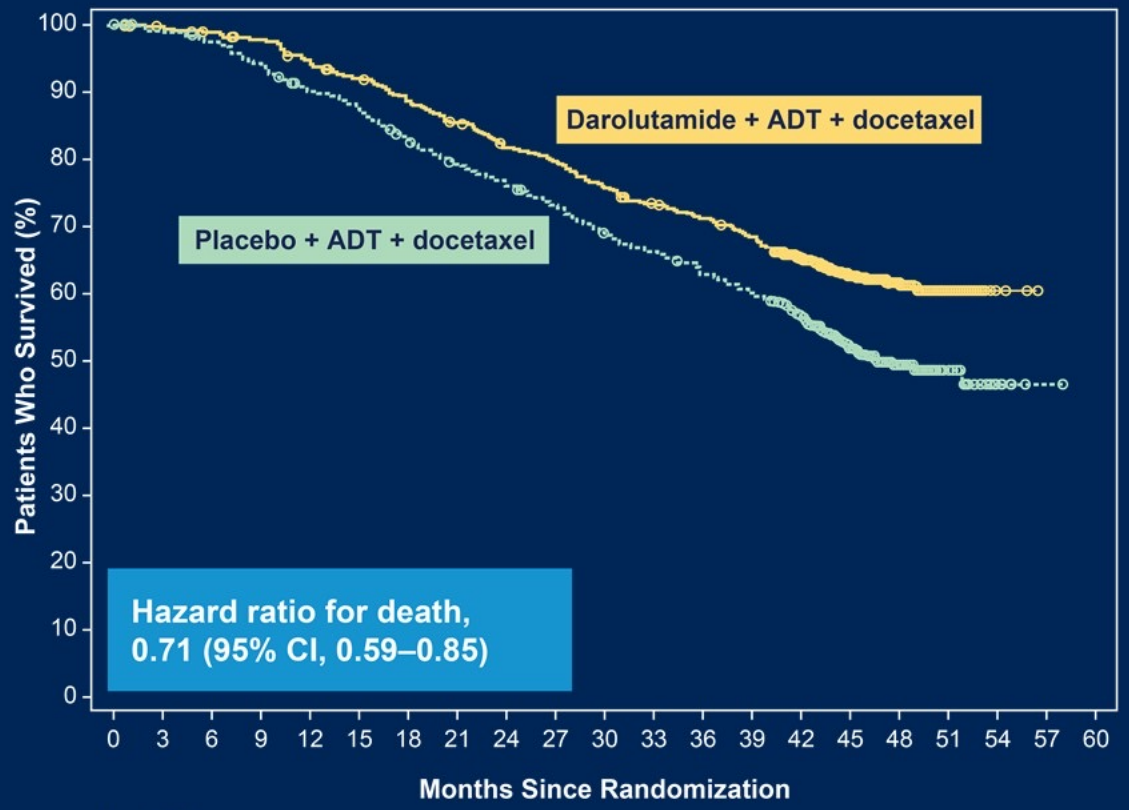
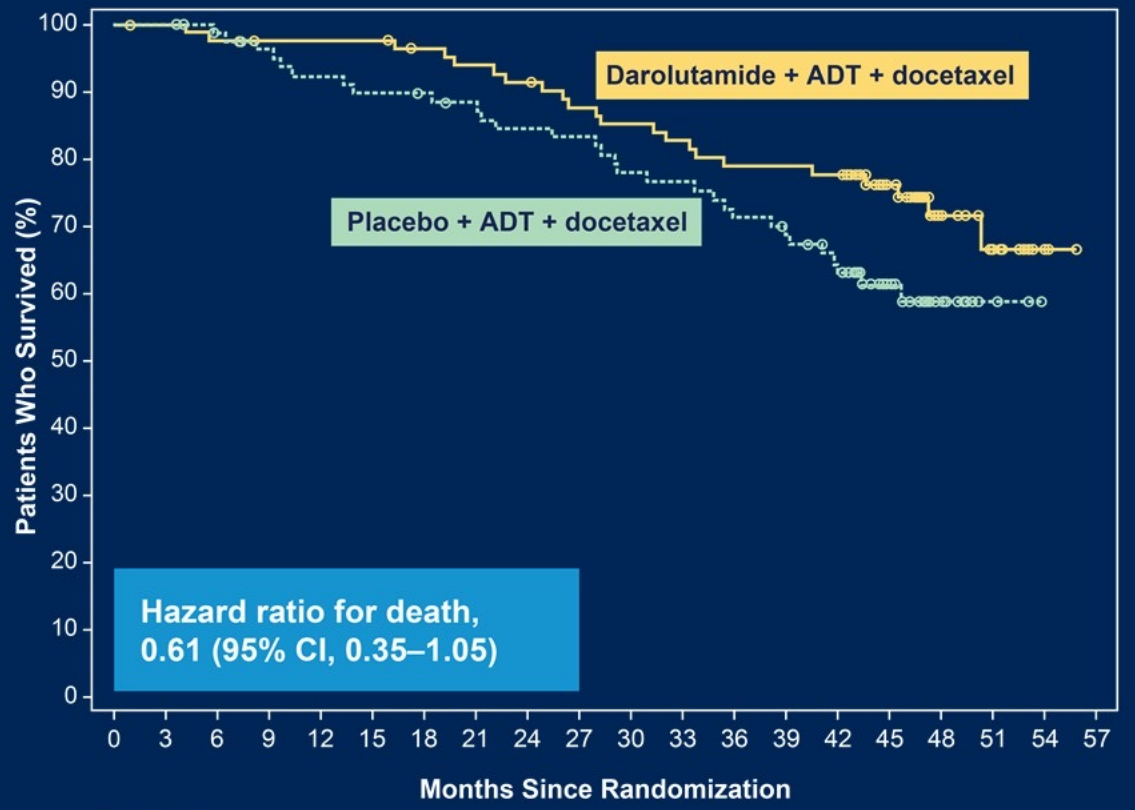
Overall Survival By Metastatic Stage at Initial Diagnosis

De novo metastatic disease



No. at Risk																				
Darolutamide	558	553	547	539	520	505	485	466	445	433	412	396	383	367	334	220	116	45	7	0	0
Placebo	566	558	546	526	503	490	461	438	420	403	378	362	344	328	292	190	93	33	6	1	0

Recurrent metastatic disease



No. at Risk																				
Darolutamide	86	85	83	81	81	81	78	76	74	70	68	66	63	63	62	43	20	11	2	0
Placebo	82	82	78	75	72	70	69	67	64	63	59	58	54	51	45	26	12	4	0	0

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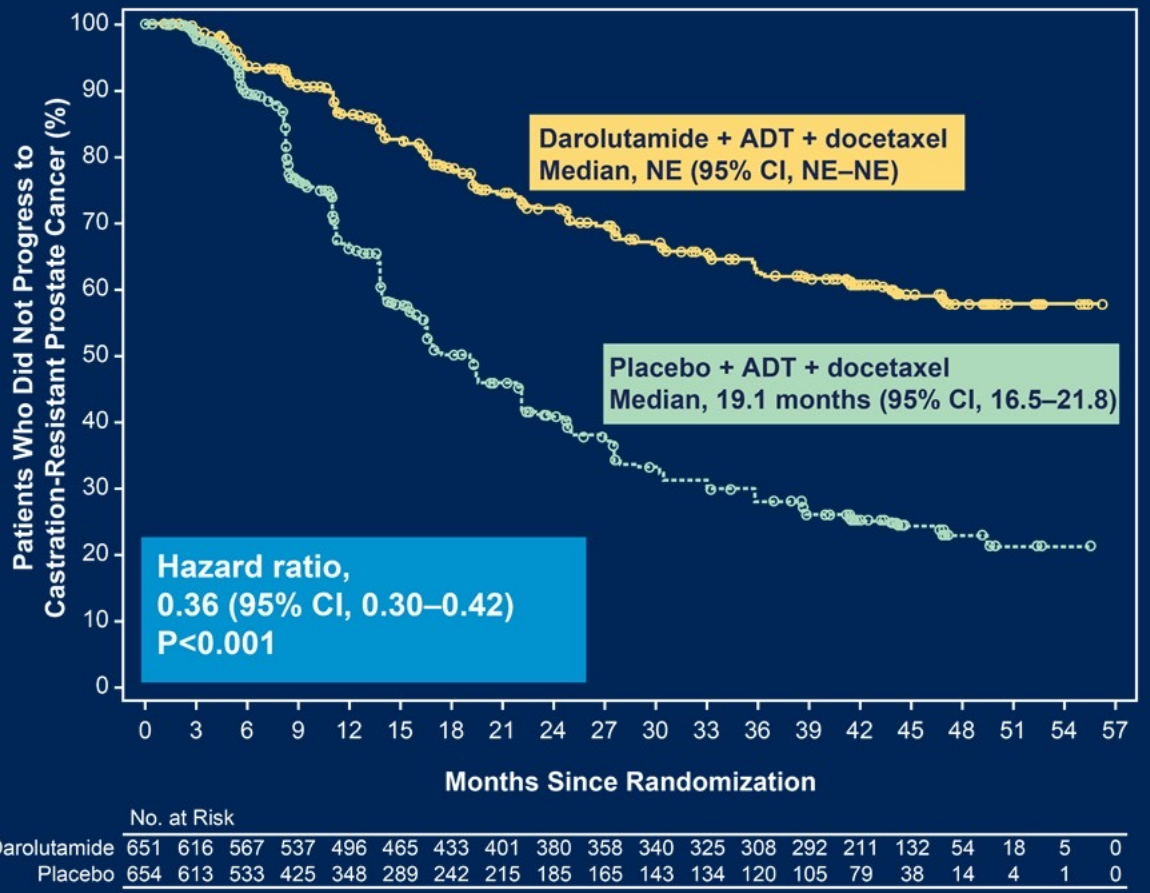
Key Secondary Endpoints

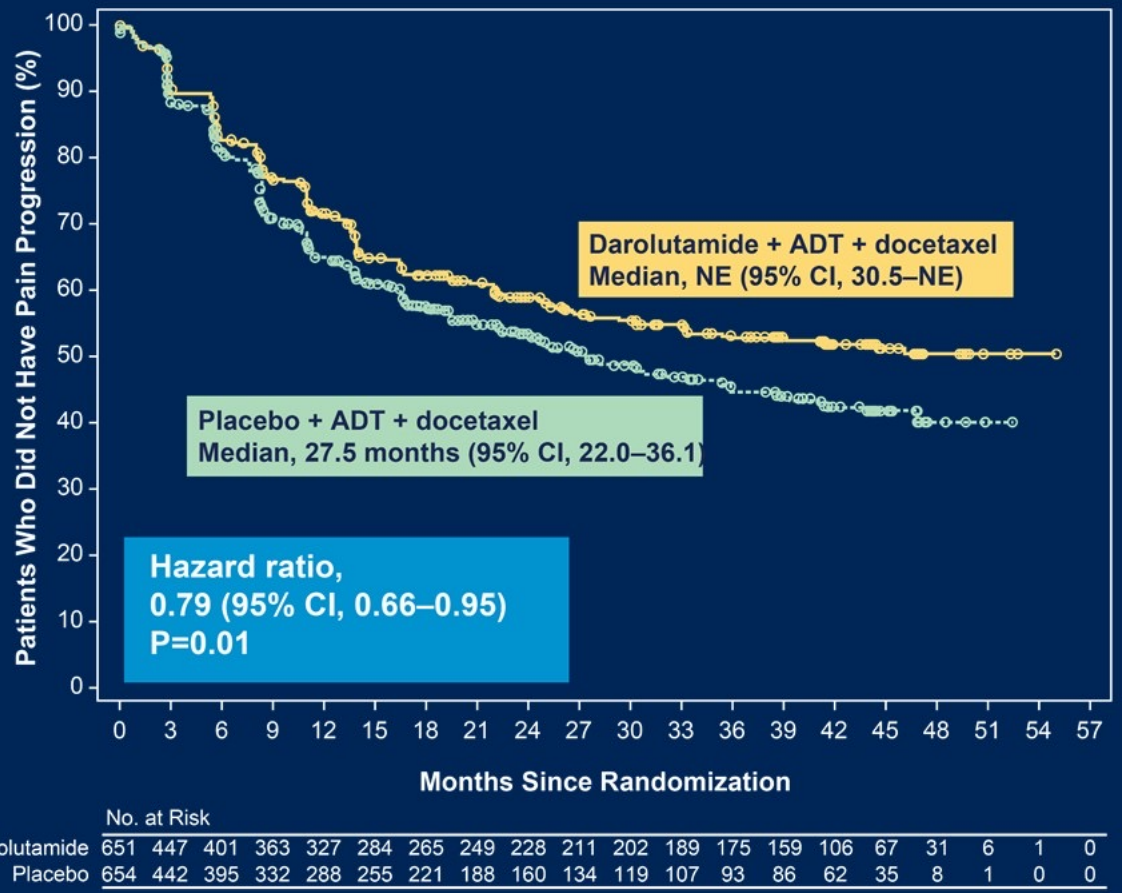
Time to CRPC



No. at Risk

Darolutamide	651	616	567	537	496	465	433	401	380	358	340	325	308	292	211	132	54	18	5	0
Placebo	654	613	533	425	348	289	242	215	185	165	143	134	120	105	79	38	14	4	1	0

Time to pain progression*



No. at Risk

Darolutamide	651	447	401	363	327	284	265	249	228	211	202	189	175	159	106	67	31	6	1	0
Placebo	654	442	395	332	288	255	221	188	160	134	119	107	93	86	62	35	8	1	0	0

*Pain progression was defined by change in the Brief Pain Inventory–Short Form questionnaire worst pain score or initiation of opioid therapy for ≥7 days.

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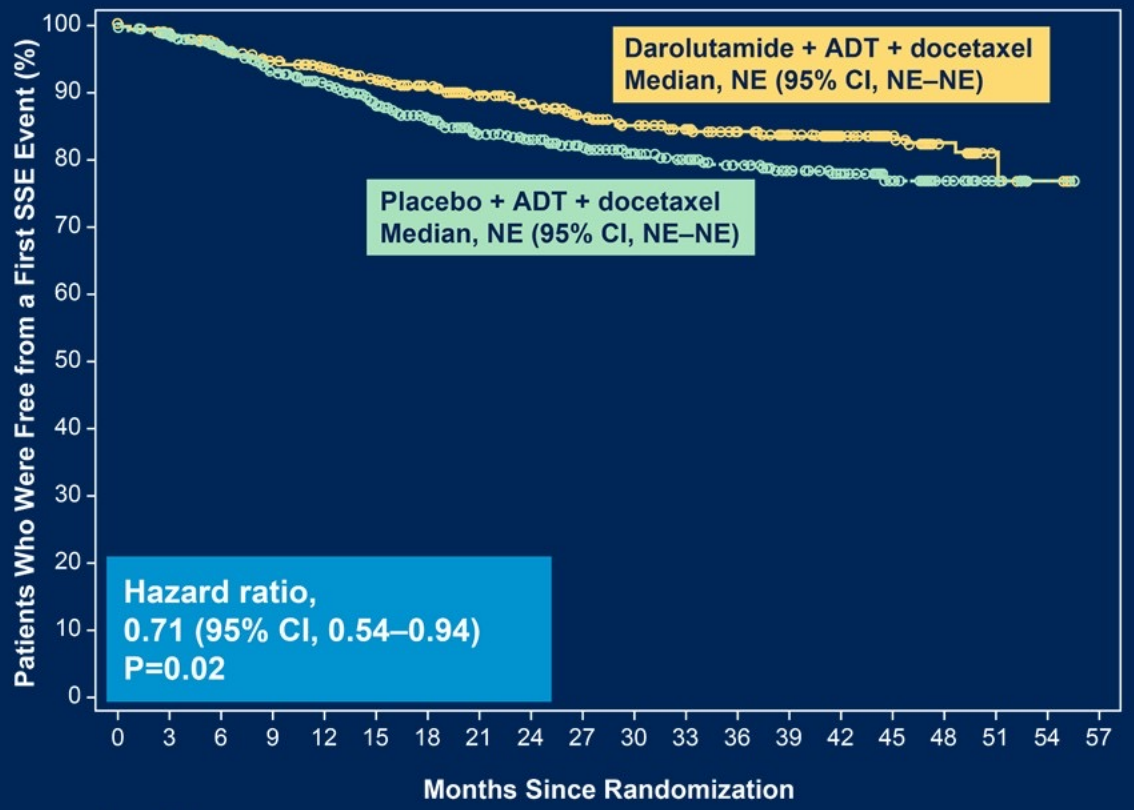
Key Secondary Endpoints

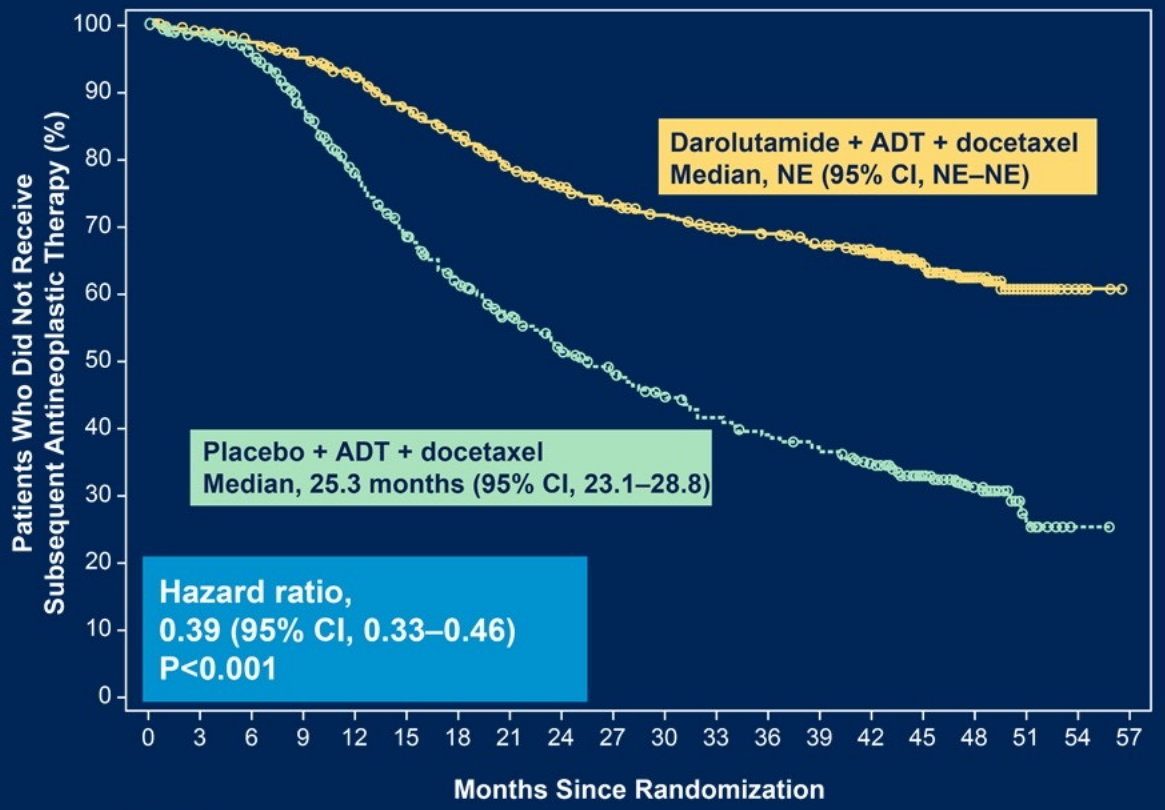
Time to first SSE



No. at Risk

Darolutamide	651	620	595	570	546	518	486	457	431	407	388	372	353	327	239	155	61	20	5	0
Placebo	654	618	582	535	494	439	399	349	309	268	238	219	202	183	134	72	28	7	1	0

Time to first subsequent antineoplastic therapy



No. at Risk

Darolutamide	651	638	621	600	570	536	503	466	442	422	406	390	380	367	342	220	113	42	8	0
Placebo	654	636	605	535	465	403	355	317	284	259	237	219	205	191	167	105	48	14	1	0

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ARASENS: Treatment-Emergent Adverse Events

TEAE, n (%)	Darolutamide + ADT + docetaxel (n=652*)	Placebo + ADT + docetaxel (n=650*)
Any	649 (99.5)	643 (98.9)
Worst grade		
Grade 1	28 (4.3)	35 (5.4)
Grade 2	162 (24.8)	169 (26.0)
Grade 3	248 (38.0)	232 (35.7)
Grade 4	183 (28.1)	181 (27.8)
Grade 5	27 (4.1)	26 (4.0)
Serious	292 (44.8)	275 (42.3)
Leading to permanent discontinuation of:		
Darolutamide/placebo	88 (13.5)	69 (10.6)
Docetaxel	52 (8.0)	67 (10.3)

Median treatment duration was 41.0 months for darolutamide-treated patients and 16.7 months for placebo-treated patients.
*Three randomized patients (all in the placebo group) were never treated and were excluded from the safety analysis set. One patient randomized to placebo but who received darolutamide was included in the darolutamide group for the safety analysis set.
TEAE, treatment-emergent adverse event.

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Grade 3–4 Adverse Events

Grade 3–4 AEs in ≥2% of darolutamide-treated patients, n (%)	Darolutamide + ADT + docetaxel (n=652)	Placebo + ADT + docetaxel (n=650)
Any AE	431 (66.1)	413 (63.5)
Neutropenia*	220 (33.7)	222 (34.2)
Febrile neutropenia	51 (7.8)	48 (7.4)
Hypertension	42 (6.4)	21 (3.2)
Anemia	31 (4.8)	33 (5.1)
Pneumonia	21 (3.2)	20 (3.1)
Hyperglycemia	18 (2.8)	24 (3.7)
Increased alanine aminotransferase	18 (2.8)	11 (1.7)
Increased aspartate aminotransferase	17 (2.6)	7 (1.1)
Increased weight	14 (2.1)	8 (1.2)
Urinary tract infection	13 (2.0)	12 (1.8)

*Neutropenia includes the preferred terms leukopenia, neutropenia, neutrophil count decreased, and white blood cell count decreased.

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Adverse Events of Special Interest for AR Pathway Inhibitors

AEs associated with AR pathway inhibitor therapy	Darolutamide + ADT + docetaxel (n=652)		Placebo + ADT + docetaxel (n=650)	
	Patients, n (%)	EAIR/100 PY*	Patients, n (%)	EAIR/100 PY*
Fatigue	216 (33.1)	12.5	214 (32.9)	17.8
Bone fracture	49 (7.5)	2.8	33 (5.1)	2.7
Falls	43 (6.6)	2.5	30 (4.6)	2.5
Rash†	108 (16.6)	6.2	88 (13.5)	7.3
Diabetes mellitus and hyperglycemia‡	99 (15.2)	5.7	93 (14.3)	7.7
Weight decreased	22 (3.4)	1.3	35 (5.4)	2.9
Vasodilatation and flushing	133 (20.4)	7.7	141 (21.7)	11.7
Breast disorders/gynecomastia‡	21 (3.2)	1.2	10 (1.5)	0.8
Hypertension‡	89 (13.7)	5.1	60 (9.2)	5.0
Cardiac disorder‡	71 (10.9)	4.1	76 (11.7)	6.3
Cerebral ischemia	8 (1.2)	0.5	8 (1.2)	0.7
Mental impairment disorder‡	23 (3.5)	1.3	15 (2.3)	1.2
Depressed mood disorder‡	21 (3.2)	1.2	24 (3.7)	2.0
Seizure	4 (0.6)	0.2	1 (0.2)	0.1

*EAIR is the number of patients with a given AE divided by the total darolutamide/placebo treatment duration of all patients in years and expressed in 100 PY. †This category combines the following MedDRA terms: rash, maculopapular rash, drug eruption, pruritic rash, erythematous rash, macular rash, papular rash, follicular rash, pustular rash, and vesicular rash. ‡This category is a MedDRA High-Level Group Term. EAIR, exposure-adjusted incidence rate; PY, patient year.

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ARASENS Conclusions

- Darolutamide in combination with ADT and docetaxel significantly improved OS compared with ADT and docetaxel in patients with mHSPC. Darolutamide reduced the risk of death by 32.5%
- Darolutamide improved OS despite a high rate of subsequent life-prolonging systemic therapy in the placebo group
- The OS benefit for darolutamide was consistent across prespecified subgroups
- Darolutamide also significantly improved key secondary endpoints, including time to castration-resistant prostate cancer, time to pain progression, time to first SSE, and time to first subsequent antineoplastic therapy
- Rates of adverse events were similar between the darolutamide and placebo groups

Darolutamide in combination with ADT and docetaxel should become a new standard of care for treatment of mHSPC

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Takeaway

- ADT alone is obsolete and should rarely be used
- Docetaxel benefit is for high volume disease
- For high volume disease ADT + darolutamide + docetaxel is superior to ADT + docetaxel

A phase 3 trial with a 2x2 factorial design in men with *de novo* metastatic castration-sensitive prostate cancer (mCSPC): Overall survival with abiraterone acetate plus prednisone in PEACE-1

Karim Fizazi, Joan Carles, Stéphanie Foulon, Guilhem Roubaud, Ray McDermott, Aude Fléchon, Bertrand Tombal, Stéphane Supiot, Dominik Berthold, Philippe Ronchin, Gabriel Kacsó, Gwenaëlle Gravis, Fabio Calabro, Jean-François Berdah, Ali Hasbini, Marlon Silva, Antoine Thiery-Vuillemin, Igor Latorzeff, Isabelle Rieger, Alberto Bossi

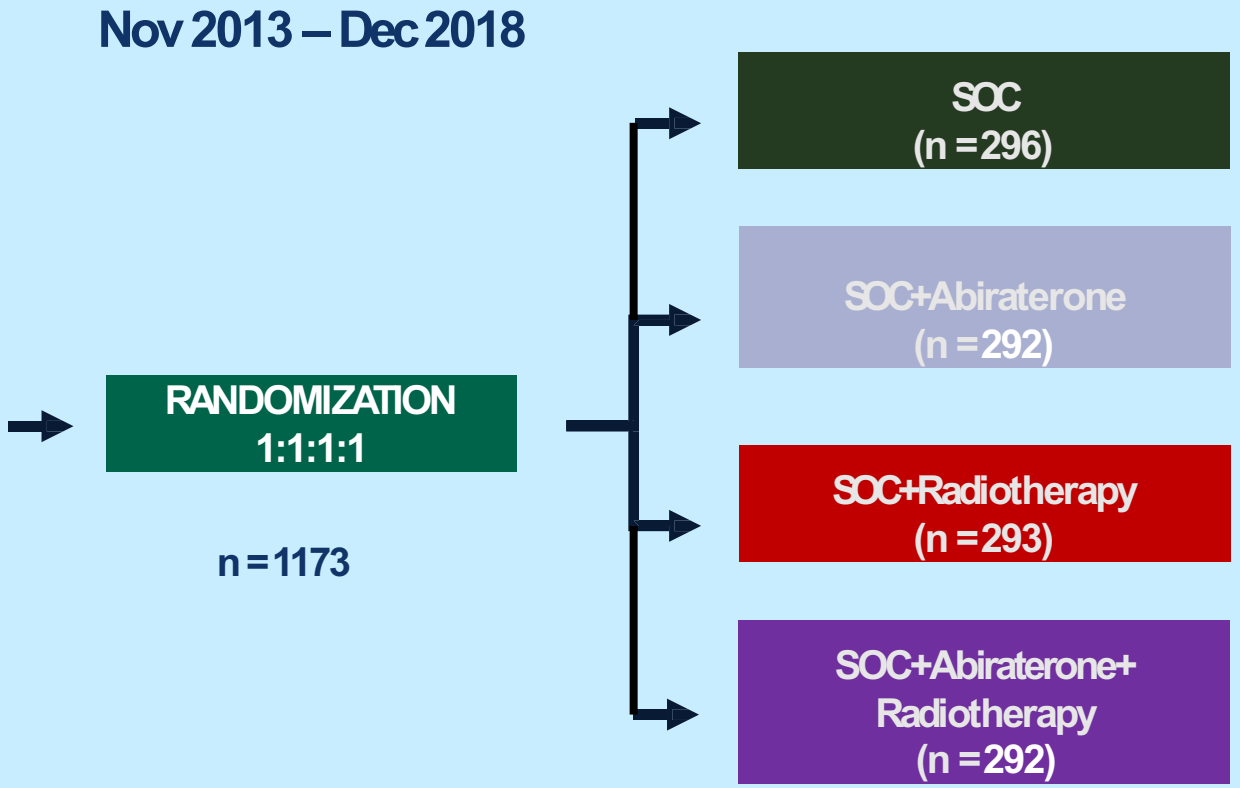
Design of PEACE-1 (2x2)

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

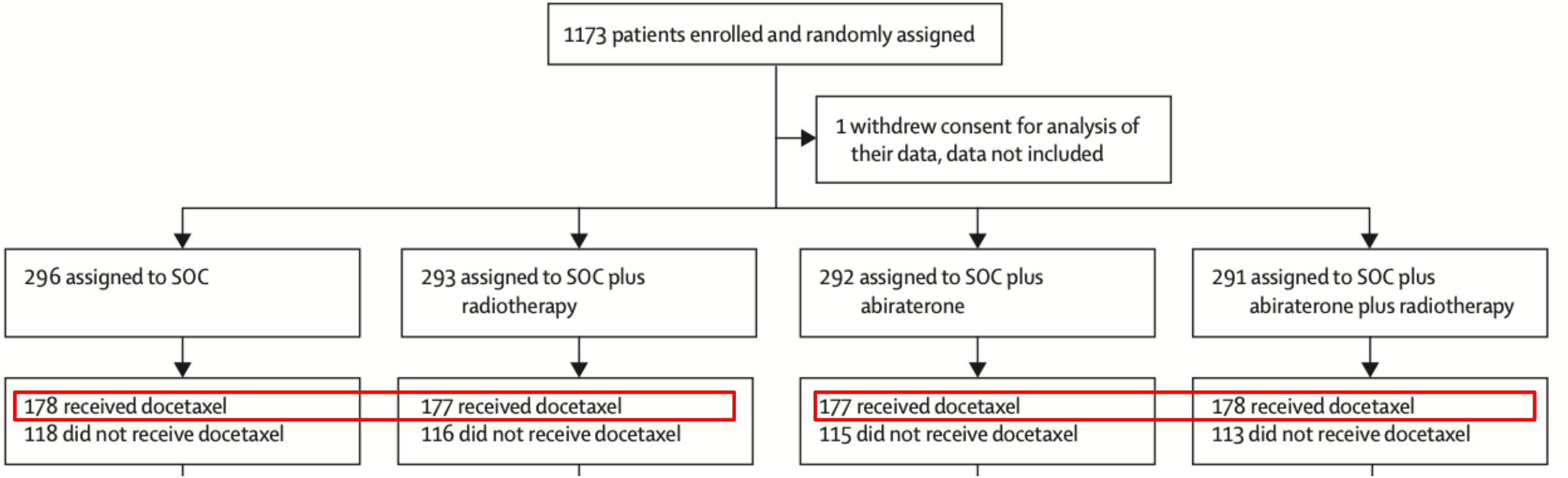


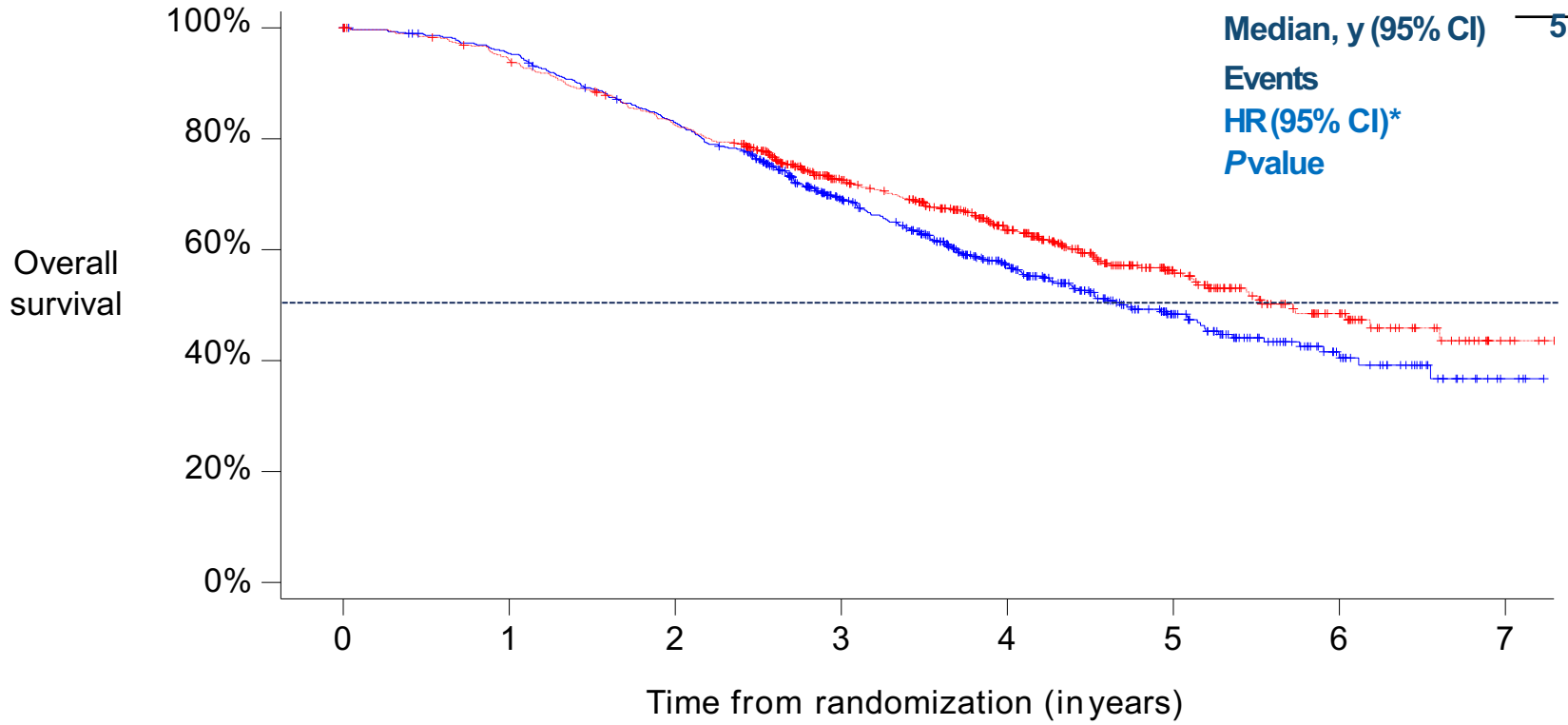
Figure 1: **Trial profile**
ADT=androgen deprivation therapy. SOC=standard of care.

Patient characteristics (ADT+docetaxel population)

		SOC (+/- RXT) + Abiraterone (n = 355)	SOC (+/- RXT) (n = 355)
Median age, year (IQR)		66 (60–70)	66 (59–70)
ECOG PS score, n (%)	0 1-2	250 (70) 105 (30)	246 (69) 109 (31)
Gleason score at initial diagnosis, n (%)	≤ 7 ≥ 8	79 (23) 270 (77)	71 (21) 276 (79)
Median time from diagnosis, month (IQR)		2.2 (1.6-3.0)	2.2 (1.4-2.9)
Metastatic sites, n (%)	Lymph nodes only Bone without visceral Visceral	27 (8) 287 (81) 41 (12)	29 (8) 279 (79) 47 (13)
Disease burden, n (%)	Low High	131 (37) 224 (63)	123 (35) 232 (65)
Median baseline PSA, ng/mL (IQR)		13.7 (2.4-58.9)	12.0 (3.0-59.9)
Docetaxel, n (%)	Yes No	355 (100) 0 (0)	355 (100) 0 (0)

OS in the Overall population

	SOC+Abi (n = 583)	SOC (n = 589)
Median, y (95% CI)	5.7 (5.1-NE)	4.7 (4.3-5.3)
Events	228	268
HR (95% CI)*	0.82 (0.69-0.98)	
P value	0.030	

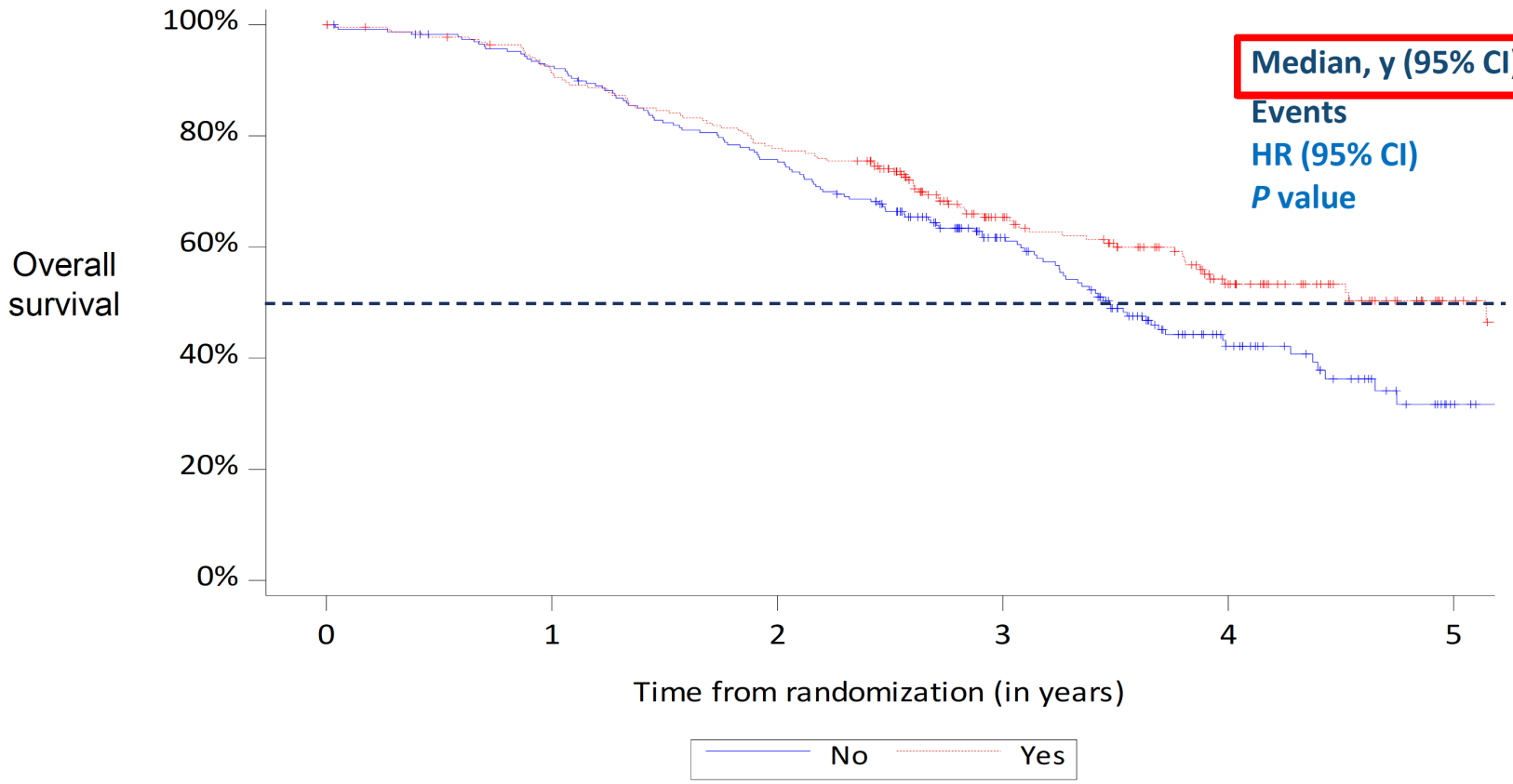


No	589	556	480	334	207	101	37	4
Yes	583	541	470	340	230	111	47	6

*Adjusted on stratification parameters (RXT, PS, type of castration, metastatic burden, docetaxel)

OS with Abiraterone in the ADT+docetaxel (+/-RXT): High-volume patients

	SOC+Abi (n = 224)	SOC (n = 232)
Median, y (95% CI)	**5.1 (3.8-NE)**	**3.5 (3.2-4.0)**
Events	92	120
HR (95% CI)	**0.72 (0.55-0.95)**	
***P* value**	0.019	



No	**232**	**210**	**171**	**101**	**39**	**6**
Yes	**224**	**201**	**171**	**103**	**57**	**16**

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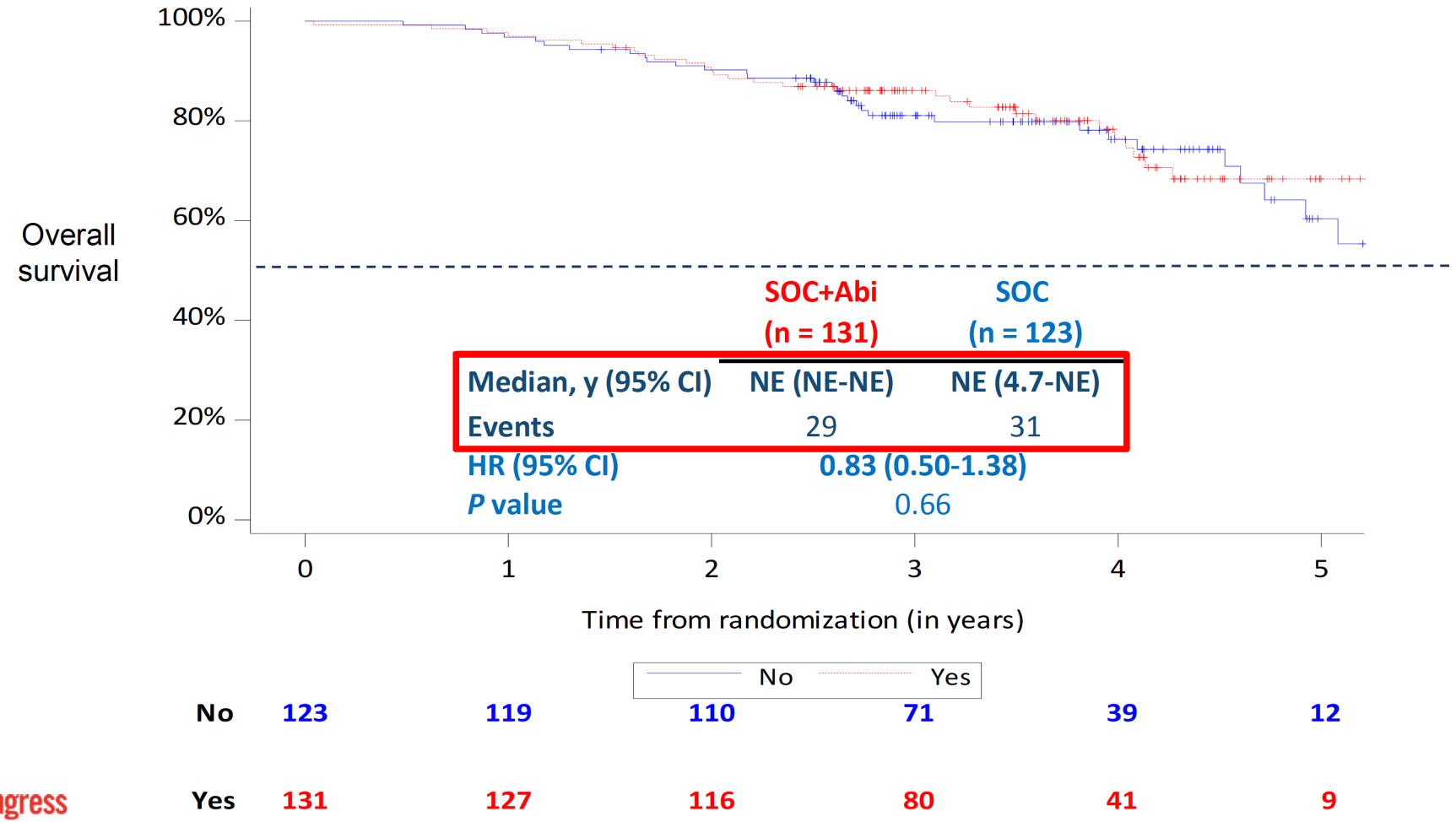
OS with Abiraterone in the ADT+docetaxel (+/-RXT): Low-volume patients



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PEACE-1 OS results in the context of recent data

Median Overall Survival
(*de novo* High-Volume mCSPC)

ADT alone

33 m CHAARTED (Kyriakopoulos CE, JCO 2018)
34 m GETUG-15 (Gravis G Eur Urol 2018)
35 m STAMPEDE (Clarke NW, Ann Oncol 2019)

ADT+docetaxel

40 m STAMPEDE doce (Clarke Ann Oncol 2019)
42 m PEACE-1
44 m GETUG-15 (Gravis G Eur Urol 2018)
48 m CHAARTED (Kyriakopoulos CE, JCO 2018)

ADT+abiraterone

50 m LATITUDE (Fizazi K Lancet Oncol 2019)
56 m STAMPEDE Abi (James N ESMO 2020)

ADT+docetaxel+abiraterone

61 m PEACE-1

Takeaway

- ADT alone is obsolete and should rarely be used
- Docetaxel benefit is for high volume disease
- For high volume disease ADT + darolutamide + docetaxel is superior to ADT + docetaxel
- Abiraterone + prednisone improves OS for those who also receive docetaxel in addition to ADT (+/- EBRT)- LV data needs to mature

RT + Combination ADT

RT + ADT + Abiraterone

RT + ADT + Abiraterone + Enzalutamide

RT + ADT + Docetaxel

2023 ASCO ANNUAL MEETING

Prostate irradiation in men with *de novo*, low-volume, metastatic castration-sensitive prostate cancer (mCSPC): Results of PEACE-1, a phase 3 randomized trial with a 2x2 design

Alberto BOSSI,
Institut Gustave Roussy, Amethyst RT Group, France

Stéphanie Foulon, Xavier Maldonado, Paul Sargos, Ray McDermott, Paul Kelly, Aude Fléchon, Bertrand Tombal, Stéphane Supiot, Dominik Berthold, Philippe Ronchin, Gabriel Kacso, Naji Salem, Fabio Calabro', Jean-François Berdah, Ali Hasbini, Marlon Silva, Jihane Boustani, Hélène Ribault, Karim Fizazi

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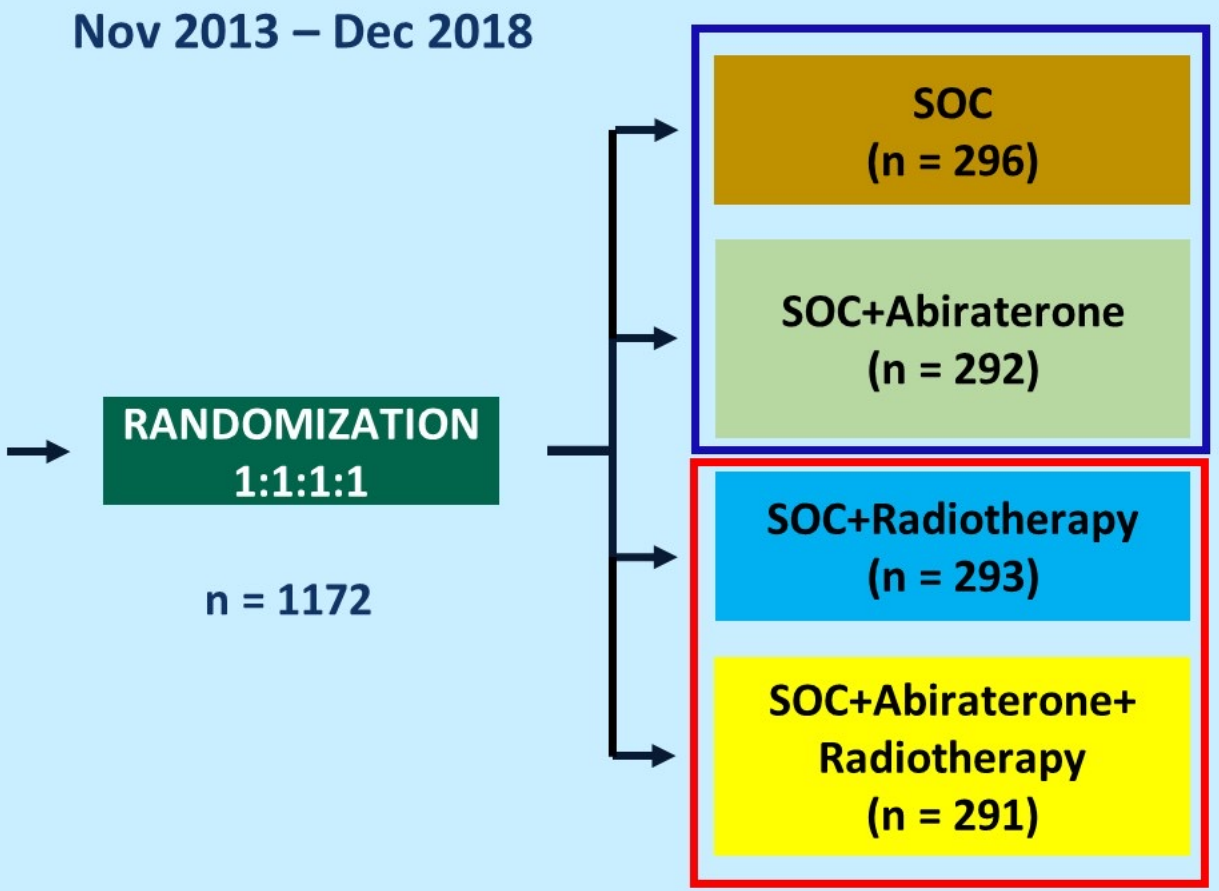
Design of PEACE-1

Key Eligibility Criteria
De novo mCSPC
Distant metastatic disease: ≥ 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

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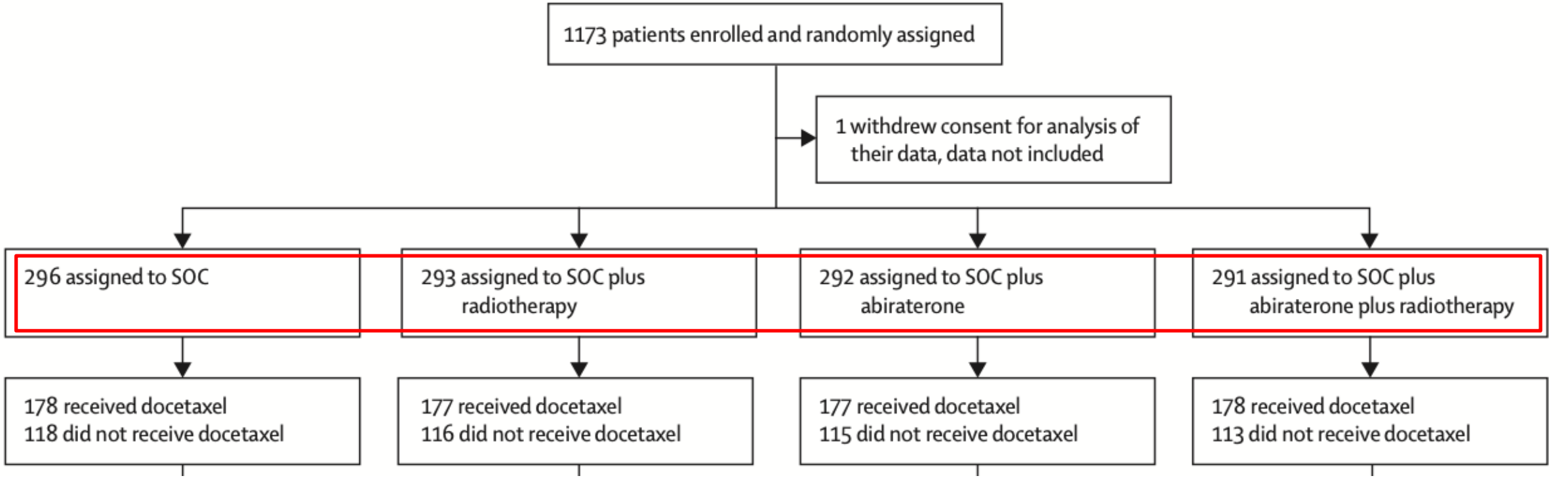
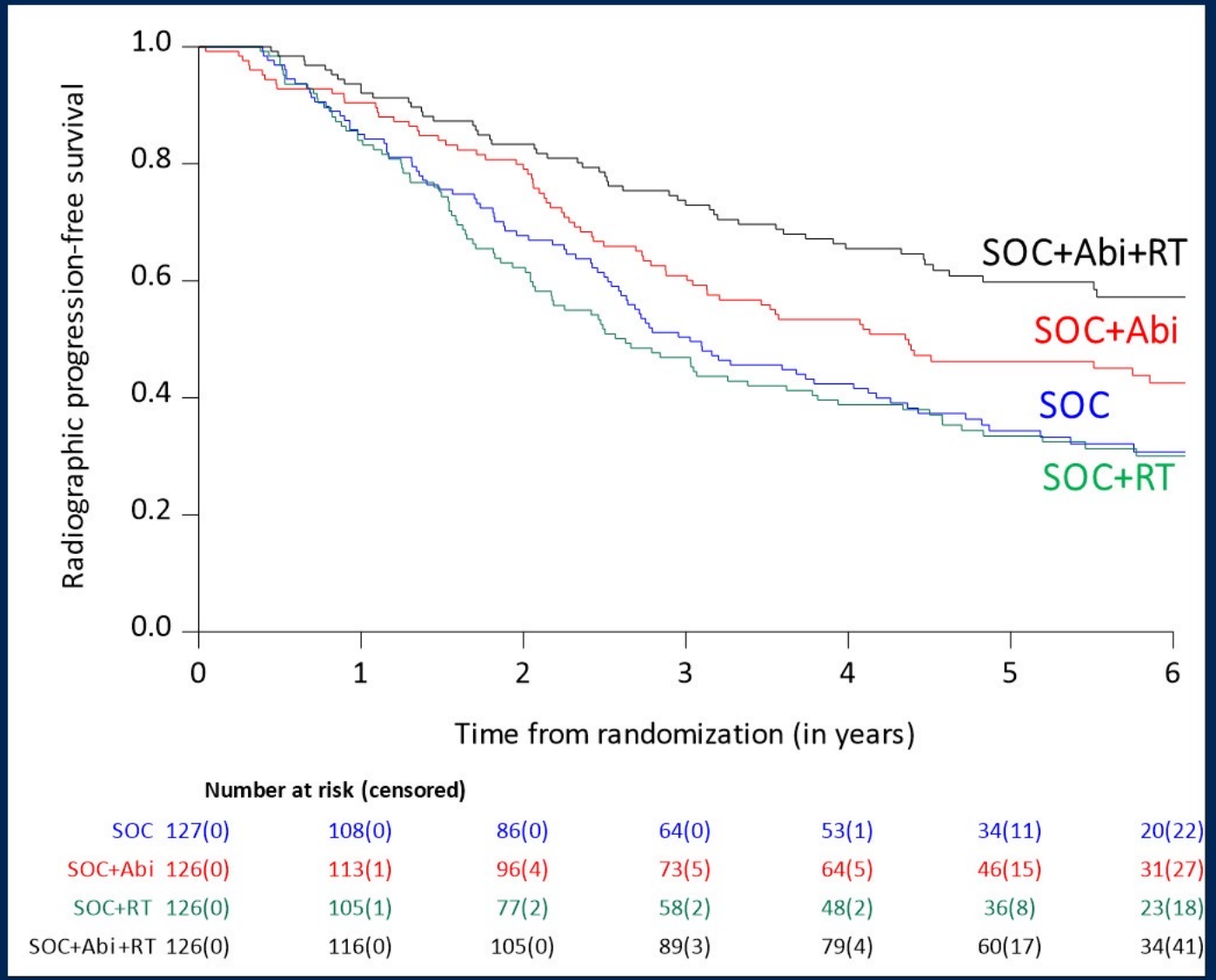


Figure 1: **Trial profile**
ADT=androgen deprivation therapy. SOC=standard of care.

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 arms w/wo Abi	0.61		0.02	

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

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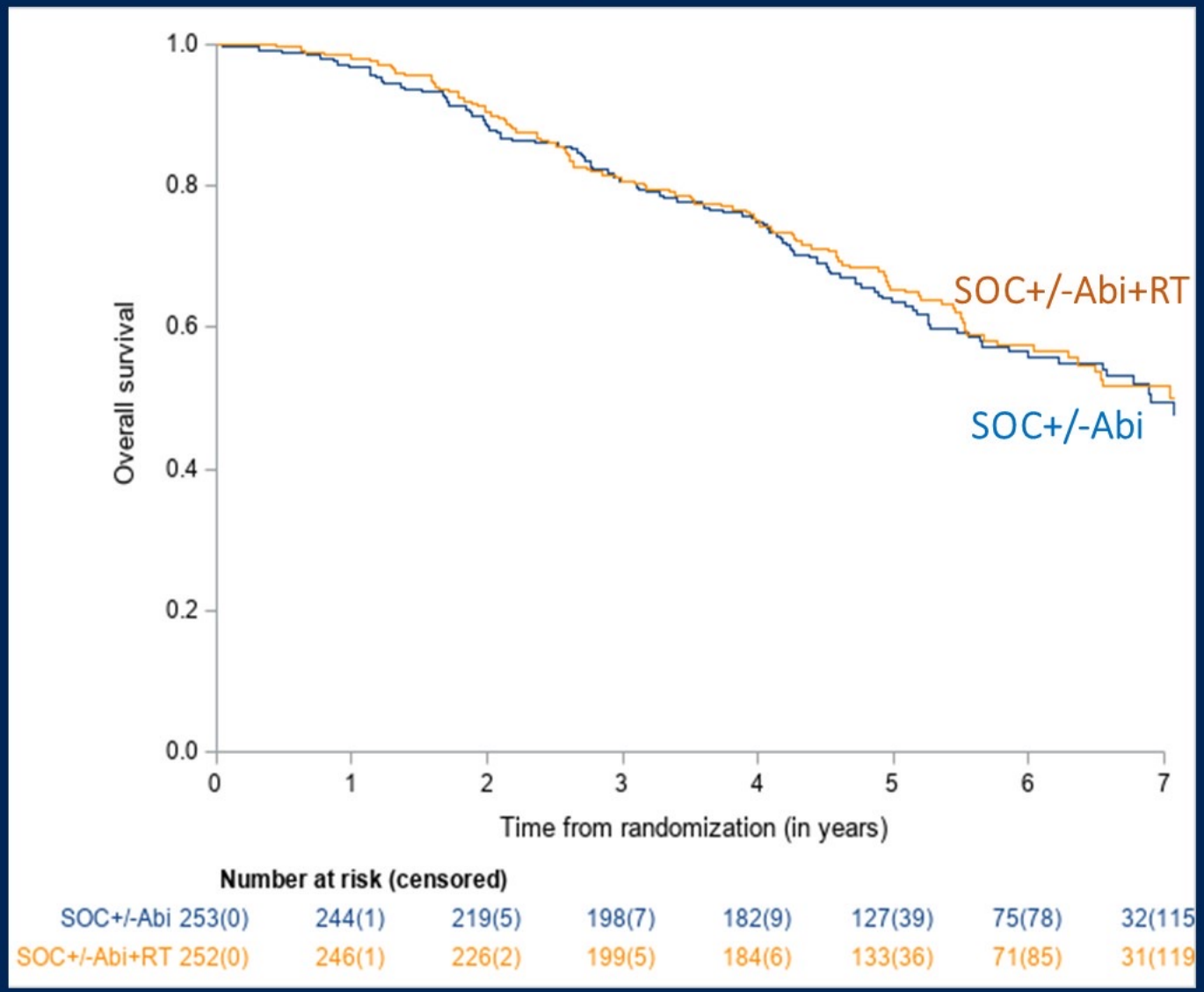
OS (low volume population)



	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 Abitraterone and stratification factors (PS, type of castration, docetaxel)

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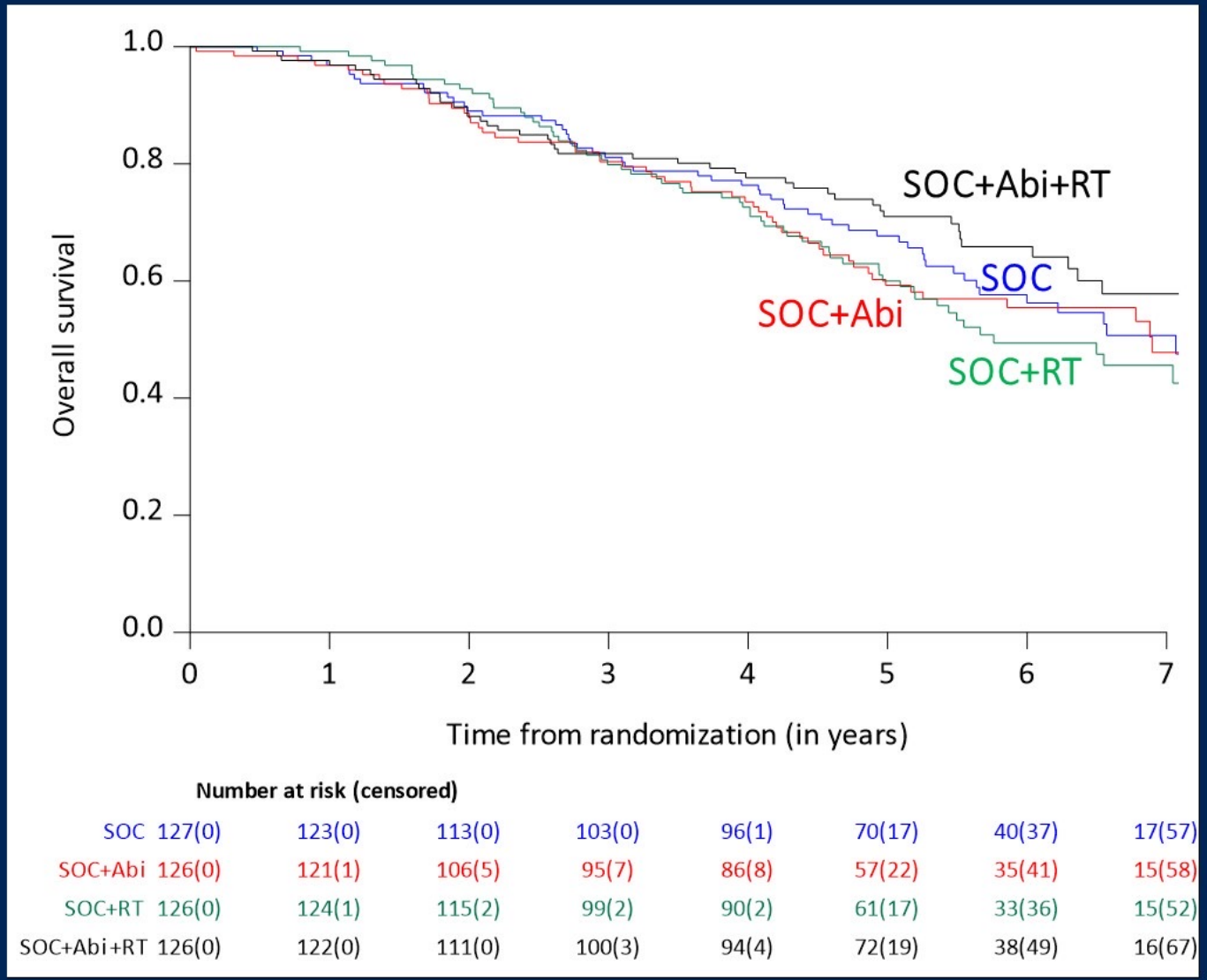
OS (low volume population)



	SOC (n=127)	SOC+RT (n=126)	SOC+Abi (n=126)	SOC+Abi+RT (n=126)
Median, ys. (95.1% CI)	7.1 (5.6-NE)	5.8 (5.1-NE)	6.9 (5.0-NE)	NE (6.4-NE)
Events, n.	57	60	54	44
HR (95.1% CI)*	Ref	1.19 (0.82-1.72)	1.05 (0.72-1.54)	0.81 (0.55-1.21
Global p-value	0.29			
HR (95.1% CI)*	Ref	1.18 (0.81-1.71)	Ref	0.77 (0.51-1.16)
P-values arms w/wo Abi	0.39		0.21	

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

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ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

Serious Genito-Urinary events (low volume population*)

	No RT (n=200)	RT (n=198)
Urinary Catheter	9	6
Double J Stent	13	12
Nephrostomy	2	1
Prostate RT or TURP	27	4 TURP (all RT)
Radical Prostatectomy	1	1

*with available data regarding Serious Genito-Urinary events

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Conclusions

- Combining prostate RT with intensified systemic treatment (Abiraterone w/wt docetaxel) improves rPFS and CRPC free-survival in men with low burden, *de-novo* mCSPC.
- No detectable impact of prostate RT on OS, minimal added toxicity.

- For the first time, PEACE-1 also establishes a role of RT in the prevention of serious GU events, irrespective of the metastatic burden.

- A triplet of ADT+Abiraterone+prostate RT should be considered a standard in men with *de-novo* low burden mCSPC (additive effect). RT may also be considered in selected men with *de-novo* high burden mCSPC ("quadruplet").

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Takeaway

- ADT alone is obsolete and should rarely be used
- Docetaxel benefit is for high volume disease
- For high volume disease ADT + darolutamide + docetaxel is superior to ADT + docetaxel
- Abiraterone + prednisone improves OS for those who also receive docetaxel in addition to ADT (+/- EBRT)- LV data needs to mature
- For low volume M1 patients, adding prostate RT to ADT+ abiraterone + prednisone +/- docetaxel, did not have OS benefit

Abiraterone acetate plus prednisolone with or without enzalutamide added to androgen deprivation therapy compared to ADT alone for men with high-risk nonmetastatic prostate cancer: primary combined analysis from two comparisons in the STAMPEDE platform protocol

Gerhardt Attard, Louise Brown, Noel Clarke, Laura Murphy, William Cross, Rob Jones, Silke Gillessen, J.Martin Russell, Adrian Cook, Jo Bowen, Anna Lydon, Ian Pedley, Omi Parikh, Simon Chowdhury, Zafar Malik, David Matheson, Chris Parker, Matthew Sydes, Mahesh Parmar, Nicholas James **on behalf of the STAMPEDE investigators***

Conducted by Medical Research Council Trials Unit at University College London, U.K.

ClinicalTrials.gov number, NCT00268476 & Current Controlled Trials number, ISRCTN78818544

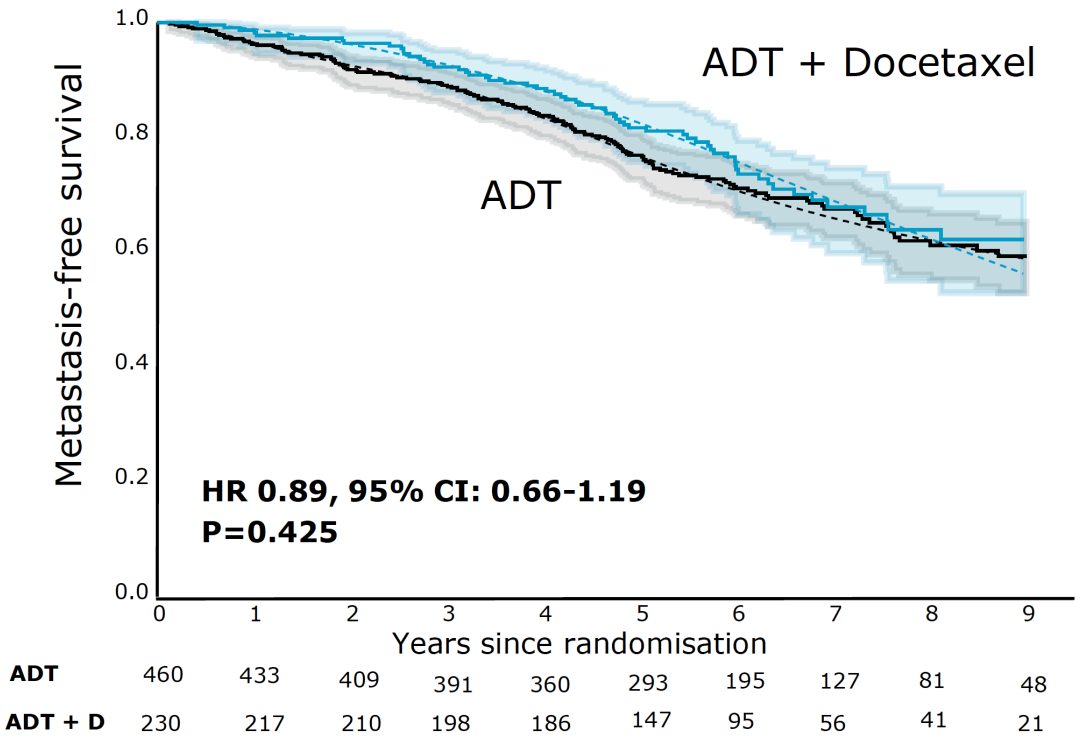
*113 U.K. and Swiss sites: list of investigators and collaborators at www.stampedetrial.org

2021 ESMO congress

Background: docetaxel

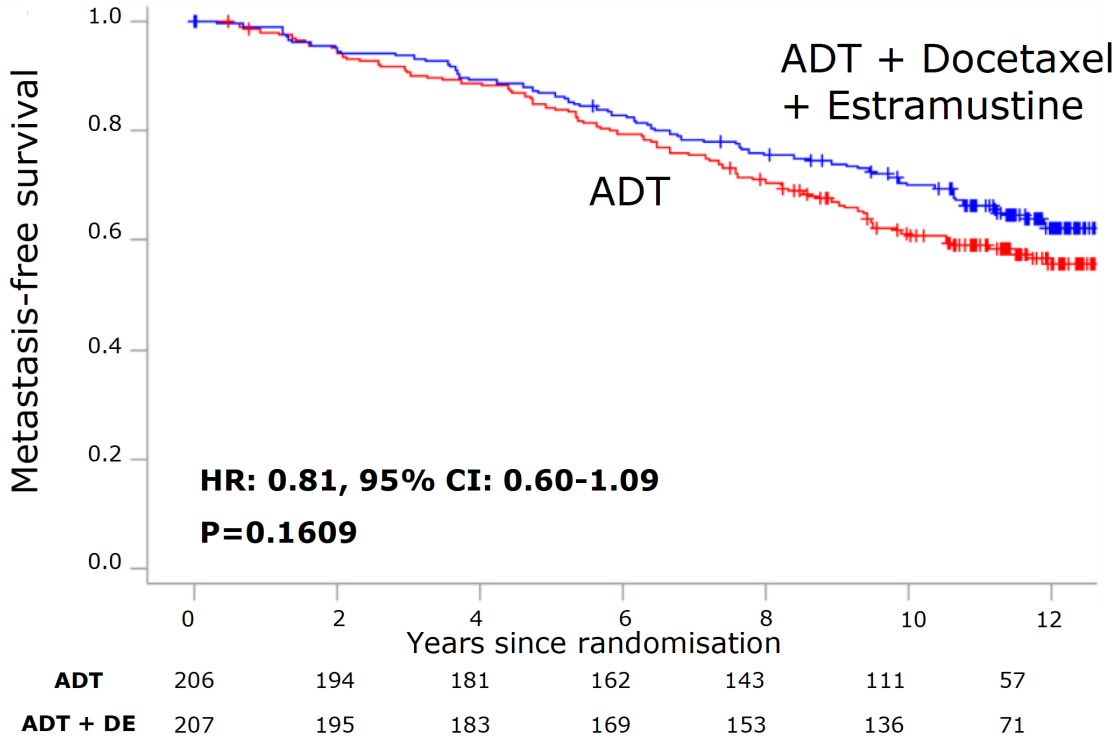
- Docetaxel improves survival in M1 PCa but **no improvement** in MFS/OS in M0

STAMPEDE trial



James et al, ESMO 2019, abstract 855PD

GETUG-12 trial



Fizazi et al, ESMO 2018, abstract 791O

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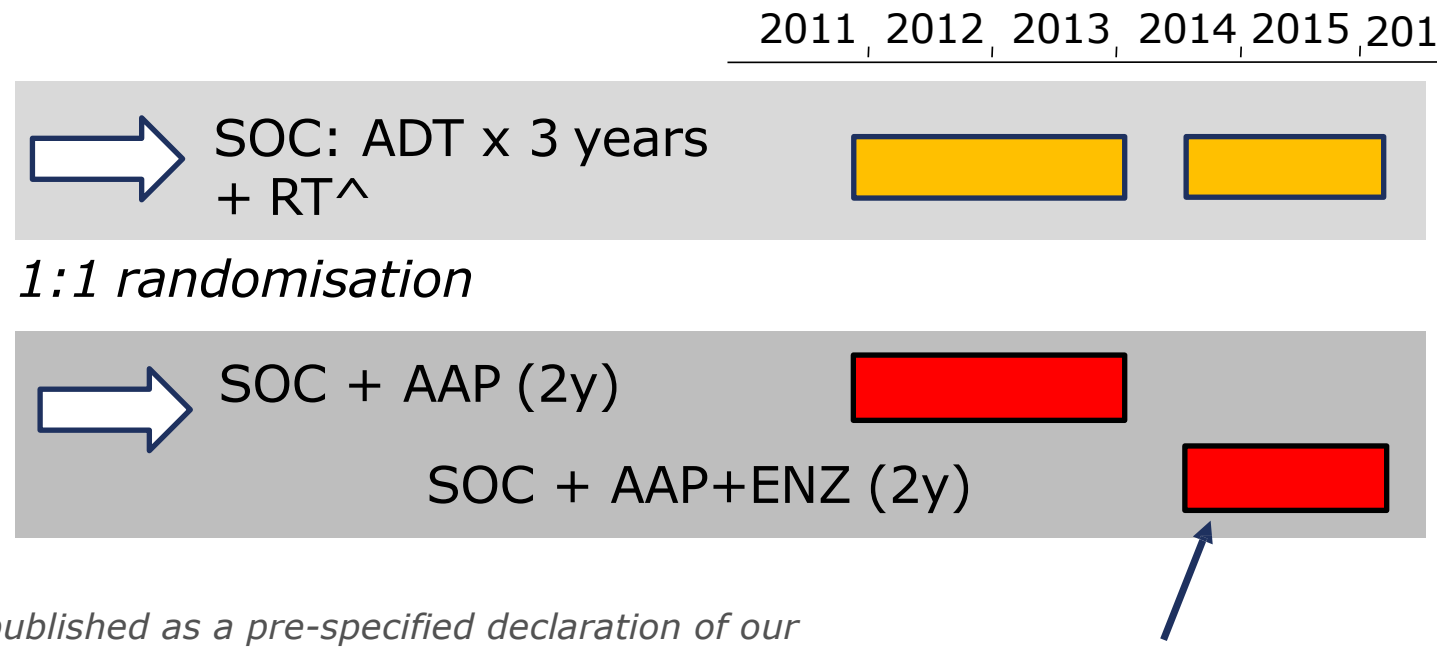
Study design

- M0 pts in AAP comparison: continued FU with **no further** efficacy inspections
- 2019 - amended the reporting plan* to split M1 & M0, power the 1^{ary} end-point on MFS, meta-analyse with new data from AAP+ENZ comparison



- No overlapping controls
- Same protocol & eligibility criteria
- 2 years AAP+/-ENZ
- No evidence of OS benefit with AAP+/-ENZ in mCRPC [1]

*published as a pre-specified declaration of our intentions: Attard G, et al. Eur Urol. Epub 2021 Jul 14

SOC, standard of care
^when indicated

[1]Morris MJ, et al. J Clin Oncol 2019;37:5008

Patient population

M0

No evidence of metastases on bone and CT scan of pelvis, abdo, chest

(pre-defined stratification criterion)

Newly-diagnosed

Any of:

- Node-Positive
- ≥2 of: Stage T3 or T4
  PSA≥40ng/ml
  Gleason 8, 9 or 10

Relapsing after previous RP or RT

Any of:

- Node-positive
- PSA≥4ng/ml, rising & doubling time <6m
- PSA≥20ng/ml

All patients

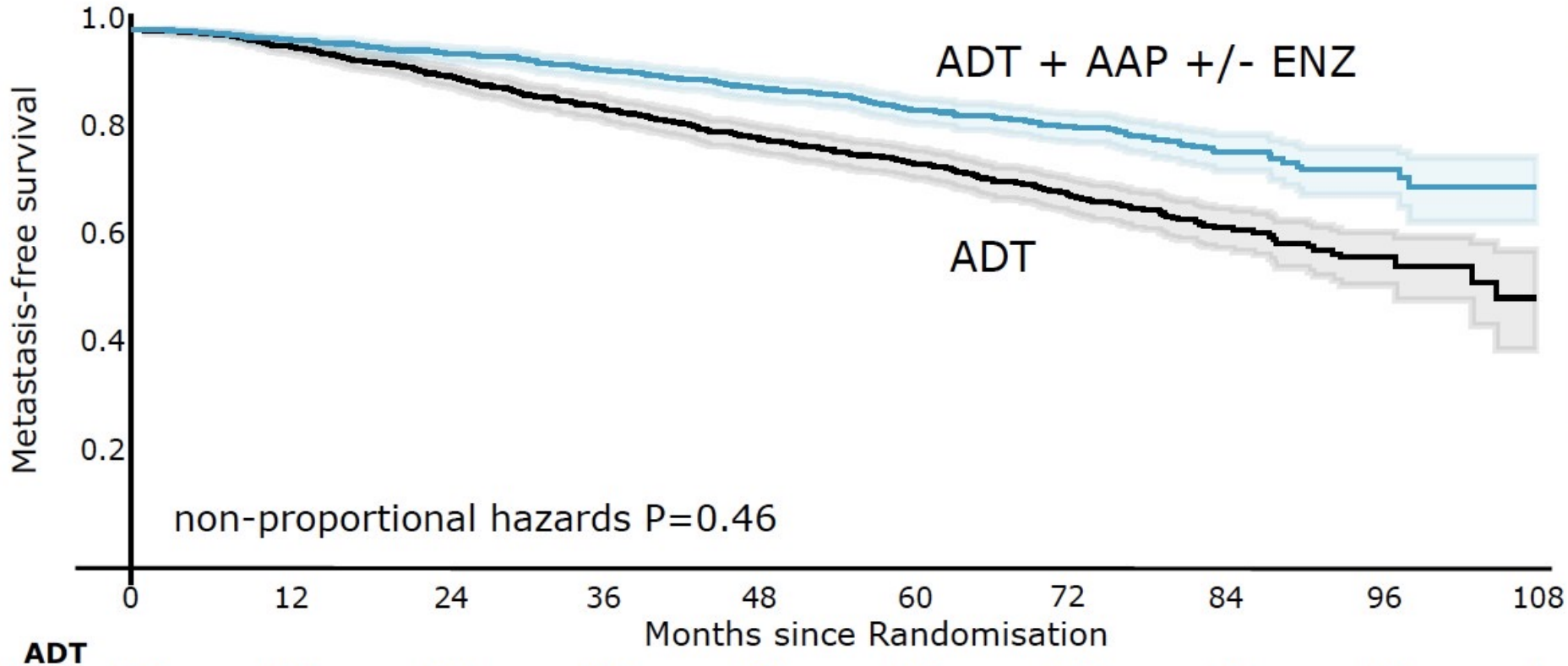
Written informed consent Fit

for all protocol treatment Fit

for follow-up

Full criteria: www.stampedetrial.org

Metastasis-free survival



ADT										
At-risk	988	950	894	836	767	550	329	172	53	9
Censored	0	8	11	14	26	201	387	522	632	673
Event	0	30	83	138	195	237	272	294	303	306
ADT+AAP+/-ENZ										
At-risk	986	948	917	884	839	622	369	198	71	14
Censored	0	21	28	31	45	225	460	615	737	792
Event	0	17	41	71	102	139	157	173	178	180

Events
180 ADT+ AAP +/- ENZ
306 ADT

HR:	**0.53**
95% CI:	0.44-0.64
P value	2.9×10^{-11}

6-year MFS improved from 69% to 82%

Kaplan-Meier estimates with 95% CI in lighter shade

Non-proportional hazards P=0.46

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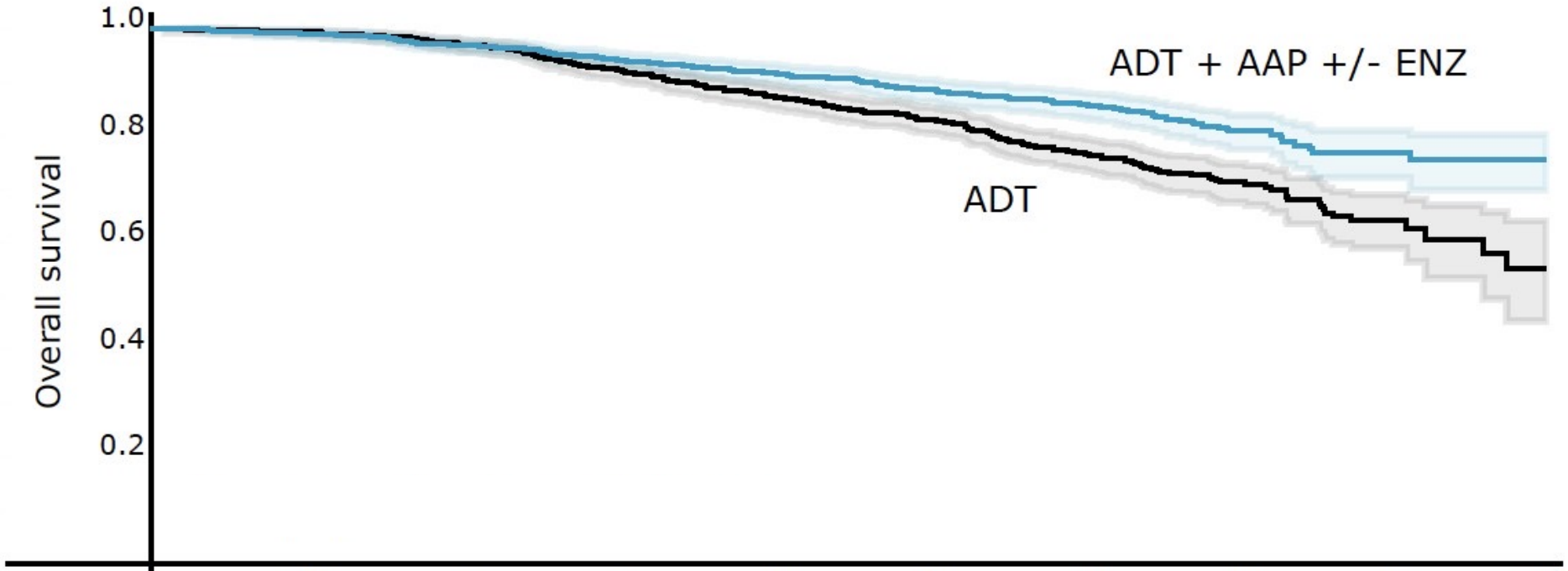
Overall survival

Events
147 ADT+AAP +/- ENZ
236 ADT



SOC										
At-risk	988	974	947	901	837	610	368	200	63	10
Censored	0	8	11	14	28	216	421	568	693	742
Event	0	6	30	73	123	162	199	220	232	236
SOC+AAP+/-ENZ										
At-risk	986	956	928	899	861	645	386	205	74	16
Censored	0	21	29	32	46	234	477	641	766	823
Event	0	9	29	55	79	107	123	140	146	147

HR:	**0.60**
95% CI	0.48 to 0.73
P value	9.3×10^{-7}

6-year survival improved from 77% to 86%

Kaplan-Meier estimates with 95% CI in lighter shade

Non-proportional hazards P=0.1

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Conclusions

- **2 years** of AAP-based therapy significantly improves MFS & overall survival of high-risk M0 PCa starting ADT and should be considered **a new standard of care**

- Adding ENZ to AAP increases toxicity but has no discernible effect on efficacy

Takeaway

- ADT alone is obsolete and should rarely be used
- Docetaxel benefit is for high volume disease
- For high volume disease ADT + darolutamide + docetaxel is superior to ADT + docetaxel
- Abiraterone + prednisone improves OS for those who also receive docetaxel in addition to ADT (+/- EBRT)- LV data needs to mature
- For low volume M1 patients, adding prostate RT to ADT+ abiraterone + prednisone +/- docetaxel, did not have OS benefit
- For M0 very high-risk patients, adding abiraterone for 2 years to ADT + RT improves MFS, OS


11/30/13
Canon 6D, Sigma 35mm, ISO 640, f/1.6, 1/30s