Triplet vs Doublet Therapy for mCSPC

Mehmet Asim Bilen, MD
mbilen@emory.edu
Winship Cancer Institute of Emory University

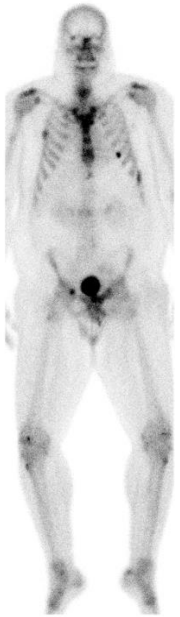
March, 2025

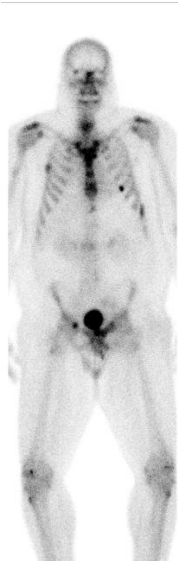
EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

Therapeutic Options for Advanced Prostate Cancer 2025

CASTRATION SENSITIVE

CASTRATION RESISTANT





ANDROGEN DEPRIVATION

Orchiectomy / GnRH Agonist

GnRH Antagonist

Antiandrogens

Docetaxel

Enzalutamide

Apalutamide

Abiraterone+/- Docetaxel

Daralutamide+ Docetaxel

IMMUNOTHERAPY

Sipuleucel-T

SECONDARY HORMONAL TREATMENTS

Bicalutamide, flutamide, nilutamide

Ketoconazole

DES

Abiraterone

Enzalutamide

M0 CRPC AGENTS

Apalutamide

Enzalutamide

Daralutamide

Radiopharmaceuticals

Radium-223

Lu-177 PSMA

CHEMOTHERAPY

Docetaxel

Cabazitaxel

CRPC with DDR

Olaparib

Rucaparib

PARP combinations

DES = diethylstilbestrol

INTRODUCTION

The landscape of mCSPC is rapidly evolving. What do we know now?...

Trial (HR)	Treatment	Reference
CHAARTED (0.72) STAMPEDE (ARM C: 0.81)	ADT+ **DOCETAXEL**	Kyriakopoulous CE, et al. J Clin Oncol. 2018 Clarke NW, et al. Ann Oncol. 2019
LATITUDE (0.66) STAMPEDE (ARM G: 0.60)	ADT + **ABIRATERONE**	Fizazi K, et al. Lancet Onc. 2019 James N, et al. ESMO 2020
ENZAMET (0.67) ARCHES (0.66)	ADT + **ENZALUTAMIDE**	Davis ID, et al. NEJM. 2019 Armstrong A, et al. ESMO 2021
TITAN (0.65)	ADT + **APALUTAMIDE**	Chi KN, et al. JCO 2021
ARANOTE	**ADT+Daralutamide**	ESMO 2024

Doublet Therapy

PEACE-1	ADT + **Docetaxel + Abiraterone**	Fizazi K et al. Lancet 2002
ARASENS	ADT + **Docetaxel + Daralutamide**	Smith MR, et al. NEJM. 2022

Triplet Therapy

McKay et al. Eur Urol Open Sci. 2022;45:41-43

ARANOTE Study Design

Global, randomized, double-blind, placebo-controlled, phase 3 study

Patients (N=669)
- mHSPC*
- ECOG PS 0–2

Stratification factors
- Visceral metastases (Y/N)
- Prior local therapy (Y/N)

2:1 randomization

Darolutamide 600 mg BID + ADT (N=446)

Placebo + ADT (N=223)

Data cut-off: June 7, 2024

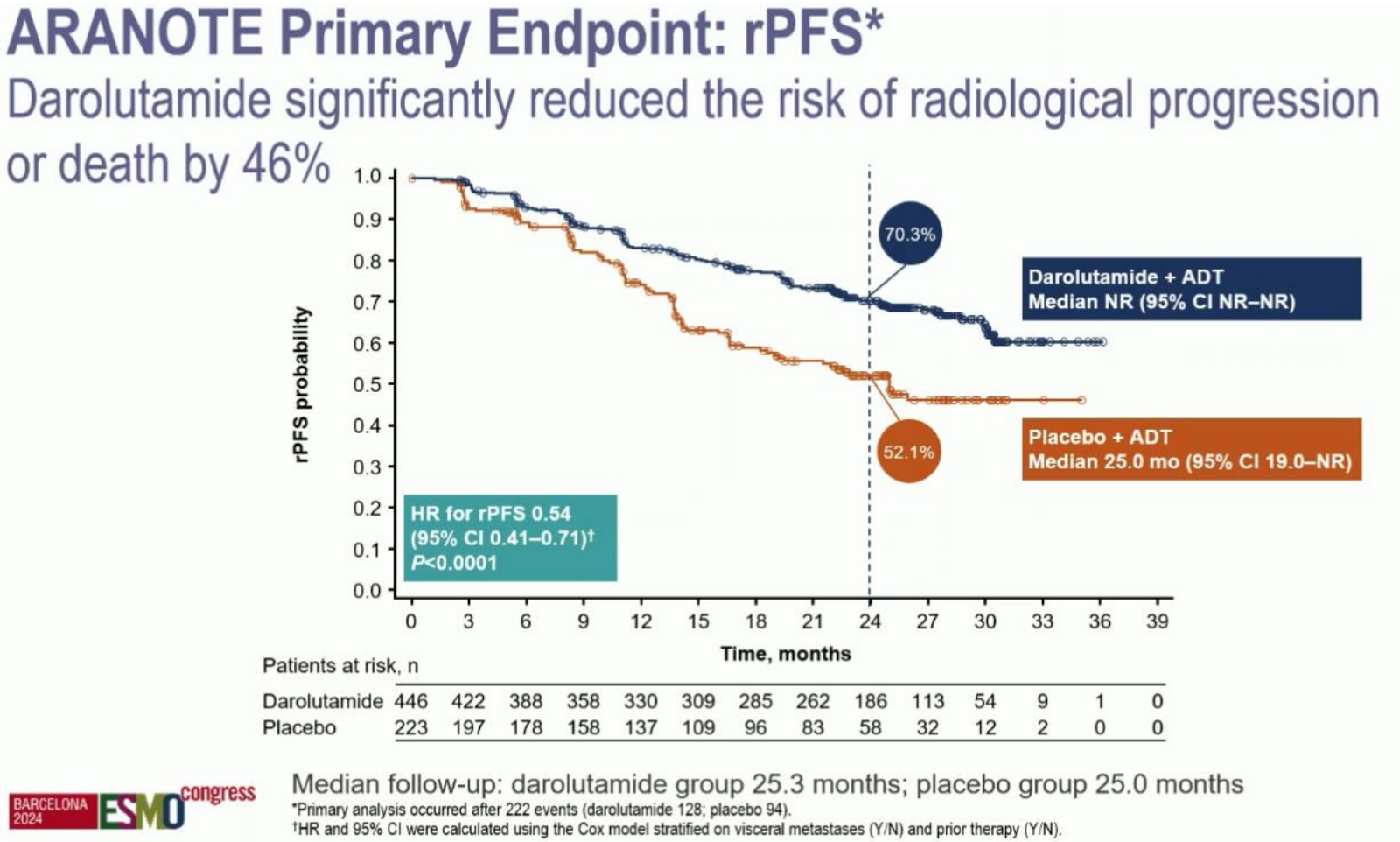
Endpoints

Primary
- rPFS by central blinded review

Secondary
- OS
- Time to initiation of subsequent anticancer therapy
- Time to mCRPC
- Time to PSA progression
- Rates of undetectable PSA (<0.2 ng/mL)
- Time to pain progression (BPI-SF)
- Safety

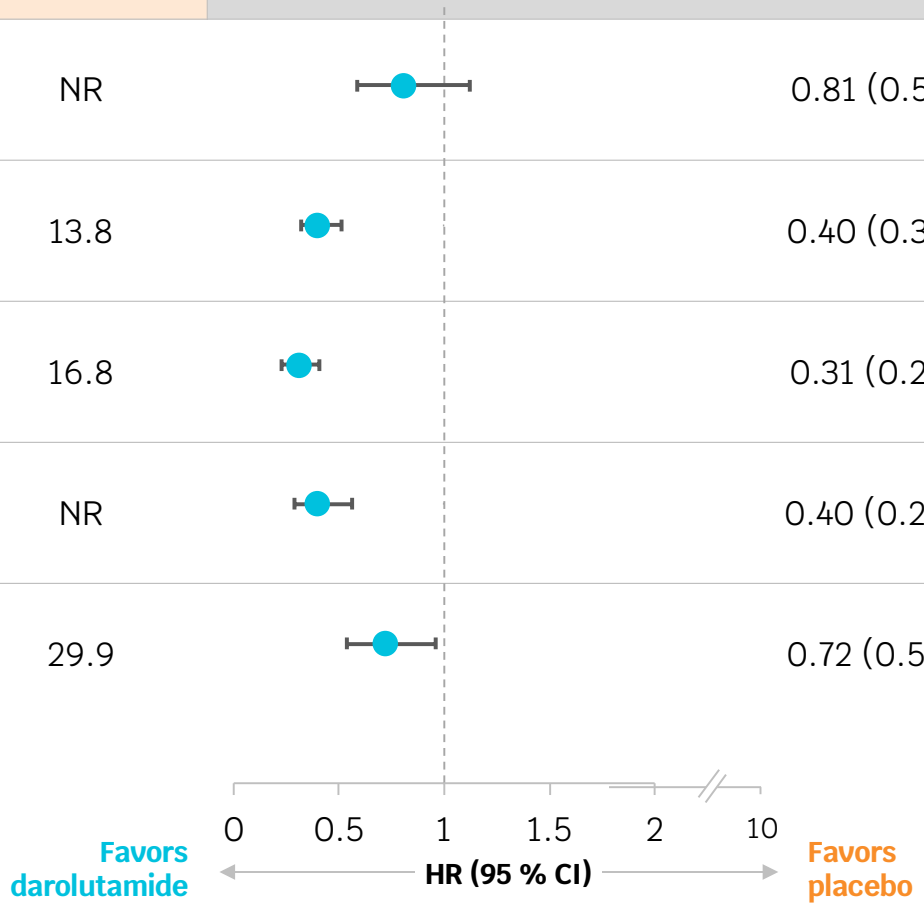
Saad F, et al. ESMO 2024

ESMO 2024: daralutamide (without docetaxel) + ADT vs. ADT+placebo



ARANOTE: Benefit across all secondary endpoints

Endpoint	Darolutamide (n=446)		Placebo (n=223)		Stratified HR (95% CI)
	n (%)	Median, months	n (%)	Median, months	
OS*	103 (23.1)	NR	60 (26.9)	NR	0.81 (0.59-1.12)
Time to mCRPC	154 (34.5)	NR	143 (64.1)	13.8	0.40 (0.32-0.51)
Time to PSA progression	93 (20.9)	NR	108 (48.4)	16.8	0.31 (0.23-0.41)
Time to initiation of subsequent systemic therapy for prostate cancer	68 (15.2)	NR	74 (33.2)	NR	0.40 (0.29-0.56)
Time to pain progression	124 (27.8)	NR	79 (35.4)	29.9	0.72 (0.54-0.96)



*At the time of primary analysis, OS data are immature.

Saad F, et al. ESMO 2024

HETEROGENEITY IN CSPC

High Volume: CHAARTED	**High Risk:** LATITUDE
	≥2 risk factors:
Visceral metastasis and/or	**Gleason score ≥8**
≥4 bone metastasis ≥1 outside axial skeleton	**≥3 bone metastasis**
	Visceral metastasis

Median OS(y) with ADT alone	**Recurrent**	**De novo**
Low Volume	**>8**	5.5
High Volume	5.5	**3**

Sweeney C, et al. N Eng J Med, 2015
Hussain et al. Journal of Clinical Oncology

ROLE OF DOUBLET THERAPY IN MHSPC

Questions to consider prior to treatment intensification in mHSPC:

Disease profile?

1) Volume: high vs low
2) Risk: high vs low
3) De novo vs recurrent disease

Patient profile?

1) Age
2) Ethnicity
3) Performance status/co-morbidities

Safety/QOL?

Genomic Markers?

PEACE-1 TRIAL

Open-label, randomized phase III trial with 2x2 factorial design

Included N=1173
- De novo mHSPC
- ECOG 0-2
- ≥ 1 lesion bone scan and/or CT imaging
- Continuous ADT

Stratified by:
- ECOG PS
- Metastatic site
- Type of castration
- Docetaxel exposure

1:1:1:1 Randomization

- **SOC (n=296)**
- **SOC + Abiraterone 1000 mg qday + 5 mg prednisone bid (n=292)**
- **SOC + Radiotherapy (n=293)**
- **SOC+Abiraterone+ RT (n=292)**

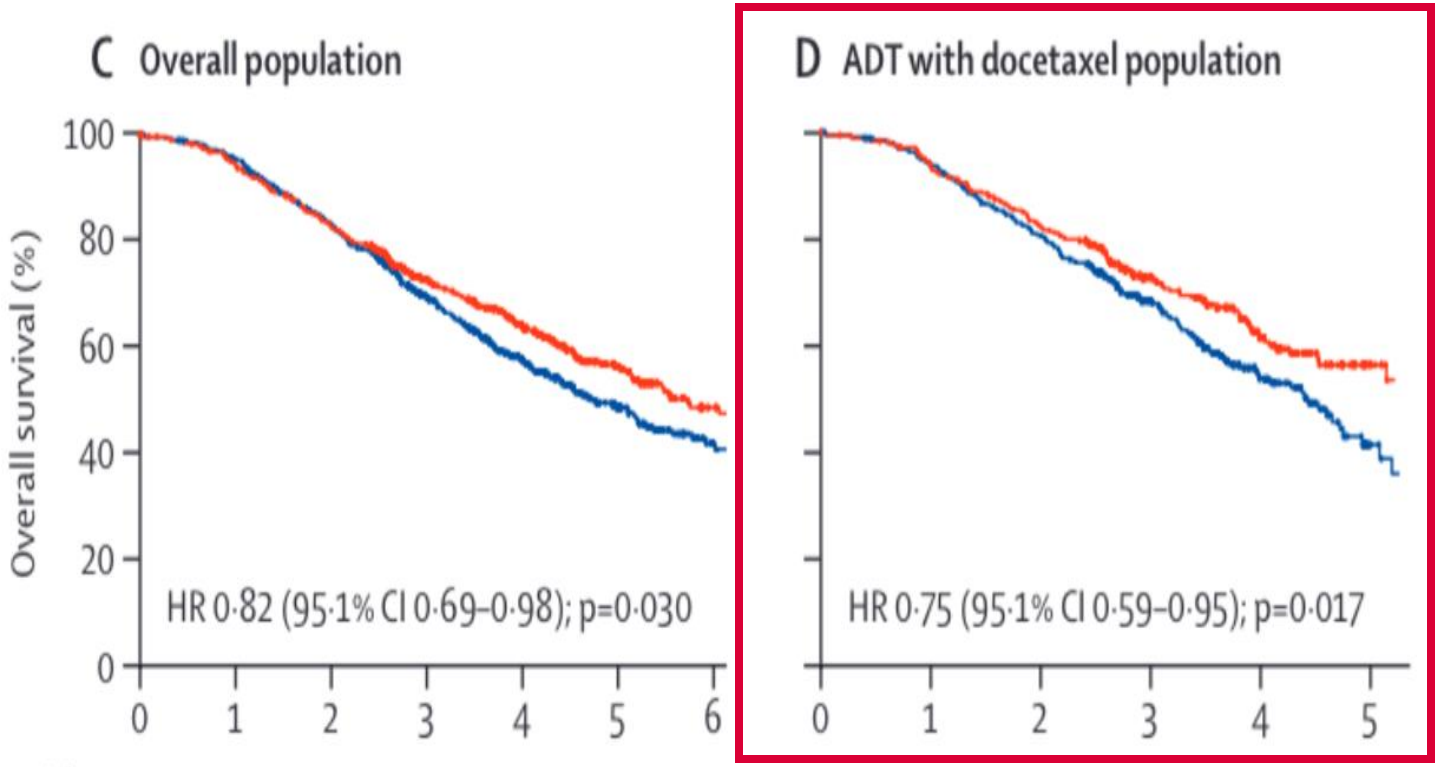
Endpoints

Primary
- Radiographic PFS
- Overall Survival

Secondary
- CRPC-free survival
- PSA response rate
- PSA at 6-8m
- Time to pain progression
- Time to chemo
- QOL

Fizazi, K. et al. *The Lancet 2022; 399*(10336), 1695–1707

RESULTS: OS



Number at risk													
SOC without abiraterone groups	589	556	480	334	207	101	37	355	329	281	172	78	18
SOC plus abiraterone groups	583	541	470	340	230	111	47	355	328	287	183	98	25

SOC+ Abi (n=355)
- Median y = NR (4.5-NE)
- Events: 355

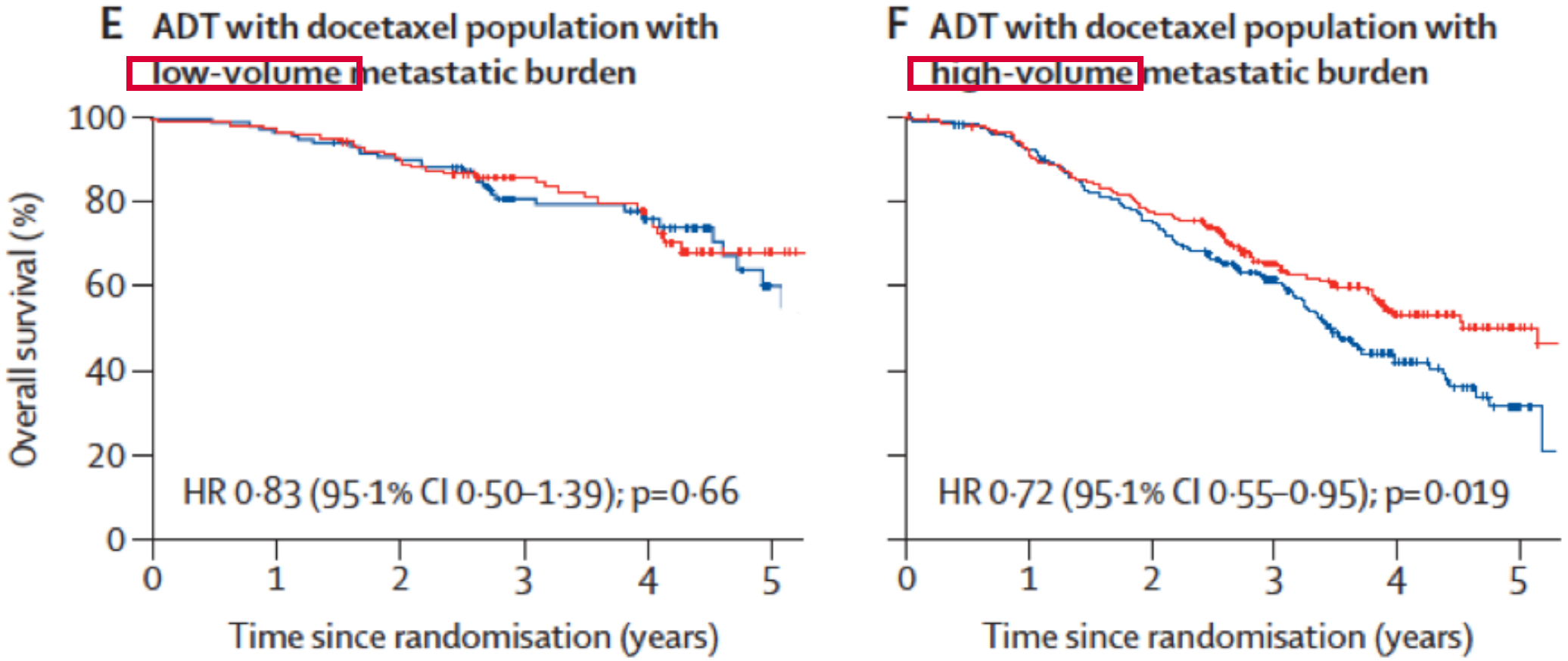
SOC (n=355)
- Median y= 4.4 (3.8-4.9)
- Events: 151

HR (95% CI) 0.75 (0.59-0.95)
P = 0.017

What if stratified by disease volume?

Fizazi, K. et al. J Clin Oncol. 39, no.15_suppl(May 20,2021) 5000-5000
Fizazi, K. et al. The Lancet 2022; 399(10336), 1695–1707

RESULTS: OS LOW VS HIGH VOLUME DISEASE



Benefit is driven in high volume disease

Fizazi, K. et al. J Clin Oncol. 39, no.15 suppl(May 20,2021) 5000-5000

ARASENS TRIAL

Randomized double-blind and placebo-controlled phase III trial

Included N=1306
- mHSPC
- ECOG 0 or 1
- Candidates for ADT + docetaxel

Stratified by:
- M1a vs M1b vs M1c
- ALP < vs >/ ULN

1:1 Randomization

Darolutamide 600 mg bid + Docetaxel x6 + ADT

Placebo + Docetaxel x6 + ADT

Endpoints

Primary
- Overall Survival

Secondary
- Time to CRPC
- Time to pain progression
- SSE-free survival
- Time to SSE
- Time to next txt
- Time to opioid
- Safety

MR Smith, et al. N Engl J Med 2022;386:1132-1142

BASELINE DEMOGRAPHICS

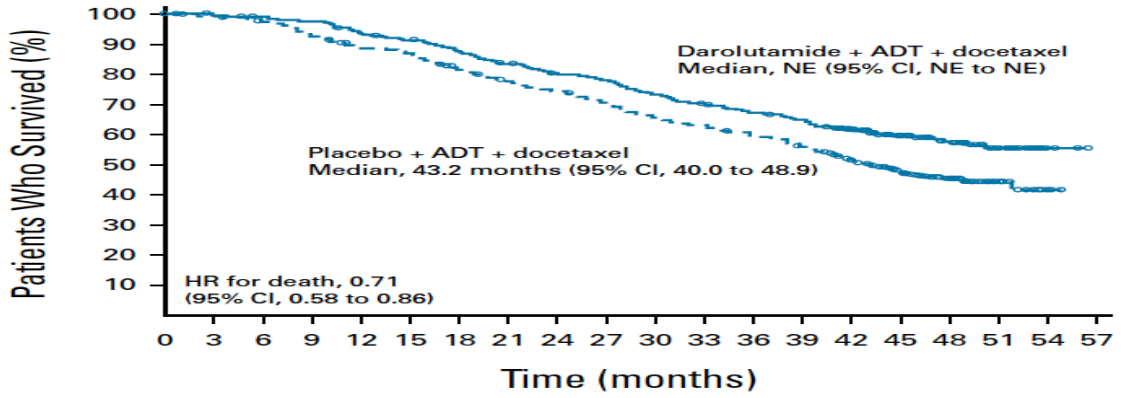
Characteristic	Darolutamide–ADT– Docetaxel (N=651)†	Placebo–ADT–Docetaxel (N=654)†
Median age (range) — yr	67 (41–89)	67 (42–86)
Age group — no. (%)		
<65 yr	243 (37.3)	234 (35.8)
65–74 yr	303 (46.5)	306 (46.8)
75–84 yr	102 (15.7)	110 (16.8)
≥85 yr	3 (0.5)	4 (0.6)
ECOG performance-status score — no. (%)‡		
0	466 (71.6)	462 (70.6)
1	185 (28.4)	190 (29.1)
Race — no. (%)§		
White	345 (53.0)	333 (50.9)
Asian	230 (35.3)	245 (37.5)
Black	26 (4.0)	28 (4.3)
Other	7 (1.1)	2 (0.3)
Not reported	43 (6.6)	46 (7.0)
Region — no. (%)		
North America	125 (19.2)	119 (18.2)
Asia-Pacific	229 (35.2)	244 (37.3)
Rest of the world¶	297 (45.6)	291 (44.5)
Gleason score at initial diagnosis — no. (%)‖		
<8	122 (18.7)	118 (18.0)
≥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 (0.0–9219.0)	24.2 (0.0–11,947.0)
Median serum ALP level (range) — U/liter**	148 (40–4885)	140 (36–7680)
ALP category — no. (%)**		
<ULN	290 (44.5)	291 (44.5)
≥ULN	361 (55.5)	363 (55.5)

77% high volume
70% high risk

MR Smith, et al. N Engl J Med 2022;386:1132-1142

High Risk

C

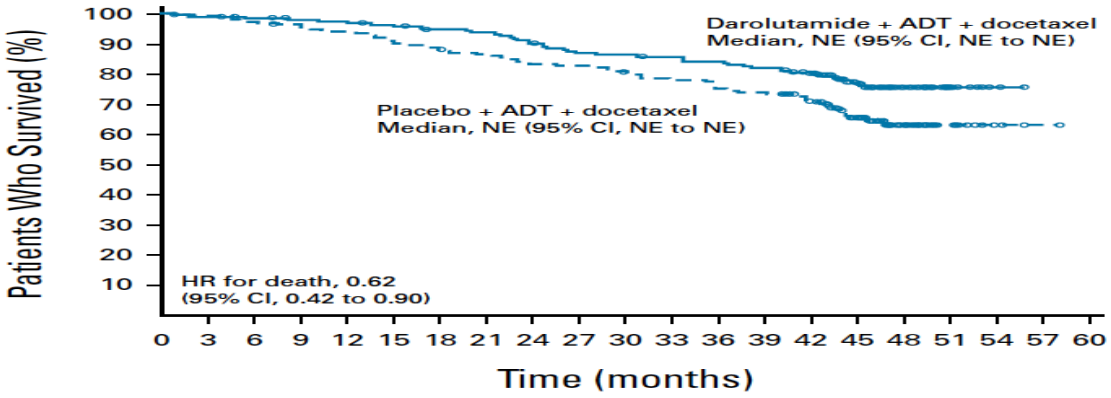


No. of high-risk patients at risk:

Darolutamide	452	450	443	437	419	407	389	369	352	344	322	308	294	282	257	177	99	42	6	0
Placebo	460	453	443	423	400	392	367	346	330	313	290	277	261	245	215	148	72	24	3	0

Low Risk

D

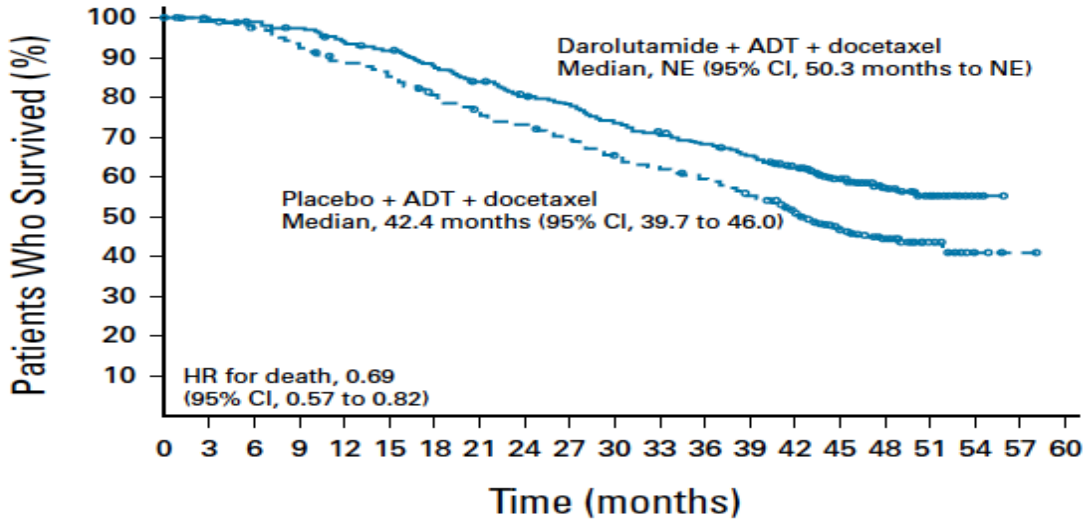


No. of low-risk patients at risk:

Darolutamide	199	195	194	190	189	186	181	179	173	165	164	160	158	154	145	90	40	14	3	0	0
Placebo	194	193	187	184	180	173	168	164	158	157	151	147	141	138	125	70	35	13	3	1	0

High Volume

A

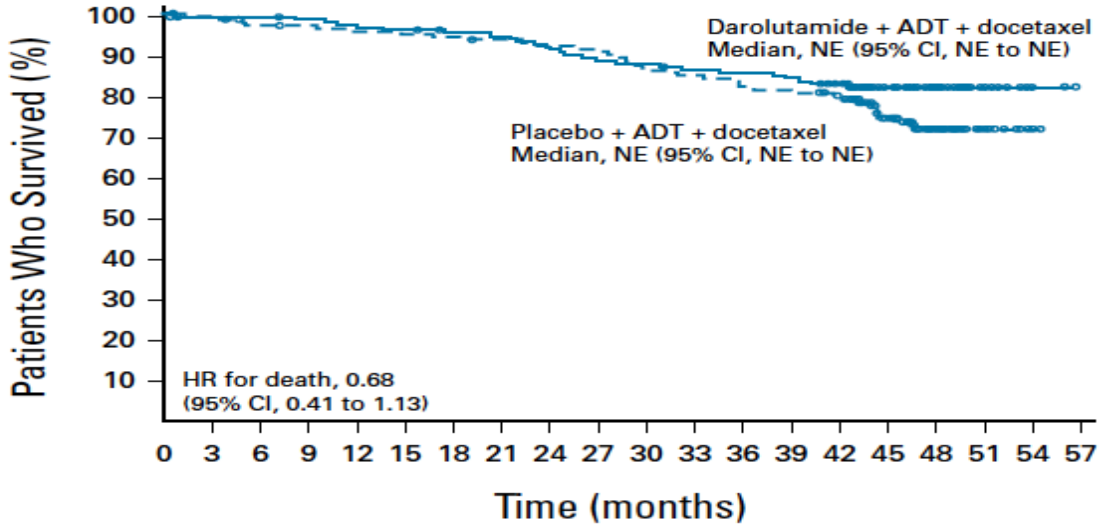


No. of high-volume patients at risk:

Darolutamide	497	494	486	479	462	449	429	408	389	378	356	341	326	312	285	193	103	43	6	0	0
Placebo	508	502	491	469	444	430	401	378	358	341	319	304	286	269	233	153	72	23	4	1	0

Low Volume

B



No. of low-volume patients at risk:

Darolutamide	154	151	151	148	146	144	141	140	136	131	130	127	126	124	117	74	36	13	3	0
Placebo	146	144	139	138	136	135	134	132	130	129	122	120	116	114	107	65	35	14	2	0

ADVERSE EVENTS

PEACE1

	ADT with docetaxel population		ADT without docetaxel population	
	SOC plus abiraterone groups (with or without radiotherapy; n=347)	SOC without abiraterone groups (with or without radiotherapy; n=350)	SOC plus abiraterone groups (with or without radiotherapy; n=226)	SOC without abiraterone groups (with or without radiotherapy; n=237)
Any adverse events	346 (100%)	349 (100%)	226 (100%)	233 (99%)
Severe (grade ≥3) adverse events	217 (63%)	181 (52%)	149 (66%)	97 (41%)
Fatal (grade 5) adverse events	7 (2%)	3 (1%)	8 (4%)	5 (2%)
Frequent severe adverse events				
Hypertension	76 (22%)	45 (13%)	66 (29%)	38 (16%)
Neutropenia	34 (10%)	32 (9%)	0	0
Hepatotoxicity	20 (6%)	2 (1%)	14 (6%)	3 (1%)
Febrile neutropenia	18 (5%)	19 (5%)	2 (1%)	1 (<1%)
Gamma-glutamyl transferase increase	17 (5%)	14 (4%)	6 (3%)	4 (2%)
Erectile dysfunction	7 (2%)	5 (1%)	12 (5%)	13 (5%)
Blood alkaline phosphatase increase	15 (4%)	12 (3%)	6 (3%)	13 (5%)
Other severe adverse events				
Fatigue	10 (3%)	15 (4%)	3 (1%)	0
Peripheral neuropathy	4 (1%)	6 (2%)	1 (<1%)	0

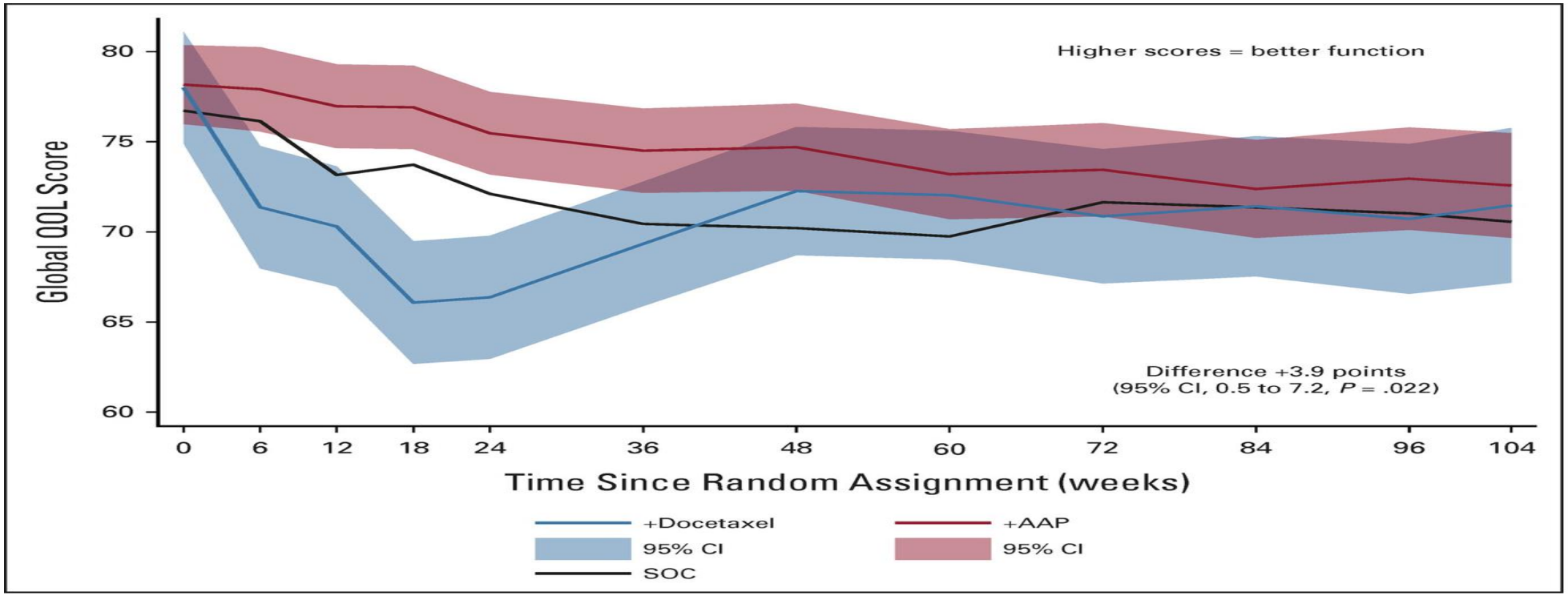
ARASENS

Event	Darolutamide–ADT–Docetaxel (N=652)†	Placebo–ADT–Docetaxel (N=650)†
	number of patients (percent)	
Any adverse event	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 adverse event	292 (44.8)	275 (42.3)
Adverse event leading to permanent discontinuation of trial agent		
Darolutamide or placebo	88 (13.5)	69 (10.6)
Docetaxel	52 (8.0)	67 (10.3)
Selected grade 3 or 4 adverse events‡		
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 ALT level	18 (2.8)	11 (1.7)
Increased AST level	17 (2.6)	7 (1.1)
Increased weight	14 (2.1)	8 (1.2)
Urinary tract infection	13 (2.0)	12 (1.8)

QUALITY OF LIFE?

- We currently do not have current trial data evaluating benefit of chemotherapy to doublet therapy *(ie chemotherapy + ARi+ ADT vs Placebo + ARi + ADT)*

- QOL is strongly affected by docetaxel chemotherapy



Rush HL et al 2021

STOPCAP: Assessing benefit of ARPIs across large trials in mHSPC

Trials

1. LATITUDE: M1, ADT +/- abiraterone
2. SWOT S1216: M1, ADT +/- TAK700 (orteronel)
3. ENZAMET: M1, ADT + bicalutamider vs ADT + enzalutamide
4. STAMPEDE: M1 or N1, arm G (abi)
5. STAMPEDE: M1 or N1, arm J (abi + enza)
6. TITAN: Apalutamide
7. PEACE-1: Abi, doce, RT

Majority of patients benefit (PFS and OS), impact less in oldest population.
No clear difference by class of agent.

PFS in ARPI trials

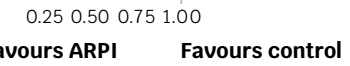
Age Group	Control n /N	ARPI N /N	Haz.ratio (95% CI)
< 65	872 / 1124	627 / 1092	0.47 (0.43, 0.53)
65 to <75	1129 / 1502	805 / 1490	0.50 (0.45, 0.54)
75+	451 / 610	381 / 649	0.63 (0.54, 0.72)

PFS in abiraterone trials

Age Group	Control n /N	ARPI N /N	Haz.ratio (95% CI)
< 65	533 / 647	394 / 626	0.49 (0.43, 0.56)
65 to <75	617 / 764	464 / 770	0.51 (0.45, 0.58)
75+	222 / 282	209 / 285	0.80 (0.66, 0.98)

OS across all trials

Class of agent and Study	ARPI n / N	Control n /N	Haz.ratio (95% CI)	% Weight
Abiraterone trials				
STAMPEDE	293 / 501	371 / 502	0.61 (0.52, 0.71)	19.97
LATITUDE	275 / 597	343 / 602	0.66 (0.56, 0.78)	18.76
PEACE-1, no RT	149 / 292	177 / 296	0.86 (0.69, 1.08)	9.74
PEACE-1, RT	138 / 291	175 / 293	0.72 (0.57, 0.90)	9.36
Subgroup	855 / 1681	1066 / 1693	0.68 (0.62, 0.75)	57.83
(Cochran Q = 6.66 on 3 d.f., p = 0.083)				
Other ARPI trials				
ENZAMET	208 / 563	268 / 562	0.67 (0.56, 0.81)	14.49
TITAN	170 / 525	235 / 527	0.59 (0.49, 0.73)	12.03
Subgroup	378 / 1088	503 / 1089	0.64 (0.56, 0.73)	26.51
(Cochran Q = 0.80 on 1 d.f., p = 0.37)				
Abiraterone + Other ARPI				
STAMPEDE	228 / 462	292 / 454	0.64 (0.54, 0.77)	15.66
Overall	**1461 / 3231**	**1861 / 3236**	**0.66 (0.62, 0.71)**	100.00
(Cochran Q = 8.33 on 6 d.f., p = 0.22)				



Adapted from Fisher D, et al. ASCO GU 2025

TAKE HOME MESSAGE

Is triplet therapy the new SOC for **all** mHSPC? → **No**

Considering current data, treatment should be at least doublet therapy

Until we have trial of docetaxel + ARi+ ADT vs ARi +ADT to answer the question of the role/benefit of docetaxel, treatment should be tailored to each patient. Factors to consider:

- **Patient preference**
- **PS and age of patient**
- **GS and disease burden**
- **De novo vs recurrent disease**
- **Racial/ethnic disparities and mutational analysis**

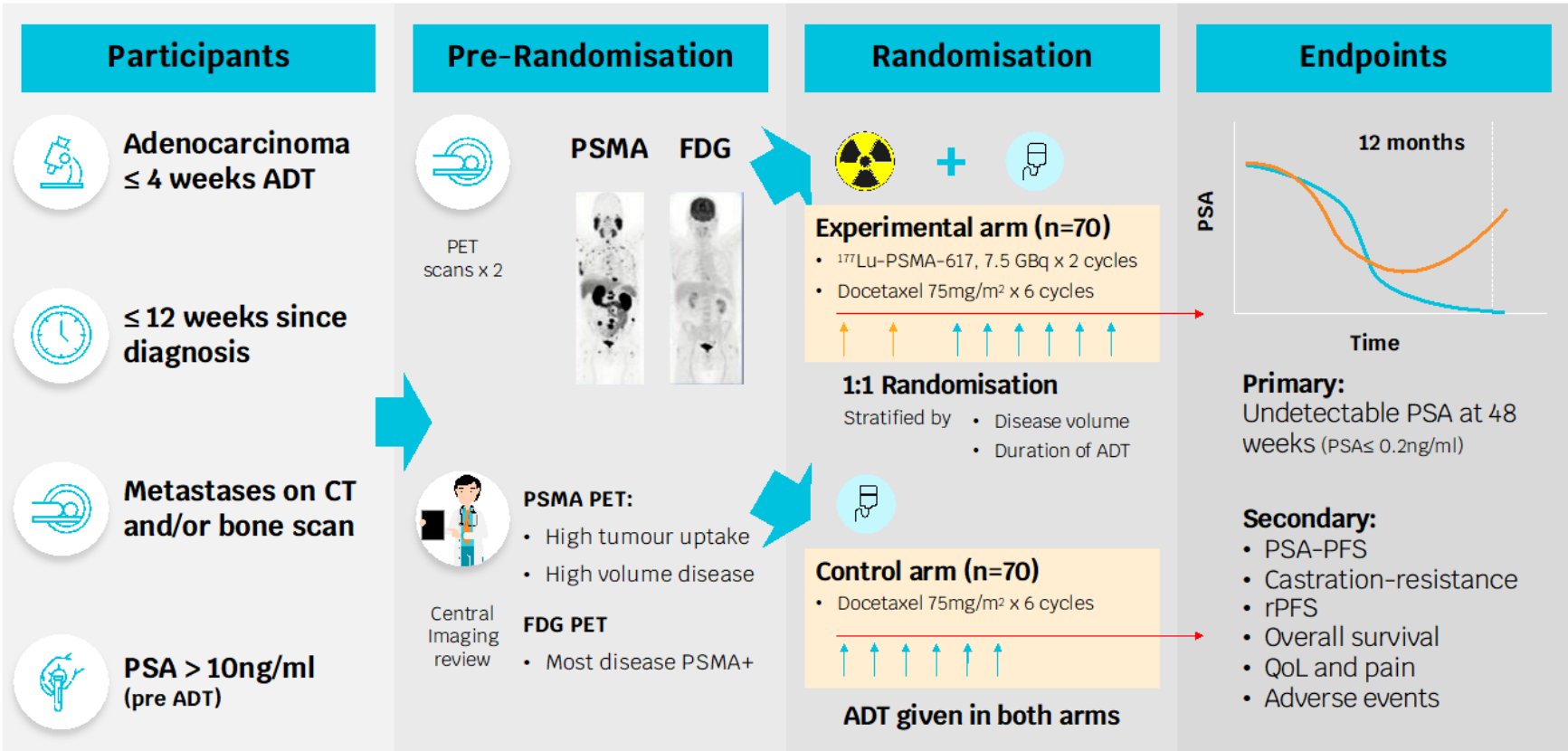
Any other treatment options for mHSPC?

UpFrontPSMA

Background/Rationale

- [^{177}Lu]Lu-PSMA-617 is approved and recommended in metastatic castration-resistant prostate cancer[1,2] but its utility in hormone-sensitive disease is uncertain
- The CHAARTED trial established androgen deprivation therapy (ADT) + docetaxel as a standard of care for de novo high-volume mHSPC. Nevertheless, outcomes remain poor for this patient cohort
- **Our hypothesis was that [^{177}Lu]Lu-PSMA-617 followed by docetaxel would enhance outcomes with minimal impact on toxicity in *de novo* high-volume mHSPC**

Study Design



Medical Oncology PI: Arun Azad Nuclear Medicine PI: Michael Hofman
https://clinicaltrials.gov/ct2/show/NCT04343885

1: Sartor O et al. N Engl J Med. 2021 Sep 16;385(12):1091-1103. 2: Hofman MS et al, Lancet. 2021 Feb 27;397(10276):797-804; Dhiantravan N, et al. BJU Int. 2021 Sep;128(3):331-342.

UpFrontPSMA

Undetectable PSA at week 48

Treatment	Lu-PSMA + docetaxel (n=61)*	Docetaxel (n=61)*
Undetectable PSA at week 48, %	41% (95% CI 30–54)	16% (95% CI 9–28)
	OR 3.88 (95% CI 1.61–9.38); p=0.002	
Undetectable PSA at any time point, %	51% (95% CI 39–63)	32% (95% CI 22–45)
	OR 2.14 (95% CI 1.03–4.46); p=0.042	
Undetectable PSA at week 12, %	17% (95% CI 10–29)	18% (95% CI 10–29)
	OR 0.94 (95% CI 0.37–2.36); p=0.895	

Adverse events

Adverse event	Lu-PSMA + docetaxel (n=63)		Docetaxel (n=63)	
	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
Any treatment-related AE	70%	29%	71%	27%
Treatment-related AEs in ≥ 20% or AESI				
Infusion-related reaction	3%	3%	8%	2%
Febrile neutropaenia	–	11%	–	10%
Peripheral sensory neuropathy	32%	2%	43%	2%
Diarrhoea	16%	6%	25%	0%
Oral mucositis	14%	3%	10%	0%
Fatigue	56%	3%	56%	0%
Alopecia	40%	0%	46%	0%
Dysgeusia	27%	0%	24%	0%
Nausea	24%	0%	24%	0%
Dry mouth	37%	0%	0%	0%

*In addition to the four patients in the docetaxel alone group who withdrew consent after randomisation, an additional four patients were not evaluable for the primary endpoint at 48 weeks (two in each group)

Azad A, et al. ESMO 2024

Future State Forecast

- Biomarker positive:
  - PSMA positive: ADT+ NHA+ PSMA RLT (**PSMAddition** phase 3 trial)
  - Genomic/IHC Biomarker:
    - AKTi for PTEN loss
    - PARPi for BRCA
    - Others (EZH2 Inh, STEP2 BITE, DLL3 BITE, etc)
- PSMA and Biomarker negative: ADT+NHA +/- chemo

THANK YOU