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Treatment Intensification with Doublet Therapy in Patients with mHSPC

Elisabeth Heath, MD, FACP
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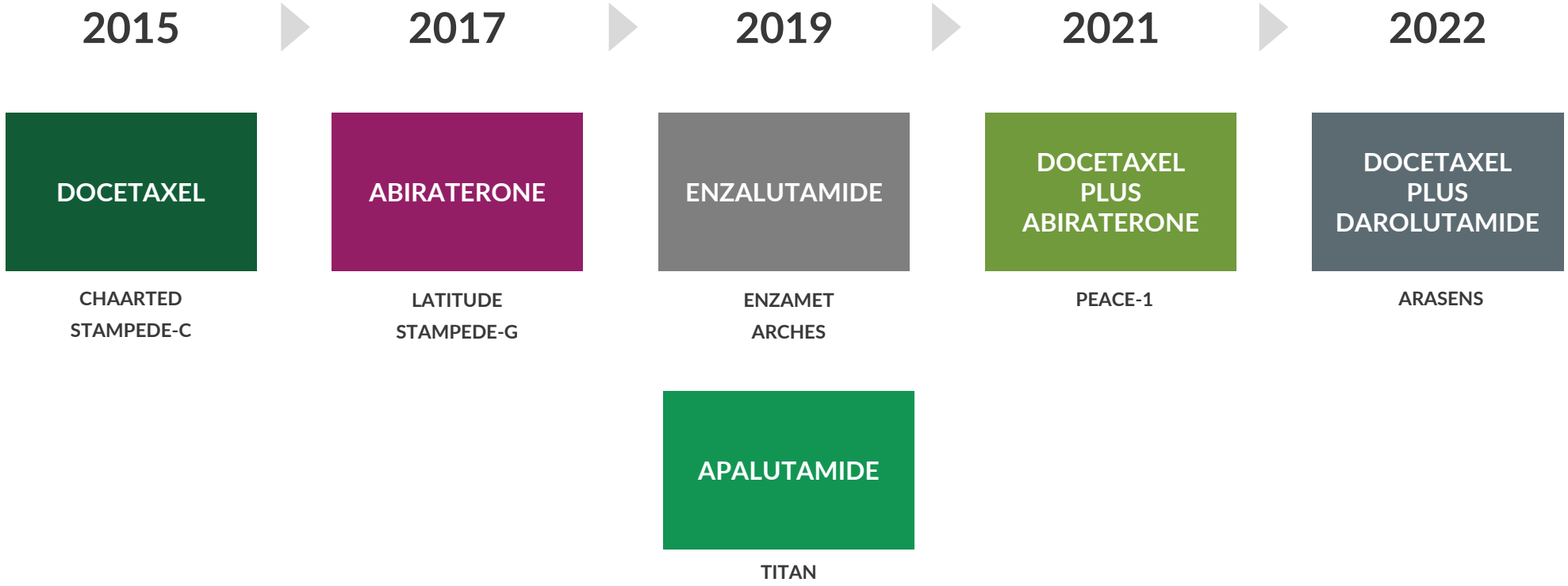
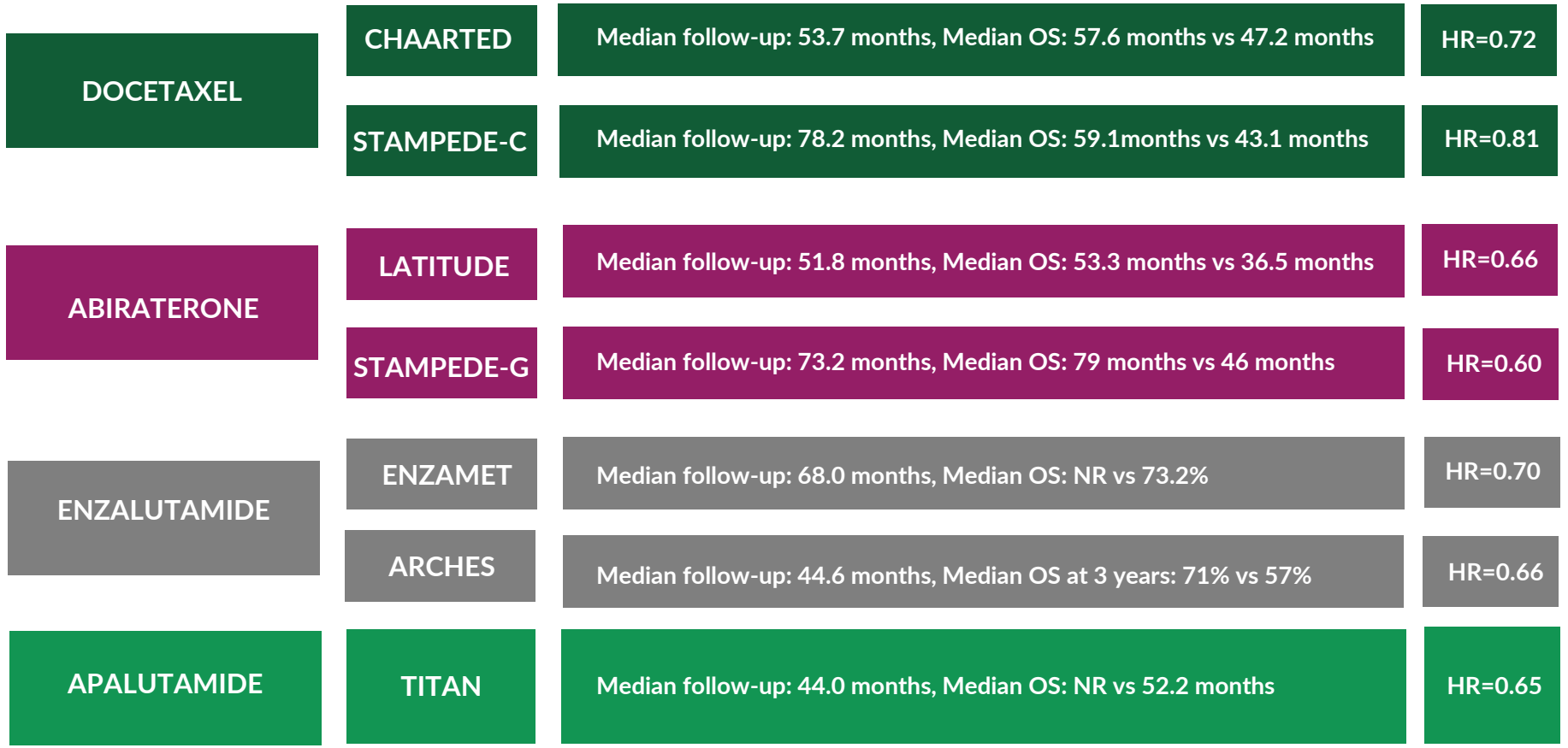
Treatment Options for mHSPC



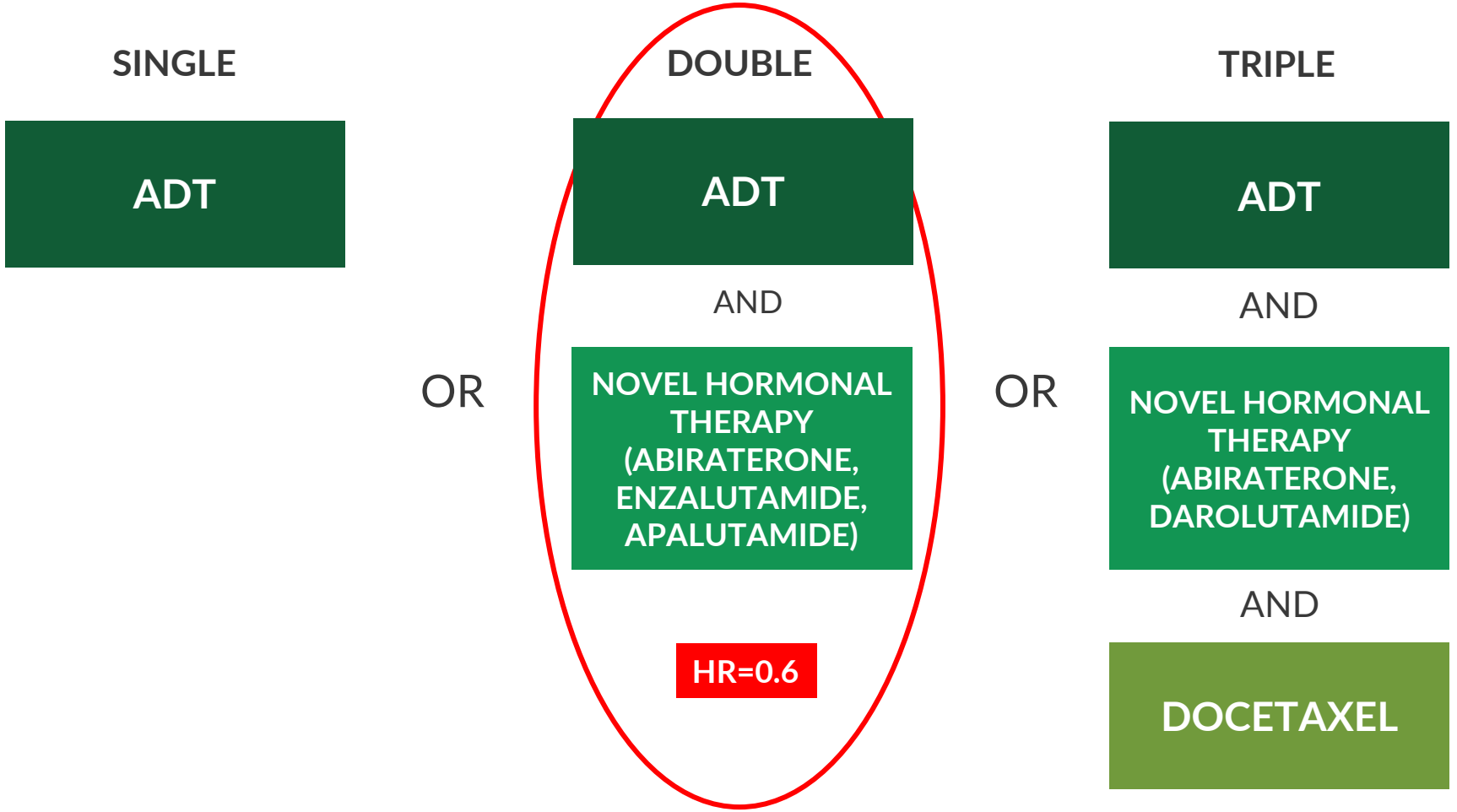
Kyriakopoulos CE et al. J Clin Oncol. 2018 Apr 10;36(11):1080-1087. Clarke NW et al. Annals of Oncology30:1992-2003, 2019. Fizazi K et al. Lancet Oncol 2019 May; 20(5):686-700. James N et al. Int J Cancer. 2022 Aug1;151(3):422-434. Davis I et al. J Clin Oncol 40, 2022 (suppl17;abstr LBA5004,), Armstrong AJ et al. Annal Oncol 2021;32(5):S1283-S1346, LBA25. Chi KN et al. J Clin Oncol. 2021 39:2294-2303.

Overall Survival Benefit With Treatment Intensification



Kyriakopoulos CE et al. J Clin Oncol. 2018 Apr 10;36(11):1080-1087. Clarke NW et al. Annals of Oncology30:1992-2003, 2019. Fizazi K et al. Lancet Oncol 2019 May; 20(5):686-700. James N et al. Int J Cancer. 2022 Aug 1;151(3):422-434. Davis I et al. J Clin Oncol 40, 2022 (suppl17;abstr LBA5004), Armstrong AJ et al. Annal Oncol 2021;32(5):S1283-S1346, LBA25. Chi KN et al. J Clin Oncol. 2021 39:2294-2303.

Treatment Strategy for mHSPC



Factors Contributing to Treatment Selection

Declining PSA

- PSA ≤ 4 ng/mL after 7 months of ADT is associated with improved survival of patients newly diagnosed with metastatic prostate cancer

Medical Co-Morbidities

- Diabetes, cardiac disease, hypertension

Financial Toxicity

- Incomplete or no coverage to oral medications

Hussain M et al. J Clin Oncol 2006;24:3984-3990. Ali A et al. JAMA Oncolo 2021;7:555-563. Morgans AK et al. J Clin Oncol 2022:40:818-824..

Factors Contributing to Treatment Selection

External Beam Radiation Therapy (EBRT)

- EBRT to primary tumor associated with overall survival benefit in patients with low metastatic burden (non-regional, lymph-node only disease OR < 4 bone metastasis and without visceral/other metastasis, using conventional imaging)

Metastatic Disease Presentation

- De novo versus recurrent

Experience with treatment options

- Office or practice process and operation

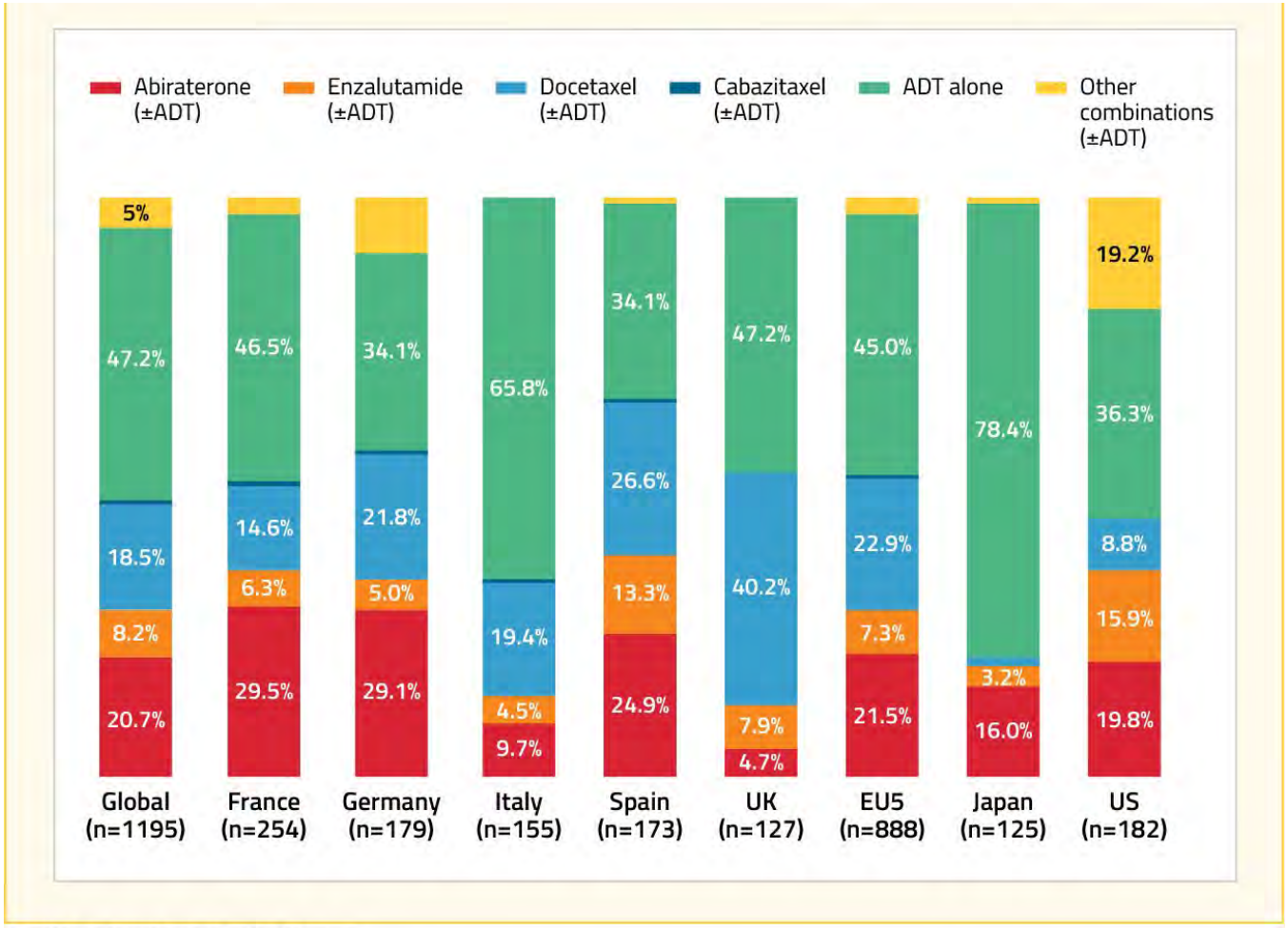
Hussain M et al. J Clin Oncol 2006;24:3984-3990. Ali A et al. JAMA Oncolo 2021;7:555-563. Morgans AK et al. J Clin Oncol 2022:40:818-824..

Real-World Treatment Intensification Patterns

Medicare Database Analysis (35,195 patients)	• < 1/3 of men received treatment intensification by 2018 • Less frequent treatment intensification in black versus white men
ConcertAI Oncology Dataset (858 patients)	• > 1/2 of men did not receive treatment intensification in 2019 • Those who did received shorter duration of treatment
IQVIA Anonymized Patient Longitudinal Data (66,844 patients)	• > 1/2 of men did not receive treatment intensification • Urology providers prescribed 12% of the time
Optum Clinformatics Data Mart Database (19,841 patients)	• < 1/2 of men received ADT only • < 7% of men received treatment intensification

Freedland S et al. J Clin Oncol 39, 2021 (suppl 15; 5073). Swami U et al. J Clin Oncol 39, 2021 (suppl15; 5072). Heath E et al. Clin Genitourin Cancer 2022 Jun 28:S1558-7673. Ryan CJ et al., J Urol. 206:1420-1429, 2021.

Real-World Utilization: Global Data



Leith A et al. BMC Urol 2022:22(1):33.

Treatment Selection Factors

- Retrospective study in 621 patients treated by 65 oncologists and 42 urologists
- Median age at initial mHSPC treatment 68 years, 58% white, 25% black, 84% de novo metastatic disease, 30% high volume disease with 22% with visceral metastasis
- Differences in adequacy of PSA reduction
  - Oncologists considered median PSA reduction of 50% as adequate compared to 75% among urologists
- Top 5 reasons why patients did not receive initial NHT
  - Drug tolerability (38%)
  - Lack of clinical trial evidence of overall survival improvement (31%)
  - Lack of reimbursement (26%),
  - Patient financial constraints (20%, questions about sequencing NHTs earlier versus later in the disease (21%))

Freedland S et al. J Clin Oncol 2022 40, no.16_suppl 5065-5065.

Patient Case

- Mr. Smith is a 77-year-old African American male with long-standing diabetes with resulting peripheral neuropathy in his hands and feet
- Originally, he was diagnosed 7 years ago with high-risk prostate cancer
  - Gleason 8, pre-treatment PSA 22 ng/dL, and clinical T2c stage
  - Negative CT scan of abdomen and pelvis, CXR, and bone scan
- Treatment plan included external beam radiation therapy along with 2 years of concurrent ADT
- PSA nadir was undetectable
- PSA after full testosterone recovery was 1.7 ng/dL
- Medications include 1 anti-hypertensive, insulin, and cholesterol lowering agent

Patient Case

- In the past year, Mr. Smith's PSA started to rise
  - PSA: 1.7 to 2.8 to 14.5 to 20.8 ng/dL
- Patient remains asymptomatic but has a 15-pound unintentional weight loss
- Imaging workup included CT scan of chest/abdomen/pelvis and bone scan
  - CT scans showed multiple enlarged lymph nodes in the retroperitoneum (largest being 2.5 cm), no visceral metastasis
  - Bone scan showed 3 bone metastasis (L5, right 4^{th} rib, right sacral ala)
- Mr. Smith is a retired high school football coach and wants to continue to attend home games to cheer for his team

Clinical Considerations

Disease Burden

- Volume of metastasis (low versus high)
  - High= Visceral or > 4 bone lesions with at least one beyond the vertebral bodies and pelvis

Disease Stage

- M1a
  - Non-regional lymph nodes only
- M1b
  - Bone metastasis +/- lymph nodes
- M1c
  - Visceral metastasis +/- lymph nodes or bone metastasis

Disease Presentation

- *De novo* (synchronous) metastatic versus recurrent (metachronous) disease

Patient Treatment: ADT and Enzalutamide (ENZAMET AND ARCHES)

- Volume of disease (p-value for interaction=0.06)
  - Low: HR 0.54 (95% CI 0.39 to 0.74)
  - High: HR 0.79 (95% CI 0.63 to 0.98)

- Timing of presentation (p-value for interaction=0.91)
  - Synchronous: HR 0.70 (95% CI 0.56 to 0.87)
  - Metachronous: HR 0.71 (95% CI 0.52 to 0.98)

Davis I et al. J Clin Oncol 40, 2022 (suppl17;abstr LBA5004). Armstrong AJ et al. Annal Oncol 2021;32(5):S1283-S1346, LBA25.

Treatment Goals for Patients with mHSPC

1. Delay progression to mCRPC
2. Prolong overall survival
3. Maintain quality of life

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Treatment Intensification with Triplet Therapy in Patients with mHSPC

Dr. Jordan Ciuro
Assistant Professor of Medicine
Georgia Cancer Center

Introduction mHSPC: Clinical Case

- 68 years old male with past medical history of hypertension
- Presents with fatigue and bone pain for 3 months
- ECOG Performance Score (PS) 1
- Prostate-Specific Antigen (PSA) 102 ng/dL, Gleason Score 8
- CT Chest Abdomen Pelvis (CAP) and bone scan display diffuse osseous involvement and evidence of hepatic metastasis
- Diagnosed with de novo metastatic HSPC
  - High volume disease ≥ 4 bone metastases with ≥ 1 outside axial skeleton or visceral disease

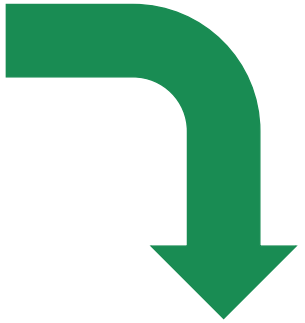
What do you offer this patient?
What treatment options are available in mHSPC?

Kyriakopoulos CE et al. *Journal of Clinical Oncology 2018*, *36*(11), 1080

Introduction

- The landscape of mHSPC is rapidly evolving…

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
★ **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

Does more therapy always = better outcomes?

What patient population should we recommend triple therapy?

Safety?

PEACE-1

ARASENS

Trial: PEACE-1

Articles

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, Dominik Berthold, Philippe Ronchin, Gabriel Kacso, Gwenaëlle Gravis, Fabio Calabro, Jean-François Berdah, Ali Hasbini, Marlon Silva, Antoine Thiery-Vuillemin, Igor Latorzeff, Loïc Mourey, Brigitte Laguerre, Sophie Abadie-Lacourtoisie, Etienne Martin, Claude El Kouri, Anne Escande, Alvar Rosello, Nicolas Magne, Friederike Schlurmann, Frank Priou, Marie-Eve Chand-Fouche, Salvador Villà Freixa, Muhammad Jamaluddin, Isabelle Rieger, Alberto Bossi, on behalf of the PEACE-1 investigators**

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

Methods

- 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), 1695–170

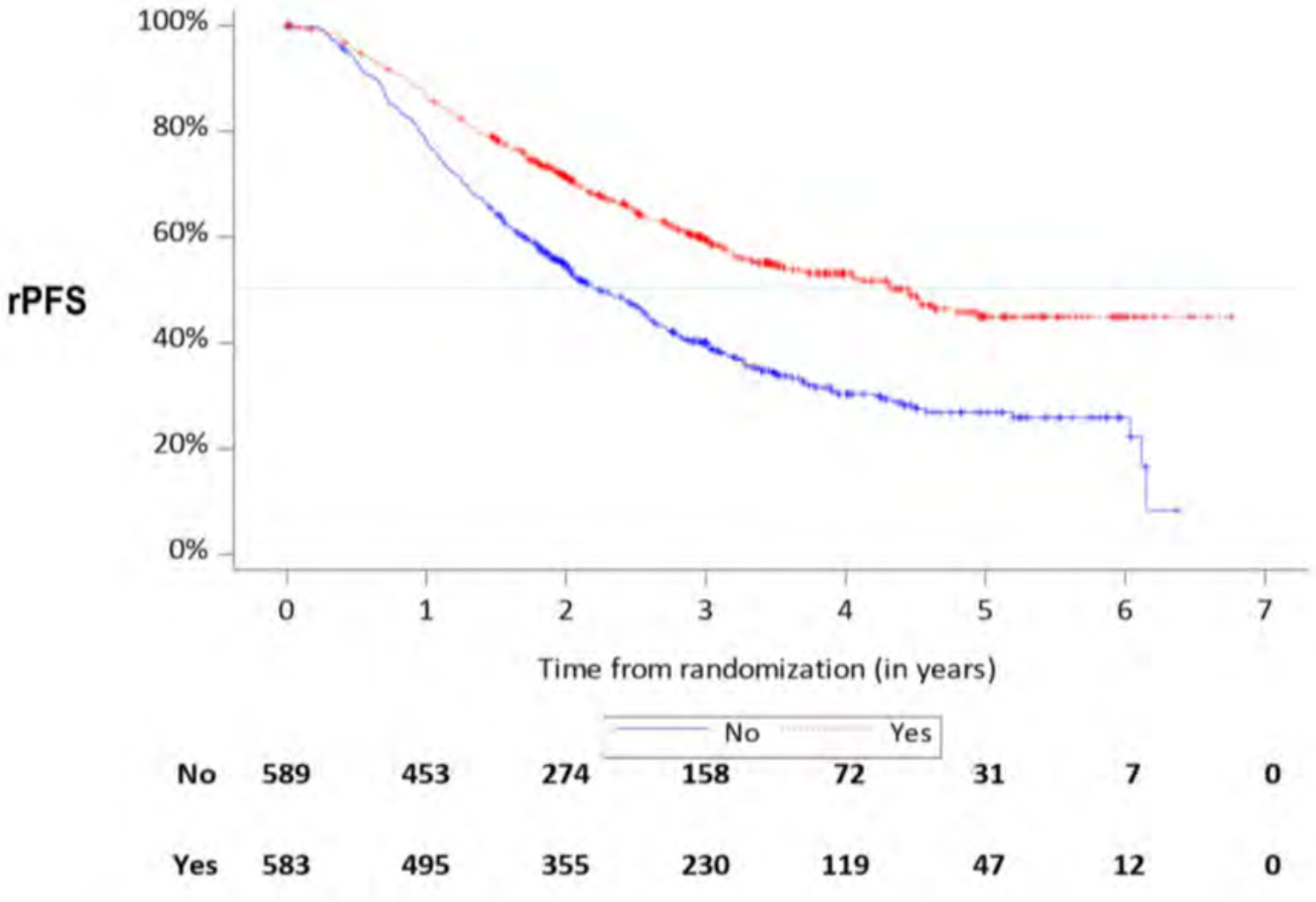
Baseline Demographics

	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 (18%)	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%)

	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)
(Continued from previous page)				
Gleason score				
≤7	145 (25%)	133 (23%)	79 (23%)	71 (20%)
8–10	429 (75%)	441 (77%)	270 (77%)	276 (80%)
Missing data	9 (2%)	15 (3%)	6 (2%)	8 (2%)
PSA at randomisation, ng/mL				
Median	14 (3–62)	11 (3–55)	14 (2–59)	12 (3–60)
Missing data	2 (<1%)	4 (1%)	0	2 (<1%)
Medical history				
Hypertension	270 (47%); N=574	241 (43%); N=562	156 (44%); N=352	148 (43%); N=344
Type 2 diabetes	62 (11%); N=566	80 (14%); N=556	33 (9%); N=351	56 (16%); N=344
High cholesterol	229 (40%); N=568	229 (41%); N=556	136 (39%); N=351	130 (38%); N=343

Fizazi, K. et al. *The Lancet 2022; 399*(10336), 1695–1707[21]
Fizazi, K. et al. J Clin Oncol. 39, no.15_suppl(May 20,2021) 5000-

Results: Radiographic PFS (rPFS)



SOC+ Abi (n=583)

- Median y = 4.5 (3.5-NE)
- Events: 252

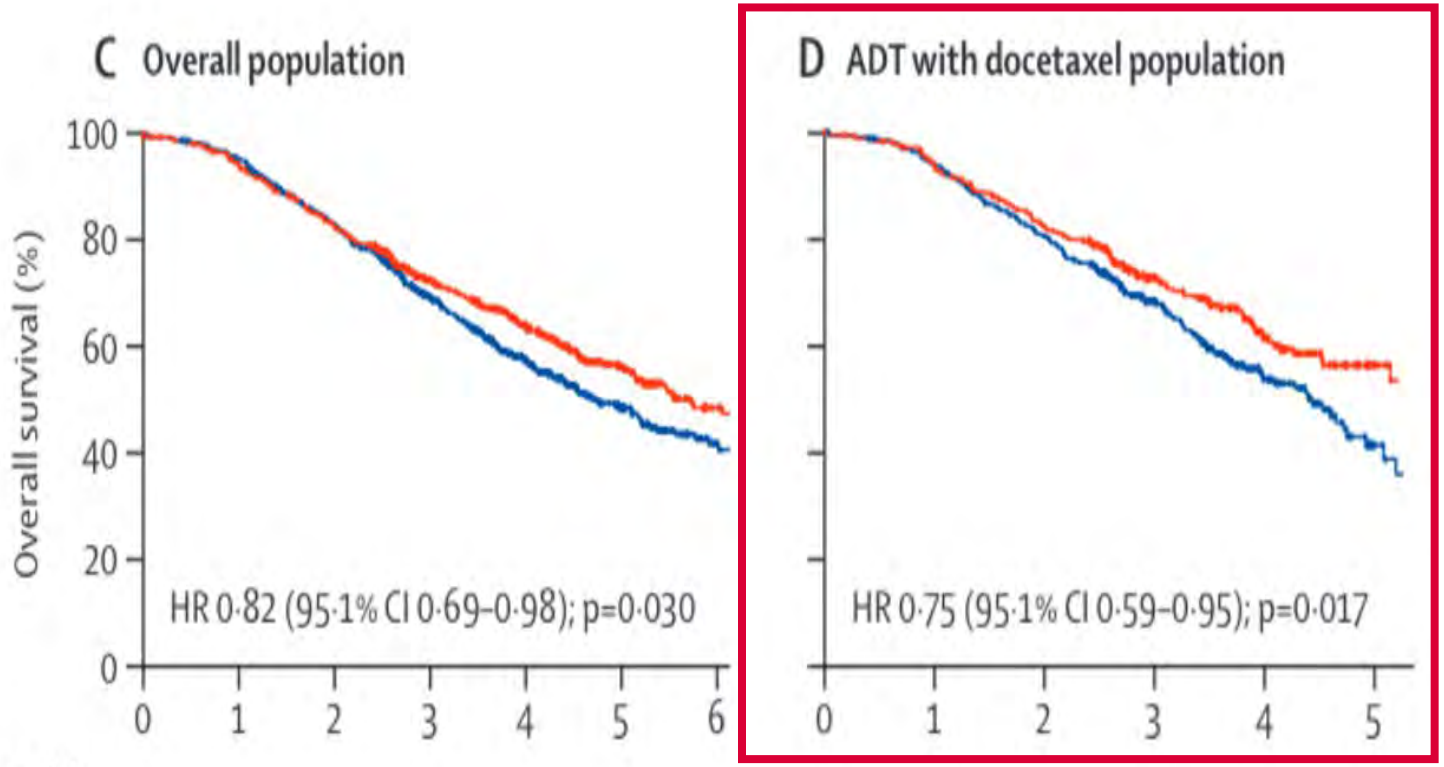
SOC (n=589)

- Median y= 2.2 (2.0-2.6)
- Events: 371

HR (95% CI) 0.54 (0.46-0.64)
P <0.0001

Fizazi, K. et al. *The Lancet 2022; 399*(10336), 1695–17(

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?

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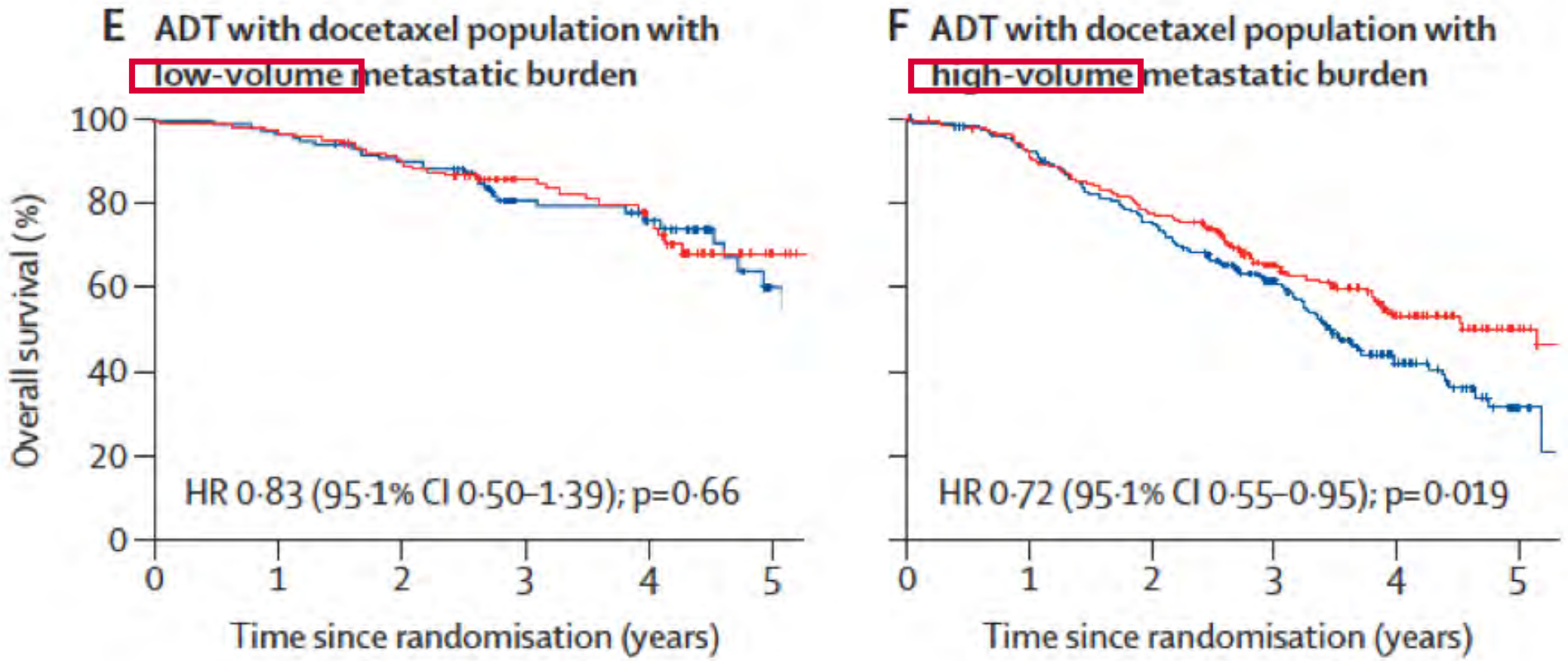
Fizazi, K. et al. J Clin Oncol. 39, no.15_suppl(May 20,2021) 5000-5
Fizazi, K. et al. The Lancet 2022; 399(10336), 1695–1707

Results: OS low vs high volume disease



No benefit of triple therapy in patients with low volume disease (p=0.66)
Benefit is driven in high volume disease

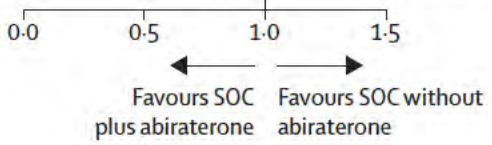
Fizazi, K. et al. J Clin Oncol. 39, no.15_suppl(May 20,2021) 5000

ADT

ADT+ Docetaxel

C

	SOC plus abiraterone groups, n/N	SOC without abiraterone groups, n/N	Overall survival HR (95·1% CI)	p value
Radiotherapy				0·86
No			0·84 (0·65–1·08)	
Yes			0·81 (0·63–1·04)	
Docetaxel				0·33
No (not yet SOC)	71/135	81/138	0·85 (0·61–1·17)	
No (physician decision)	36/93	36/96	1·11 (0·70–1·76)	
Yes (as SOC)	121/355	151/355	0·75 (0·59–0·95)	
ECOG performance status				0·39
0	144/412	173/412	0·78 (0·62–0·97)	
1–2	84/171	95/177	0·91 (0·68–1·22)	
ADT type				0·52
GnRH agonist	144/392	171/392	0·77 (0·62–0·97)	
GnRH antagonist	82/189	95/195	0·93 (0·69–1·25)	
Surgical castration	2/2	2/2	0·46 (0·06–3·31)	
Metastatic burden				0·33
High	152/331	183/336	0·77 (0·62–0·96)	
Low	76/252	85/253	0·93 (0·69–1·28)	
Overall	**228/583**	**268/589**	**0·82 (0·69–0·98)**	



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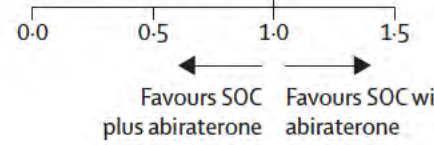
SOC plus abiraterone groups, n/N	SOC without abiraterone groups, n/N	Overall survival HR (95·1% CI)	p value
			0·85
		0·73 (0·52–1·03)	
		0·76 (0·54–1·08)	
			NA
			0·93
76/250	93/246	0·75 (0·56–1·02)	
45/105	58/109	0·74 (0·50–1·09)	
			0·98
72/219	88/222	0·76 (0·56–1·04)	
47/134	62/132	0·73 (0·50–1·06)	
2/2	1/1	0·71 (0·06–8·00)	
			0·64
92/224	120/232	0·72 (0·55–0·95)	
29/131	31/123	0·83 (0·50–1·39)	
121/355	**151/355**	**0·75 (0·59–0·95)**	



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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

Safety?

Adverse Events

	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

63 vs 52% grade ≥ AE in abiraterone arm

Most common AE:
Hypertension (22 vs 13%)
Neutropenia (10 vs 9%)
Hepatotoxicity (6 vs 1%)

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

Conclusion: PEACE-1

- Triple therapy in de novo mHSPC using abiraterone + docetaxel + ADT:
  - Significantly improved OS and rPFS when compared to SOC doublet therapy
  - Survival benefit >1.5y in men with high volume disease
  - 2.5y improvement in median rPFS

- Benefit was driven in patients with high volume disease

- Overall tolerable and expected toxicity profile
  - Minimum increase in grade ≥ 3 hypertension in abiraterone arm

ARASENS Trial

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*

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

Introduction

- Previous investigations:
  - **ARAMIS**
    - Included nmCRPC with doubling time of </ 10m
    - Evaluated Darolutamide + ADT vs placebo + ADT
    - Results:
      - Darolutamide arm reduced the risk of death by 31%
      - Improved metastasis free survival by 2 years
  - **CHAARTED**
    - Included mHSPC
    - Evaluated ADT + Docetaxel vs ADT alone
    - Results:
      - Addition of Docetaxel to ADT improved OS by 13.6m
      - Improved rPFS (20.2m vs 11.7m in ADT alone)

Combination

Darolutamide+ Docetaxel + ADT

in mHSPC?...

Fizazi, K. et al. 2019 *New England Journal of Medicine*; 380(13),1235-1246
Sweeney, C. J et al. 2015. *New England Journal of Medicine*, *373*(8), 737–746

Methods

- 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

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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)

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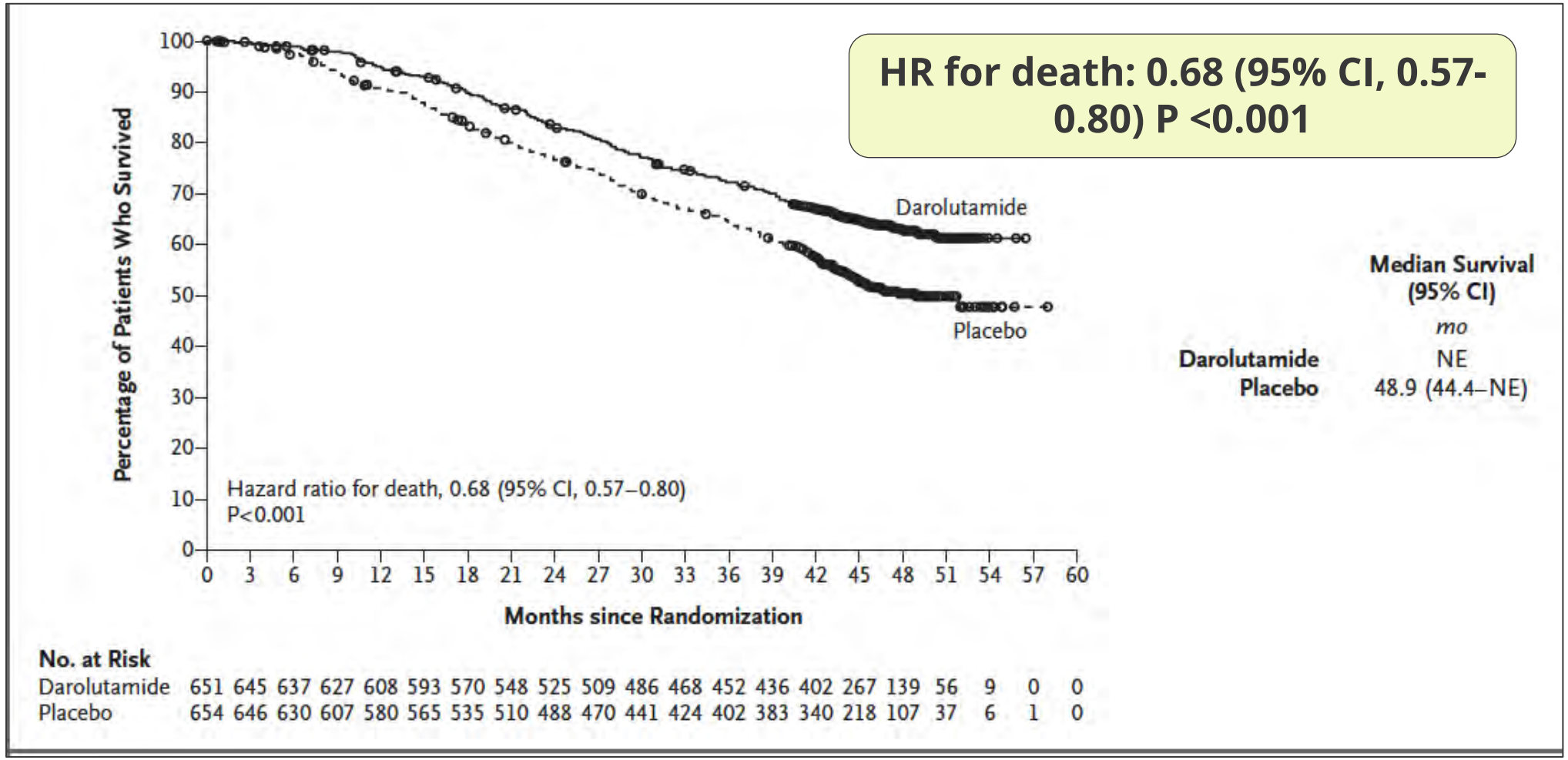
Results

Results: Primary Endpoint



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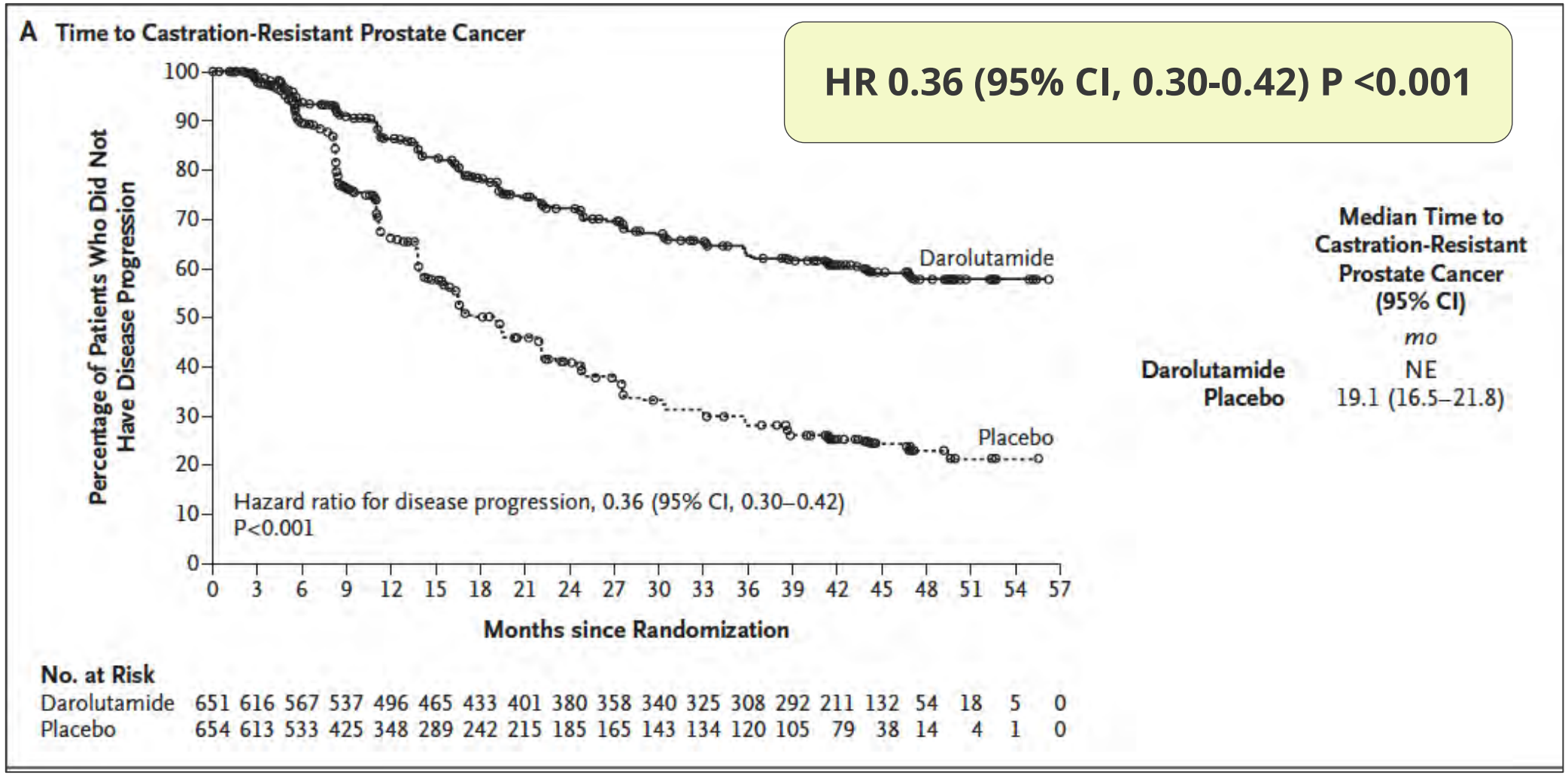
Secondary Endpoints:



HR 0.36 (95% CI, 0.30-0.42) P <0.001

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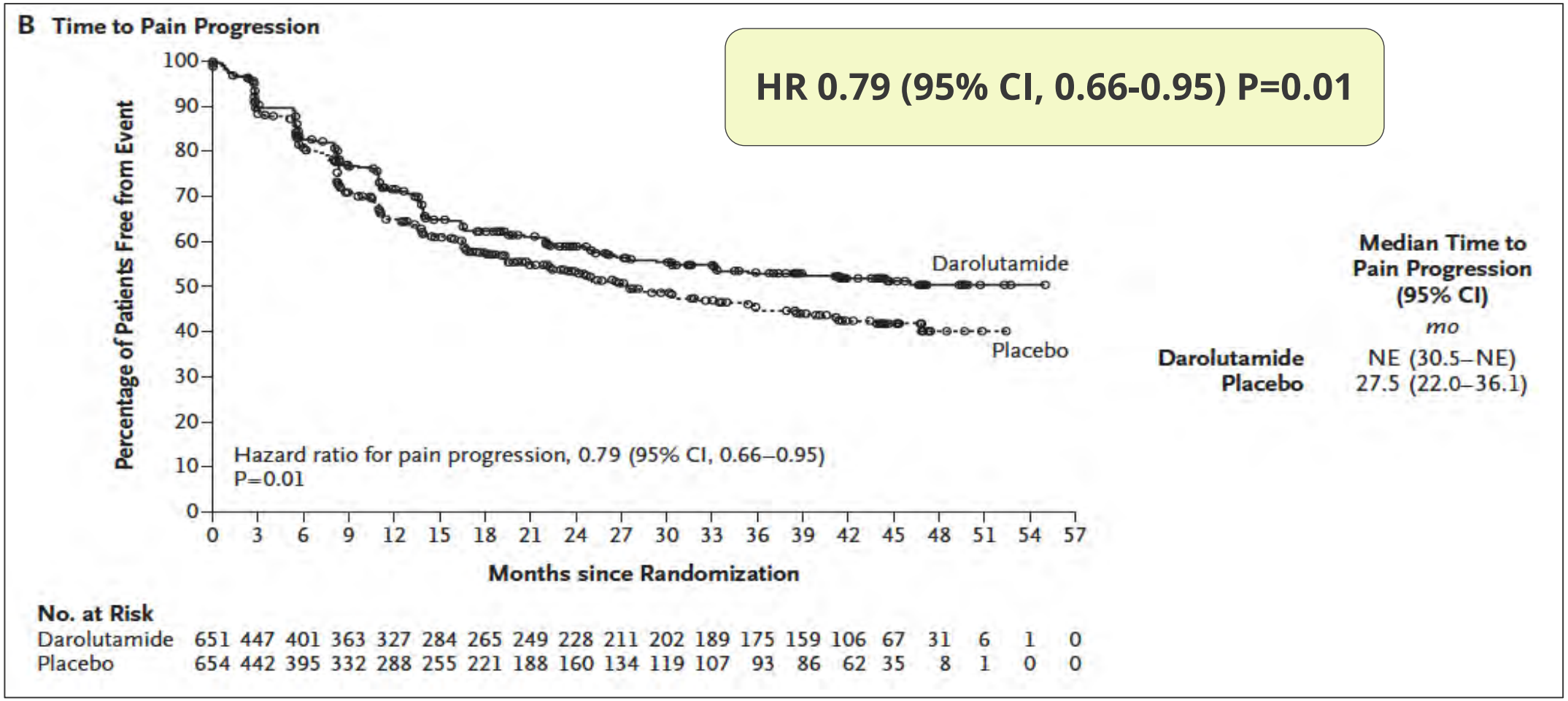
Secondary Endpoints:



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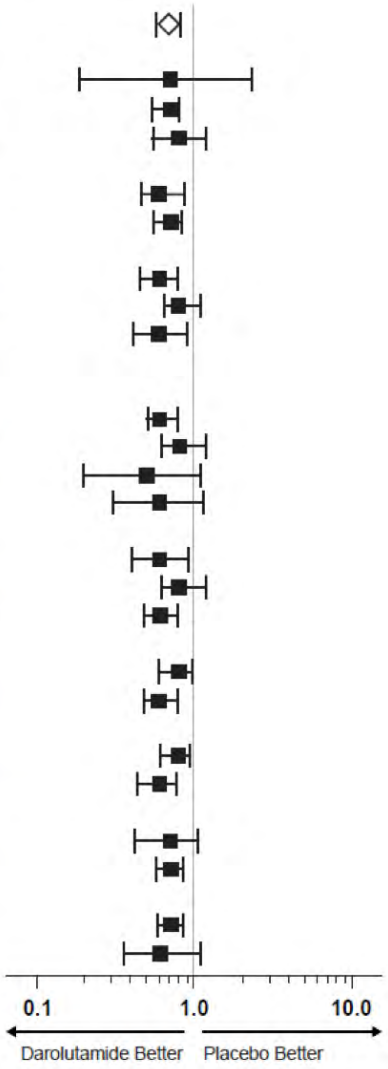
ARASENS OS: Subgroup Analyses

	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)			
Non-regional 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)



ARASENS did not stratify per disease volume

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Safety?

Adverse Events

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)

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Conclusion: ARASENS

- Triple therapy in mHSPC using darolutamide + docetaxel + ADT significantly improved OS
  - Triple therapy reduced risk of death by 32.5%
- The OS benefit was seen consistently across all subgroup analysis
  - Did not stratify by disease volume
- Darolutamide improved all secondary endpoints including:
  - Time to castrate resistant prostate cancer
  - Time to pain progression
  - Time to first subsequent therapy
- Treatment was tolerable with similar adverse event rates in both arms

Back to patient case…

Introduction mCSPC: Clinical Case

- 68 years old male with PMH HTN presents with fatigue and bone pain over the last 3 months
- ECOG PS 1
- PSA 102 ng/dL, Gleason Score 8
- CT CAP and bone scan display diffuse osseous involvement and evidence of hepatic metastasis
- Diagnosed with de novo metastatic HSPC
  - High volume disease ≥ 4 bone metastases with ≥ 1 outside axial skeleton or visceral disease

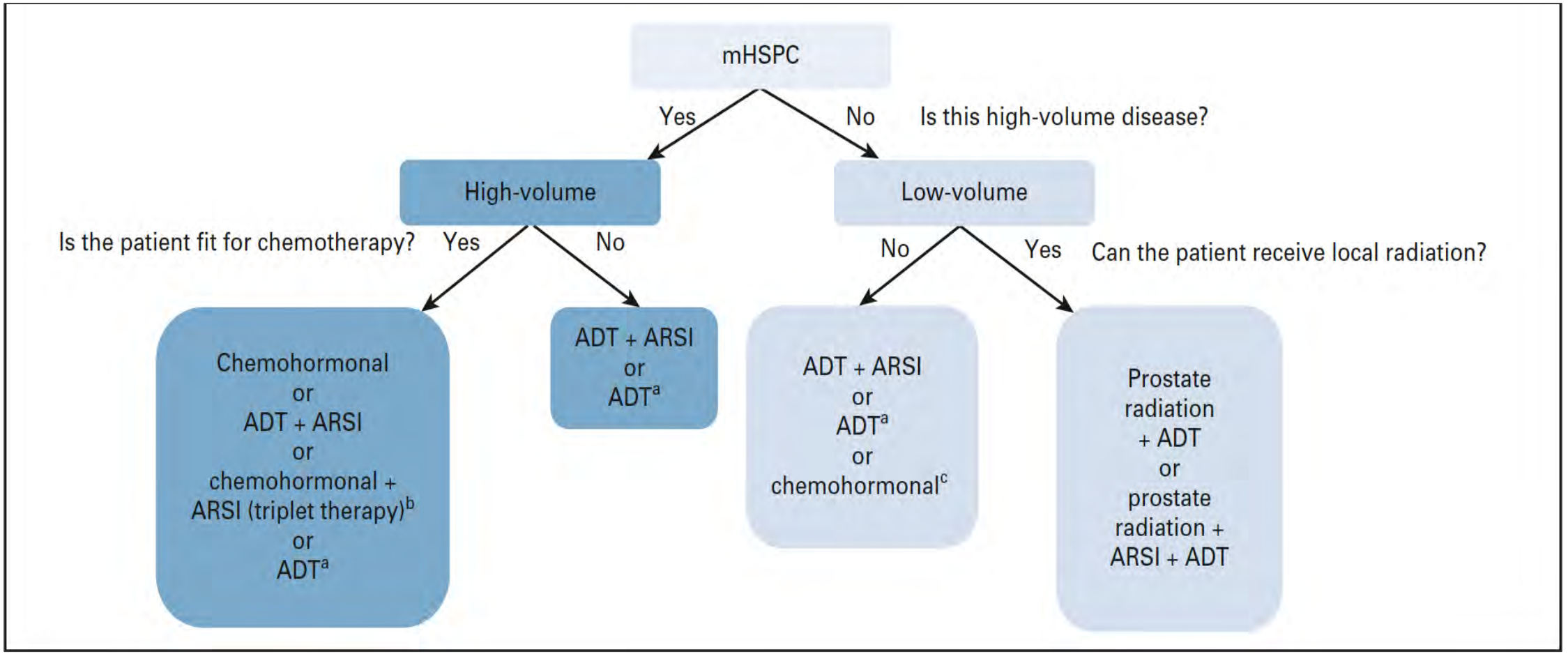
What do you offer this patient?
What treatment options are available in mCSPC?

Doublet or Triplet therapy are all reasonable
Patient specific discussion…

Take Home Message

- Is triple therapy the new SOC for all mHSPC? → **No, not always…**
  - Considering both trials, treatment depends on:
    - **Patient preference**
    - **PS of patient**
    - **GS**
    - **Disease burden**
    - **De novo vs recurrent disease**
    - **Racial/ethnic disparities and mutational analysis**

Final Points: new algorithm?



Morgans. A. et. Al. J Clin Oncol. January 2022

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