Systemic therapy for mHSPC: doublet or triplet therapy - who, when and how?

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Conflicts of interest

- Employment: None
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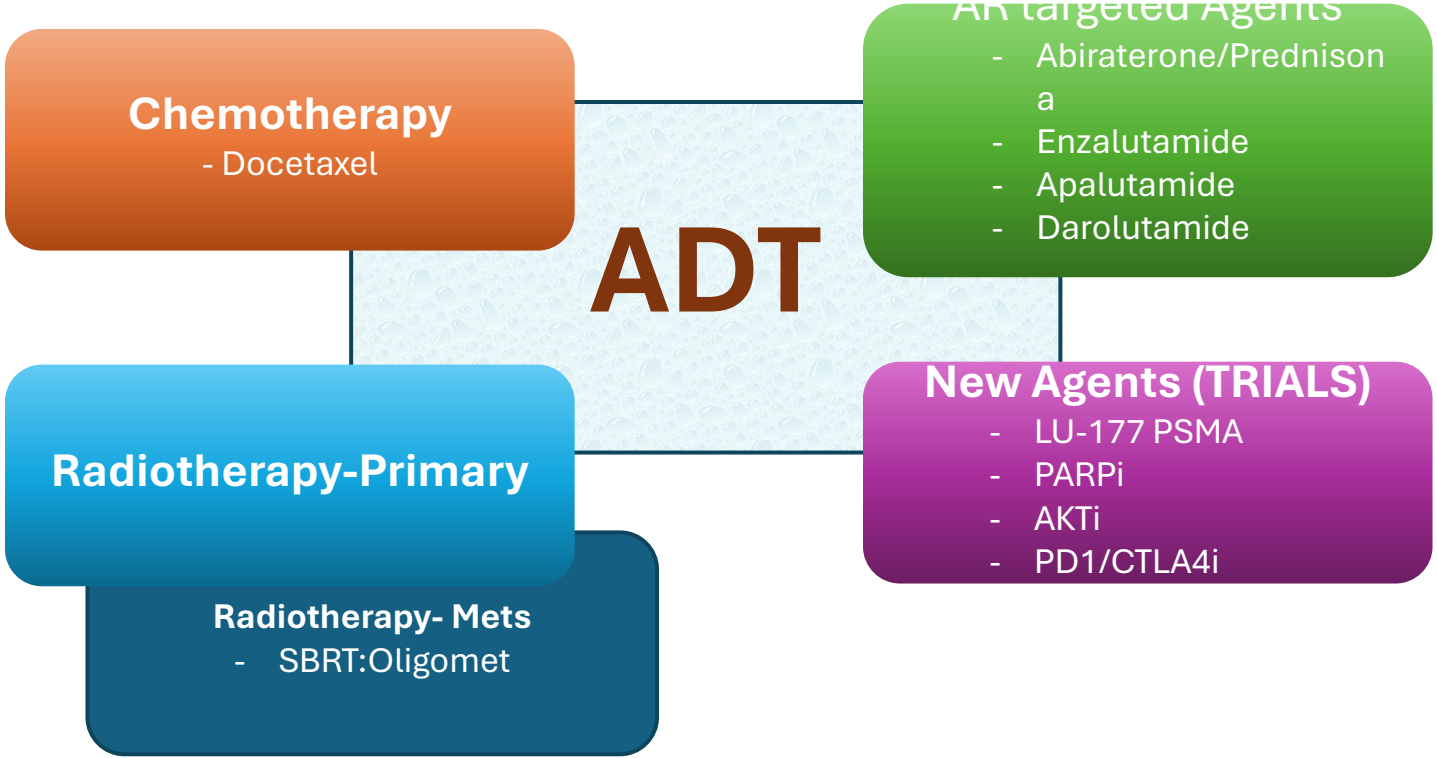
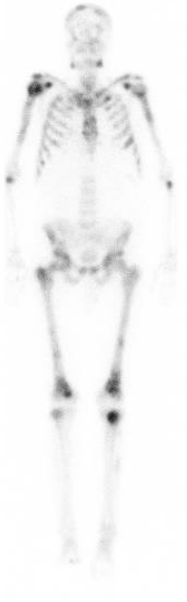
- Grant support: None
- Other (Speaking and travel grants): Janssen, Astellas, Pfizer, Ipsen, Bristol, Astra-Zeneca, Roche, MSD

Treatments available in mCSPC

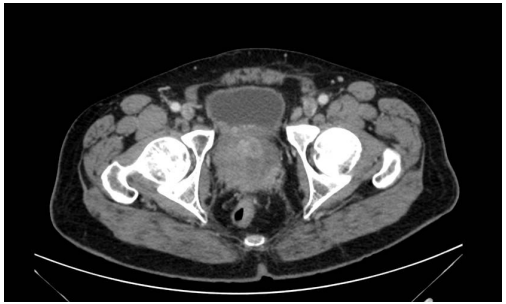


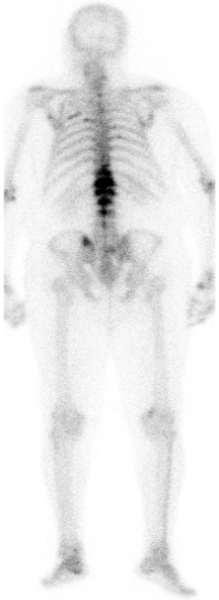
Male 71y gBRCA2mut. cT2N1M1b High Volume PSA >1000 ng/ml



Male 55 y. Prostate Cancer cT4N0M1b

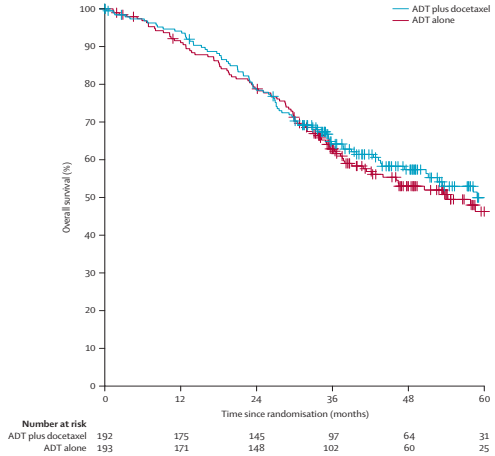
Adenocarcinoma Gleason 8, PSA 84 ng/mL



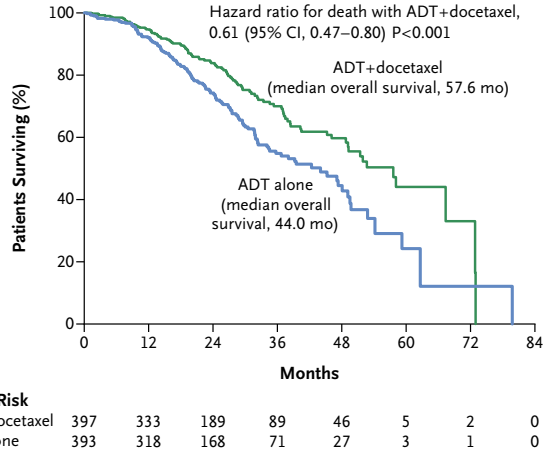


Randomized trials using ADT +/- Docetaxel

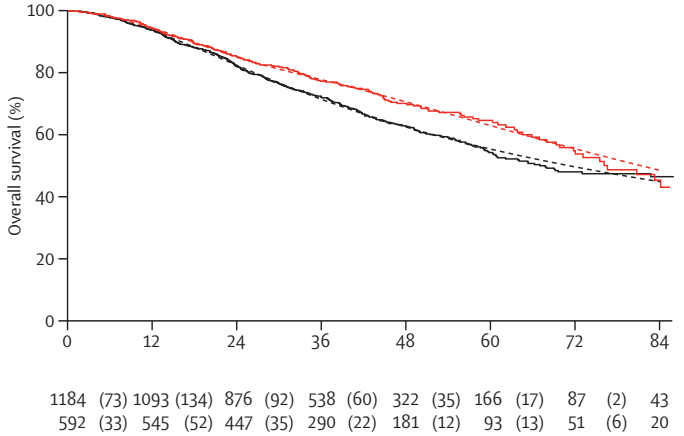
GETUG-15



CHAARTED



STAMPEDE



Study	HR	95% CI
GETUG-15	0,88	0.68-1.14
CHAARTED	0,72	0.59-0.89
STAMPEDE	0,78	0.66-0.92

Gravis G. Lancet Oncol 2013
Sweeney C. N Engl J Med 2015
Kyriakopoulos. J Clin Oncol 2018
James N. N Engl J Med 2016

STOPCAP M1 Meta-analysis Individual data

- **Individual data from 3 Clinical trials**
- **2261 patients (98% of those randomised)**
- **Median follow-up of 72 months (IQR 55–85)**
- **No strong evidence of differences in effect between trials**

	GETUG-AFU15[5]	CHAARTED[2]	STAMPEDE[7]
Accrual period	October, 2004, to December, 2008	July, 2006, to November, 2012	November, 2005, to March, 2013
Number of patients randomly assigned	385	790	1086
Control group treatment	ADT (LHRH agonist or LHRH agonist plus anti-androgen therapy or surgical castration)	ADT (LHRH agonist or LHRH antagonist or surgical castration); oral calcium carbonate 500 mg daily; oral vitamin D 400 IU daily	ADT (GRH agonists or antagonists or orchidectomy)
Intervention group treatment	ADT (LHRH agonist or LHRH agonist plus antiandrogen therapy or surgical castration) plus docetaxel (75 mg/m² intravenously every 3 weeks for a maximum of nine cycles); premedication with an oral corticosteroid (8 mg dexamethasone or equivalent) the evening before, on the day of, and on the day after docetaxel infusion plus subcutaneous injection of G-CSF from day 5 for 5 days	ADT (LHRH agonist or LHRH antagonist or surgical castration) plus docetaxel (75 mg/m² intravenously every 3 weeks for six cycles); oral dexamethasone (8 mg approximately 12 h, 3 h, and 1 h before docetaxel); oral diphenhydramine optional; 500 mg oral calcium carbonate once daily; 400 IU oral vitamin D once daily	ADT (GRH agonists or antagonists or orchidectomy) plus docetaxel (75 mg/m² intravenously every 3 weeks for six cycles) plus oral prednisolone (10 mg once daily)
Median follow-up for all participants (IQR),	84 (79–89)	54 (42–67)	78 (63–96)

OS HR:**0·79** (95%CI 0·70-0·88; p<0·0001)

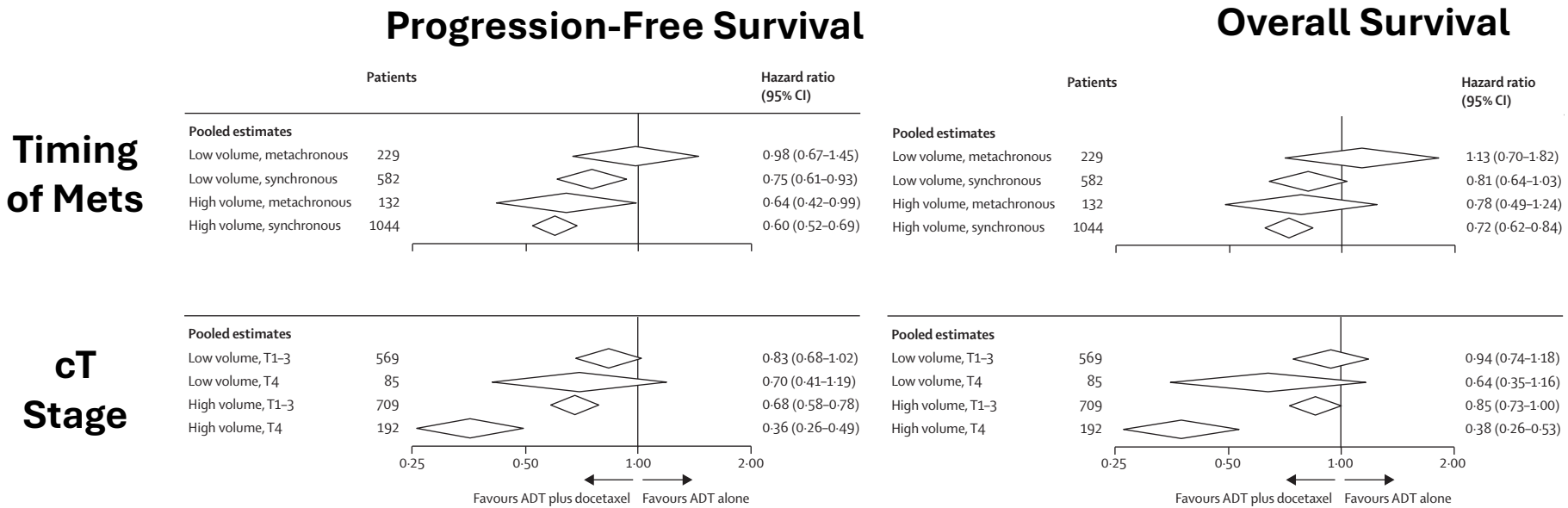
PFS HR **0·70**, (95%CI 0·63 to 0·77; p<0·0001)

FFS HR **0·64**, (95%CI 0·58 to 0·71; p<0·0001)

5-year absolute improvements ~ 9–11%

Vale CL. Lancet Oncol **2023; 24: 78**

Docetaxel benefits all patients except Low volumen and Metachronous or low clinical T ≤3



Vale CL. Lancet Oncol 2023; 24: 78

- **Docetaxel compared with ADT monotherapy does not Benefit low volumen and metachronous or cT≤3**

Phase 3 Clinical Trials including new antiandrogens in mHSPC

	Inclusion Criteria	Control	Active Arm	N	Primary Endpoint
LATITUDE	Naïve High Risk	**ADT**	ADT + Abiraterone	1209	OS & rPFS
STAMPEDE	Naïve	**ADT** ADT + Docetaxel	ADT + Abiraterone	1917 566	OS
ARCHES	Naïve or ADT + Doc x6 <2 m	**ADT**/ ADT +- Doc	Ctrl + Enzalutamide	1150	rPFS
ENZAMET	Naïve	**ADT** / ADT + Doc	ADT ± Doc + Enzalutamide	1125	OS
TITAN	Naïve* or ADT + Doc x 6 <2 m	**ADT**	ADT + Apalutamide	1052	OS & rPFS
PEACE-1	Naïve *Excludes Visceral or LN only metastasis.	**ADT + Doc**	ADT + Doc + Abi ADT + Doc + RT ADT + Doc + Abi + RT	1168	OS & rPFS
SWOG 1216	Naïve	**ADT + bicalutamide**	ADT + TAK-700	1313	OS
ARASENS	Naïve	**ADT + Doc**	ADT + Doc + ODM-201	1303	OS
ARANOTE	Naïve	**ADT**	**ADT + darolutamide**	669 (2:1)	rPFS

New Hormonal Agents Benefit All patients HR OS

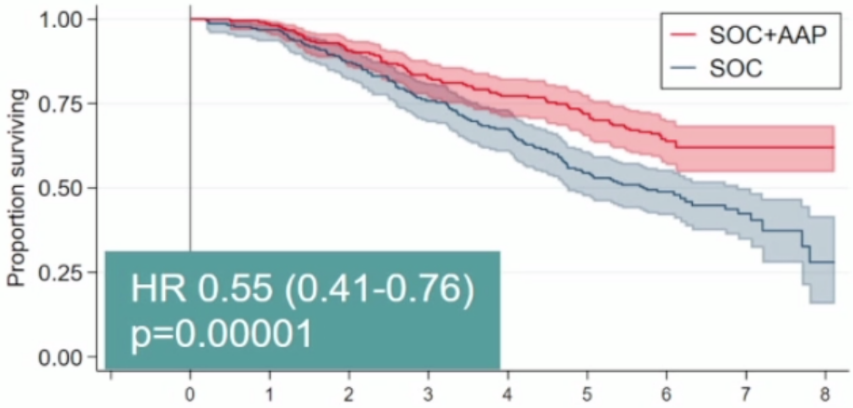
M1 HSPC ARTA	Characteristics	ALL-M1	High-Volume	Low Volume	Metachronous M1
LATITUDE Abi/P	de novo High-Risk N=1199	0.66 (0.58-0.78)	0.62 (0.52-0.74)	-	NA
STAMPEDE Abi/P	>90% de novo N=999	0.60 (0.49-0.71)	0.54(0.43-0.69)	0.55 (0.41-0.76)	NA
ENZAMET Enzalutamide	45% doce concurrent	0.67 (0.52-0.86)	0.53 (0.42-1.09)	0.39 (0.21-0.71)	0.56 (0.29-1.06)
ARCHES Enzalutamide	18% Doce previously	0.66 (0.53-0.81)	0.66 (0.52-0.88)	0.66 (0.43-1.03)	NA
TITAN Apalutamide	19% Doce previously	0.65 (0.53-0.79)	0.70 (0.56-0.88)	0.52 (0.35-0.79)	0.39 (0.22-0.69)

Fizazi et al. ASCO 2019; Hoyle et al EU 2019; James ESMO 2020; Davis et al NEJM 2019; Chi et al NEJM 2019; Chi GU ASCO 2021

VIRTUAL 2020 ESMO congress

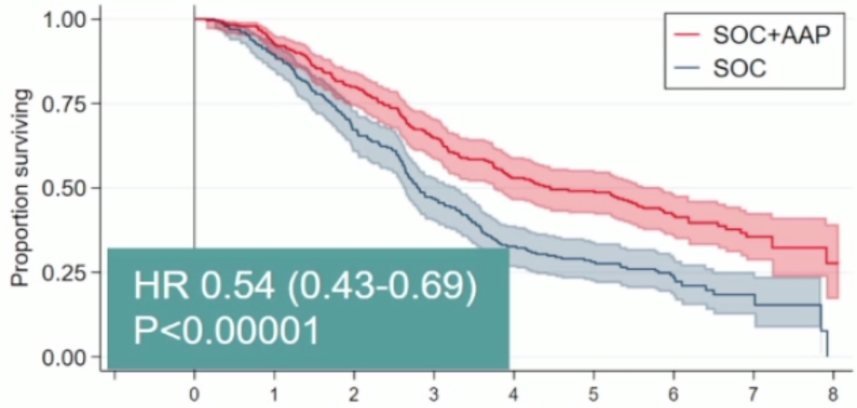
STAMPEDE: OS by risk group (LATITUDE)

Low risk



SOC									
At-risk	222	213	191	165	146	109	62	29	1
Censored	0	2	3	4	5	14	50	77	101
Died	0	7	28	53	71	99	110	116	120
SOC+AAP									
At-risk	214	211	192	172	161	149	95	31	5
Censored	0	0	2	5	5	6	44	106	132
Died	0	3	20	37	48	59	75	77	77

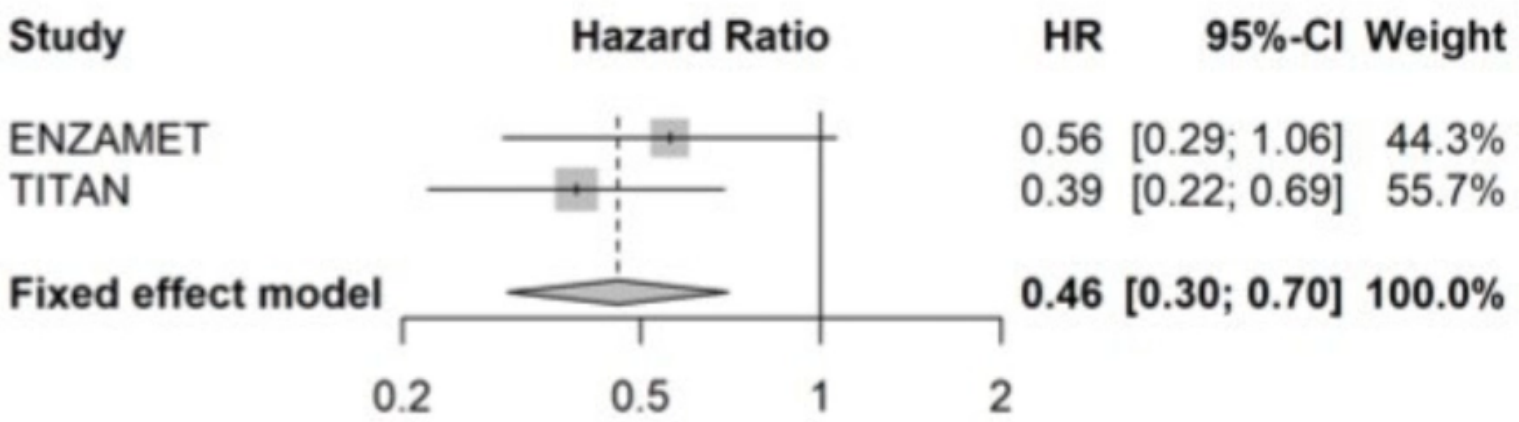
High risk



SOC									
At-risk	232	206	152	106	73	56	28	6	0
Censored	0	2	5	5	6	13	33	51	54
Died	0	24	75	121	153	163	171	175	178
SOC+AAP									
At-risk	241	221	191	154	124	111	66	19	1
Censored	0	2	2	3	5	9	39	79	95
Died	0	18	48	84	112	121	136	143	145

James N. ESMO 2020

Metachronic M1 benefit from adding NHA

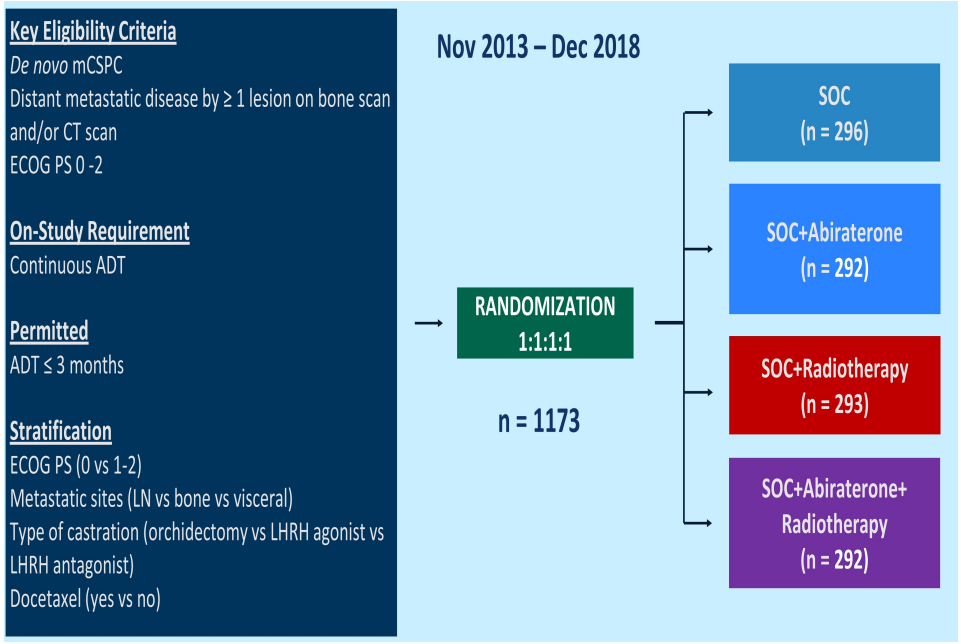


Sweeney C. Eur Urol 2021

- **NHAs benefit all subgroups independent of the volumen of disease and timing**
  - **Age might be important for patient selection**

Abiraterone plus prednisone added to androgen deprivation therapy and docetaxel in de novo metastatic castration-sensitive prostate cancer (PEACE-1): a multicentre, open-label, randomised, phase 3 study with a 2 × 2 factorial design

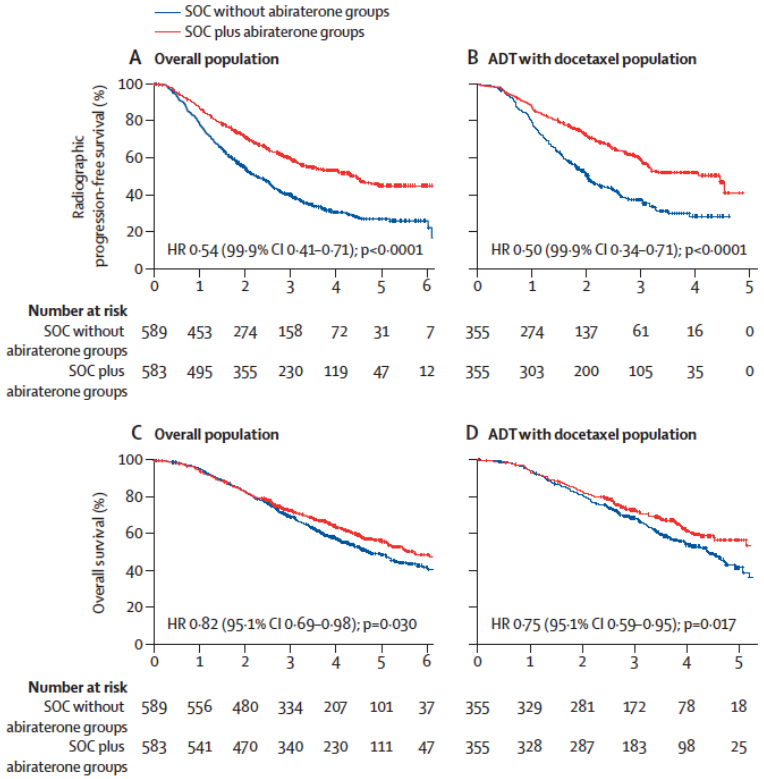
Karim Fizazi, Stéphanie Foulon, Joan Carles, Guilhem Roubaud, Ray McDermott, Aude Fléchon, Bertrand Tombal, Stéphane Supiot,



Fizazi K. Lancet 2022

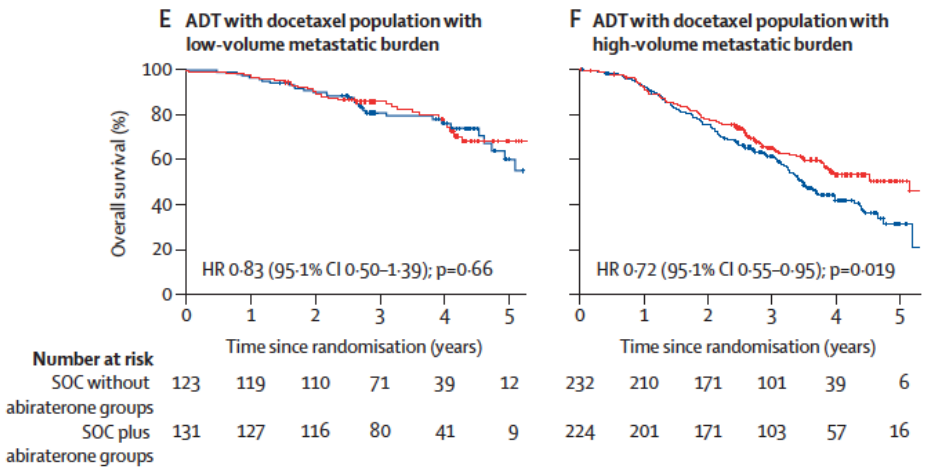
AAP benefits patients treated with Docetaxel plus ADT

	Overall population (n=1172)		ADT with docetaxel population (n=710)*	
	SOC plus abiraterone groups (with or without radiotherapy; n=583)	SOC without abiraterone groups (with or without radiotherapy; n=589)	SOC plus abiraterone groups (with or without radiotherapy; n=355)	SOC without abiraterone groups (with or without radiotherapy; n=355)
Assigned to receive radiotherapy	291 (50%)	293 (50%)	178 (50%)	177 (50%)
Country				
Belgium	29 (5%)	25 (4%)	16 (5%)	16 (5%)
France	458 (79%)	462 (78%)	278 (78%)	280 (79%)
Ireland	30 (5%)	30 (5%)	17 (5%)	13 (4%)
Italy	1 (<1%)	3 (1%)	0	0
Romania	4 (1%)	5 (1%)	0	0
Spain	55 (9%)	56 (10%)	38 (11%)	39 (11%)
Switzerland	6 (1%)	8 (1%)	6 (2%)	7 (2%)
Age, years				
Median	67 (61-72)	66 (59-72)	66 (60-70)	66 (59-70)
Range	37-94	43-87	37-85	44-84
ECOG performance status				
0	412 (71%)	412 (70%)	250 (70%)	246 (69%)
1-2	171 (29%)	177 (30%)	105 (30%)	109 (31%)
T stage				
T1	23 (4%)	23 (4%)	10 (3%)	13 (4%)
T2	109 (19%)	94 (16%)	64 (19%)	45 (13%)
T3	287 (51%)	310 (53%)	167 (49%)	189 (55%)
T4	98 (17%)	99 (17%)	68 (20%)	65 (19%)
Tx	45 (8%)	54 (9%)	32 (9%)	35 (10%)
Missing data	21 (4%)	9 (2%)	14 (4%)	8 (2%)
N stage				
N1	307 (55%)	325 (57%)	198 (58%)	207 (60%)
N0	186 (33%)	174 (30%)	99 (29%)	97 (28%)
NX	69 (12%)	76 (13%)	43 (13%)	39 (11%)
Missing data	21 (4%)	14 (2%)	15 (4%)	12 (3%)
Time from diagnosis, months				
Median	2·3 (1·6-3·2)	2·3 (1·4-3·1)	2·2 (1·6-3·0)	2·2 (1·4-2·9)
Missing data	10 (2%)	10 (2%)	6 (2%)	7 (2%)
Metastatic localisation				
Bone†	472 (81%)	475 (81%)	287 (81%)	279 (79%)
Lymph node only	47 (8%)	52 (9%)	27 (8%)	29 (8%)
Visceral‡	64 (11%)	62 (11%)	41 (12%)	47 (13%)
Metastatic burden§				
High burden	331 (57%)	336 (57%)	224 (63%)	232 (65%)
Low burden	252 (43%)	253 (43%)	131 (37%)	123 (35%)

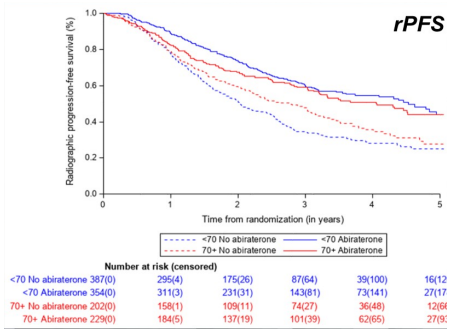


Fizazi K. Lancet 2022

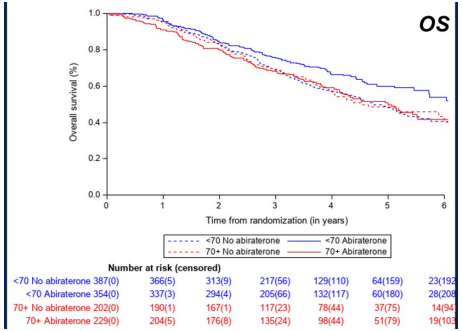
Subgroup exploratory analysis shows greater benefit for High volumen and younger patients volumen



Fizazi K. Lancet 2022



Age <70 y; HR 0.49, 95% CI 0.35-0.69
Age ≥ 70 y; HR 0.65, 95% CI 0.42-1.01



Age <70 y; HR 0.73, 95% CI 0.58-0.92
Age ≥ 70 y; HR 0.95, 95% CI 0.72-1.25

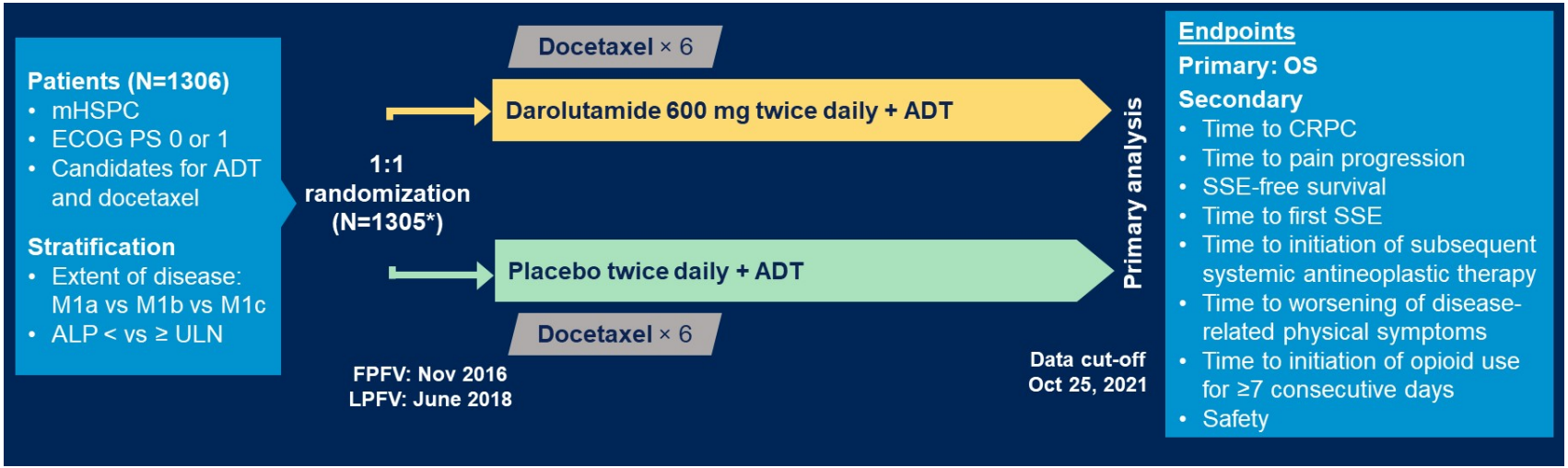
Mourey L. ASCO-GU 2023

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Darolutamide and Survival in Metastatic, Hormone-Sensitive Prostate Cancer

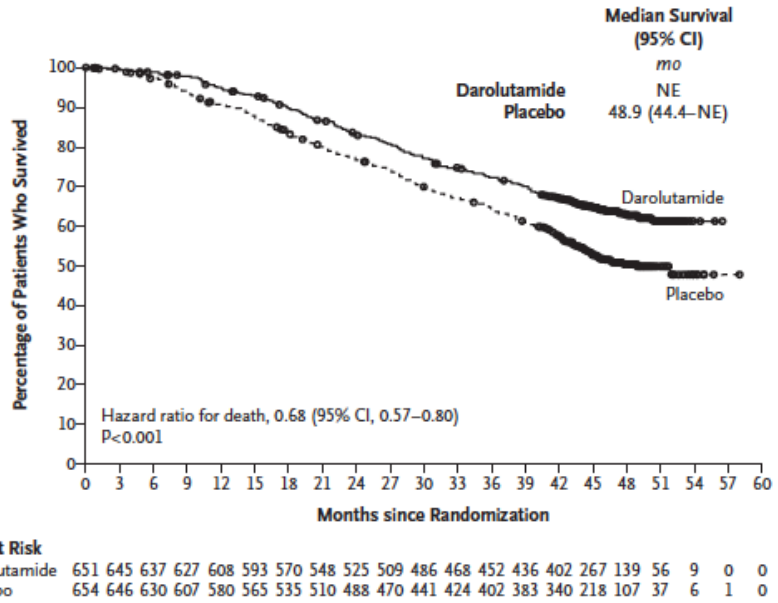
Matthew R. Smith, M.D., Ph.D., Maha Hussain, M.D., Fred Saad, M.D.,



Smith MR. N Engl J Med 2022

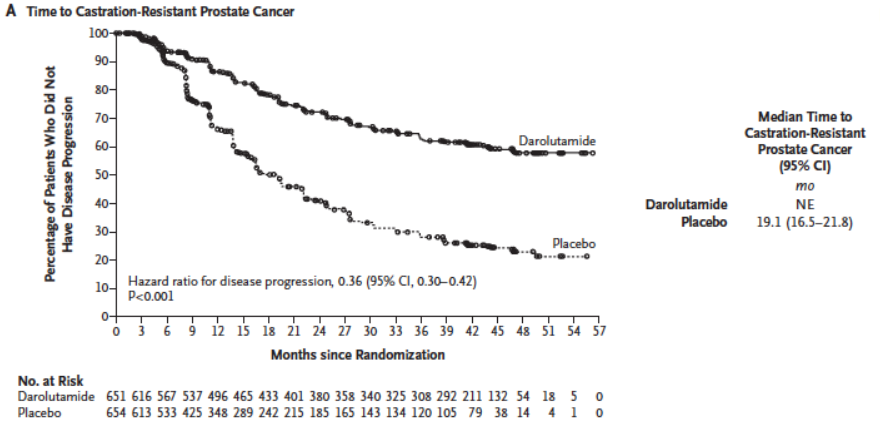
Darolutamide improves OS when added to ADT and Docetaxel

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)

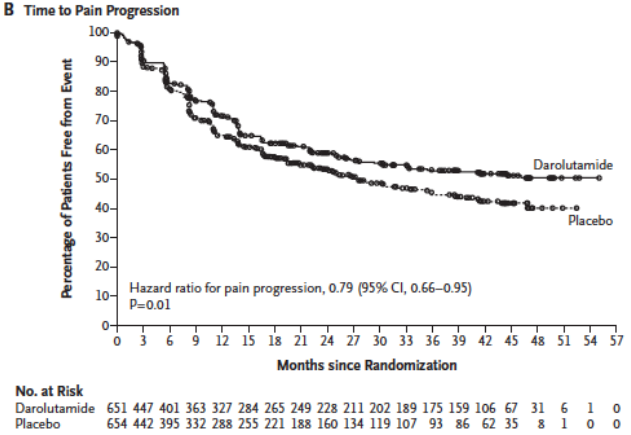


Smith MR. N Engl J Med 2022

Key Secondary endpoints



	Median Time to Castration-Resistant Prostate Cancer (95% CI)
	mo
Darolutamide	NE
Placebo	19.1 (16.5–21.8)



	Median Time to Pain Progression (95% CI)
	mo
Darolutamide	NE (30.5–NE)
Placebo	27.5 (22.0–36.1)

Table 2. Secondary Efficacy End Points (Full Analysis Set).*

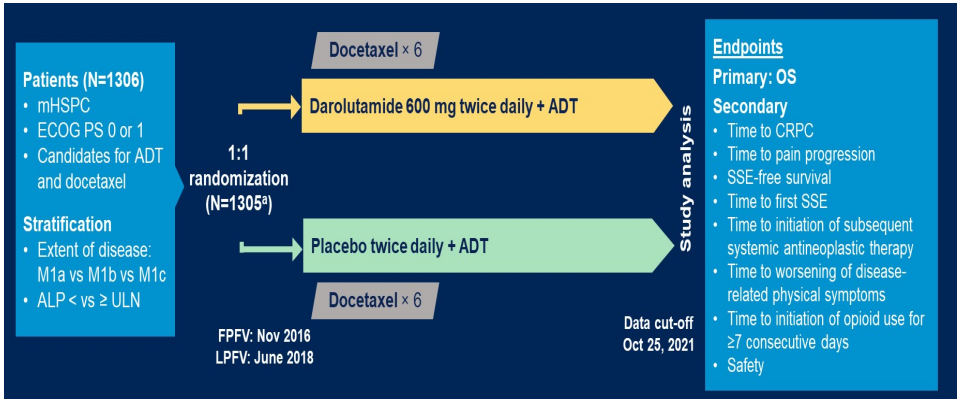
End Point	Darolutamide–ADT–Docetaxel (N=651)†		Placebo–ADT–Docetaxel (N=654)†		Hazard Ratio (95% CI)	P Value
	Median	Patients with Event	Median	Patients with Event		
	mo	*no. (%)*	*mo*	*no. (%)*		
Time to castration-resistant prostate cancer	NR	225 (35)	19.1	391 (60)	0.36 (0.30–0.42)	<0.001
Time to pain progression	NR	222 (34)	27.5	248 (38)	0.79 (0.66–0.95)	0.01
Symptomatic skeletal event–free survival	51.2	257 (40)	39.7	329 (50)	0.61 (0.52–0.72)	<0.001
Time to first symptomatic skeletal event	NR	95 (15)	NR	108 (17)	0.71 (0.54–0.94)	0.02
Time to initiation of subsequent systemic antineoplastic therapy	NR	219 (34)	25.3	395 (60)	0.39 (0.33–0.46)	<0.001
Time to worsening of disease-related physical symptoms	19.3	351 (54)	19.4	308 (47)	1.04 (0.89–1.22)	0.59
Time to initiation of opioid use for ≥7 consecutive days	NR	92 (14)	NR	117 (18)	0.69 (0.52–0.91)	NA

Smith MR. N Engl J Med 2022

original reports

Darolutamide Plus Androgen-Deprivation Therapy and Docetaxel in Metastatic Hormone-Sensitive Prostate Cancer by Disease Volume and Risk Subgroups in the Phase III ARASENS Trial

Maha Hussain, MD[1]; Bertrand Tombal, MD, PhD[2]; Fred Saad, MD[3]; Karim Fizazi, MD, PhD[4]; Cora N. Sternberg, MD[5]; E. David Crawford, MD[6]; Neal Shore, MD[7]; Evgeny Kopyltsov, MD[8]; Arash Rezazadeh Kalebasty, MD[9]; Martin Bögemann, MD[10]; Dingwei Ye, MD[11]; Felipe Cruz, MD, PhD[12]; Hiroyoshi Suzuki, MD, PhD[13]; Shivani Kapur, MD[14]; Shankar Srinivasan, PhD[15]; Frank Verholen, MD[16]; Iris Kuss, MD[17]; Heikki Joensuu, MD[18]; and Matthew R. Smith, MD, PhD[19]



Characteristic at Baseline	High Volume		Low Volume	
	Darolutamide (n=497)	Placebo (n=508)	Darolutamide (n=154)	Placebo (n=146)
Age, median (range), y	67.0 (41–89)	67.0 (44–86)	67.0 (41–84)	67.5 (42–81)
Gleason score at initial diagnosis ≥8, n (%)	381 (76.7)	403 (79.3)	124 (80.5)	113 (77.4)
Metastasis stage at initial diagnosis, n (%)[a]				
De novo	**432 (86.9)**	**445 (87.6)**	**126 (81.8)**	**121 (82.9)**
Recurrent	58 (11.7)	59 (11.6)	28 (18.2)	23 (15.8)
Metastasis stage at screening, n (%)				
M1a (nonregional LN only)	0	0	23 (14.9)	15 (10.3)
M1b (bone ± LN)	386 (77.7)	390 (76.8)[b]	131 (85.1)	131 (89.7)
M1c (visceral ± LN or bone)	111 (22.3)	118 (23.2)	0	0
Serum PSA, median (range), ng/mL[c]	38.7 (0–9219.0)	27.9 (0–11,947.0)	11.7 (0–3771.0)	14.5 (0–3372.9)

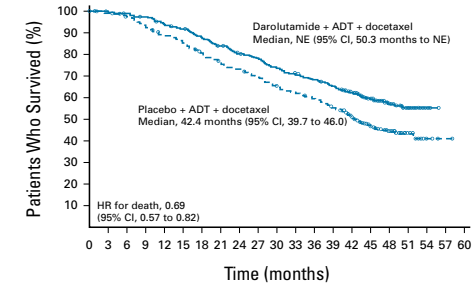
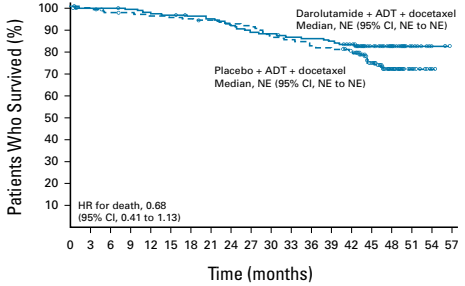
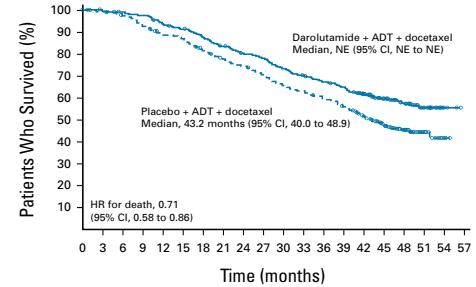
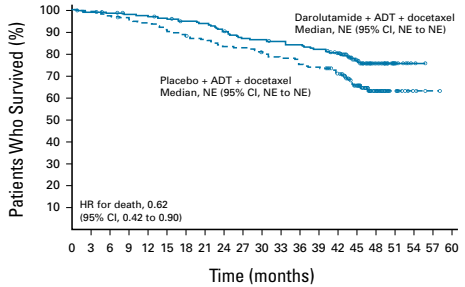
Characteristic at Baseline	High Risk		Low Risk	
	Darolutamide (n=452)	Placebo (n=460)	Darolutamide (n=199)	Placebo (n=194)
Age, median (range), y	67.0 (41–86)	67.0 (44–86)	67.0 (41–89)	67.0 (42–85)
Gleason score at initial diagnosis ≥8, n (%)	428 (94.7)	440 (95.7)	77 (38.7)	76 (39.2)
Metastasis stage at initial diagnosis, n (%)[a]				
De novo	**416 (92.0)**	**419 (91.1)**	**142 (71.4)**	**147 (75.8)**
Recurrent	33 (7.3)	39 (8.5)	53 (26.6)	43 (22.2)
Metastasis stage at screening, n (%)				
M1a (nonregional LN only)	0	0	23 (11.6)	15 (7.7)
M1b (bone ± LN)	345 (76.3)	354 (77.0)[b]	172 (86.4)	167 (86.1)
M1c (visceral ± LN or bone)	107 (23.7)	106 (23.0)	4 (2.0)	12 (6.2)
Serum PSA, median (range), ng/mL[c]	34.0 (0–9219.0)	30.0 (0–11,947.0)	19.2 (0–4173.0)	12.4 (0–3372.9)

M. Hussain. JCO 2023

ADT + Doce + ARTAs consistently improves OS compared with ADT + Docetaxel

Trial	ARTA	N	Doce (%)	Timing	rPFS HR (95%CI)	OS HR (95% CI)	Ref
PEACE-1	Abi/P	1172	710 (60%)	Conc.	0.50 (0.40-0.62)	0.75 (0.59-0.95)	Fizazi. ESMO 2021
ARASENS	Daro	1300	1300 (100%)	Conc.	NA	0.68 (0.57-0.80)	Smith MR. NEJM 2022
ENZAMET	**Enza**	**1125**	**503 (45%)**	**Conc.**	**0.48 (0.37-0.62)**	**0.73 (0.55-0.99)**	**Davis I. NEJM 2019 Proc ASCO 2022**
ARCHES	Enza	1150	205 (17%)	Sec.	NA	0.74 (0.59-2.12)	Chi K. JCO 2021
TITAN	Apa	1052	113 (10%)	Sec.	0.47 (0.22-1.01)	1.12 (0.59-2.12)	Chi K. JCO 2021

OS subanalysis by volumen or risk

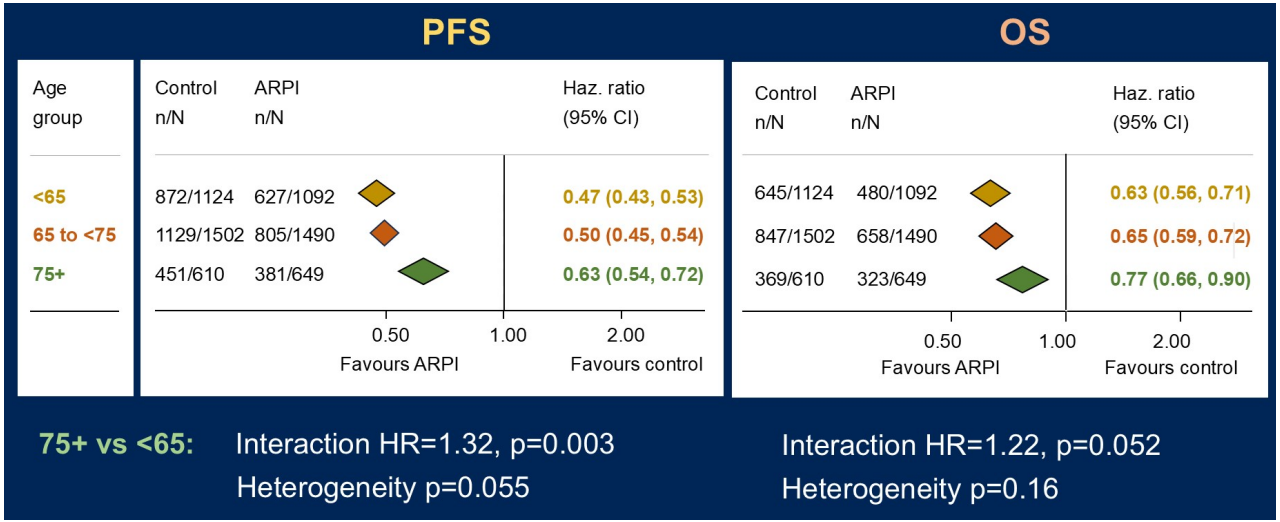
	HIGH	LOW
VOLUME		
RISK		

M. Hussain. JCO 2023

Which patients with metastatic hormone-sensitive prostate cancer (mHSPC) benefit more from androgen receptor pathway inhibitors (ARPIs)?

STOPCAP meta-analysis of individual participant data

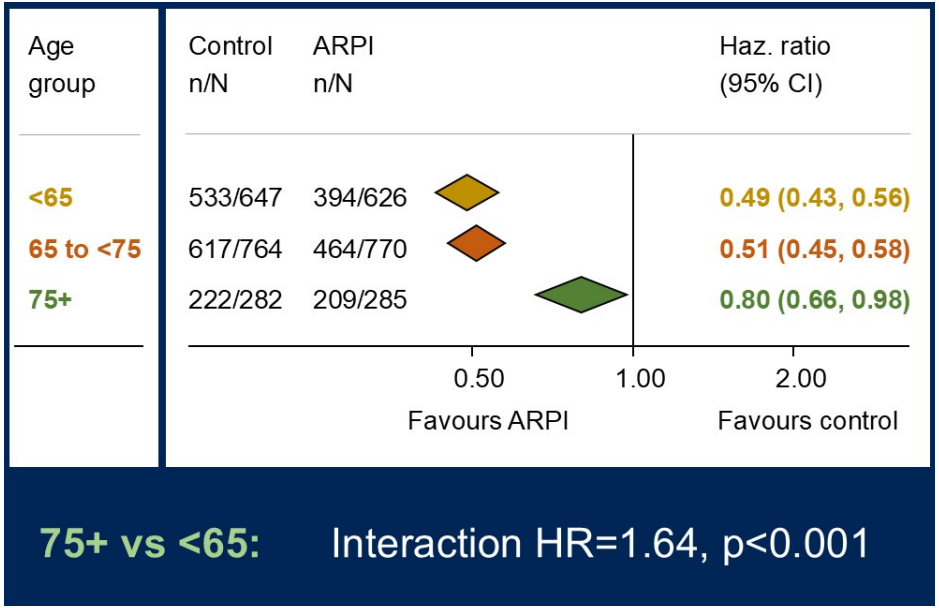
David Fisher, C Vale, L Rydzewska, P Godolphin, N Agarwal, G Attard, K Chi, N Clarke, I Davis, K Fizazi, S Gillessen, G Gravis, N James, D Matheson, R Oldroyd, M Parmar, C Sweeney, B Tombal, I White, J Tierney



Fischer D. ASCO GU 2025

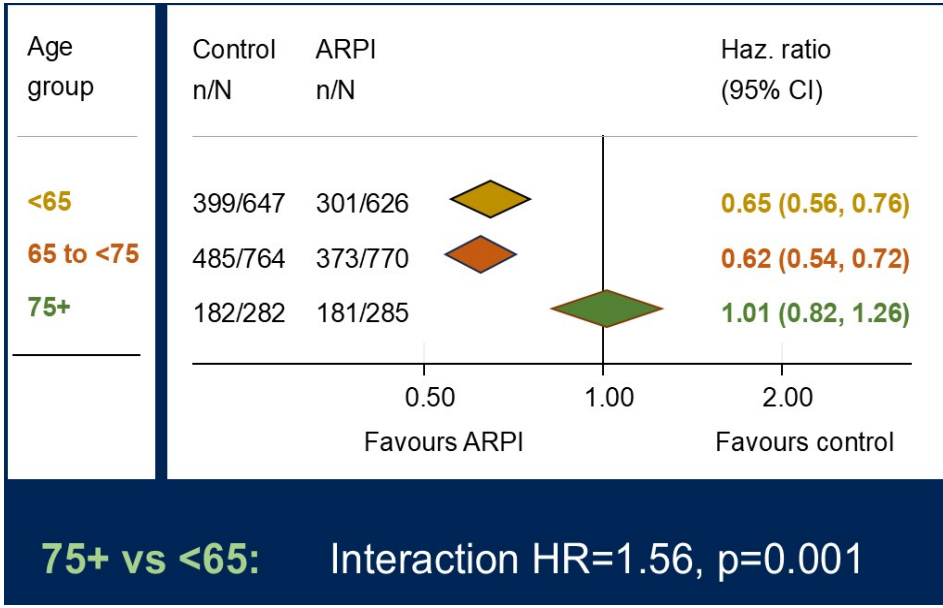
Effects of ARPI by age group: abiraterone trials

PFS



75+ vs <65: Interaction HR=1.64, p<0.001

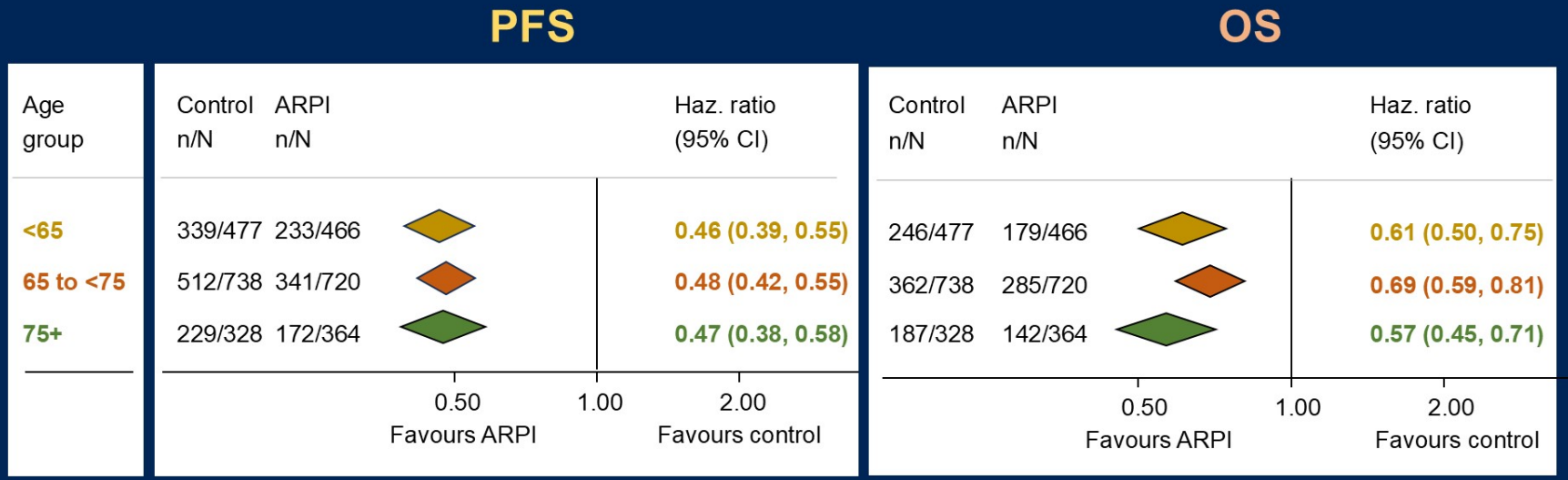
OS



75+ vs <65: Interaction HR=1.56, p=0.001

Fischer D. ASCO GU 2025

Effects of ARPIs by age subgroup: “amide” trials

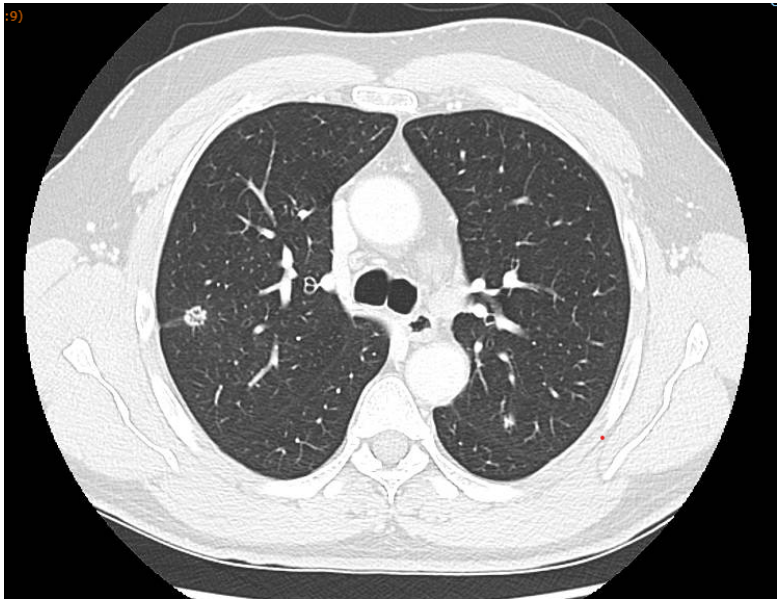


75+ vs <65: Interaction HR=1.02, p=0.88 Interaction HR=0.93, p=0.61

Note: 48% available data at present

Fischer D. ASCO GU 2025

Male 67y TxN1M1c (Lung metastases; 2 nodules and lymph nodes)



What is your preferred option?:

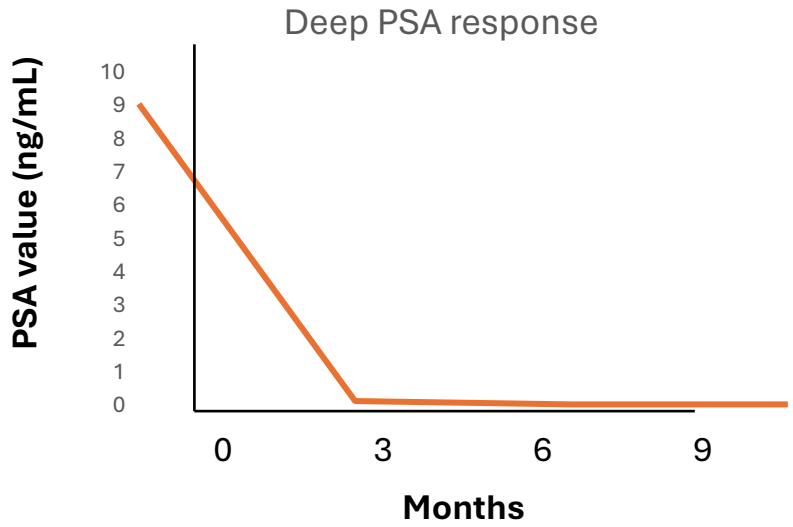
A) ADT + SBRT

B) ADT + docetaxel

C) ADT + ARPI + docetaxel

D) Clinical trial

Clinical trial (ARPI + PARPi) for nonHRR mut



PSA response

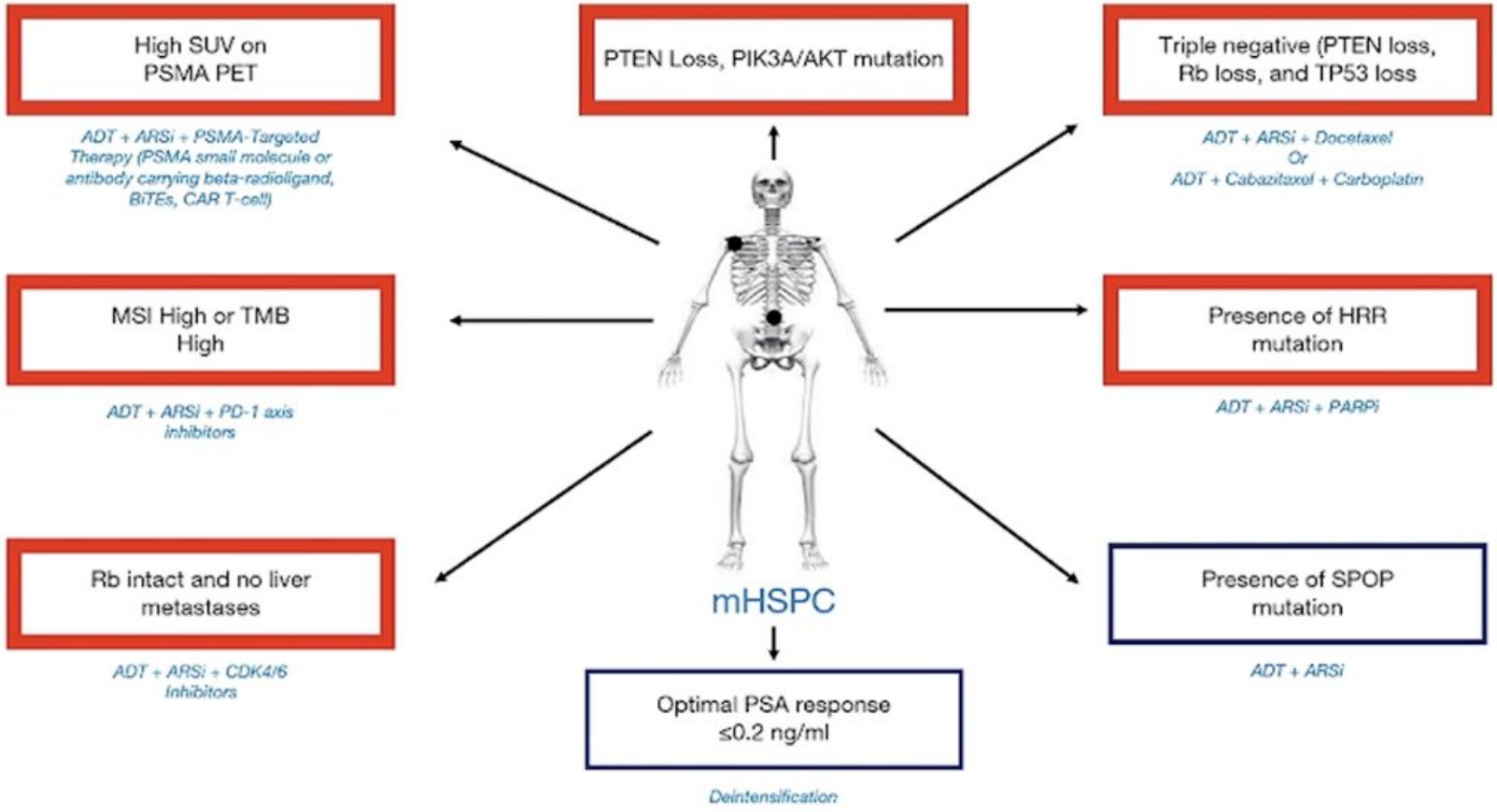
<0.006 ng/ml		29/08/2025
<0.006 ng/ml		01/08/2025
<0.006 ng/ml		04/07/2025
<0.006 ng/ml		06/06/2025
0.01 ng/ml		09/05/2025
0.04 ng/ml		11/04/2025
0.15 ng/ml		14/03/2025
0.64 ng/ml		07/02/2025
9.00 ng/ml		01/01/2025

Are new strategies posible?

¿How could we improve outcomes?

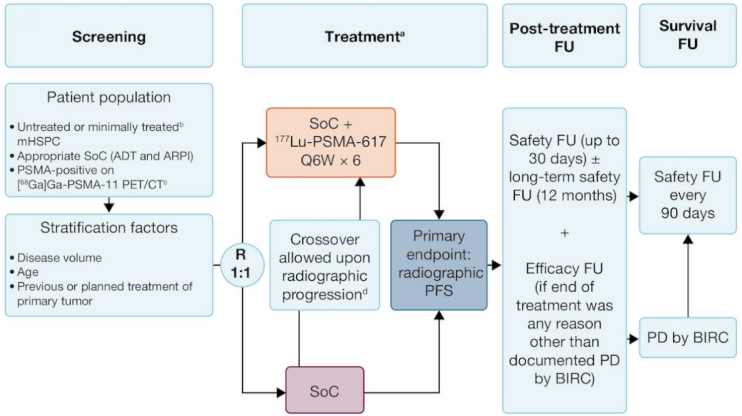
- Better Patient Selection
- Better Treatments

The Future of the Treatment of mHSPC



ADT: androgen deprivation therapy, ARPE androgen receptor signaling inhibitor, IMB: tumor mutational burden, BiTEs: bispecific T cell engager, CAR T cell: chimeric antigen receptor T cell, CDK4/6: Cyclin D Kinase 4/6; HRR: homologous recombination repair, mHSPC: metastatic hormone sensitive prostate cancer, MSI: microsatellite instability, PARPi poly adenosine diphosphate ribose polymerase inhibitor, PSMA: prostate specific membrane antigen; PD-1: programmed cell death protein 1

PSMA Addition



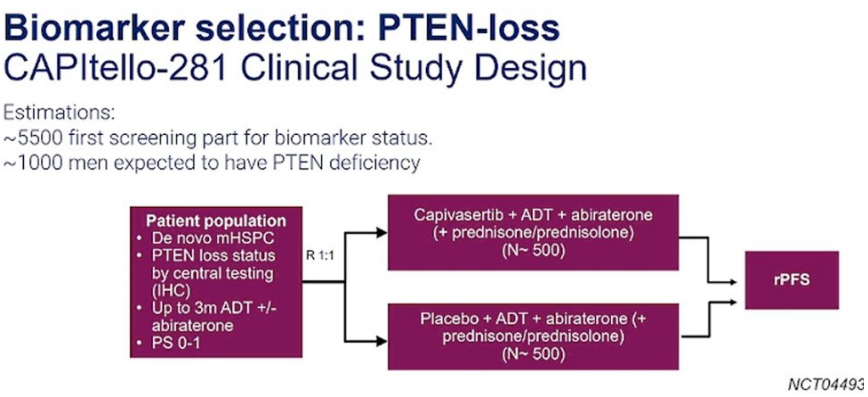
Novartis Pluvicto™ demonstrates statistically significant and clinically meaningful rPFS benefit in patients with PSMA-positive metastatic hormone-sensitive prostate cancer

Jun 02, 2025

Ad hoc announcement pursuant to Art. 53 LR

- *At interim analysis, PSMAddition trial met its primary endpoint showing statistically significant and clinically meaningful benefit for Pluvicto™ plus hormone therapy versus hormone therapy alone, with positive trend in overall survival (OS)[1]*

CAPITELLO



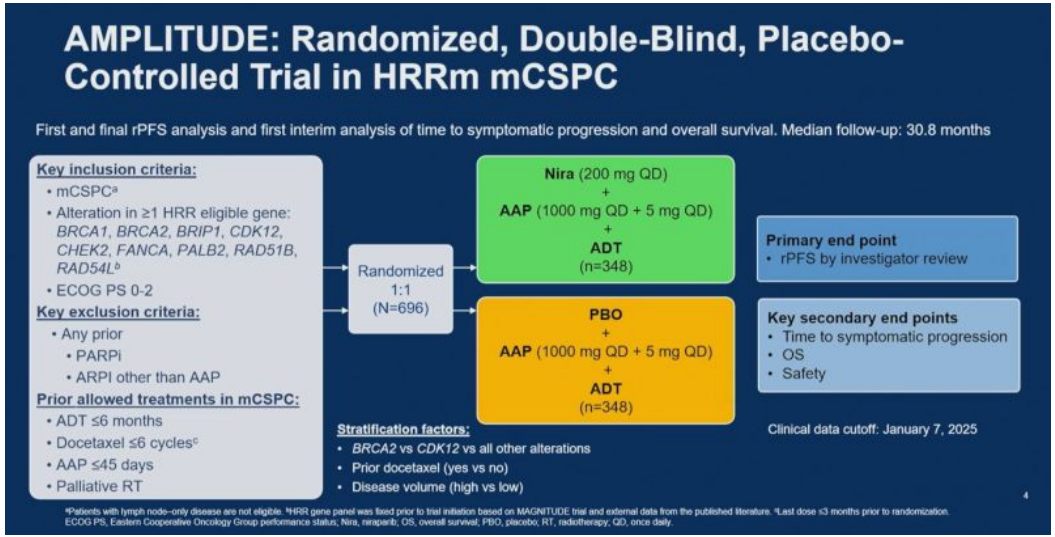
TRUQAP® (capivasertib) combination in PTEN-deficient metastatic hormone-sensitive prostate cancer demonstrated statistically significant and clinically meaningful improvement in radiographic progression-free survival in CAPItello-281 Phase III trial

PUBLISHED
25 November 2024

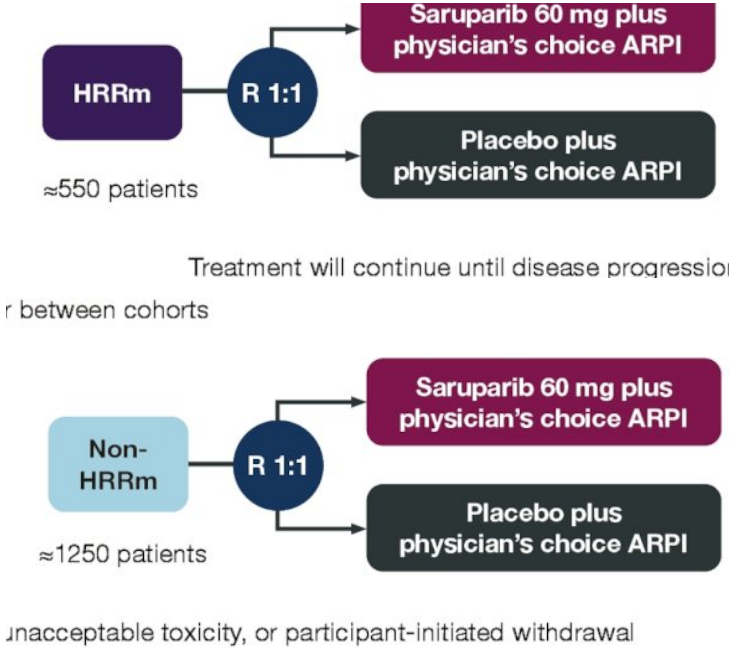
Genomics

BRCA2/1 and other HRR genes	Genomic profiles	PTEN Loss
	• PAM50 • Decypher	

PARP inhibitors in mHSPC
HRRm and not mutated



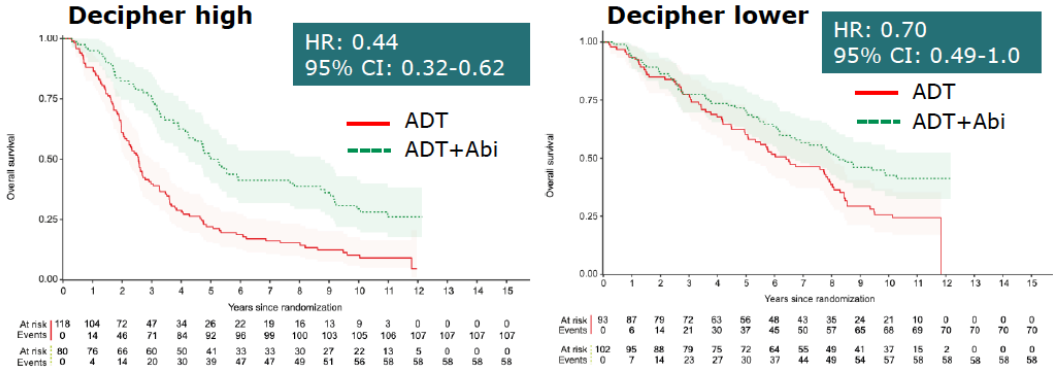
EVO-PARP



Decypher might be predictive for docetaxel

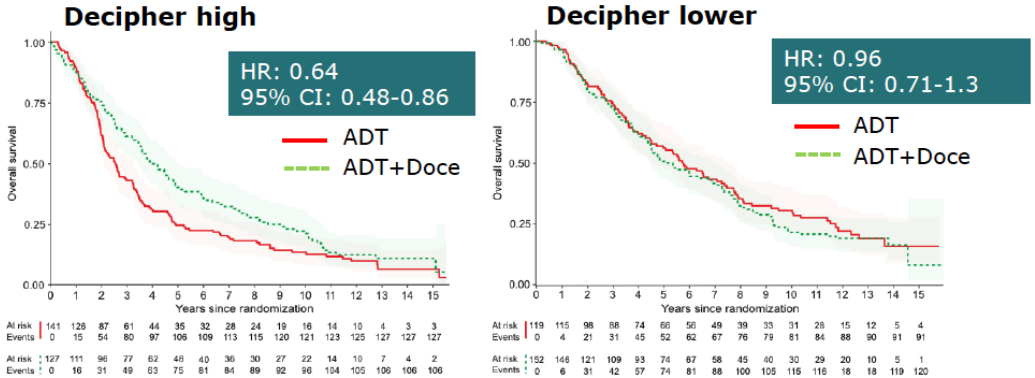
Grist E. ESMO 2024

Abiraterone



Biomarker-treatment interaction not statistically-significant (p=0.061), nor clinically-relevant

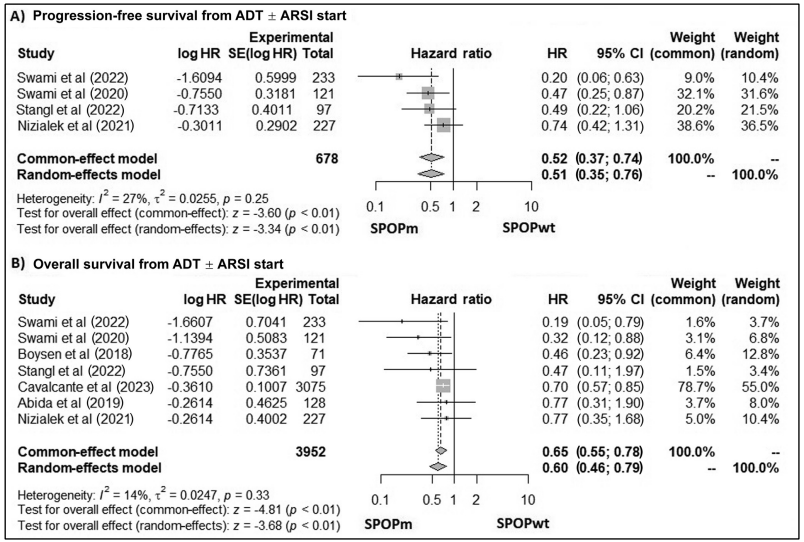
Docetaxel



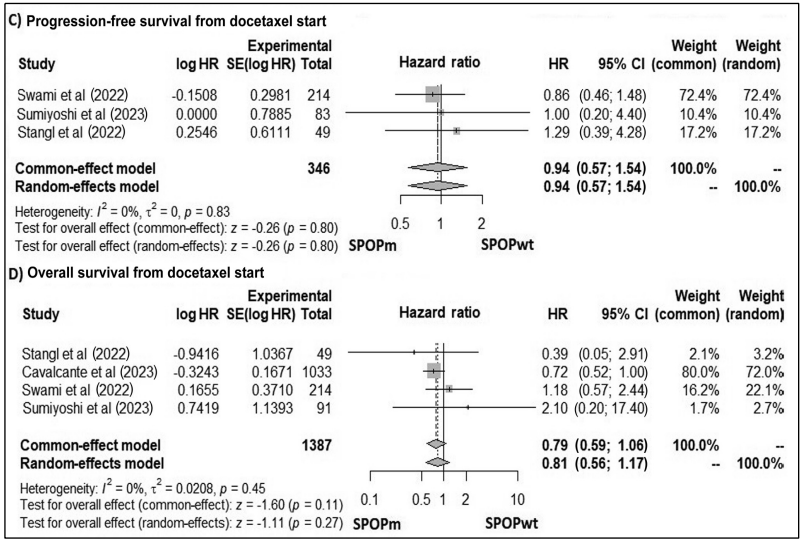
High Decipher score identifies patients more likely to benefit from docetaxel
Biomarker-treatment interaction effect p value= 0.039*

SPOP mutants are associated with improved prognosis and increased sensitivity to AR targeted agents, but not to docetaxel

ADT +- ARSI

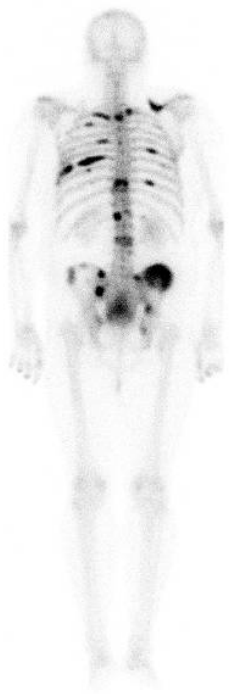


ADT + docetaxel



Pedrani et al. Eur Urol Oncol 2024

Male 57y T2N1M1b High Volume PSA 1430 ng/mL and



ADT and 2 weeks later comes to the hospital due to a Disseminated intravascular coagulation (DIC) .

What is your preferred option:

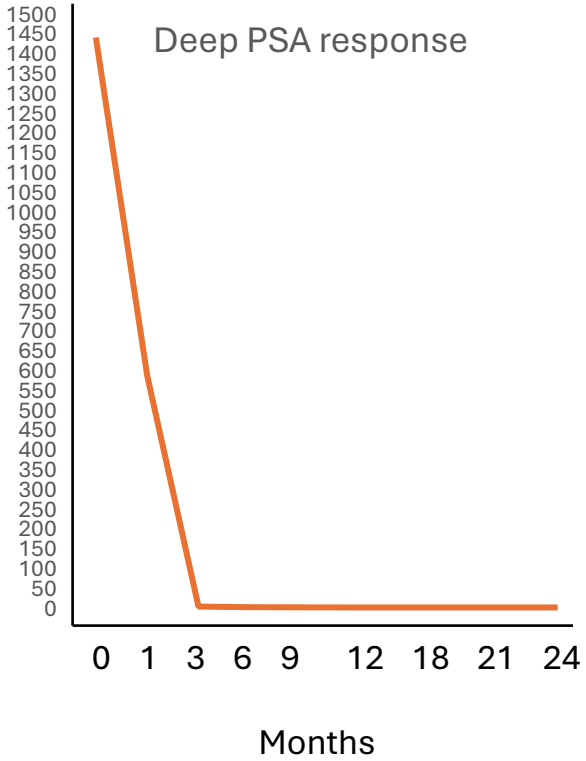
A) Continue ADT alone

B) ADT + docetaxel

C) ADT + ARPI

D) ADT + ARPI + docetaxel

ADT + ARPI induced a deep PSA response



PSA	0.13 ng/ml		07/05/2025
PSA	0.11 ng/ml		27/01/2025
PSA	0.10 ng/ml		28/10/2024
PSA	0.16 ng/ml		15/07/2024
PSA	0.18 ng/ml		05/04/2024
PSA	0.50 ng/ml		29/12/2023
PSA	0.86 ng/ml		26/09/2023
PSA	2.28 ng/ml		04/08/2023
PSA	585.40 ng/ml		31/05/2023
PSA	1438.00 ng/ml		24/04/2023

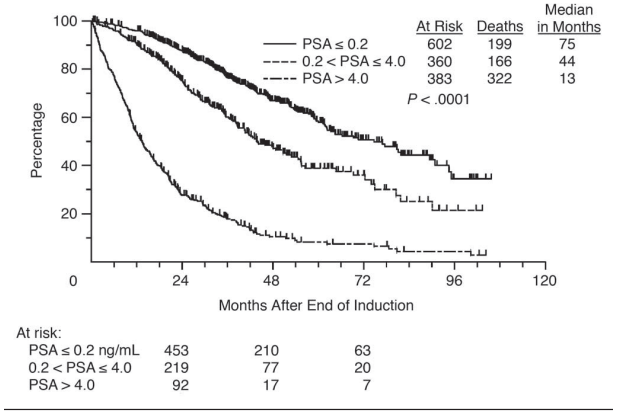
VOLUME 24 · NUMBER 24 · AUGUST 20 2006

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Absolute Prostate-Specific Antigen Value After Androgen Deprivation Is a Strong Independent Predictor of Survival in New Metastatic Prostate Cancer: Data From Southwest Oncology Group Trial 9346 (INT-0162)

Maha Hussain, Catherine M. Tangen, Celestia Higano, Paul F. Schelhammer, James Faulkner, E. David Crawford, George Wilding, Atif Akdas, Eric J. Small, Bryan Donnelly, Gary MacVicar, and Derek Raghavan

From the University of Michigan, Ann Arbor, MI; Southwest Oncology Group

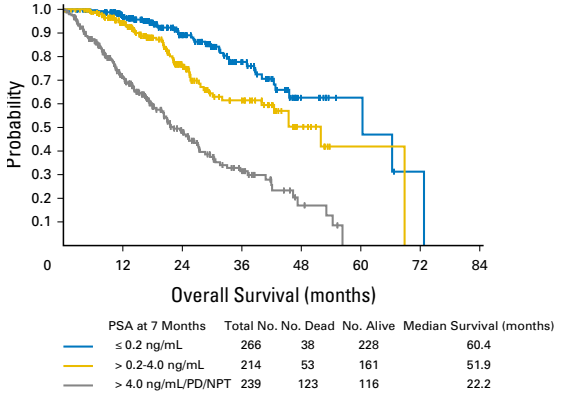


VOLUME 36 · NUMBER 4 · FEBRUARY 1, 2018

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

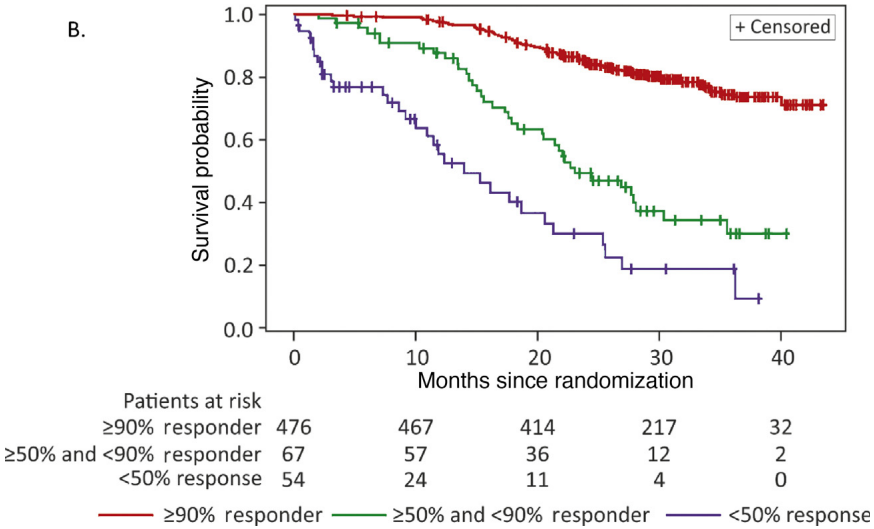
Seven-Month Prostate-Specific Antigen Is Prognostic in Metastatic Hormone-Sensitive Prostate Cancer Treated With Androgen Deprivation With or Without Docetaxel

Lauren C. Harshman, Yu-Hui Chen, Glenn Liu, Michael A. Carducci, David Jarrard, Robert Dreicer, Noah Hahn, Jorge A. Garcia, Maha Hussain, Daniel Shevrin, Mario Eisenberger, Manish Kohli, Elizabeth R. Plimack, Matthew Cooney, Nicholas J. Vogelzang, Joel Picus, Robert Dipaola, and Christopher J. Sweeney on behalf of the ECOG-ACRIN 3805 Investigators



Correlation of Prostate-specific Antigen Kinetics with Overall Survival and Radiological Progression-free Survival in Metastatic Castration-sensitive Prostate Cancer Treated with Abiraterone Acetate plus Prednisone or Placebos Added to Androgen Deprivation Therapy: Post Hoc Analysis of Phase 3 LATITUDE Study

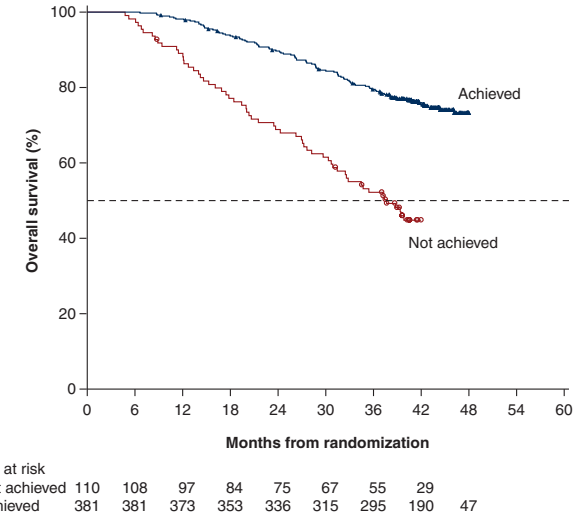
Nobuaki Matsubara [a,], Kim N. Chi [b], Mustafa Özgüroğlu [c], Alfredo Rodriguez-Antolin [d], Susan Feyerabend [e], Luis Fein [f], Boris Y. Alekseev [g], Giri Sulur [h], Andrew Protheroe [i], Susan Li [j], Suneel Mundle [k], Peter De Porre [l], Namphuong Tran [h], Karim Fizazi [m]*



Matsubara N. Eur Urol 2024

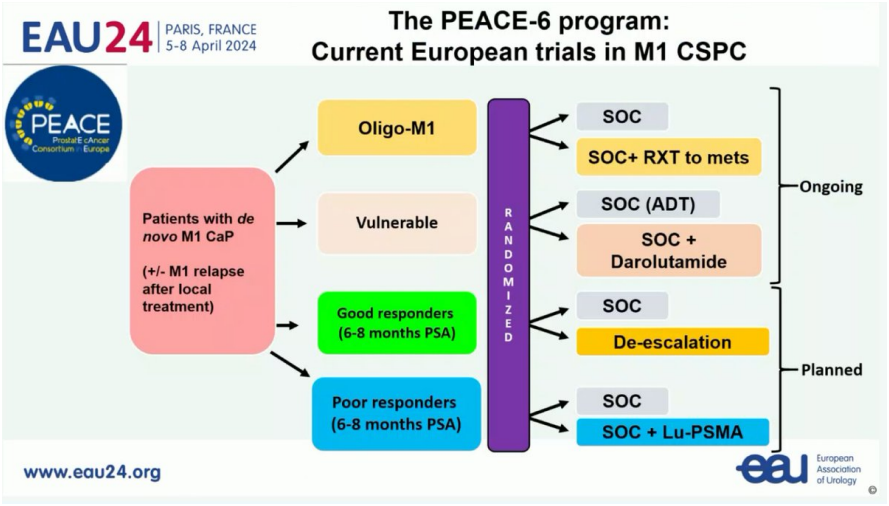
Deep, rapid, and durable prostate-specific antigen decline with apalutamide plus androgen deprivation therapy is associated with longer survival and improved clinical outcomes in TITAN patients with metastatic castration-sensitive prostate cancer☆☆

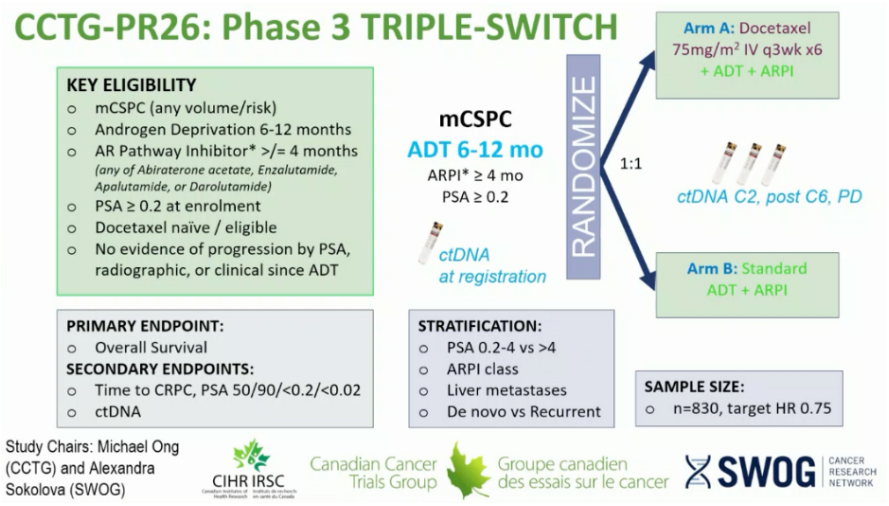
S. Chowdhury[1,*], A. Bjartell[3], N. Agarwal[4], B. H. Chung[5], R. W. Given[6], A. J. Pereira de Santana Gomes[7], A. S. Merseburger[8], M. Özgüroğlu[9], Á. Juárez Soto[10], H. Uemura[11], D. Ye[12], S. D. Brookman-May[13,14], A. Londhe[15], A. Bhaumik[15], S. D. Mundle[16], J. S. Larsen[17], S. A. McCarthy[16] & K. N. Chi[18]



Ann Oncol 2023

TRIALS WITH A NEW DESIGN:
IS APPROPRIATE TO INTENSIFY ONLY THOSE PATIENTS WITHOUT A GOOD PSA RESPONSE?





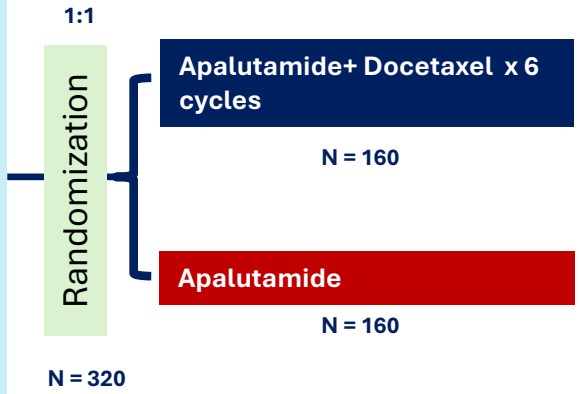
REINFORCE study design
Randomized Phase 3 trial

Broad Patient Population

Key inclusión criteria
- mCSPC
- ECOG PS 0-1
- Apalutamide as first line mCSPC
- Lack of achievement of Optimal PSA response at 6 months*

Exclusion Criteria
- Tumor progression to first line**
- Prior docetaxel

Stratification factors
- *Synchronous vs Metachronous*
- *Visceral mts (yes/no)*
- *PSA ≤4 vs >4 ng/ml*



PRIMARY ENDPOINT
- Event-Free Survival †

SECONDARY ENDPOINTS
- PSA progression-free survival
- Time to Castration Resistance
- Time to Subsequent treatment
- Overall Survival
- Symptomatic Skeletal event free survival (SSE-FS)
- Time to initiation of opioid use (≥ 7 days)
- Safety and Security

* **Optimal PSA response** is defined as 6 months PSA ≤ 0.2 ng/ml or PSA response ≥ 90% and PSA >4 ng/ml
** **Tumor progression** defined according to PCGW3 criteria and RECIST 1.1 for measurable disease.
† **Event-Free Survival** is defined as PSA progression or radiological progression of soft-tissue, visceral, or bone lesions according to PCWG3 and RECIST 1.1 for measurable disease or death from any cause.

Study Design: Multicenter Ph3 Randomized Study.

Population: Spain (GUARD). Collaboration with other country groups preferred (France, ...).Number of Centers N=20.

Sample size: 80% power to detect a 35% decrease in the risk of developing an event in the apalutamide plus docetaxel group versus the control group. One-sided alpha level of 0.1 and a 1:1 randomization. Estimated to observe 133 failure-free survival events (56 events in the experimental arm, 77 events in the control arm), allowing for a 7% dropout rate.

Accrual period: 24 months; **Treatment Duration:** 24 months

Total duration: 48 months

First Patient In: April 2026

TAKE HOME MESSAGES

WHO: ADT and ARPI is the cornerstone treatment

Select based on

-Your plan: Doublet (AAP, Enza, Apa, Daro,) vs Triplet (Daro or AAP)

-Patients characteristics: Toxicity profile, concomitant drugs and and AGE

When: **Begin with ADT** (LHRH analogs /LHRH antagonists of Surgical Castr.)

When your plan is clear add the apropriate ARPI

For selected patients add Docetaxel when the PS is appropriate

How: Take it easy.....and make decissions with your the multidisciplinary team

¡Thank You!

egbillalabeitia@salud.Madrid.org