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EARLY TREATMENT INTENSIFICATION FOR METASTATIC CASTRATION SENSITIVE PROSTATE CANCER: OPTIMISING PATIENT SELECTION AND TREATMENT

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NOVEMBER 2022

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This content is supported by an Independent Educational Grant from Bayer.

Prof. Evan Yu has received received financial support/sponsorship from the following companies:

- **Consulting:** AbbVie, Advanced Accelerator Applications, Bayer, Clovis, Exelixis, Genzyme, Janssen, Merck, Oncternal
- **Research Funding to Institution:** Bayer, Blue Earth, Daiichi-Sankyo, Dendreon, Lantheus, Merck, Seagen, Taiho

EDUCATIONAL OBJECTIVES

- Recognise how the mCSPC treatment landscape has evolved highlighting the need for treatment intensification
- Understand the available data and how this can be applied to select the most appropriate treatment for mCSPC patients

CLINICAL TAKEAWAYS

- ADT alone is no longer sufficient treatment for mCSPC patients
- Treatment intensification with either doublet or triplet therapy should occur
- Patients with *de novo*, high-volume disease who are fit for chemotherapy should be considered for triplet therapy with ADT + docetaxel + NHA
- Patients who are unfit for chemotherapy or have low volume disease should be considered for doublet therapy with ADT + NHA

ADT, androgen deprivation therapy; mCSPC, metastatic castration sensitive prostate cancer; NHA, novel hormonal agents

mCSPC: EVOLVING TREATMENT LANDSCAPE

mCSPC, metastatic castration sensitive prostate cancer

THE DEVELOPMENT OF NOVEL HORMONE THERAPY AND CHEMOTHERAPY IN mCSPC

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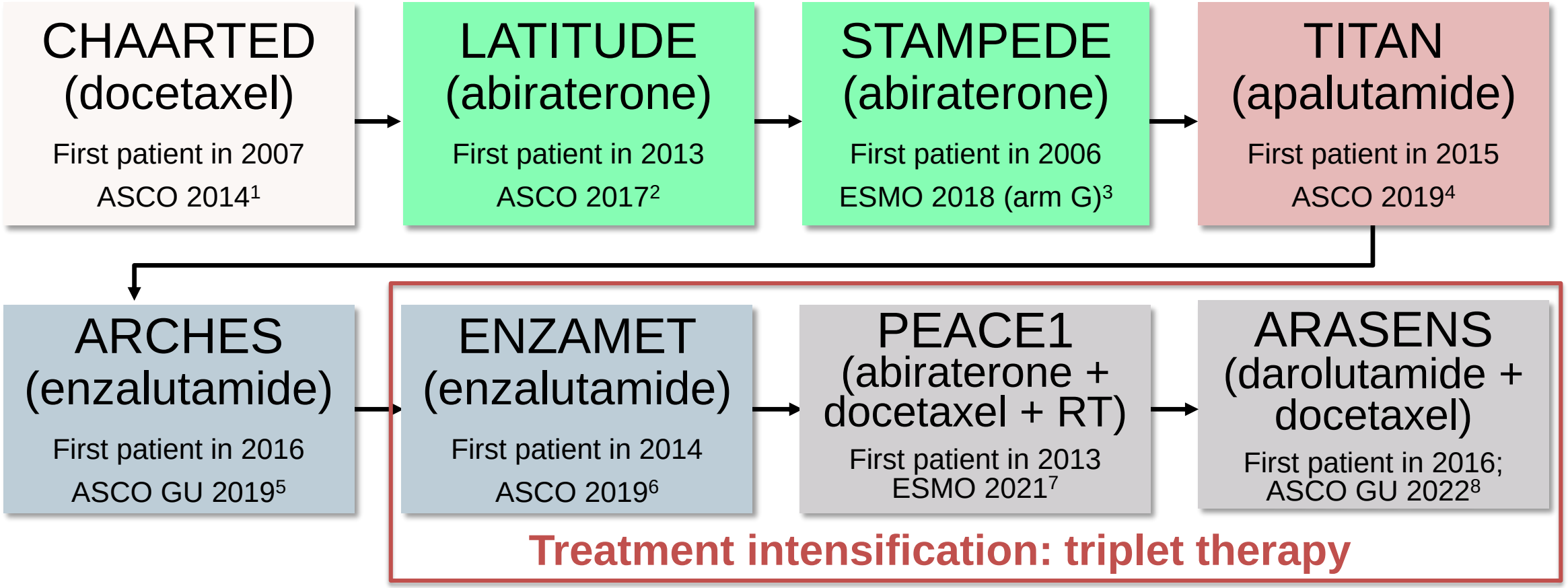


ADT, androgen deprivation therapy; ARPI, androgen receptor pathway inhibitor; ASCO, American Society of Clinical Oncology; ESMO, European Society for Medical Oncology; GU, genitourinary; mCSPC, metastatic castration-sensitive prostate cancer; RT, radiation therapy

1. Sweeney C, et al. J Clin Oncol. 2014;32(5s):(suppl; abstr LBA2); 2. Fizazi K, et al. J Clin Oncol. 2017;35(suppl):LBA3; 3. Hoyle AP, et al. Ann Oncol. 2018;29(suppl 8):viii722 (abstract LBA4);
4. Chi KN, et al. J Clin Oncol. 2019;37(suppl):5006; 5. Armstrong AJ, et al. J Clin Oncol. 2019;37(suppl 7S):687; 6. Sweeney C, et al. J Clin Oncol. 2019;37(suppl):LBA2;
7. Fizazi K, et al. Abstract #LBA5_PR. ESMO 2021. Oral presentation; 8. Smith M, et al. J Clin Oncol 2022; 40, (suppl 6; abstr 13) (ASCO GU 2022, oral presentation)

CHAARTED STUDY DESIGN

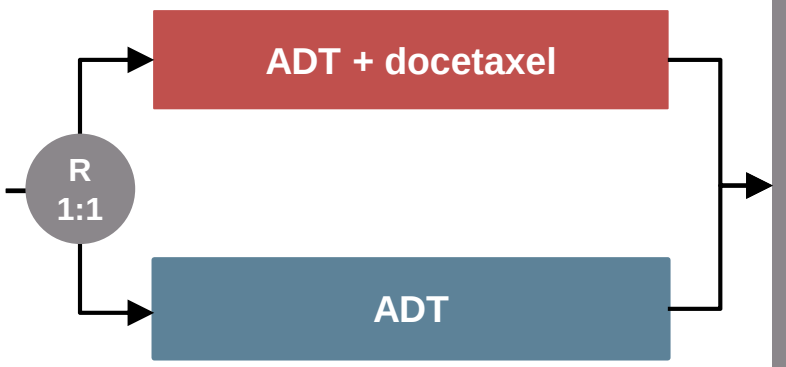
CHAARTED: Randomised phase 3 trial designed to determine whether docetaxel therapy at initiation of ADT in patients with mCSPC can increase overall survival compared with ADT alone

mCSPC (N=790)

- On ADT <120 days
- ECOG PS 0–2
- Prior ADT allowed if:
  - Prior adjuvant use, if duration was ≤24 mo and progression occurred >12 mo after completion of therapy
  - Receiving ADT for metastatic disease with no evidence of progression and treatment commencing within 120 days prior to randomisation

Stratification

- Age (<70 y vs ≥70 y)
- ECOG PS (0 or 1 vs 2)
- CAB > 30 days (yes vs no)
- SRE prevention (yes vs no)
- Prior ADT (<12 mo vs ≥12 mo)
- Extent of metastasis (low vs high)



Primary Endpoint

- Overall survival

Secondary Endpoints

- Time to CRPC
- Time to clinical progression
- Percent patients with PSACR at 6 months
- Percentage of patients with PSACR at 12 months
- QoL

ADT, androgen deprivation therapy; CAB, combined androgen blockade; CRPC, castration-resistant prostate cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; mCSPC, metastatic castration sensitive prostate cancer; mo, month; PSACR, prostate-specific antigen complete response; QoL, quality of life; R, randomisation; SRE, skeletal-related event; y, year

Sweeney CJ, et al. N Engl J Med. 2015;373:737-46

CHAARTED: COMBINATION ADT + DOCETAXEL RESULTED IN SIGNIFICANTLY LONGER OVERALL SURVIVAL THAN ADT ALONE

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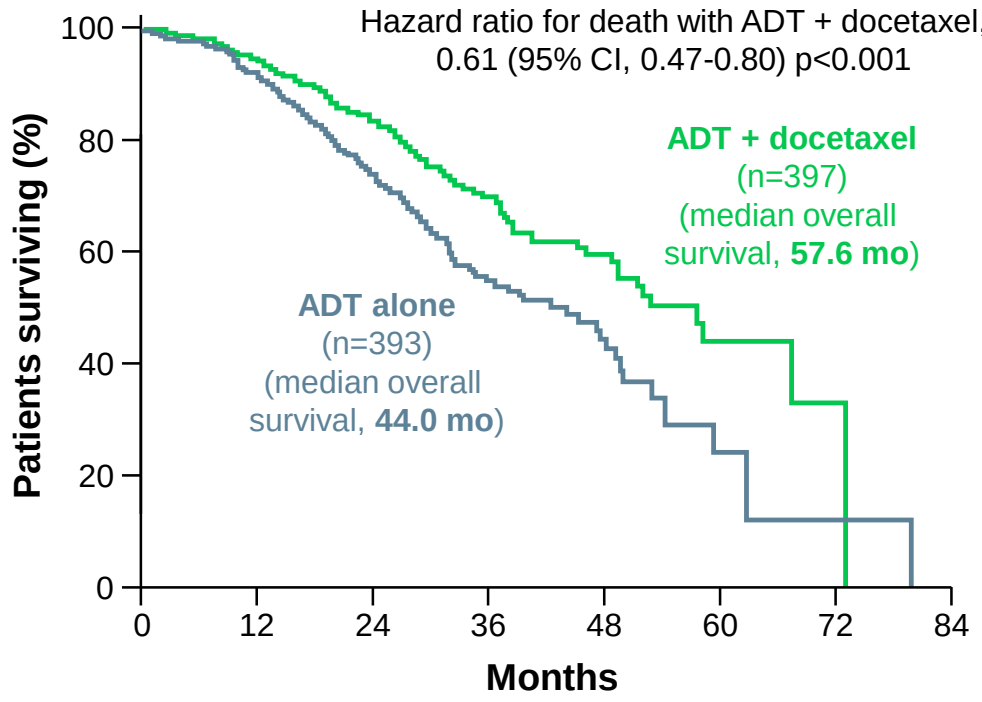
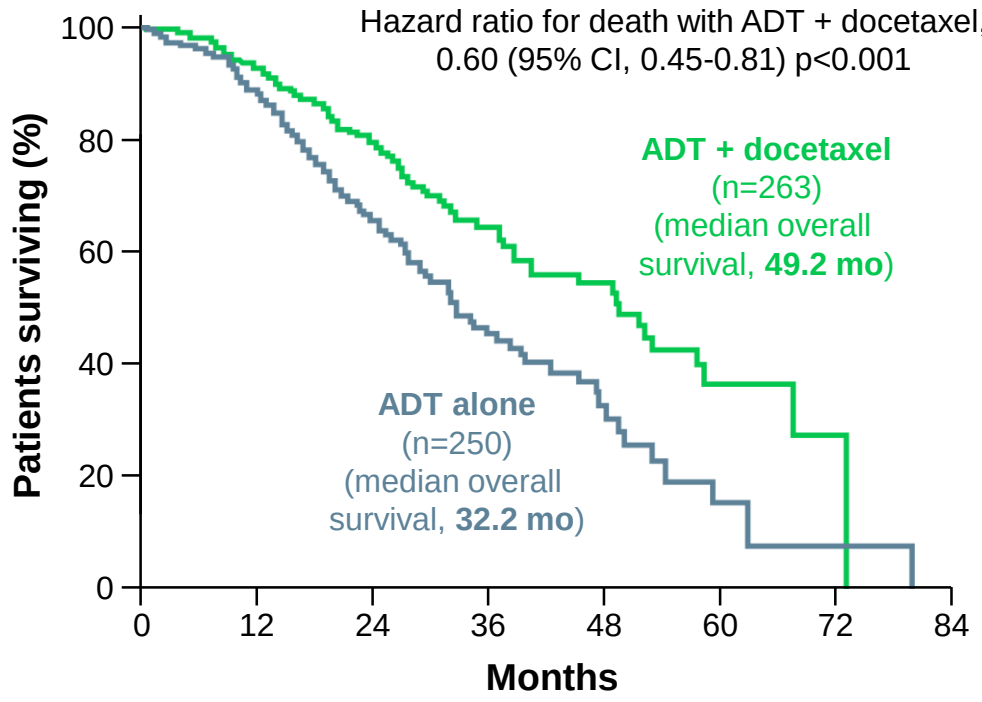
Median Overall Survival – All Patients

13.6 months longer with ADT + docetaxel



Median Overall Survival – High-Volume Disease[a]

17.0 months longer with ADT + docetaxel



[a] High-volume disease was defined as the presence of visceral metastases or ≥4 bone metastases lesions with ≥1 beyond the vertebral bodies and pelvis

ADT, androgen deprivation therapy; CI, confidence interval; mo, months

Sweeney CJ, et al. N Engl J Med. 2015;373:737-46

TREATMENT INTENSIFICATION: CONSIDERATIONS

TREATMENT INTENSIFICATION – SUITABLE FOR WHICH PATIENTS?

- Fit for chemotherapy or not?
- High-volume or low-volume disease?
- Symptomatic or non-symptomatic?
- Contraindications to particular treatments or not?

CONSIDERATIONS WHEN SELECTING BETWEEN ANDROGEN PATHWAY INHIBITORS

- **Abiraterone** – liver function test abnormalities, hypokalaemia, oedema, hypertension, hyperglycaemia (from exogenous glucocorticoids)[1,2]
- **Enzalutamide** – fatigue, falls, restless leg syndrome[3,4]
- **Apalutamide** – rash[5,6]
- **Darolutamide** – only approved in combination with docetaxel by FDA (can start up to 6 weeks prior to starting docetaxel), fewer unfavourable drug-drug interactions[7,8,9]

FDA, Food and Drug Administration; PI, Prescribing Information; SmPC, Summary of Product Characteristics

1. Abiraterone (Zytiga) PI (Aug 21); 2. Abiraterone (Zytiga) SmPC (08 Sep 22); 3. Enzalutamide (Xtandi) PI (Sep 22); 4. Enzalutamide (Xtandi) SmPC (08 Sep 22); 5. Apalutamide (Erleada) PI (Nov 22); 6. Apalutamide (Erleada) SmPC (13 Jul 22); 7. Darolutamide (Nubeqa) PI (Aug 22); 8. Darolutamide (Nubeqa) SmPC (27 Mar 22); 9. Olivier KM, et al. Int J Urol Nurs. 2021;15:47-58

POTENTIAL DRUG-DRUG INTERACTIONS OF NHA'S WITH COMMONLY USED PC MEDICATIONS

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Interaction	**Substrate** AR inhibitor increases plasma level of comedication May increase risk of AEs associated with comedication	**Substrate** AR inhibitor decreases plasma level of comedication May lead to a decrease in activity of comedication	**Inducer** Comedication decreases plasma level of AR inhibitor May lead to a decrease in activity of AR inhibitor	**Inhibitor** Comedication increases plasma level of AR inhibitor May increase risk of AEs associated with AR inhibitor

Medicinal product		Apalutamide	Enzalutamide	Darolutamide
Antithrombotics	Clopidogrel		✗	
	Dabigatran	CAUTION	CAUTION	
	Rivaroxaban	✗	✗	
	Warfarin	✗	✗	
Calcium channel blockers	Amlodipine	CAUTION	CAUTION	
	Diltiazem		✓	
	Nifedipine, felodipine	✗	✗	
	Verapamil		CAUTION	
Cardiac glycosides	Digoxin	CAUTION	CAUTION	
Proton pump inhibitor	Omeprazole	✗	✗	
Analgesics	Fentanyl	CAUTION	✗	
Hypnotics	Diazepam	✗	✗	
	Midazolam	✗	✗	
Antipsychotics	Haloperidol	✗	✗	
Antibiotics	Clarithromycin	CAUTION		CAUTION
	Rifampicin		✗	✗
Anticonvulsants	Carbamazepine		✗	✗
Statins	Rosuvastatin	CAUTION		✗

Note: Recommendations provided in the US PI, EMA SPC, and NICE BNF. ✓ Comedication can be combined with AR inhibitor. ✗ Avoidance or substitution of comedication is recommended. CAUTION indicates comedication should be administered with caution and/or dose adjustment based on efficacy/tolerability is recommended.

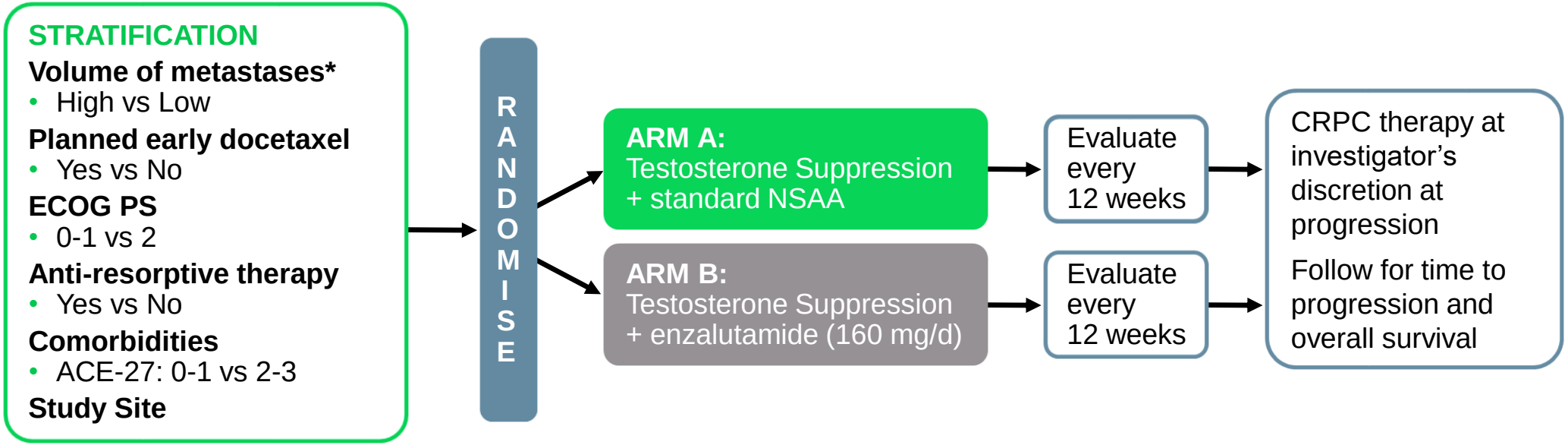
AE, adverse event; AR, androgen receptor; BNF, British National Formulary; EMA, European Medicines Agency; NICE, National Institute for Health and Care Excellence; PC, prostate cancer; PI, prescribing information; SPC, summary of product characteristics

Olivier KM, et al. Int J Urol Nurs. 2021;15:47-58

mCSPC TRIPLET THERAPY TRIALS

mCSPC, metastatic castration sensitive prostate cancer

ENZAMET STUDY DESIGN



Prior to randomisation testosterone suppression up to 12 weeks and 2 cycles of docetaxel was allowed; intermittent ADT and cyproterone were not allowed; NSAA: bicalutamide; nilutamide; flutamide

* High volume: visceral metastases and/or 4 or more bone metastases (at least 1 beyond pelvis and vertebral column);

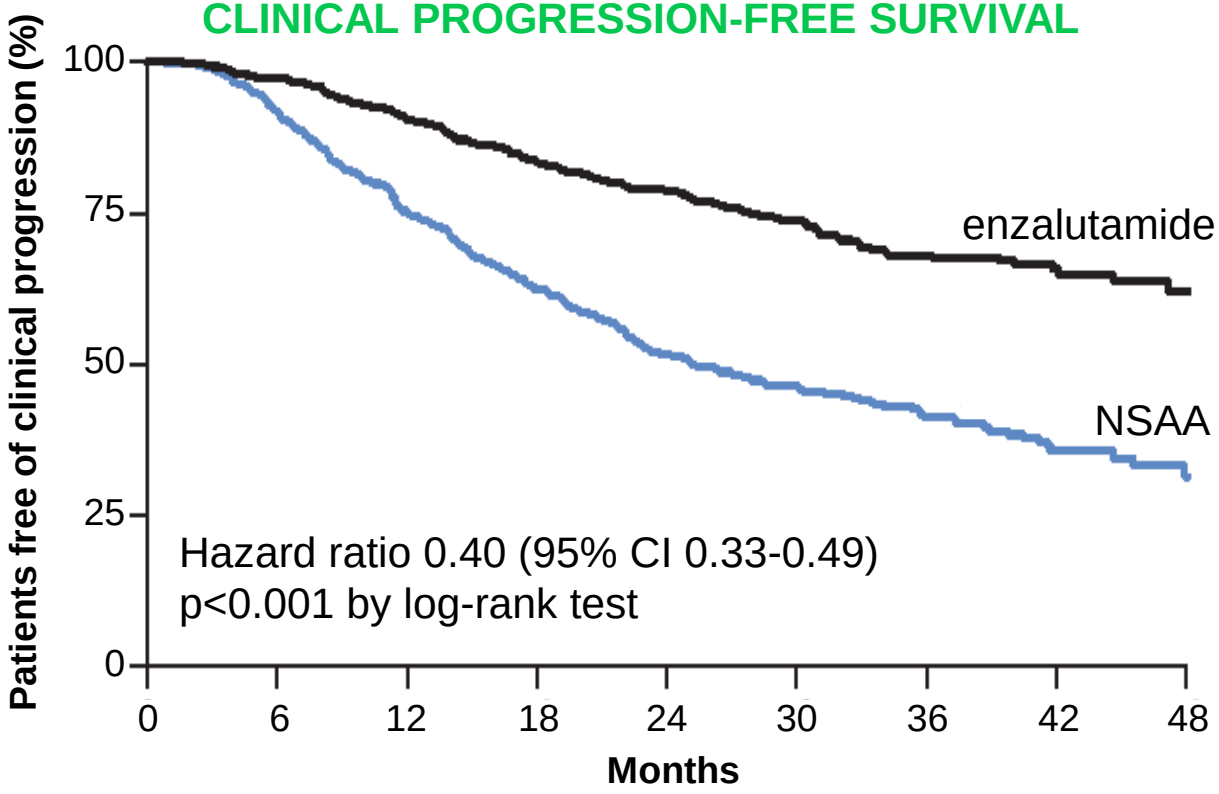
ACE-27, adult comorbidity evaluation-27; ADT, androgen deprivation therapy; CRPC, castration resistant prostate cancer; d, day; ECOG PS, Eastern Cooperative Oncology Group performance status; NSAA, nonsteroidal antiandrogen

Sweeney C, et al. J Clin Oncol. 2019;37(suppl):LBA2; Davis I, et al. N Engl J Med. 2019; 381:121-31 (inc. protocol)

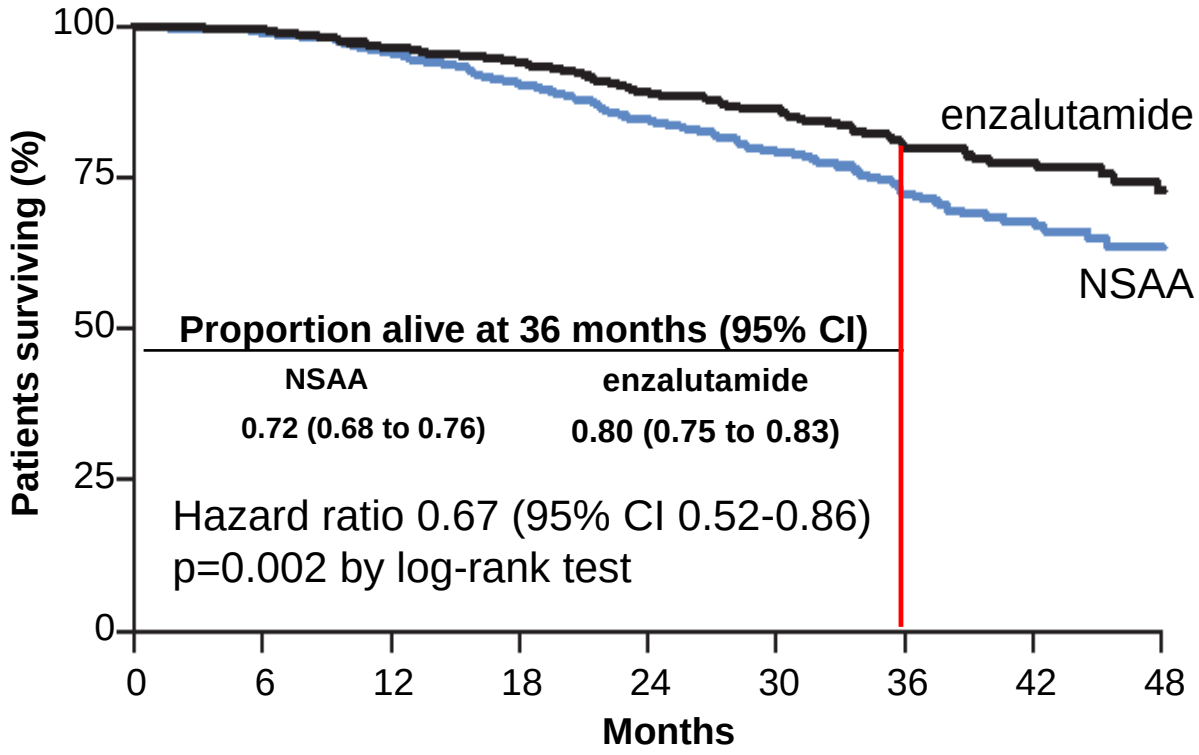
ENZAMET: ENZALUTAMIDE FOR mCSPC

- **Varied inclusion criteria:** high and low volume, *de novo* vs metachronous metastasis, concurrent docetaxel, many permutations

CLINICAL PROGRESSION-FREE SURVIVAL



OVERALL SURVIVAL (Primary endpoint)



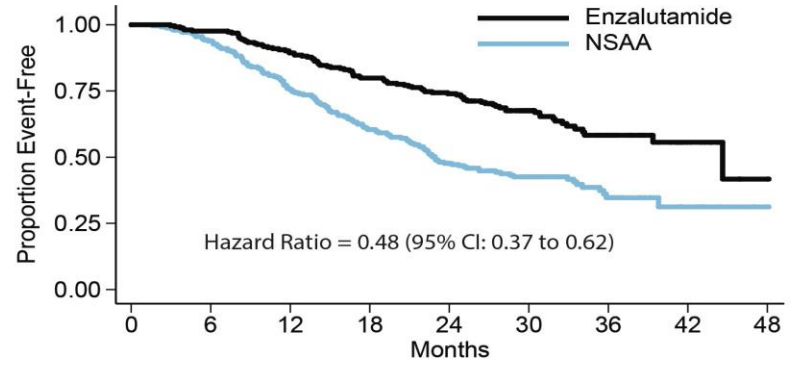
CI, confidence interval; mCSPC, metastatic castration-sensitive prostate cancer; NSAA, nonsteroidal antiandrogen

Sweeney C, et al. J Clin Oncol. 2019;37(suppl):LBA2; Davis ID, et al. N Engl J Med. 2019;381:121-31

ENZAMET: CONCURRENT DOCETAXEL

Testosterone suppression + docetaxel n=503 (71% high volume)

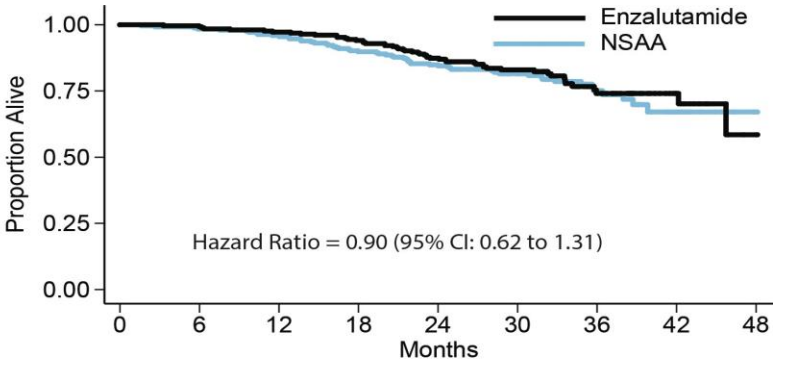
CLINICAL PROGRESSION-FREE SURVIVAL



Number at risk

NSAA	249	230	185	148	112	73	21	6	1
Enzalutamide	254	248	226	202	178	109	35	12	2

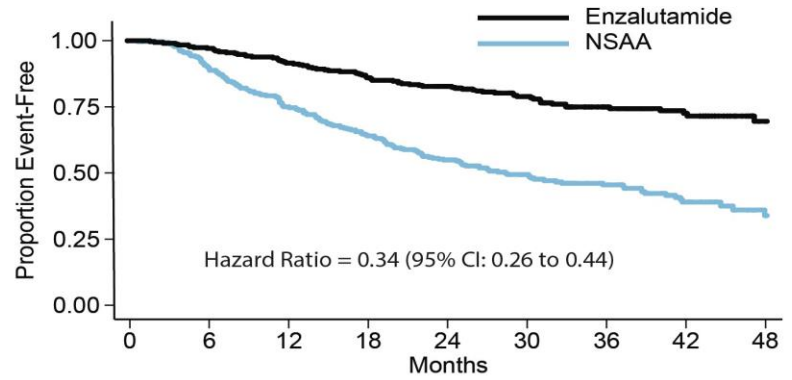
OVERALL SURVIVAL



Number at risk

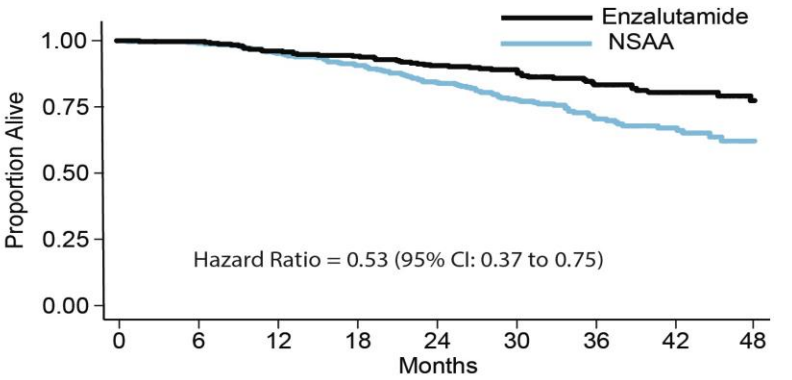
NSAA	249	241	235	220	203	135	56	13	2
Enzalutamide	254	252	246	238	210	139	54	19	3

Testosterone suppression + no docetaxel n=622 (37% high volume)



Number at risk

NSAA	313	282	233	198	160	109	75	44	16
Enzalutamide	309	299	281	266	246	175	121	72	34



Number at risk

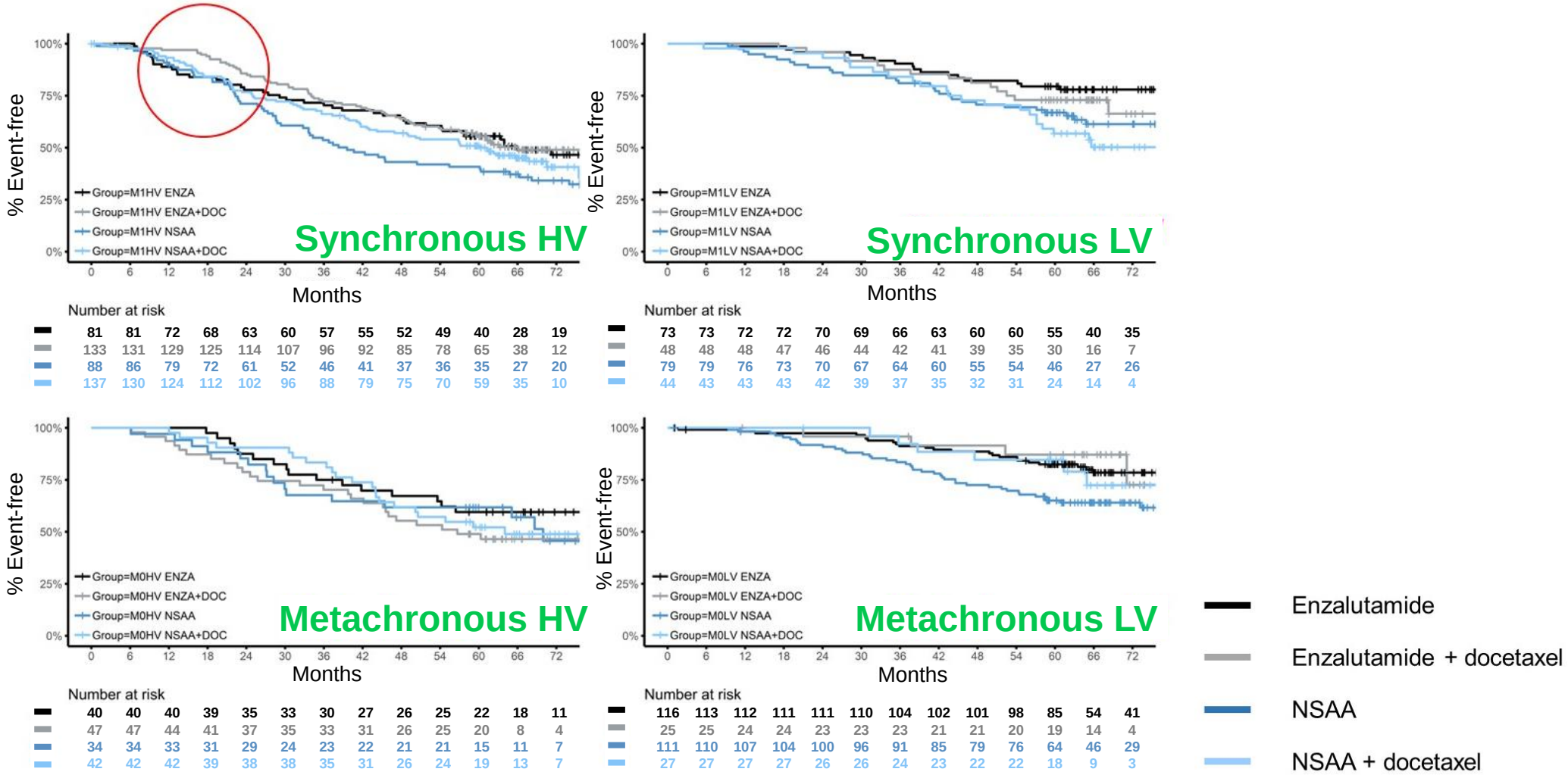
NSAA	313	310	296	281	249	176	118	73	30
Enzalutamide	309	306	295	289	270	201	135	87	42

CI, confidence interval; NSAA, nonsteroidal antiandrogen

Sweeney C, et al. J Clin Oncol. 2019;37(suppl):LBA2; Davis ID, et al. N Engl J Med. 2019;381:121-31

ENZAMET: UPDATED OVERALL SURVIVAL

EXPLORATORY ANALYSIS: VOLUME, M1 TIMING, DOCETAXEL



HV, high volume; LV, low volume

Davis, IJ Clin Oncol 40, 2022 (suppl 17; abstr LBA5004)

ENZAMET: SELECTED AEs ALL PATIENTS AT ANYTIME

Selected AEs*	TS + NSAA N=558		TS + ENZA N=563	
SAE rate per year of Rx exposure	0.33	95% CI: 0.28-0.39	0.34	95% CI: 0.29-0.40
AEs of Interest	**N**	**%**	**N**	**%**
G3 Hypertension	24	4	43	8
G2 Hypertension	30	5	60	11
G3 Fatigue	4	1	31	6
G2 Fatigue	80	14	142	25
G3 Falls	2	<1	6	1
G2 Falls	8	1	28	5
Syncope	7	1	20	4
Concentration impairment (G1/2)	6	1	24	4
Any seizure	0	0	7	1

*Worst grade shown

NSAA, nonsteroidal antiandrogen; TS, testosterone suppression

Sweeney C, et al. J Clin Oncol. 2019;37(suppl):LBA2

PEACE-1 STUDY DESIGN

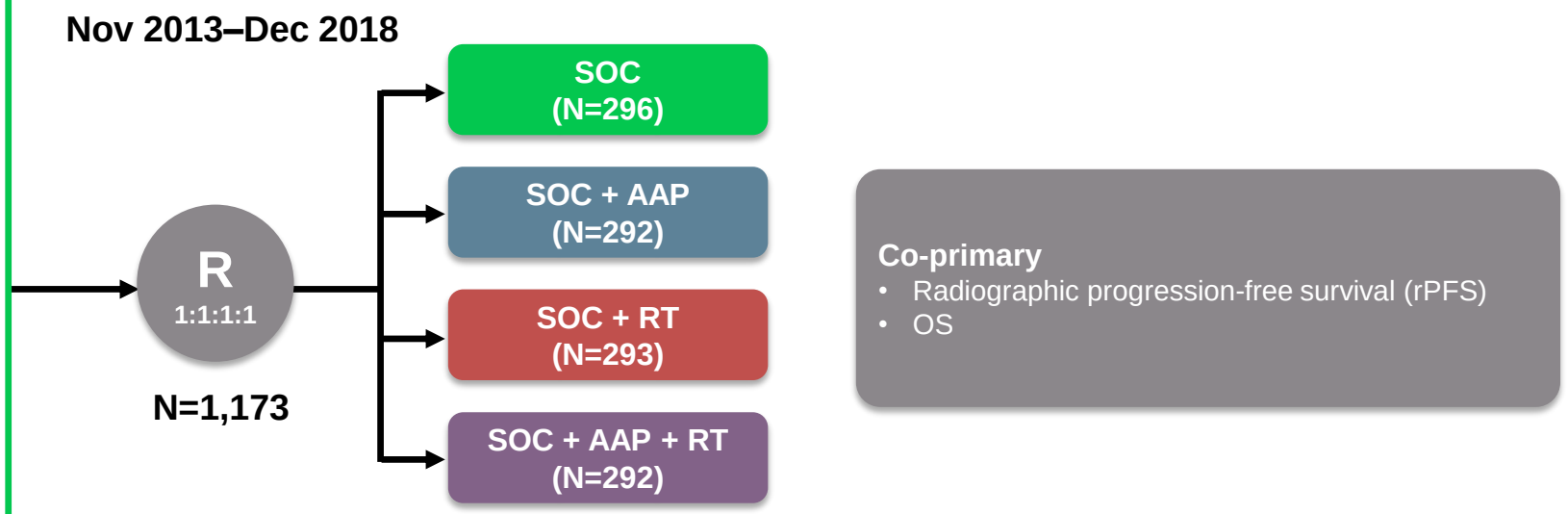
PEACE-1: A phase 3 trial with 2x2 factorial design investigating overall survival of abiraterone acetate + docetaxel + ADT in *de novo* mCSPC patients

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 (lymph node vs bone vs visceral)
- Type of castration (orchidectomy vs LHRH agonist vs LHRH antagonist)
- Docetaxel (yes vs no)



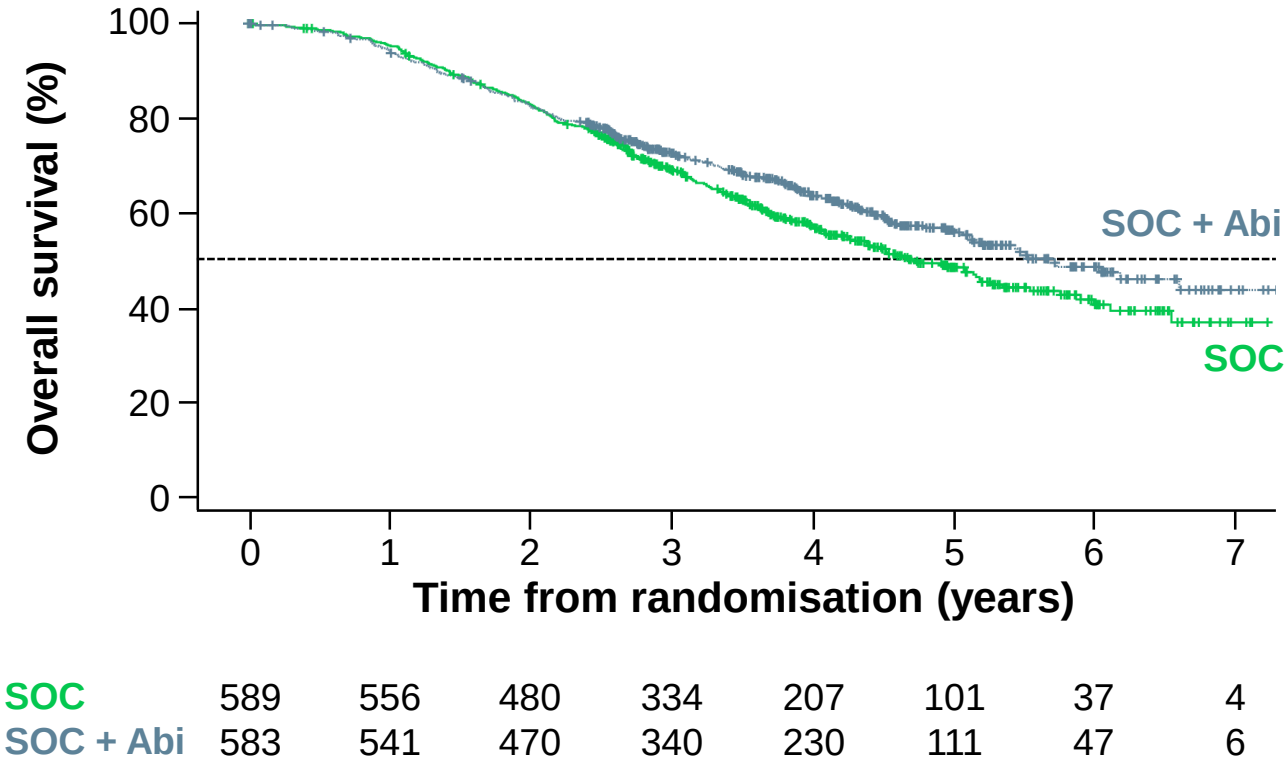
2x2 factorial design

SOC = ADT and docetaxel 75 mg/m^2 every 3 weeks for 6 cycles

AAP, abiraterone and prednisone; ADT, androgen deprivation therapy; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; LHRH, luteinising hormone releasing hormone; mCSPC, metastatic castration-sensitive prostate cancer; OS, overall survival; PCWG 2, Prostate Cancer Working Group 2; PSA, prostate specific antigen; R, randomisation; rPFS, radiographic progression-free survival; RT, radiotherapy; SOC, standard of care

Fizazi K, et al. Abstract #LBA5_PR. ESMO 2021. Oral presentation; Fizazi K, et al. The Lancet 2022; 399 (103360): 1695-1707

PEACE-1 TRIAL – OVERALL SURVIVAL FOR THE ENTIRE 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	

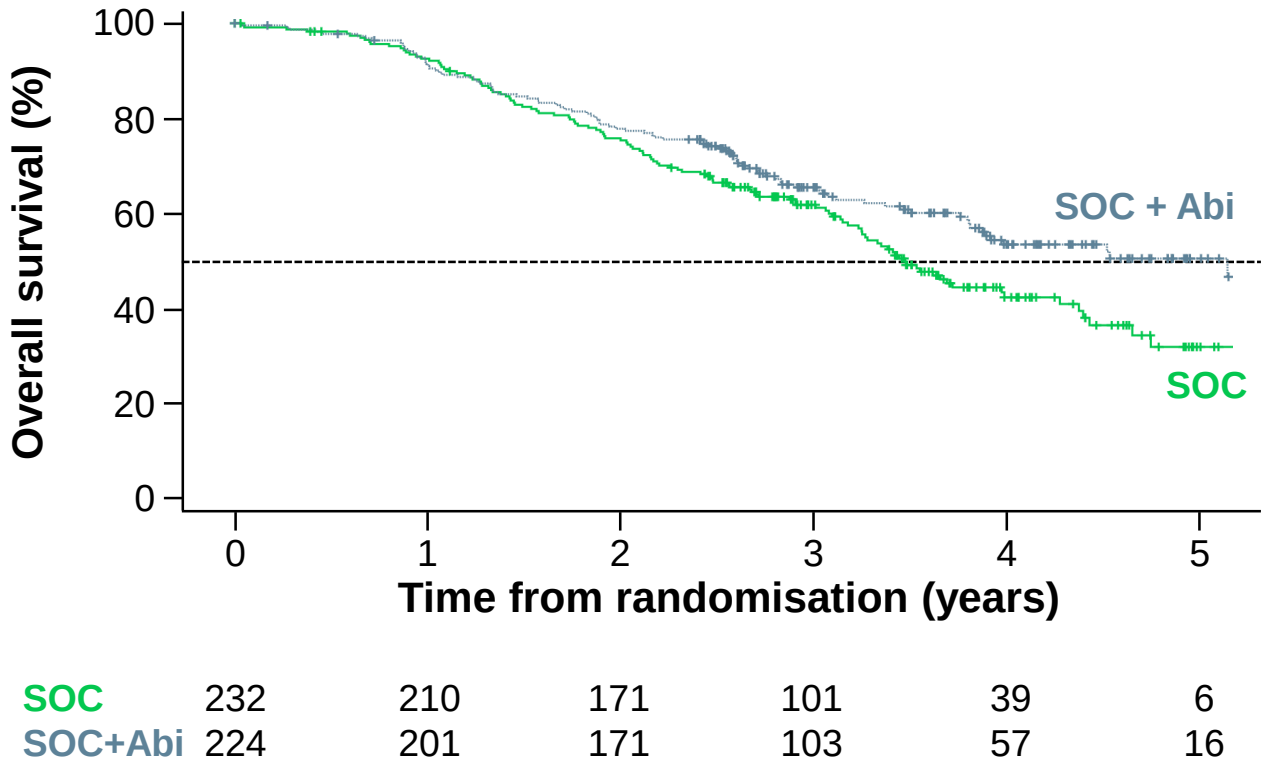
* Adjusted on stratification parameters (RXT, PS, type of castration, metastatic burden, docetaxel)

Abi, abiraterone; CI, confidence interval; HR, hazard ratio; NE, not estimable; OS, overall survival; PS, performance status; RXT, radiotherapy to primary tumour; SOC, standard of care; y, year

Fizazi K, et al. Abstract #LBA5_PR. ESMO 2021. Oral presentation

PEACE-1 TRIAL – OVERALL SURVIVAL WITH ABIRATERONE + ADT + DOCETAXEL (+/- RT) IN HIGH-VOLUME PATIENTS

- Abiraterone + ADT + docetaxel provides lifetime gain of more than 1.5 years in high-volume patients (5.1y vs 3.5y)



	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	

Abi, abiraterone; ADT, androgen deprivation therapy; CI, confidence interval; HR, hazard ratio; NE, not estimable; RT, radiotherapy; SOC, standard of care; y, year

Fizazi K, et al. Abstract #LBA5_PR. ESMO 2021. Oral presentation

PEACE-1: SAFETY DATA

G3-5 TOXICITY ON STUDY TREATMENTS (ADT + DOCETAXEL SAFETY POPULATION)

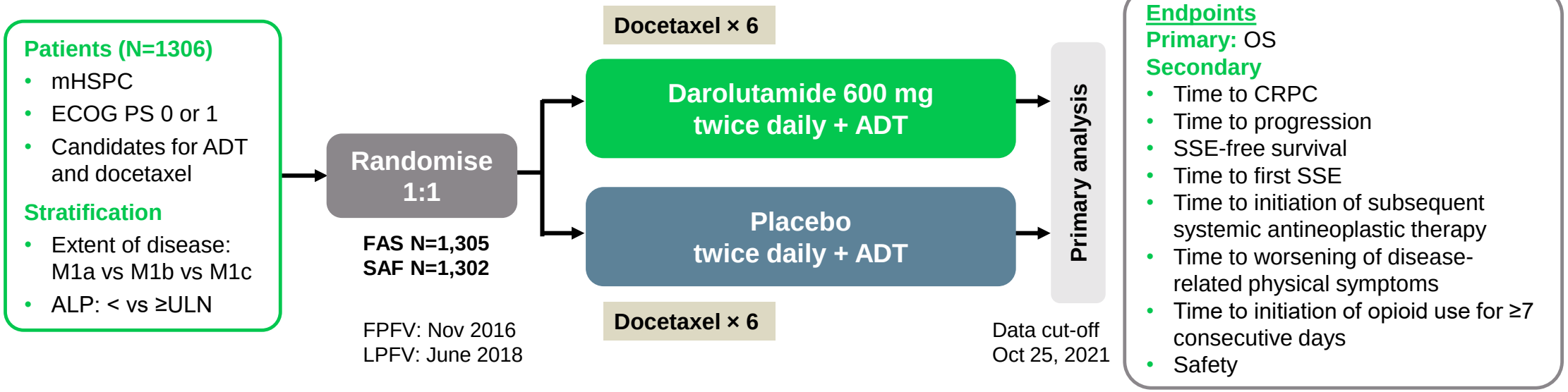
Toxicity, N (%)	SOC (+/- RXT) + Abiraterone (n=346)	SOC (+/- RXT) (n=350)
Neutropenia	34 (10)	32 (9)
Febrile neutropenia	18 (5)	19 (5)
Liver	20 (6)	2 (1)
Hypertension	76 (22)	45 (13)
Hypokalemia	11 (3)	1 (0)
Cardiac	6 (2)	5 (1)
Fatigue	10 (3)	15 (4)
Gastrointestinal	14 (4)	18 (5)
Grade 5	7 (2)	3 (1)

Abi, abiraterone; ADT, androgen deprivation therapy; RXT, radiotherapy; SOC, standard of care

Fizazi K, et al. Abstract #LBA5_PR. ESMO 2021. Oral presentation

ARASENS STUDY DESIGN

Randomised, double-blind, placebo-controlled, global, phase 3 study (NCT02799602)
Conducted at 286 centres in 23 countries



- The final analysis was conducted after 533 deaths
- Secondary efficacy endpoints were tested hierarchically

ADT, androgen deprivation therapy; ALP, alkaline phosphatase; CRPC, castration-resistant prostate cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; FAS, full analysis set; FPFV, first patient first visit; LPFV, last patient first visit; M1a, nonregional lymph node metastases; M1b, bone metastases +/- lymph node metastases; M1c, visceral metastases +/- lymph node or bone metastases; mHSPC, metastatic hormone sensitive prostate cancer; OS, overall survival; SAF, safety analysis set; SSE, symptomatic skeletal event; ULN, upper limit of normal

Smith M, et al. J Clin Oncol 2022; 40, (suppl 6; abstr 13) (ASCO GU 2022, oral presentation); Smith M, et al. N Engl J Med. 2022; 386(12):1132-42

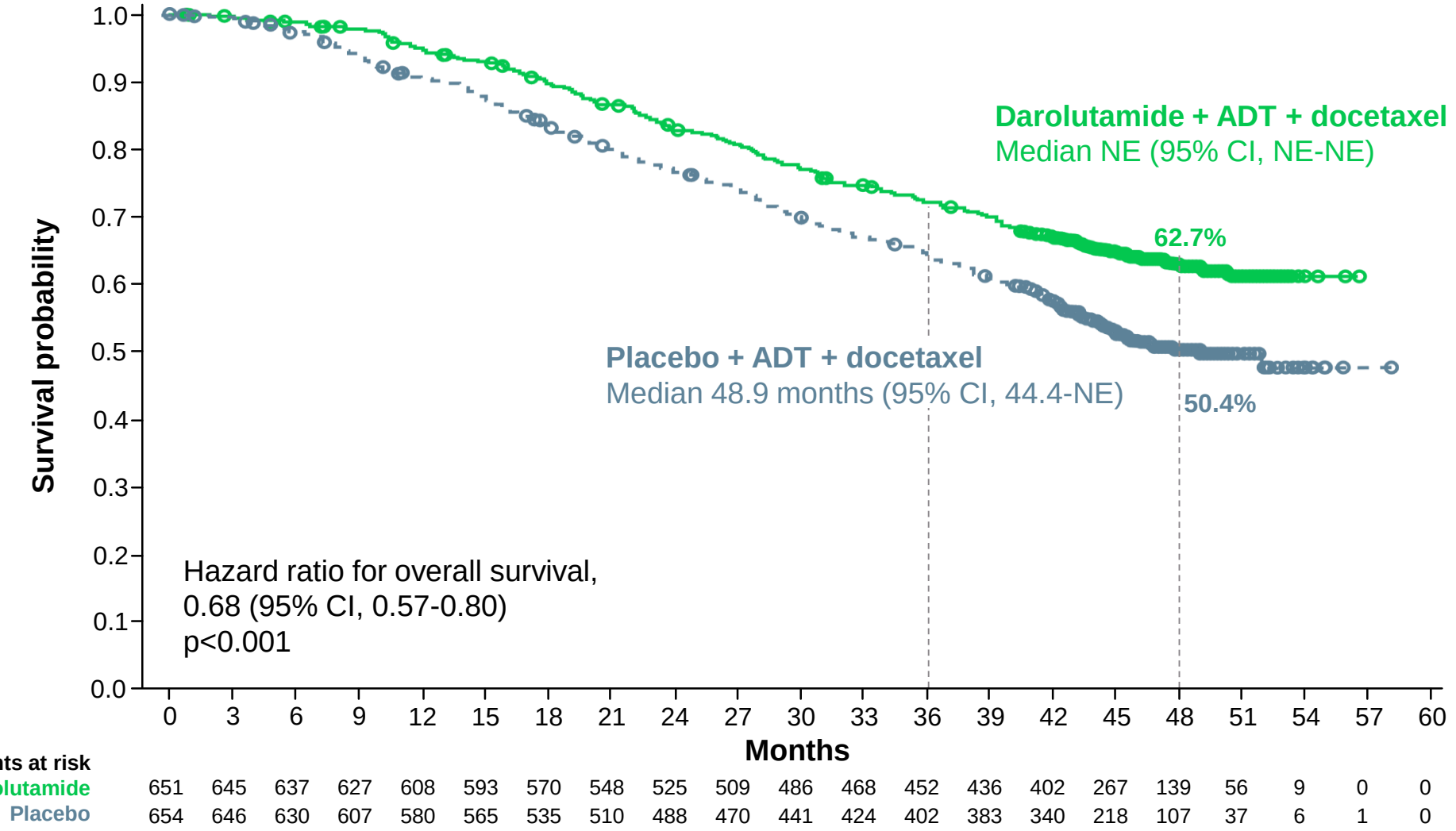
ARASENS: SELECTED CLINICAL CHARACTERISTICS AT BASELINE

Characteristic	Darolutamide–ADT– docetaxel (N=651)	Placebo–ADT– docetaxel (N=654)
Gleason score at initial diagnosis — no. (%)		
<8	122 (18.7)	118 (18)
≥8	505 (77.6)	516 (78.9)
Data missing	24 (3.7)	20 (3.1)
Metastasis stage at initial diagnosis – no. (%)		
M1, distant metastasis	558 (85.7)	566 (86.5)
M0, no distant metastasis	86 (13.2)	82 (12.5)
MX, distant metastasis not assessed	7 (1.1)	6 (0.9)
Metastasis stage at screening — no. (%)		
M1a, nonregional lymph-node metastases only	23 (3.5)	16 (2.4)
M1b, bone metastases with or without lymph-node metastases	517 (79.4)	520 (79.5)
M1c, visceral metastases with or without lymph-node or bone metastases	111 (17.1)	118 (18.0)
Median serum PSA level (range) – ng/ml	30.3 (0.0-9,219.0)	24.2 (0.0-11,947.0)
Median serum ALP level (range) – U/liter	148 (40-4,885)	140 (36-7,680)
ALP category – no. (%)		
<ULN	290 (44.5)	291 (44.5)
≥ULN	361 (55.5)	363 (55.5)

ADT, androgen deprivation therapy; ALP, alkaline phosphatase; PSA, prostate specific antigen; ULN, upper limit of normal

Smith M, et al. N Engl J Med. 2022;386(12):1132-42

ARASENS: OVERALL SURVIVAL



Number of patients 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

ADT, androgen deprivation therapy; CI, confidence interval; NE, not estimable

Smith M, et al. N Engl J Med. 2022;386(12):1132-42; Smith M, et al. J Clin Oncol 2022; 40, (suppl 6; abstr 13) (ASCO GU 2022, oral presentation)

ARASENS: OS BY *DE NOVO* AND RECURRENT SUBSETS

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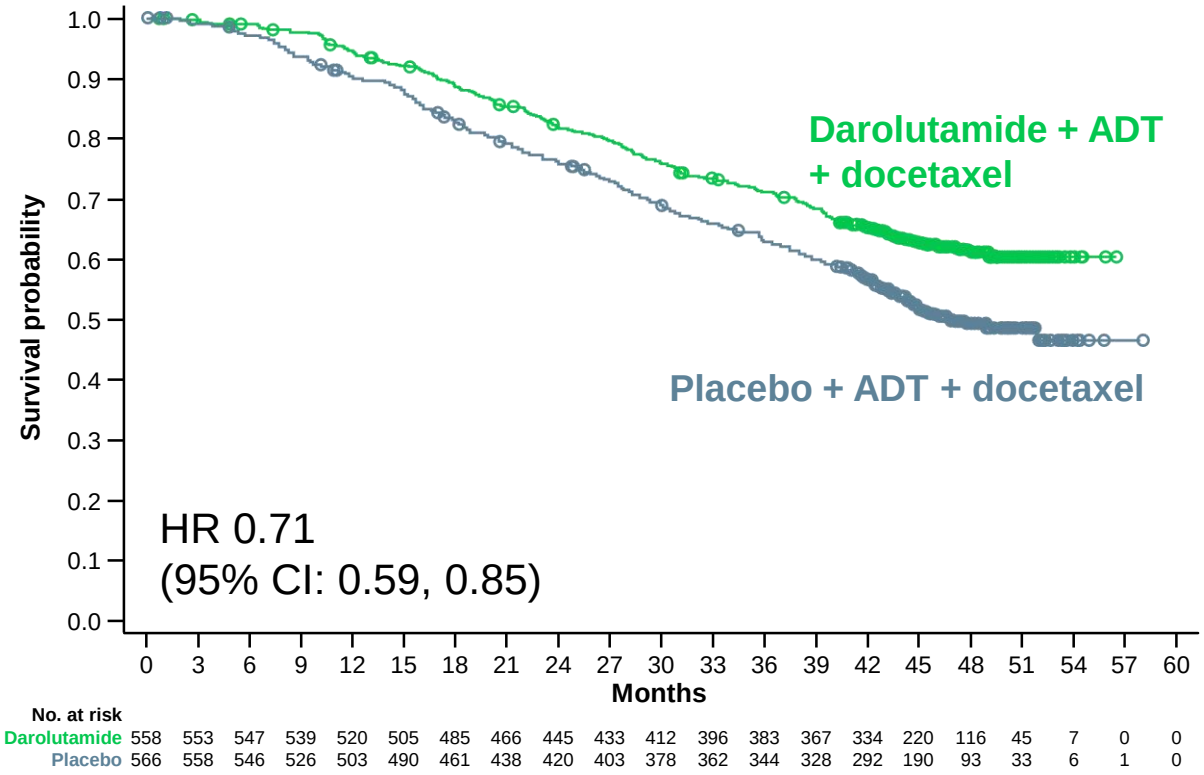
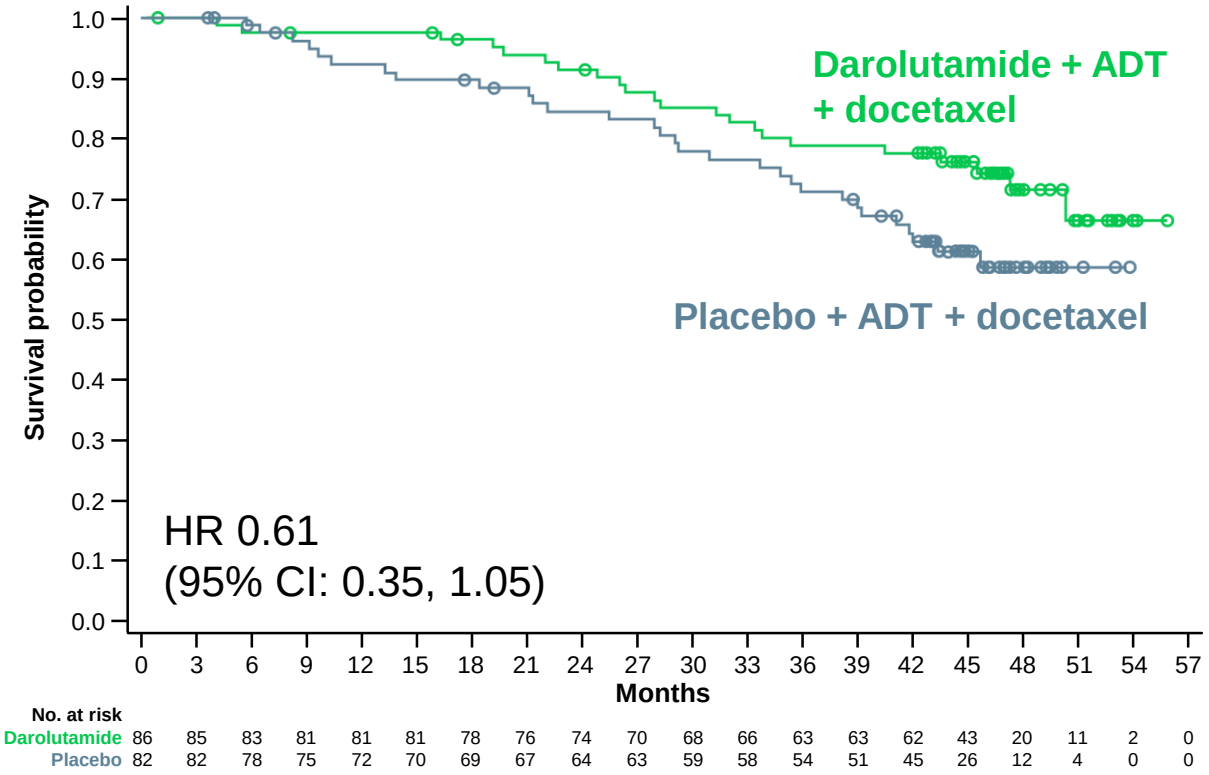
De novo mHSPC
(M1 at initial diagnosis; 86.1% of patients)



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 mHSPC
(M0 at initial diagnosis; 12.9% of patients)



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	

ADT, androgen deprivation therapy; CI, confidence interval; HR, hazard ratio; M0, non-metastatic; M1, metastatic; mHSPC, metastatic hormone sensitive prostate cancer; OS, overall survival

Smith M, et al. N Engl J Med. 2022;386(12):1132-42 (supplementary appendix); Fizazi K, et al. Ann Oncol. 2022;33 (suppl_7): S616-S652 (ESMO 2022, oral presentation)

ARASENS: ADVERSE EVENTS OF INTEREST

Adverse Event	Darolutamide + ADT + docetaxel (N=652)	Placebo + ADT + docetaxel (N=650)
	No. of patients (%)	No. of patients (%)
Events commonly associated with ADT or ARPI therapy		
Fatigue	216 (33.1)	214 (32.9)
Vasodilatation and flushing	133 (20.4)	141 (21.7)
Rash	108 (16.6)	88 (13.5)
Diabetes mellitus and hyperglycemia	99 (15.2)	93 (14.3)
Hypertension	89 (13.7)	60 (9.2)
Cardiac disorder	71 (10.9)	76 (11.7)
Cardiac arrhythmia	52 (8.0)	55 (8.5)
Coronary artery disorder	19 (2.9)	13 (2.0)
Heart failure	4 (0.6)	13 (2.0)
Bone fracture	49 (7.5)	33 (5.1)
Falls, including accident	43 (6.6)	30 (4.6)
Mental-impairment disorder	23 (3.5)	15 (2.3)
Weight decreased	22 (3.4)	35 (5.4)
Depressed-mood disorder	21 (3.2)	24 (3.7)
Breast disorders/gynecomastia	21 (3.2)	10 (1.5)
Cerebral ischemia	8 (1.2)	8 (1.2)
Seizure	4 (0.6)	1 (0.2)

Most AEs of interest were similar between the treatment arms except for rash and hypertension

ADT, androgen deprivation therapy; AE, adverse event; ARPI, androgen receptor pathway inhibitor

Smith M, et al. N Engl J Med. 2022; 386(12):1132-42

SUMMARY

- For patients fit for docetaxel with mCSPC, consideration should be given to add either darolutamide or abiraterone to ADT + docetaxel
  - Especially for those patients with de novo, high-volume prostate cancer
- As the above are a highly selected group of patients, this triple combination is not the only standard of care, yet treatment intensification for mCSPC patients of some sort needs to be strongly considered
- Patient comorbidities, side effects of androgen pathway inhibitors and drug-drug interactions should be factored into appropriate agent selection
- Further post-hoc information is forthcoming on high volume vs low volume disease subgroups
- Do patients who present with metachronous, rather than synchronous metastatic hormone sensitive prostate cancer benefit from triple combination therapy?

ADT, androgen deprivation therapy; mCSPC, metastatic castration sensitive prostate cancer

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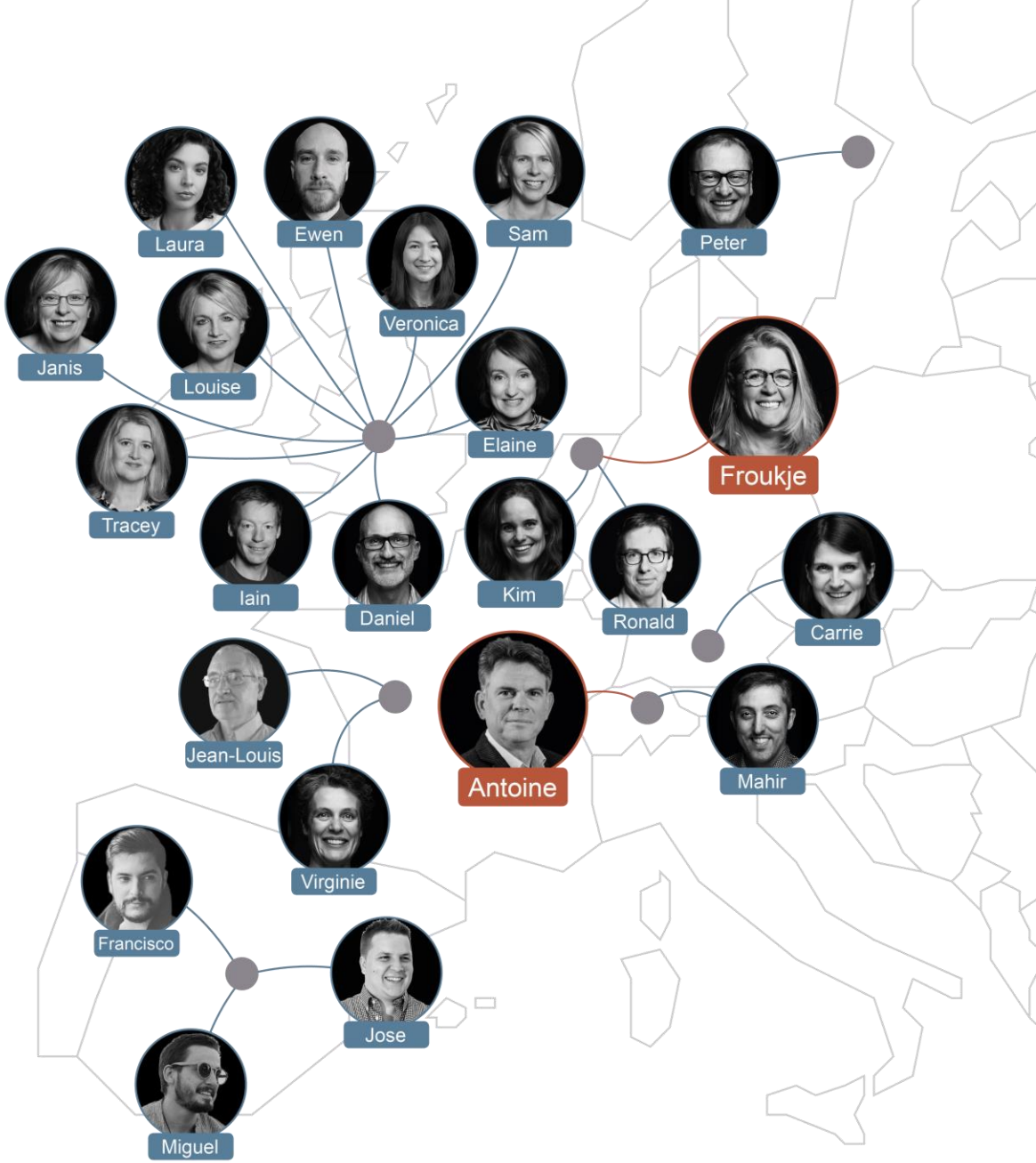

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