ACC MED

ACCADEMIA NAZIONALE DI MEDICINA

Il paziente con mHSPC: intensificazione del trattamento per migliorare la sopravvivenza, preservando la qualità di vita

Prolungare la sopravvivenza e mantenere la qualità di vita in tutto il percorso del paziente con mHSPC: linee guida ed evidenze scientifiche nel trattamento di prima linea e il possibile ruolo della radioterapia

Ciro Franzese

Humanitas University Humanitas Research Hospital
Milano

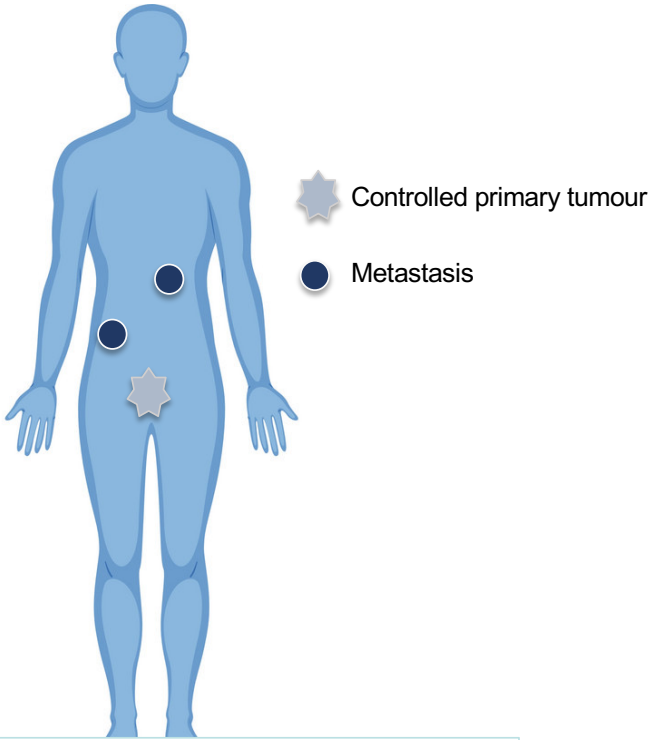
The burden of prostate cancer

1.4 million men worldwide each year

It’s estimated that cases of PC will rise to around 4 million in 2040

Sung H et al. CA Cancer J Clin 2021;71:209–49.

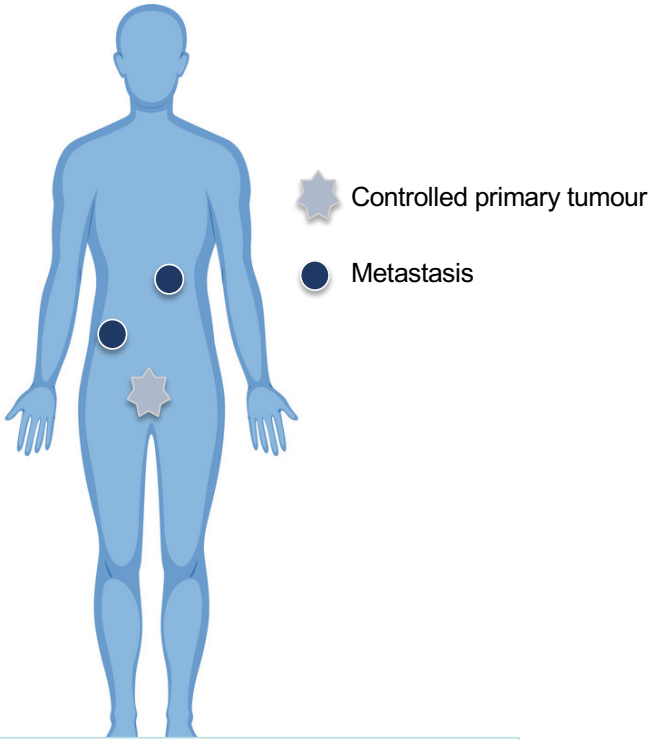
Metastatic prostate cancer



20% of patients with localized PC progress to metastatic HSPC within 5 years (mHSPC)

Clin Oncol 2017;35:3097–104

De novo metastatic prostate cancer



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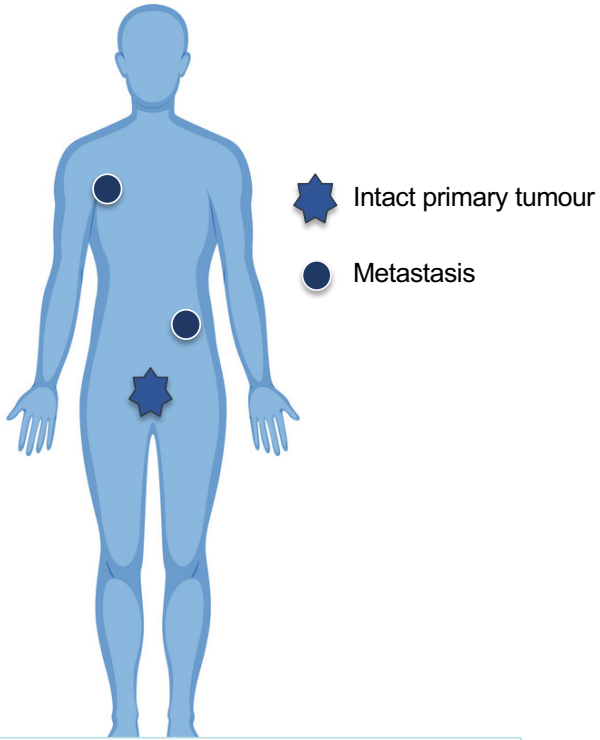
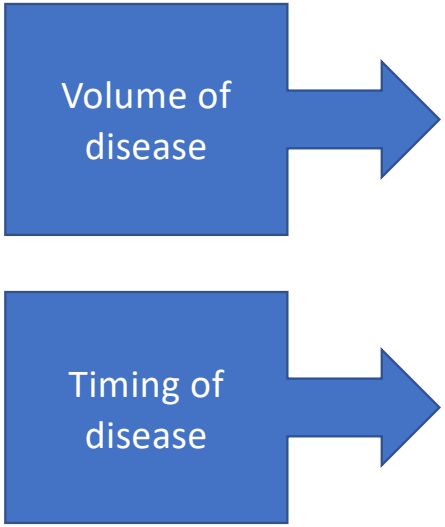
Clin Oncol 2017;35:3097–104



6–8% of patients are directly diagnosed in the metastatic stage (de novo mHSPC)

Morb Mortal Wkly Rep 2020;69:1473–80

What we know?

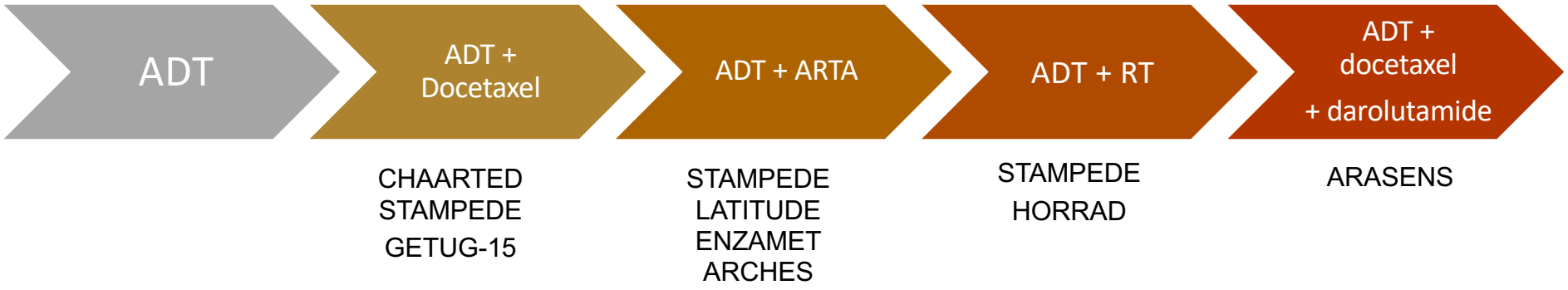


Metastatic hormone-sensitive PC

Low volume patients - better outcome - compared to **high volume** patients

Metachronous disease - better outcome - compared to **synchronous disease**

Spectrum of treatments of mHSPC



Role of chemotherapy

Burden of Metastatic Castrate Naive Prostate Cancer Patients, to Identify Men More Likely to Benefit from Early Docetaxel: Further Analyses of CHAARTED and GETUG-AFU15 Studies

Gwenaelle Gravis[a,*], Jean-Marie Boher[b], Yu-Hui Chen[c], Glenn Liu[d], Karim Fizazi[e], Michael A. Carducci[f], Stephane Oudard[g], Florence Joly[h], David M. Jarrard[d], Michel Soulie[i], Mario J. Eisenberger[f], Muriel Habibian[j], Robert Dreicer[k], Jorge A. Garcia[l], Maha H.M. Hussain[m], Manish Kohli[n], Nicholas J. Vogelzang[o], Joel Picus[p], Robert DiPaola[q], and Christopher Sweeney[r]

Meta-analysis results of the aggregate data showed **significant heterogeneity in ADT + D versus ADT** effect sizes between **HV and LV subgroups** (p=0.017).

Adding Docetaxel in patients with HV disease has a consistent effect in improving median OS (HR 0.68, 95%CI 0.56 - 0.82)

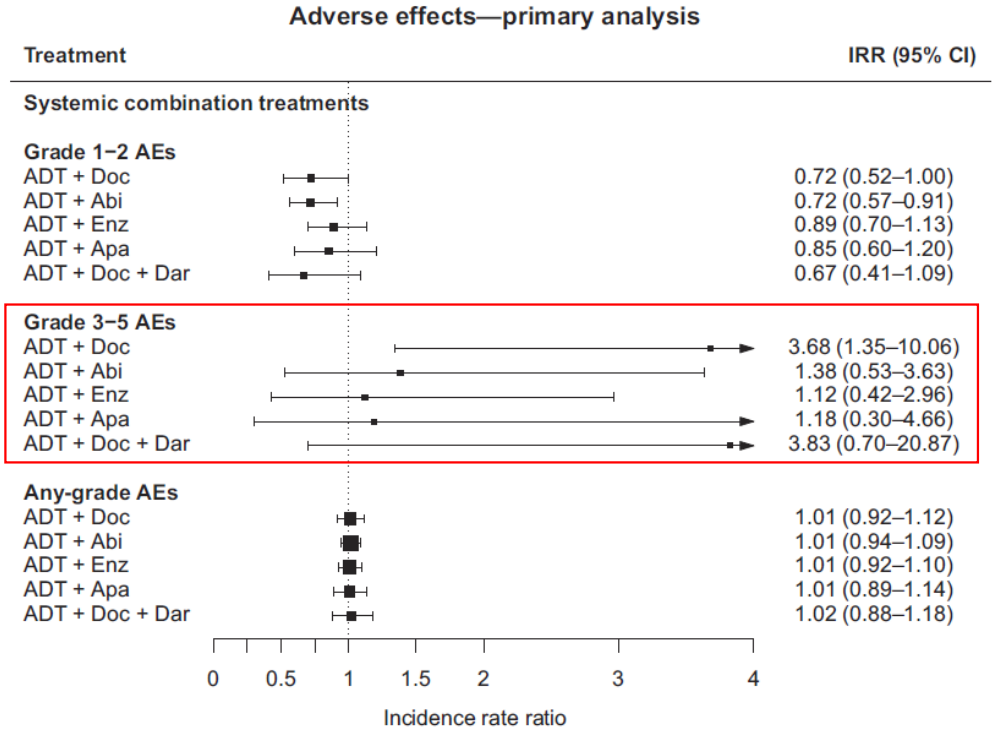
Patients with **LV disease** showed much longer OS, **without evidence that Docetatxel improved OS** (HR 1.03, 95%CI 0.77 - 1.38)

Eur Urol. 2018 June ; 73(6): 847–855.

Quality of life and systemic treatments

Treatments for Metastatic Hormone-sensitive Prostate Cancer: Systematic Review, Network Meta-analysis, and Benefit-harm assessment

Dominik Menges [a,*], *Henock G. Yebyo* [a], *Sergio Sivec-Muniz* [a], *Sarah R. Haile* [a], *Michaela C. Barbier* [b], *Yuki Tomonaga* [a], *Matthias Schwenkglenks* [a,b], *Milo A. Puhan* [a]



European Urology 2022, Article in press

The ARCHES trial

ARCHES: A Randomized, Phase III Study of Androgen Deprivation Therapy With Enzalutamide or Placebo in Men With Metastatic Hormone-Sensitive Prostate Cancer

Andrew J. Armstrong, MD, ScM[1]; Russell Z. Szmulewitz, MD[2]; Daniel P. Petrylak, MD[3]; Jeffrey Holzbeierlein, MD[4]; Arnauld Villers, MD[5]; Arun Azad, MBBS, PhD[6]; Antonio Alcaraz, MD, PhD[7]; Boris Alekseev, MD[8]; Taro Iguchi, MD, PhD[9]; Neal D. Shore, MD[10]; Brad Rosbrook, MS[11]; Jennifer Sugg, MS[12]; Benoit Baron, MS[13]; Lucy Chen, MD[12]; and Arnulf Stenzl, MD[14]

Inclusion criteria:

- N=1150
- mHSPC
- ECOG PS 0–1
- ADT duration ≤3 mesi, with use of docetaxel: ADT ≤6 mesi
- Allowed previous treatment on primary tumor and docetaxel

R 1:1

Enzalutamide 160mg QD + ADT[1] n=574

Placebo QD + ADT[1] n=576

J Clin Oncol. 2019 Nov 10;37(32):2974-2986

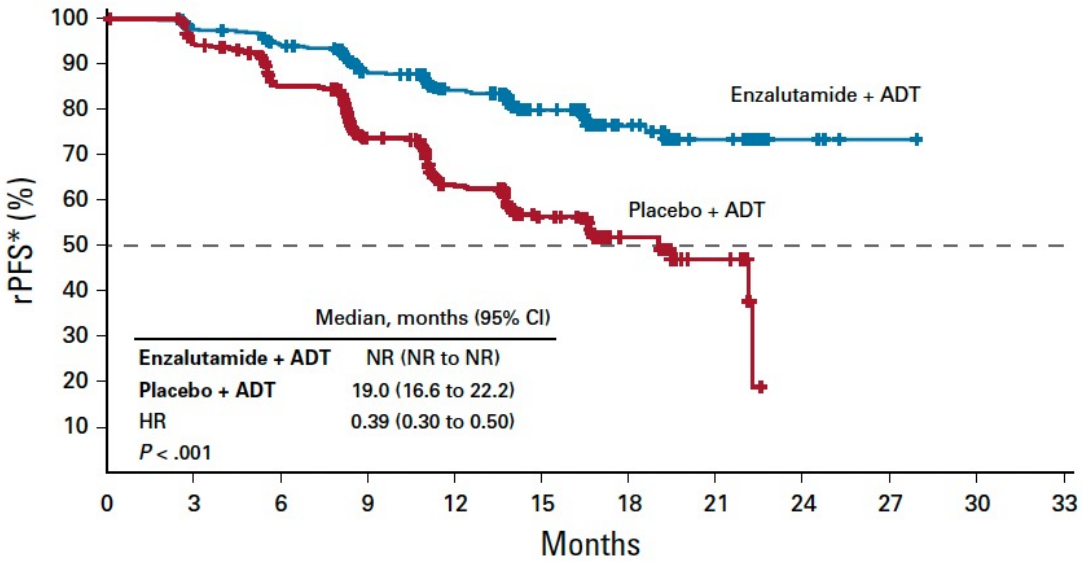
The ARCHES trial

From March, 2016, to January, 2018, a total of 1,150 patients were randomly assigned 1:1 from 202 centers

The risk of **radiographic progression or death was significantly reduced by 61%** with enzalutamide plus ADT versus placebo plus ADT (HR, 0.39; 95%CI, 0.30 to 0.50; P <.001)

Enza + ADT significantly reduced also:

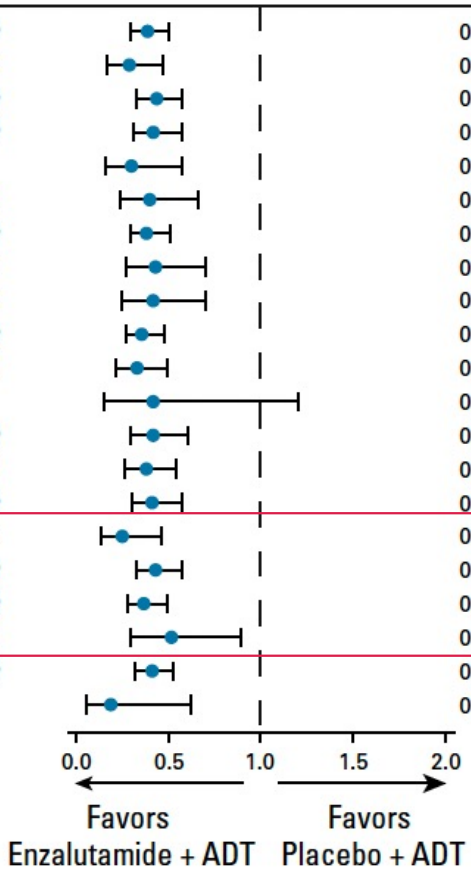
- the fiirst symptomatic skeletal event
- the castration resistance
- the pain progression



J Clin Oncol. 2019 Nov 10;37(32):2974-2986

The ARCHES trial - outcome

Subgroup	Enzalutamide + ADT No. of patients (E)	Placebo + ADT No. of patients (E)	HR (95% CI)[†]
All patients	574 (91)	576 (201)	0.39 (0.30 to 0.50)
Age < 65 years	148 (21)	152 (58)	0.29 (0.17 to 0.47)
Age ≥ 65 years	426 (70)	424 (143)	0.44 (0.33 to 0.58)
Geographic region – Europe	341 (55)	344 (122)	0.42 (0.31 to 0.58)
Geographic region – North America	86 (14)	77 (29)	0.30 (0.16 to 0.57)
Geographic region – rest of the world	147 (22)	155 (50)	0.40 (0.24 to 0.66)
ECOG status 0 at baseline	448 (67)	443 (146)	0.38 (0.29 to 0.51)
ECOG status 1 at baseline	125 (24)	133 (55)	0.43 (0.27 to 0.70)
Gleason score at initial diagnosis < 8	171 (21)	187 (47)	0.42 (0.25 to 0.70)
Gleason score at initial diagnosis ≥ 8	386 (65)	373 (151)	0.36 (0.27 to 0.48)
Disease localization at baseline – bone only	268 (35)	245 (82)	0.33 (0.22 to 0.49)
Disease localization at baseline – soft tissue only	51 (5)	45 (12)	0.42 (0.15 to 1.20)
Disease localization at baseline – bone and soft tissue	217 (50)	241 (104)	0.42 (0.30 to 0.60)
Baseline PSA value at or below overall median	293 (41)	305 (96)	0.38 (0.26 to 0.54)
Baseline PSA value above overall median	279 (50)	269 (104)	0.41 (0.30 to 0.58)
Low volume of disease	220 (14)	203 (47)	0.25 (0.14 to 0.46)
High volume of disease	354 (77)	373 (154)	0.43 (0.33 to 0.57)
No prior docetaxel therapy	471 (70)	474 (166)	0.37 (0.28 to 0.49)
Prior docetaxel therapy	103 (21)	102 (35)	0.52 (0.30 to 0.89)
Previous use of ADT or orchiectomy	535 (88)	515 (179)	0.41 (0.32 to 0.53)
No previous use of ADT or orchiectomy	39 (3)	61 (22)	0.19 (0.06 to 0.62)



J Clin Oncol. 2019 Nov 10;37(32):2974-2986

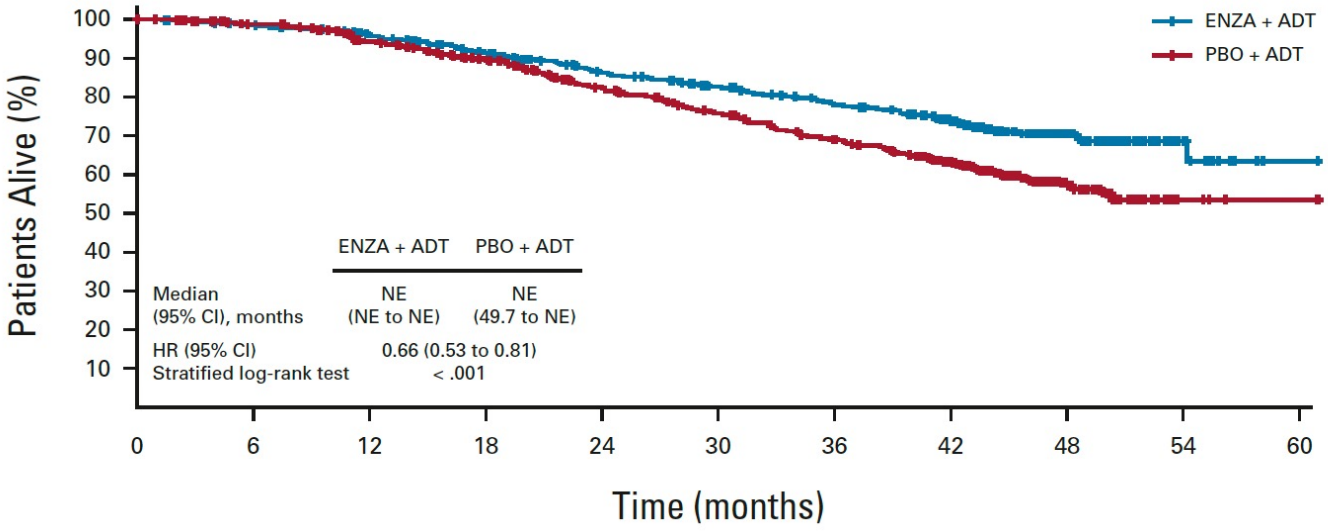
The ARCHES trial – update 2022

Improved Survival With Enzalutamide in Patients With Metastatic Hormone-Sensitive Prostate Cancer

Andrew J. Armstrong, MD, ScM[1]; Arun A. Azad, MBBS, PhD[2,3]; Taro Iguchi, MD, PhD[4]; Russell Z. Szmulewitz, MD[5]; Daniel P. Petrylak, MD[6]; Jeffrey Holzbeierlein, MD[7]; Arnauld Villers, MD[8]; Antonio Alcaraz, MD, PhD[9]; Boris Alekseev, MD[10]; Neal D. Shore, MD[11]; Francisco Gomez-Veiga, MD, PhD[12,13]; Brad Rosbrook, MS[14]; Fabian Zohren, MD, PhD[14]; Shunsuke Yamada, MEng[15]; Gabriel P. Haas, MD[15]; and Arnulf Stenzl, MD[16]

Final prespecified OS analysis and an update on rPFS

Patients assigned to **enzalutamide plus ADT** had a **34% reduction** in the risk of death versus placebo plus ADT (HR 0.66; 95% CI, 0.53 to 0.81; P < .001)



J Clin Oncol. 2022 May 20;40(15):1616-1622

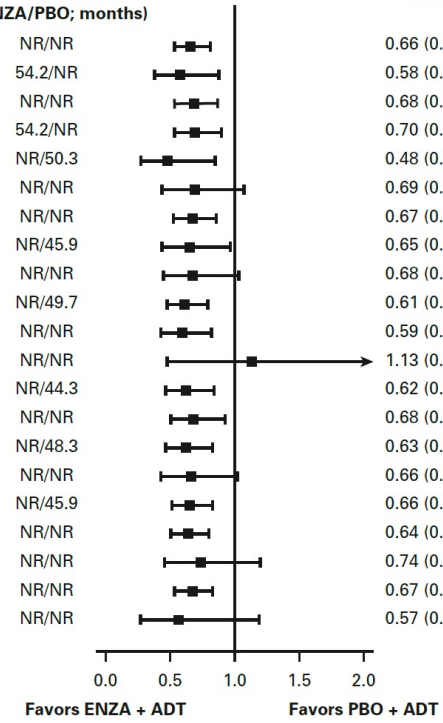
The ARCHES trial – overall survival

Median duration of tx:

- Enzalutamide + ADT: 40,2 months
- Placebo + ADT: 13,8 months
- Crossover + ADT: 23,9 months

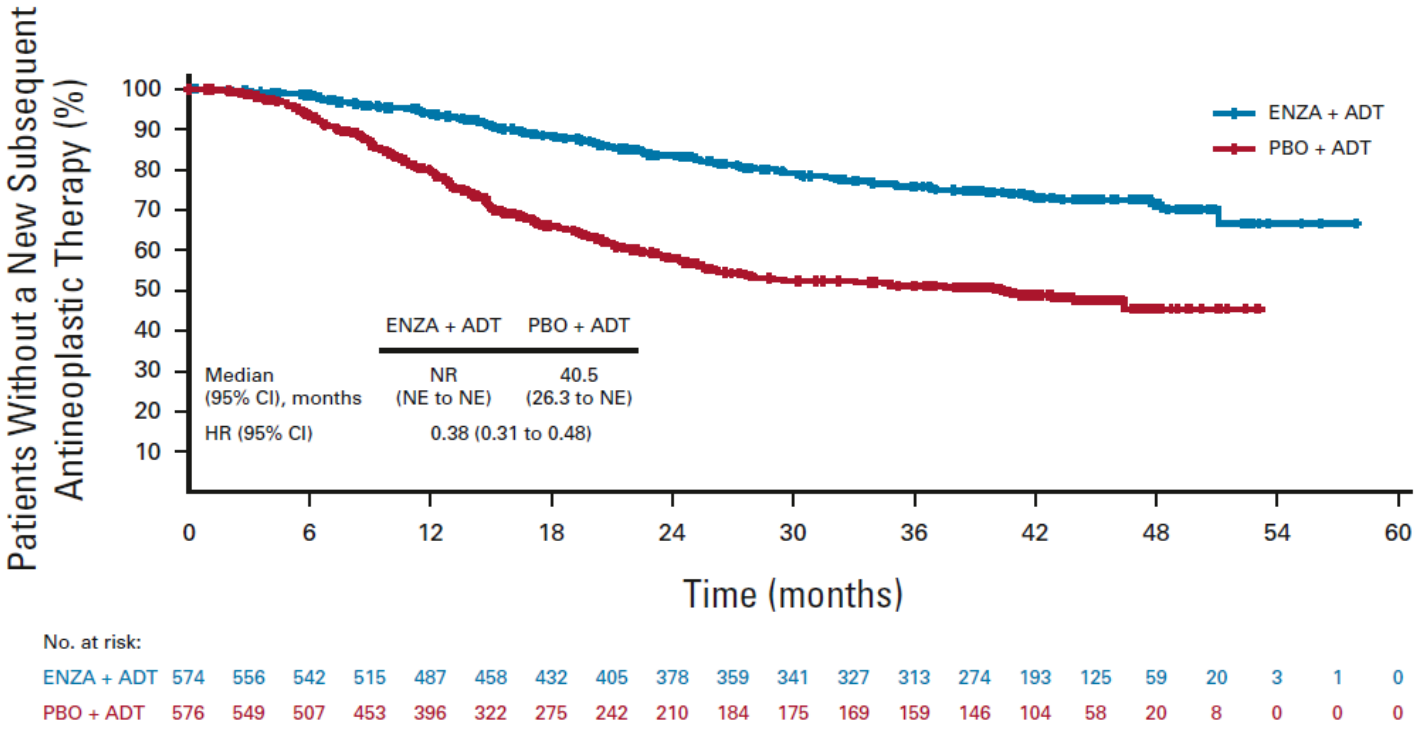
The clinical benefit of enzalutamide plus ADT was generally **consistent across prespecified subgroups**, except in patients with only soft tissue disease at baseline

Subgroup	ENZA + ADT No. (E)	PBO + ADT No. (E)	Median (ENZA/PBO; months)	HR (95% CI)
All subgroups	574 (154)	576 (202)	NR/NR	0.66 (0.53 to 0.81)
Age < 65 years	148 (39)	152 (52)	54.2/NR	0.58 (0.38 to 0.88)
Age ≥ 65 years	426 (115)	424 (150)	NR/NR	0.68 (0.54 to 0.87)
Geographic region—Europe	341 (100)	344 (129)	54.2/NR	0.70 (0.54 to 0.90)
Geographic region—North America	86 (20)	77 (28)	NR/50.3	0.48 (0.27 to 0.85)
Geographic region—RoW	147 (34)	155 (45)	NR/NR	0.69 (0.44 to 1.08)
ECOG status 0 at baseline	448 (112)	443 (143)	NR/NR	0.67 (0.52 to 0.86)
ECOG status 1 at baseline	125 (42)	133 (59)	NR/45.9	0.65 (0.44 to 0.97)
Gleason score at initial diagnosis < 8	171 (38)	187 (51)	NR/NR	0.68 (0.44 to 1.04)
Gleason score at initial diagnosis ≥ 8	386 (108)	373 (145)	NR/49.7	0.61 (0.48 to 0.79)
Disease localization at baseline—bone only	268 (64)	245 (84)	NR/NR	0.59 (0.43 to 0.82)
Disease localization at baseline—soft tissue only	51 (12)	45 (9)	NR/NR	1.13 (0.48 to 2.69)
Disease localization at baseline—bone and soft tissue	217 (72)	241 (106)	NR/44.3	0.62 (0.46 to 0.84)
Baseline PSA value at or below overall median	291 (72)	303 (97)	NR/NR	0.68 (0.50 to 0.93)
Baseline PSA value above overall median	279 (82)	269 (105)	NR/48.3	0.63 (0.47 to 0.84)
Low volume of disease	220 (35)	203 (46)	NR/NR	0.66 (0.43 to 1.03)
High volume of disease	354 (119)	373 (156)	NR/45.9	0.66 (0.52 to 0.83)
No prior docetaxel therapy	471 (124)	474 (165)	NR/NR	0.64 (0.51 to 0.81)
Prior docetaxel therapy	103 (30)	102 (37)	NR/NR	0.74 (0.46 to 1.20)
Previous use of ADT or orchiectomy	535 (144)	515 (179)	NR/NR	0.67 (0.54 to 0.83)
No previous use of ADT or orchiectomy	39 (10)	61 (23)	NR/NR	0.57 (0.27 to 1.20)



J Clin Oncol. 2022 May 20;40(15):1616-1622

The ARCHES trial – time to next systemic therapy



J Clin Oncol. 2022 May 20;40(15):1616-1622

The ARCHES trial – safety

TABLE 2. Summary of TEAEs and Exposure-Adjusted TEAEs of Special Interest (safety analysis set)

TEAEs	ENZA + ADT (n = 572)	PBO + ADT[a] (n = 574)
Median treatment duration, months (range)	40.2 (0.2-58.1)	13.8 (0.2-27.6)
Total exposure, PY	1,521.5	733.2
Any TEAE, No. (%)	520 (90.9)	504 (87.8)
Any grade 3-4 TEAE, No. (%)	224 (39.2)	160 (27.9)
Any TEAE leading to death, No. (%)	30 (5.2)	12 (2.1)
Any study drug-related TEAE, No. (%)	339 (59.3)	273 (47.6)
Any study drug-related TEAE leading to death, No. (%)	0	1 (0.2)
Any TEAE of special interest, No. (%)	416 (72.7)	327 (57.0)

J Clin Oncol. 2022 May 20;40(15):1616-1622

The ARCHES trial – safety

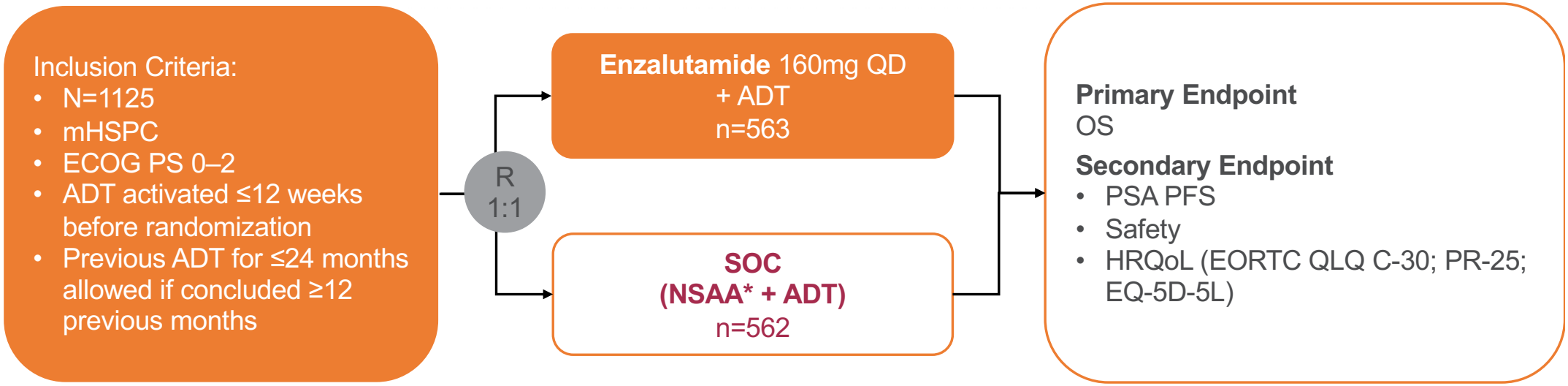
	Enza + ADT				Placebo + ADT			
	All Grades		Grade 3-4		All Grades		Grade 3-4	
TEAE of Special Interest by Group Term[b]	No. (%)	Events (rate)[c]	No. (%)	Events (rate)[c]	No. (%)	Events (rate)[c]	No. (%)	Events (rate)[c]
Convulsions	3 (0.5)	3 (0.2)	3 (0.5)	3 (0.2)	3 (0.5)	3 (0.4)	2 (0.3)	2 (0.3)
Hypertension	82 (14.3)	88 (5.8)	29 (5.1)	30 (2.0)	39 (6.8)	40 (5.5)	13 (2.3)	13 (1.8)
Decreased neutrophil count	8 (1.4)	10 (0.7)	4 (0.7)	5 (0.3)	4 (0.7)	6 (0.8)	2 (0.3)	4 (0.5)
Cognitive/memory impairment	38 (6.6)	46 (3.0)	4 (0.7)	5 (0.3)	15 (2.6)	15 (2.0)	0	0
Ischemic heart disease	26 (4.5)	31 (2.0)	7 (1.2)	8 (0.5)	11 (1.9)	14 (1.9)	8 (1.4)	9 (1.2)
Other selected cardiovascular events	25 (4.4)	33 (2.2)	10 (1.7)	11 (0.7)	10 (1.7)	11 (1.5)	4 (0.7)	5 (0.7)
Posterior reversible encephalopathy syndrome	0	0	0	0	0	0	0	0
Fatigue	184 (32.2)	216 (14.2)	16 (2.8)	26 (1.7)	118 (20.6)	126 (17.2)	11 (1.9)	12 (1.6)
Renal disorders	11 (1.9)	13 (0.9)	2 (0.3)	2 (0.1)	4 (0.7)	5 (0.7)	0	0
Second primary malignancies	22 (3.8)	23 (1.5)	15 (2.6)	16 (1.1)	11 (1.9)	14 (1.9)	7 (1.2)	7 (1.0)
Falls	58 (10.1)	86 (5.7)	7 (1.2)	10 (0.7)	19 (3.3)	20 (2.7)	3 (0.5)	4 (0.5)
Fractures	77 (13.5)	106 (7.0)	20 (3.5)	23 (1.5)	31 (5.4)	36 (4.9)	9 (1.6)	12 (1.6)
Loss of consciousness	15 (2.6)	16 (1.1)	9 (1.6)	10 (0.7)	2 (0.3)	2 (0.3)	1 (0.2)	1 (0.1)
Thrombocytopenia	3 (0.5)	7 (0.5)	0	16 (1.1)	3 (0.5)	3 (0.4)	0	0
Musculoskeletal events	223 (39.0)	395 (26.0)	14 (2.4)	1 (0.1)	170 (29.6)	257 (35.1)	17 (3.0)	20 (2.7)
Severe cutaneous adverse reactions	1 (0.2)	1 (0.1)	0	0	1 (0.2)	1 (0.1)	0	0
Angioedema	10 (1.7)	11 (0.7)	1 (0.2)	1 (0.1)	1 (0.2)	1 (0.1)	0	0
Rash	22 (3.8)	26 (1.7)	0	0	10 (1.7)	12 (1.6)	0	0
Hepatic disorder	34 (5.9)	43 (2.8)	8 (1.4)	11 (0.7)	34 (5.9)	55 (7.5)	4 (0.7)	9 (1.2)

J Clin Oncol. 2022 May 20;40(15):1616-1622

The ENZAMET trial

Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer

I.D. Davis, A.J. Martin, M.R. Stockler, S. Begbie, K.N. Chi, S. Chowdhury, X. Coskinas, M. Frydenberg, W.E. Hague, L.G. Horvath, A.M. Joshua, N.J. Lawrence, G. Marx, J. McCaffrey, R. McDermott, M. McJannett, S.A. North, F. Parnis, W. Parulekar, D.W. Pook, M.N. Reaume, S.K. Sandhu, A. Tan, T.H. Tan, A. Thomson, E. Tu, F. Vera-Badillo, S.G. Williams, S. Yip, A.Y. Zhang, R.R. Zielinski, and C.J. Sweeney, for the ENZAMET Trial Investigators and the Australian and New Zealand Urogenital and Prostate Cancer Trials Group*



N Engl J Med 2019;381:121-31

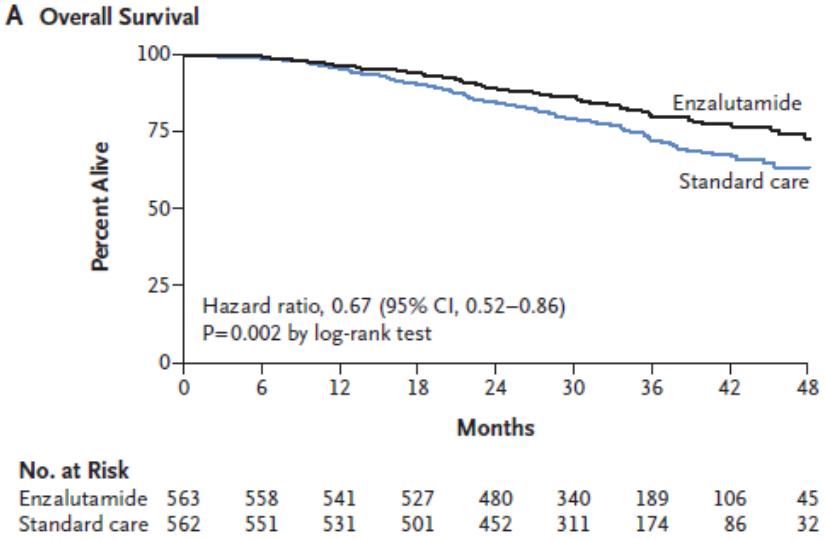
The ENZAMET trial

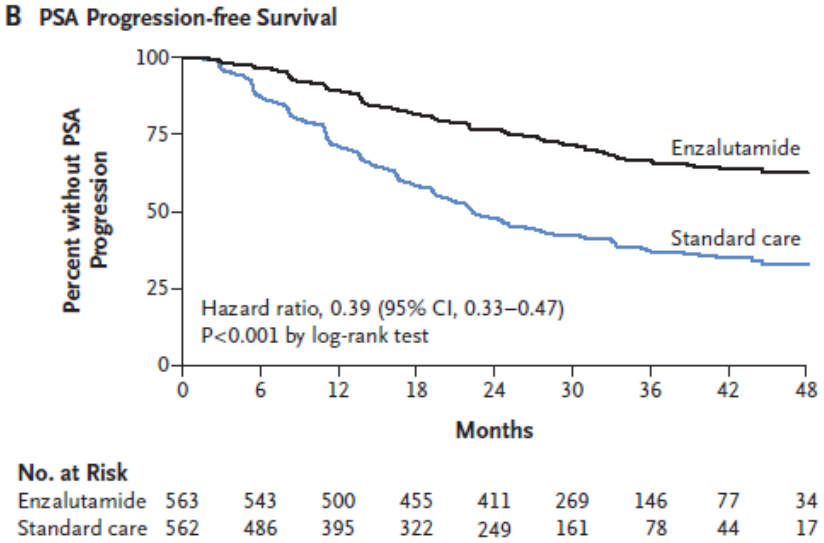
A total of 1125 men underwent randomization and the median follow-up was 34 months

Volume of disease — no. (%)		
High	291 (52)	297 (53)
Low	272 (48)	265 (47)
Visceral metastases — no. (%)	62 (11)	67 (12)
No. of months since diagnosis of metastasis		
Mean	2.9±6.9	3.1±7.2
Median (IQR)	1.9 (0.9–2.8)	1.9 (1.0–2.8)
Gleason score — no. (%)†		
≤7	152 (27)	163 (29)
8–10	335 (60)	321 (57)
Missing data	76 (13)	78 (14)
Previous therapy — no. (%)		
Adjuvant androgen-deprivation therapy	58 (10)	40 (7)
Antiandrogen therapy‡	285 (51)	316 (56)
LHRHA‡	411 (73)	418 (74)
Bilateral orchiectomy	5 (1)	8 (1)
Docetaxel‡	95 (17)	83 (15)

N Engl J Med 2019;381:121-31

The ENZAMET trial - outcome

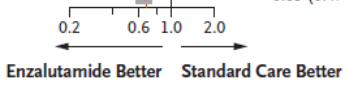




N Engl J Med 2019;381:121-31

The ENZAMET trial – subgroup analysis

Subgroup	Enzalutamide	Standard Care	Hazard Ratio (95% CI)	P Value for Interaction	Adjusted P Value
	no. of events/total no.				
All patients	102/563	143/562	0.67 (0.52–0.86)		
Volume of disease				0.04	0.14
Low	22/272	46/265	0.43 (0.26–0.72)		
High	80/291	97/297	0.80 (0.59–1.07)		
Early docetaxel planned				0.04	0.14
Yes	52/254	55/249	0.90 (0.62–1.31)		
No	50/309	88/313	0.53 (0.37–0.75)		
ACE-27 score				0.73	0.81
2 or 3	31/141	42/143	0.73 (0.46–1.16)		
0 or 1	71/422	101/419	0.65 (0.48–0.88)		
Antiresorptive therapy				0.006	0.06
Yes	17/55	11/58	1.77 (0.83–3.77)		
No	85/508	132/504	0.59 (0.45–0.77)		
Region				0.25	0.42
Ireland and United Kingdom	22/102	22/93	1.04 (0.57–1.88)		
North America	21/117	31/129	0.72 (0.41–1.25)		
Australia and New Zealand	59/344	90/340	0.58 (0.42–0.81)		
Gleason score				0.66	0.81
≤7	13/152	23/163	0.59 (0.30–1.16)		
8 to 10	66/335	84/321	0.70 (0.50–0.96)		
ECOG performance status				0.96	0.96
1 or 2	44/158	59/157	0.66 (0.45–0.98)		
0	58/405	84/405	0.66 (0.47–0.92)		
Age				0.16	0.33
≥70 yr	47/257	79/257	0.56 (0.39–0.81)		
<70 yr	55/306	64/305	0.81 (0.56–1.15)		
Visceral metastases				0.16	0.33
Yes	18/62	18/67	1.05 (0.54–2.02)		
No	84/501	125/495	0.62 (0.47–0.82)		
Previous local treatment				0.72	0.81
Yes	39/238	49/235	0.72 (0.47–1.09)		
No	63/325	94/327	0.65 (0.47–0.89)		



N Engl J Med 2019;381:121-31

The ENZAMET trial - safety

Adverse Event	Enzalutamide (N=563)	Standard Care (N=558)
Any adverse event — no. of patients (%)*		
Grade 1	40 (7)	77 (14)
Grade 2	202 (36)	230 (41)
Grade 3	277 (49)	194 (35)
Grade 4	38 (7)	40 (7)
Grade 5	6 (1)	7 (1)
Serious adverse event		
No. of patients (%)	235 (42)	189 (34)
No. of events	385	297
Rate during treatment exposure (95% CI) — no./yr†	0.34 (0.29–0.40)	0.33 (0.28–0.39)
Adverse event leading to treatment discontinuation at any time — no. of patients	33	14

N Engl J Med 2019;381:121-31

Update from ASCO 2022

Meeting Abstract | 2022 ASCO Annual Meeting II

GENITOURINARY CANCER—PROSTATE, TESTICULAR, AND PENILE

Updated overall survival outcomes in ENZAMET (ANZUP 1304), an international, cooperative group trial of enzalutamide in metastatic hormone-sensitive prostate cancer (mHSPC).

Ian D. Davis, Andrew James Martin, Robert Richard Zielinski, Alastair Thomson, Thean Hsiang Tan, Shahneen Sandhu, ...

Enzalutamide added to TS provided clinically meaningful **improvements in OS** for the combined overall cohort, which persisted **with an additional 3 years of follow-up**.

The benefits were more pronounced in pts with **low volume disease**, and were also seen in the subgroup with M1 **high volume** mHSPC

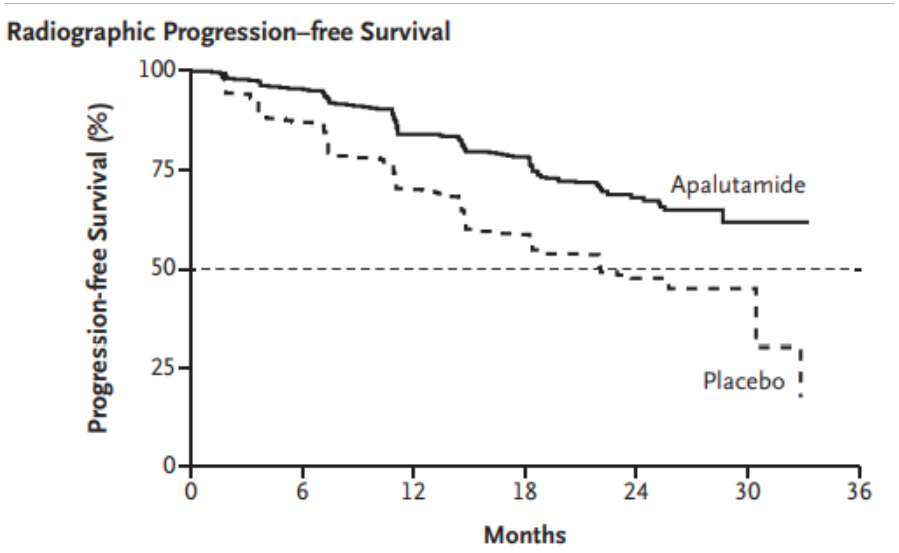
	Enzalutamide		NSAA		HR (95% CI)
	Deaths/Total	5y OS %	Deaths/Total	5y OS %	
All participants	208/563	67	268/562	57	0.70 (0.58 to 0.84)
Concurrent docetaxel					
No	100/310	72	145/312	58	0.60 (0.47 to 0.78)
Yes	108/253	61	123/250	56	0.82 (0.63 to 1.06)
Volume of Disease (Vol)					
Low	59/262	80	97/261	66	0.54 (0.39 to 0.74)
High	149/301	55	171/301	49	0.79 (0 .63 to 0.98)

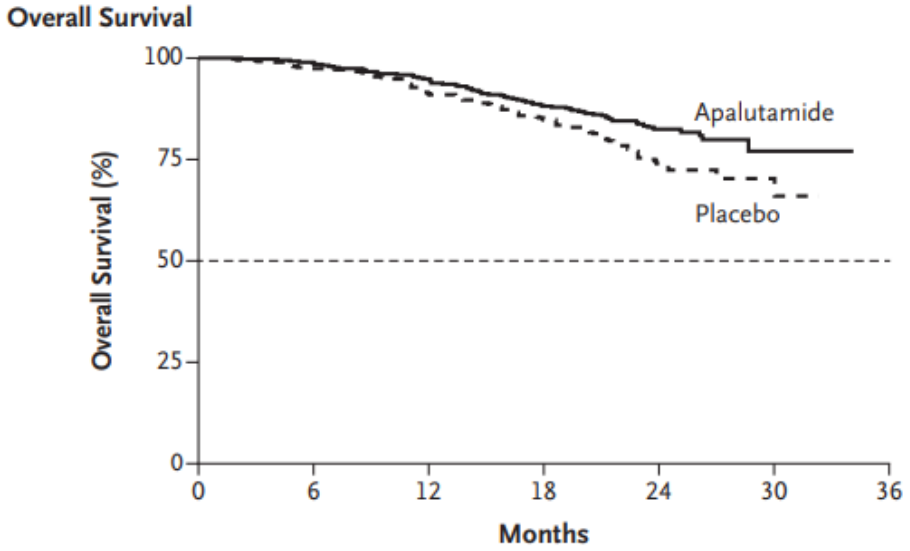
TITAN trial

Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer

Kim N. Chi, M.D., Neeraj Agarwal, M.D., Anders Bjartell, M.D., Byung Ha Chung, M.D., Andrea J. Pereira de Santana Gomes, M.D., Robert Given, M.D., Álvaro Juárez Soto, M.D., Axel S. Merseburger, M.D., Mustafa Özgüroğlu, M.D., Hirotsugu Uemura, M.D., Dingwei Ye, M.D., Kris Deprince, M.D., Vahid Naini, Pharm.D., Jinhui Li, Ph.D., Shinta Cheng, M.D., Margaret K. Yu, M.D., Ke Zhang, Ph.D., Julie S. Larsen, Pharm.D., Sharon McCarthy, B.Pharm., and Simon Chowdhury, M.D., for the TITAN Investigators*

Phase 3 trial, 525 patients with metastatic, castration-sensitive prostate cancer, randomly assigned patients to receive apalutamide (240 mg per day) or placebo, added to ADT





N Engl J Med 2019;381:13-24.

Treatments' comparison for mHSPC

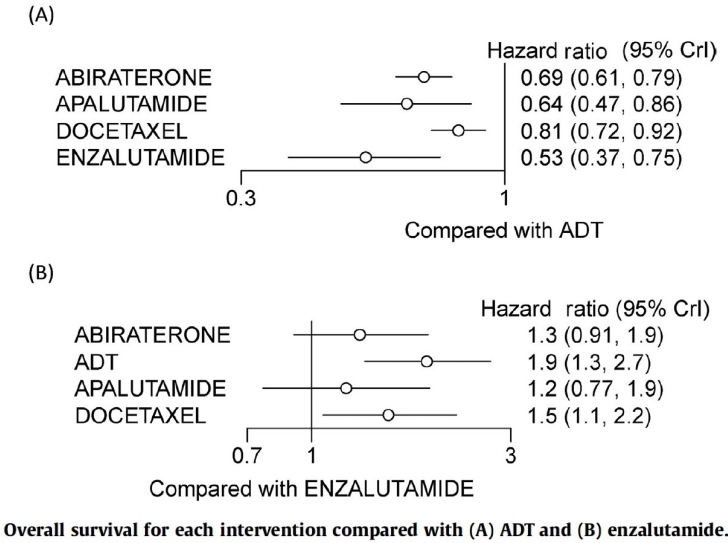
Indirect Comparisons of Efficacy between Combination Approaches in Metastatic Hormone-sensitive Prostate Cancer: A Systematic Review and Network Meta-analysis

Niranjan J. Sathianathen [a,b], Samantha Koschel [a], Isaac A. Thangasamy [a], Jiasian Teh [a], Omar Alghazo [a], Georgiana Butcher [a,c], Harriet Howard [a,c], Jada Kapoor [a], Nathan Lawrentschuk [a,b], Shankar Siva [d,e], Arun Azad [e,f], Ben Tran [f], Damien Bolton [b], Declan G. Murphy [a,e,]*

All 4 interventions demonstrated **significantly improved OS compared with ADT alone.**

These four interventions were statistically comparable to each other with none being clearly superior.

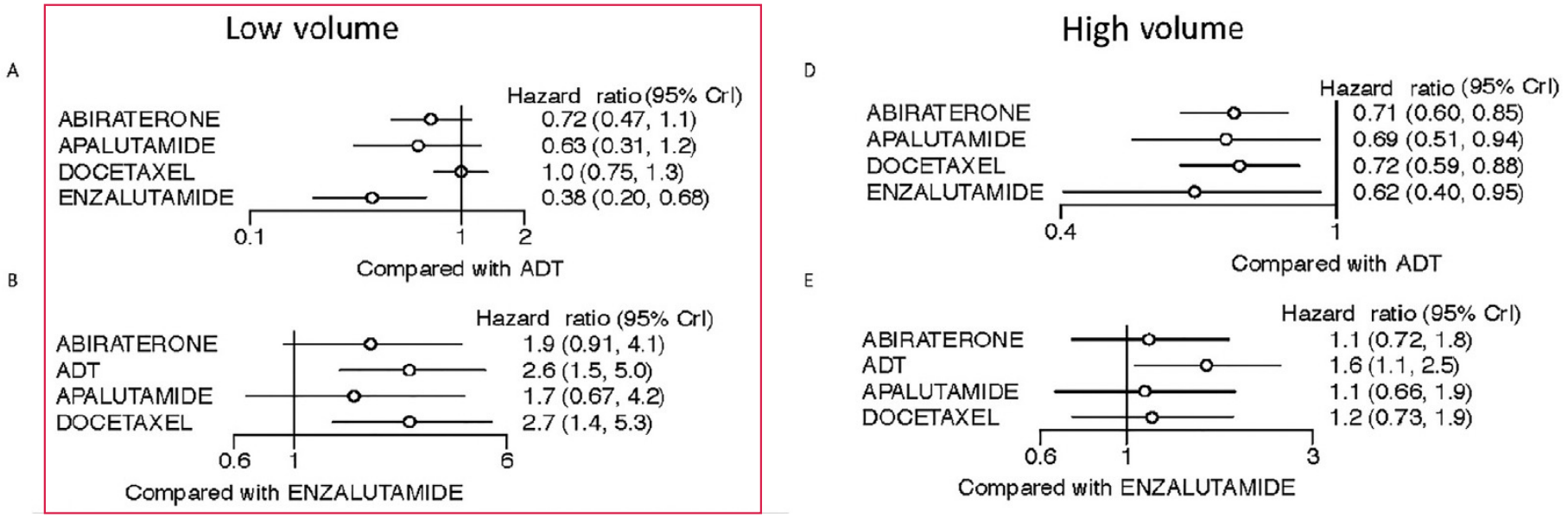
However, **enzalutamide + ADT had the absolute lowest HR compared with ADT alone** (HR 0.53, 95%CI 0.37–0.75).



Overall survival for each intervention compared with (A) ADT and (B) enzalutamide.

European Urology 78 (2020) 347 – 357

Treatments' comparison for mHSPC

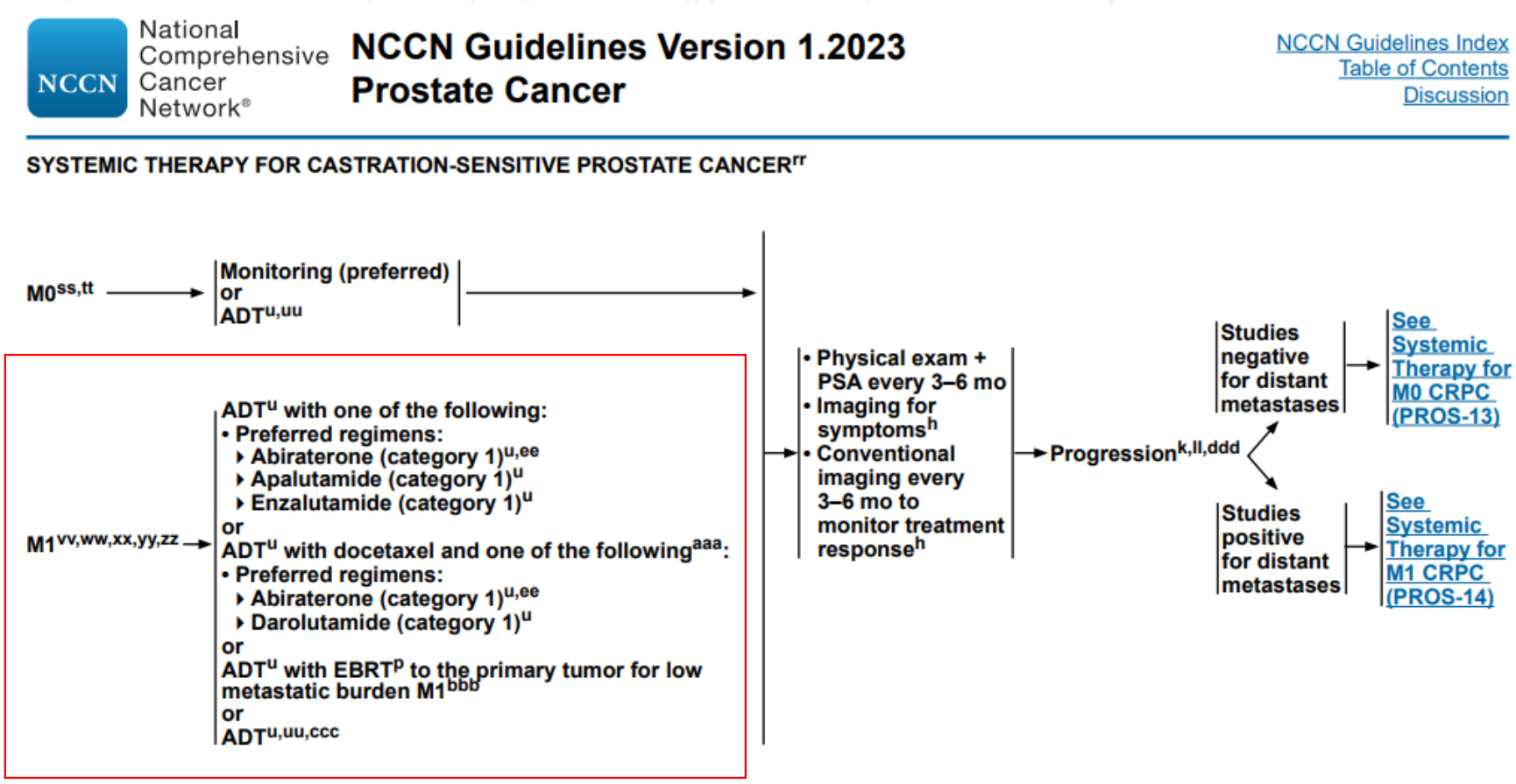


For **low-volume disease**, only **Enza demonstrated improved survival** compared with ADT, with the lowest absolute HR (HR 0.38, 95%CI 0.20–0.68).

Enzalutamide appeared to be superior to docetaxel in men with low-volume disease (HR 0.38, 95%CI 0.19–0.72).

European Urology 78 (2020) 347 – 357

Guidelines

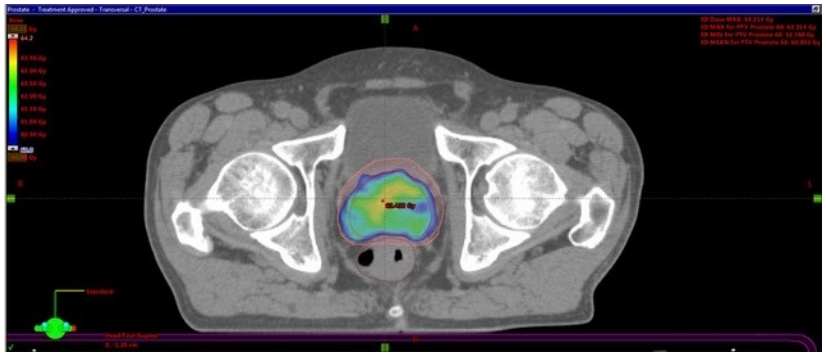

National Comprehensive Cancer Network®
NCCN Guidelines Version 1.2023
Prostate Cancer
NCCN Guidelines Index
Table of Contents
Discussion
SYSTEMIC THERAPY FOR CASTRATION-SENSITIVE PROSTATE CANCER[rr]
M0[ss,tt]
Monitoring (preferred)
or
ADT[u,uu]
M1[vv,ww,xx,yy,zz]
ADT[u] with one of the following:
• Preferred regimens:
▸ Abiraterone (category 1)[u,ee]
▸ Apalutamide (category 1)[u]
▸ Enzalutamide (category 1)[u]
or
ADT[u] with docetaxel and one of the following[aaa]:
• Preferred regimens:
▸ Abiraterone (category 1)[u,ee]
▸ Darolutamide (category 1)[u]
or
ADT[u] with EBRT[p] to the primary tumor for low metastatic burden M1[bbb]
or
ADT[u,uu,ccc]
• Physical exam + PSA every 3–6 mo
• Imaging for symptoms[h]
• Conventional imaging every 3–6 mo to monitor treatment response[h]
Progression[k,ll,ddd]
Studies negative for distant metastases
See Systemic Therapy for M0 CRPC (PROS-13)
Studies positive for distant metastases
See Systemic Therapy for M1 CRPC (PROS-14)

Guidelines

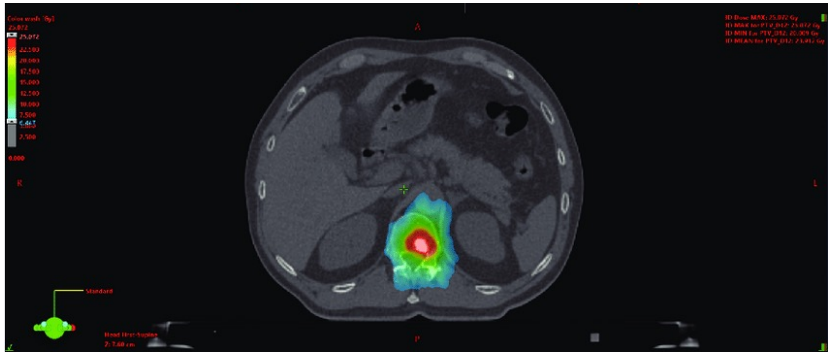
EAU - EANM - ESTRO - ESUR - ISUP - SIOG Guidelines on Prostate Cancer

Recommendations	Strength rating
Offer immediate systemic treatment with androgen deprivation therapy (ADT) to palliate symptoms and reduce the risk for potentially serious sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction) to M1 symptomatic patients.	Strong
Offer luteinising hormone-releasing hormone (LHRH) antagonists or orchiectomy before starting ADT, especially to patients with impending clinical complications like spinal cord compression or bladder outlet obstruction.	Strong
Offer early systemic treatment to M1 patients asymptomatic from their tumour.	Strong
Offer short-term administration of an older generation androgen receptor (AR) antagonist to M1 patients starting LHRH agonist to reduce the risk of the 'flare-up' phenomenon.	Weak
Do not offer AR antagonist monotherapy to patients with M1 disease.	Strong
Discuss combination therapy including ADT plus systemic therapy with all M1 patients.	Strong
Do not offer ADT monotherapy to patients whose first presentation is M1 disease if they have no contraindications for combination therapy and have a sufficient life expectancy to benefit from combination therapy (≥ 1 year) and are willing to accept the increased risk of side effects.	Strong
Offer ADT combined with chemotherapy (docetaxel) to patients whose first presentation is M1 disease and who are fit for docetaxel.	Strong
Offer ADT combined with abiraterone acetate plus prednisone or apalutamide or enzalutamide to patients whose first presentation is M1 disease and who are fit enough for the regimen.	Strong
Offer ADT combined with prostate radiotherapy (RT) (using the doses and template from the STAMPEDE study) to patients whose first presentation is M1 disease and who have low volume of disease by CHAARTED criteria.	Strong
Do not offer ADT combined with any local treatment (RT/surgery) to patients with high-volume (CHAARTED criteria) M1 disease outside of clinical trials (except for symptom control).	Strong
Do not offer ADT combined with surgery to M1 patients outside of clinical trials.	Strong
Only offer metastasis-directed therapy to M1 patients within a clinical trial setting or well-designed prospective cohort study.	Strong

Radiotherapy in mHSPC



Which role for radiotherapy in mHSPC ?



RT in mHSPC - STAMPEDE TRIAL

Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial

Christopher C Parker, Nicholas D James, Christopher D Brawley, Noel W Clarke, Alex P Hoyle, Adnan Ali, Alastair W S Ritchie, Gerhardt Attard, Simon Chowdhury, William Cross, David P Dearnaley, Silke Gillessen, Clare Gilson, Robert J Jones, Ruth E Langley, Zafar I Malik, Malcolm D Mason, David Matheson, Robin Millman, J Martin Russell, George N Thalmann, Claire L Amos, Roberto Alonzi, Amit Bahl, Alison Birtle, Omar Din, Hassan Douis, Chinnamani Eswar, Joanna Gale, Melissa R Gannon, Sai Jonnada, Sara Khaksar, Jason F Lester, Joe M O'Sullivan, Omi A Parikh, Ian D Pedley, Delia M Pudney, Denise J Sheehan, Narayanan Nair Srihari, Anna T H Tran, Mahesh K B Parmar, Matthew R Sydes*, on behalf of the Systemic Therapy for Advanced or Metastatic Prostate cancer: Evaluation of Drug Efficacy (STAMPEDE) investigators†*

2061 newly diagnosed metastatic prostate cancer randomized to

a) **Standard of care**: lifelong androgen deprivation therapy (with up-front docetaxel permitted from December, 2015)

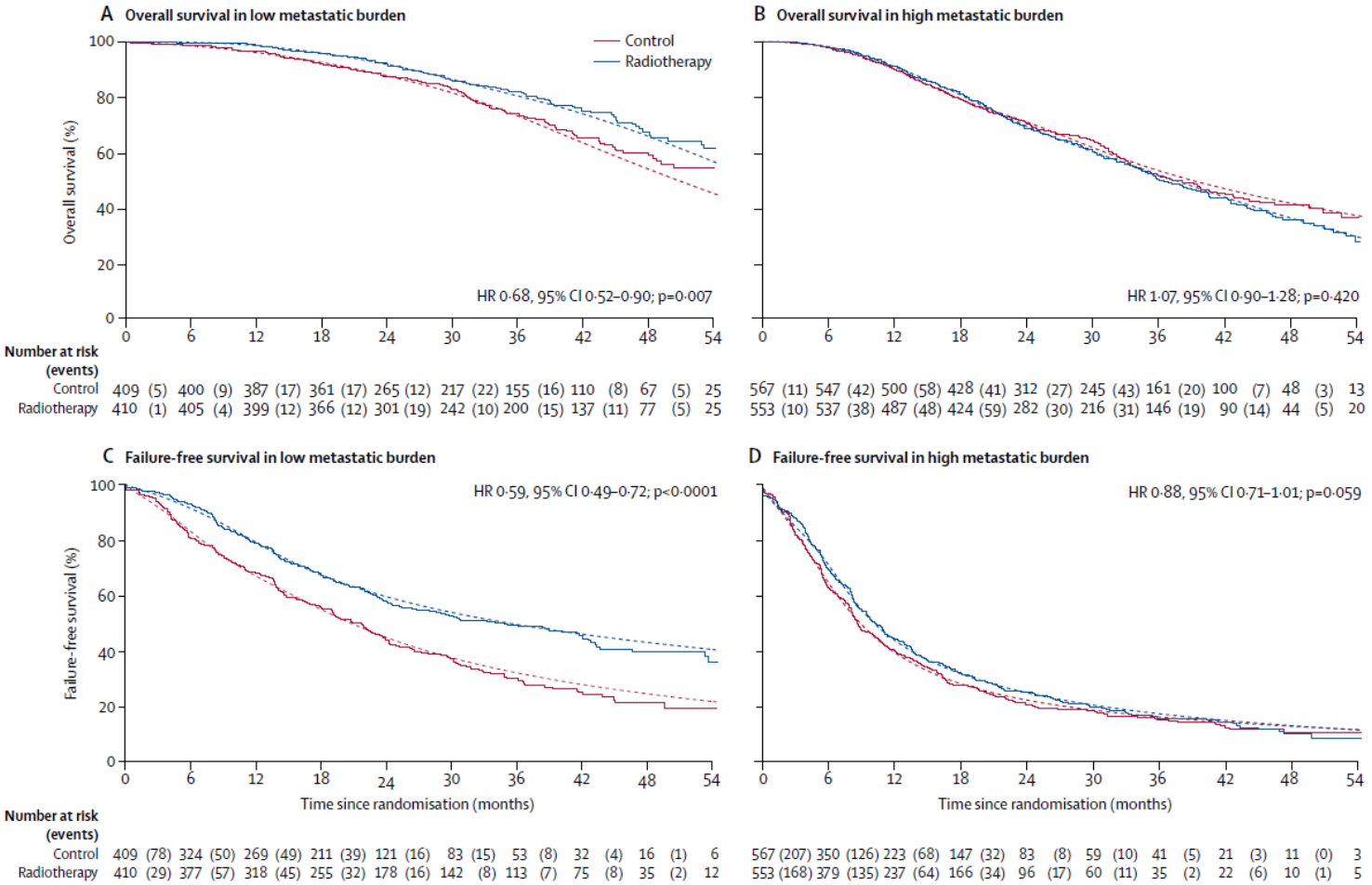
b) **Standard of care** plus **radiotherapy** to the primary tumore

Men allocated to radiotherapy received either:

- 55 Gy in 20 daily fractions
- 36 Gy in 6 weekly fractions

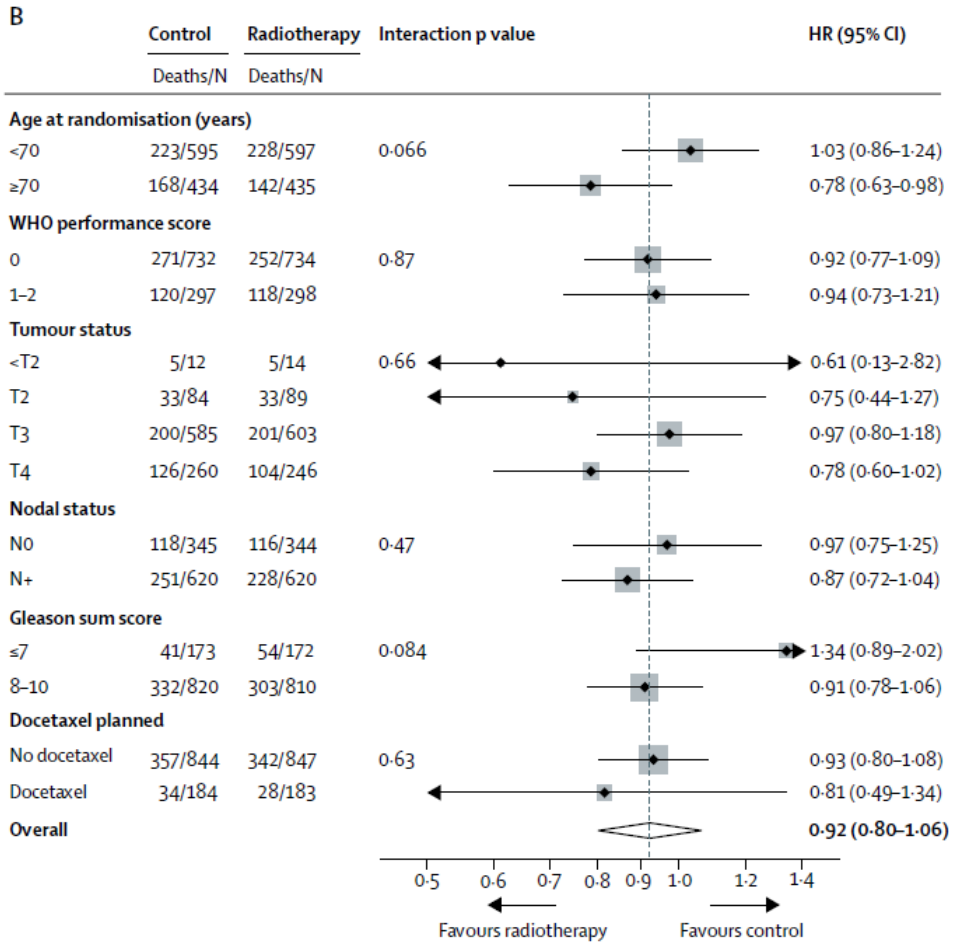
RT in mHSPC - STAMPEDE TRIAL

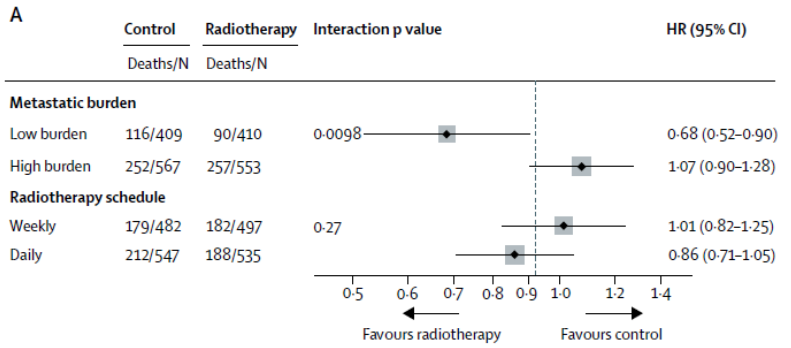
LOW VOLUME



HIGH VOLUME

RT in mHSPC - STAMPEDE TRIAL





	Within treatment window		After treatment window	
	Control (n=1029)	Radiotherapy (n=1032)	Control (n=1029)	Radiotherapy (n=1032)
Transurethral resection of the prostate	9 (1%)	13 (1%)	23 (2%)	24 (2%)
Ureteric stent	5 (<1%)	3 (<1%)	16 (2%)	7 (1%)
Surgery for bowel obstruction	0 (0%)	0 (0%)	0 (0%)	1 (<1%)
Urinary catheter	14 (1%)	18 (2%)	35 (3%)	36 (3%)
Nephrostomy	2 (<1%)	2 (<1%)	8 (1%)	3 (<1%)
Colostomy	0 (0%)	0 (0%)	2 (<1%)	1 (<1%)
Acute kidney injury	2 (<1%)	6 (1%)	31 (3%)	35 (3%)
Urinary tract infection	14 (1%)	31 (3%)	49 (5%)	75 (7%)
Urinary tract obstruction	4 (<1%)	7 (1%)	24 (2%)	17 (2%)
Prostate cancer death	2 (<1%)	1 (<1%)	327 (32%)	313 (30%)

Treatment window defined as 12 weeks from randomisation for patients in either treatment group who did not receive docetaxel, and 28 weeks from randomisation for those who did.

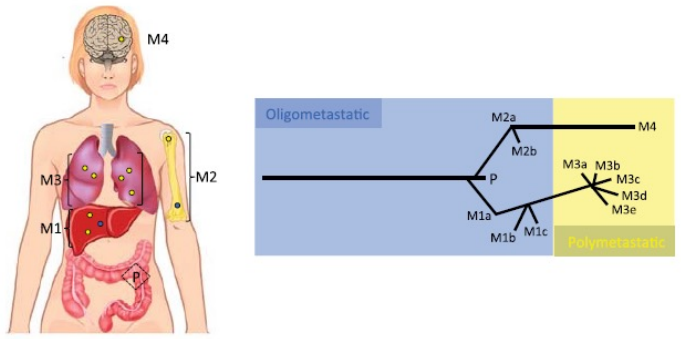
Table 3: **Incidence of symptomatic local events reported before and after treatment period**

Role of RT for metastases?

Stereotactic Body Radiotherapy for Oligometastasis

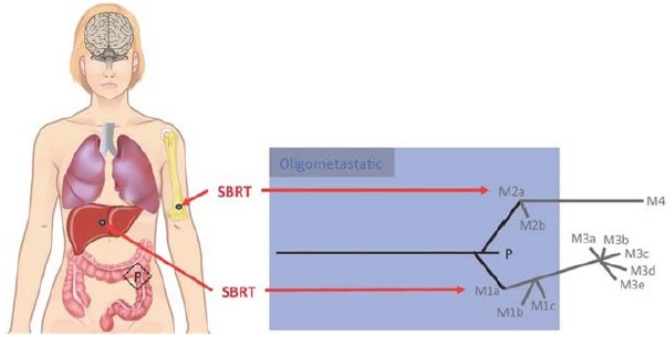
Opportunities for Biology to Guide Clinical Management

Linear Progression Model of Metastasis Evolution (with Metastatic Cascades):



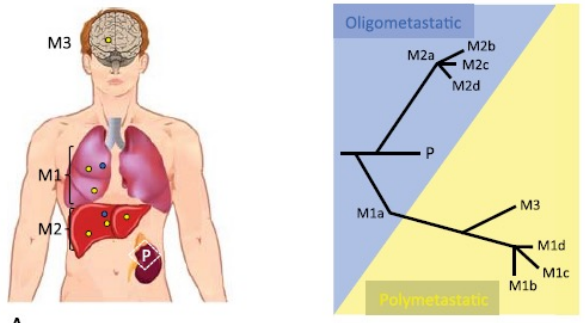
A

Potential Effect of Ablative Therapy:



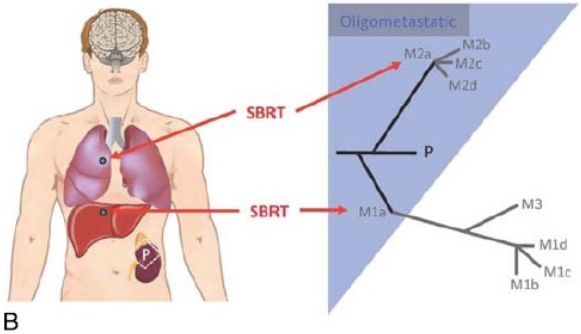
B

Parallel Progression Model of Metastasis Evolution (with Metastatic Cascades):



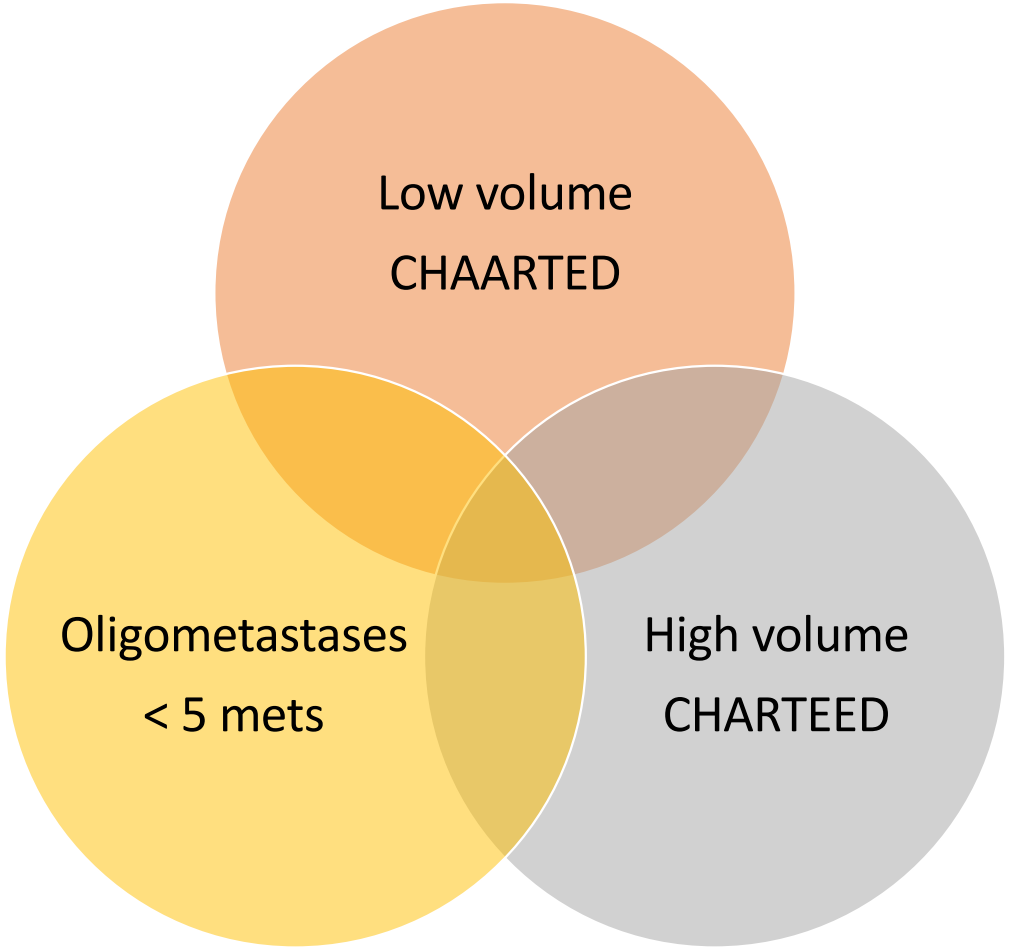
A

Potential Effect of Ablative Therapy:



B

Matter of definition



Oligometastatic state is not the same as low-volume according to CHAARTED

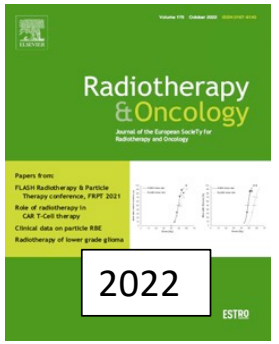
Low-volume CHARTEED may have large number of mets to lymph nodes and axial bone

Oligometastatic setting is defined as <= 5 mets

MDT in de novo mHSP

Recommendations for radiation therapy in oligometastatic prostate cancer: An ESTRO-ACROP Delphi consensus

Thomas Zilli [a,b,c,*], Vérane Achard [b,c], Alan Dal Pra [d], Nina Schmidt-Hegemann [e], Barbara Alicja Jereczek-Fossa [f,g], Andrea Lancia [h], Gianluca Ingrosso [i], Filippo Alongi [j,k], Shafak Aluwini [l], Stefano Arcangeli [m], Pierre Blanchard [n,o], Antonio Conde Moreno [p], Felipe Couñago [q,r,s], Gilles Créhange [t], Piet Dirix [u], Alfonso Gomez Iturriaga [v], Matthias Guckenberger [w], David Pasquier [x,y], Paul Sargos [z], Marta Scorsetti [aa], Stéphane Supiot [ab], Alison C. Tree [ac], Almudena Zapatero [ad], Jennifer Le Guevelou [b,c], Piet Ost [ae,af], Claus Belka [e]



5. For which presentation setting (de novo, oligorecurrent, oligoprogressive) do you recommend MDRT?	**For de novo, oligorecurrent and oligoprogressive**	**Consensus Round 1: 68%; round 2: 88%**
7. Which imaging modalities do you recommend to select candidates for MDRT?	**PSMA PET imaging**	**Consensus Round 1: 64%; round 2: 80%; round 3: 88%**
8. Do you recommend a confirmatory biopsy to suspicious lesions for MDRT?	**Only for selected cases**	**Consensus Round 1: 84%**
Synchronous de novo oligometastatic castration-sensitive PCa		
9. For patients with untreated primary with de novo oligometastatic PCa on conventional imaging, which confirmatory imaging do you recommend?	**PSMA PET imaging**	**Consensus Round 1: 60%; round 2: 84%**
10. For patients with untreated primary with de novo oligometastatic PCa, which type of treatment do you recommend?	Systemic therapy and treatment of the prostate (±pelvic nodes) and all metastatic lesions	Agreement Round 1: 68%; round 2: 76%; round 3: 76%
13. For patients with untreated primary with de novo oligometastatic PCa treated to primary and all metastatic lesions, which duration of systemic therapy do you propose?	Long-course, 18–36 months	Agreement Round 1: 72%; round 2: 72%; round 3: 76%
14. For patients with untreated primary with de novo oligometastatic PCa treated to the primary, for which SITES do you consider using MDRT?	Pelvic and extra-pelvic nodal disease + bone lesions	Agreement Round 1: 52%; round 2: 60%; round 3: 76%

Local and metastatic curative radiotherapy in patients with de novo oligometastatic prostate cancer

C. Reverberi, M. Massaro✉, M. F. Osti, D. Anzellini, L. Marinelli, A. Montalto, V. De Sanctis & M. Valeriani

Scientific Reports | (2020) 10:17471

37 de novo Oligo-PCa patients treated with RT on primary tumor and metastases

- Radiotherapy was delivered in 5 weeks, the median dose to the pelvis was 45 Gy (1.8 Gy/fraction), and 68.75 Gy (2.75 Gy/fraction) for the prostate.
- For bone metastases the dose used was 45–55 Gy/25 fractions, while loco-regional nodal metastases were usually treated with 55–60 Gy/25 fractions.
- Extra-pelvic metastases were more commonly treated with SBRT in 1–5 fractions.

MDT in de novo mHSP

The median OS was 68.8 months, the 2- and 5-year OS rates were 96.9% and 65.4%.

The median b-RFS was 58 months and the 2- and 5-year b-RFS rates were 73.3% and 39.3%.

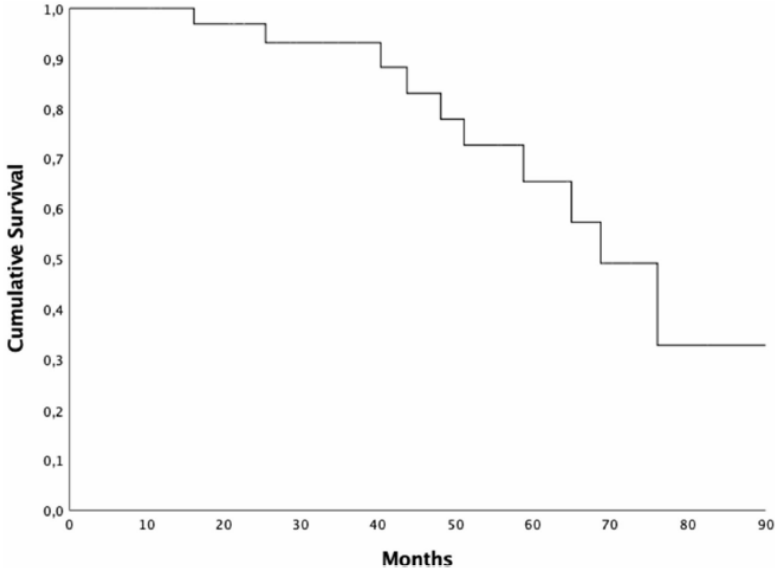


Figure 1. Kaplan-Meyer overall survival curve.

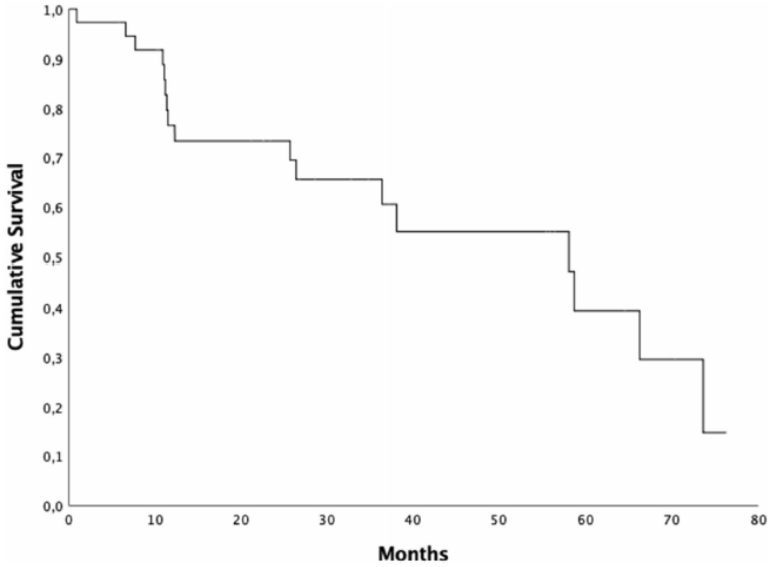


Figure 3. Kaplan Meyer biochemical relapse free survival curve.

MDT in de novo mHSP

The median OS was 68.8 months, the 2- and 5-year OS rates were 96.9% and 65.4%.

The median b-RFS was 58 months and the 2- and 5-year b-RFS rates were 73.3% and 39.3%.

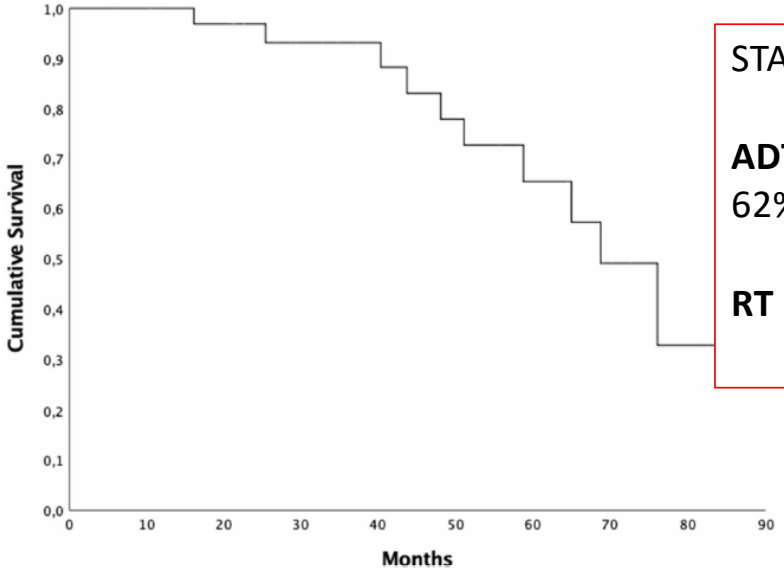


Figure 1. Kaplan-Meyer overall survival curve.

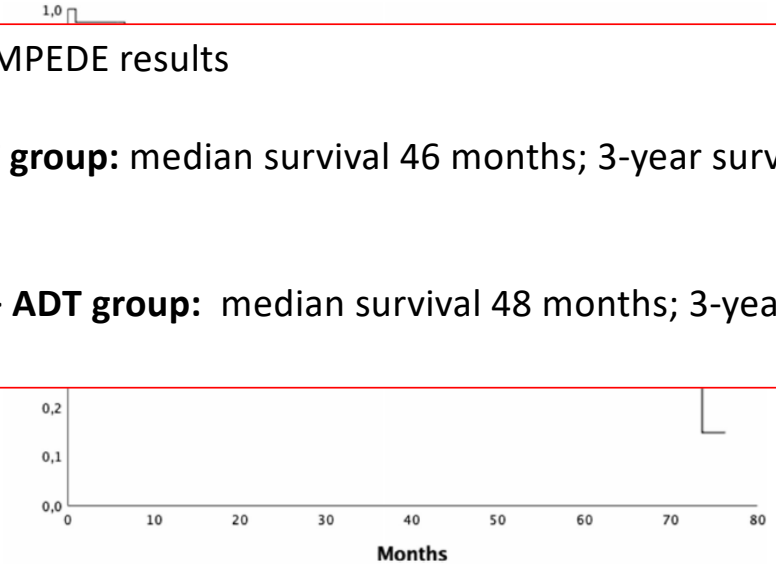


Figure 3. Kaplan Meyer biochemical relapse free survival curve.

STAMPEDE results

ADT group: median survival 46 months; 3-year survival 62%

RT + ADT group: median survival 48 months; 3-year survival 65

Metastasis-directed Therapy (SBRT) Guided by PET-CT ^{18}F-CHOLINE Versus PET-CT ^{68}Ga-PSMA in Castration-sensitive Oligorecurrent Prostate Cancer: A Comparative Analysis of Effectiveness

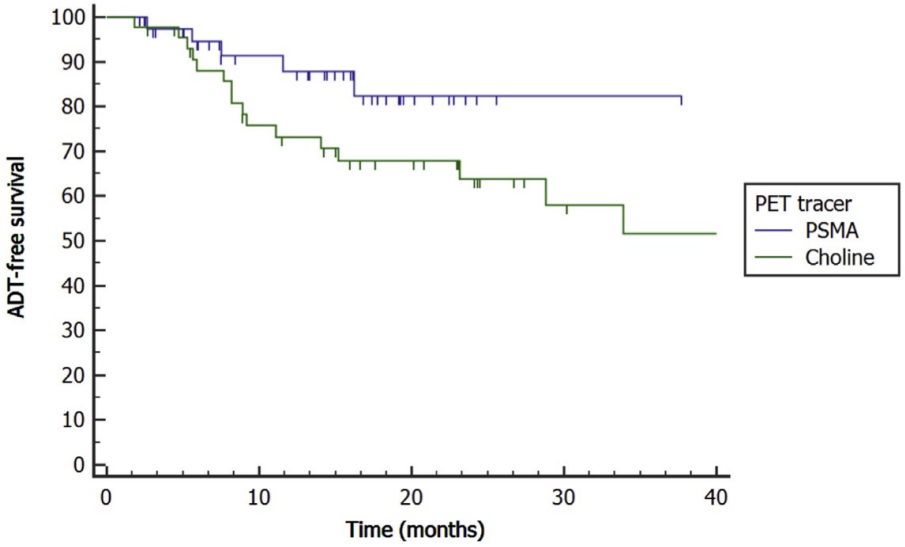
Rosario Mazzola,[1] Giulio Francolini,[2] Luca Triggiani,[3] Giuseppe Napoli,[1] Francesco Cuccia,[1] Luca Nicosia,[1] Lorenzo Livi,[2] Stefano Maria Magrini,[3] Matteo Salgarello,[4] Filippo Alongi[1,2]

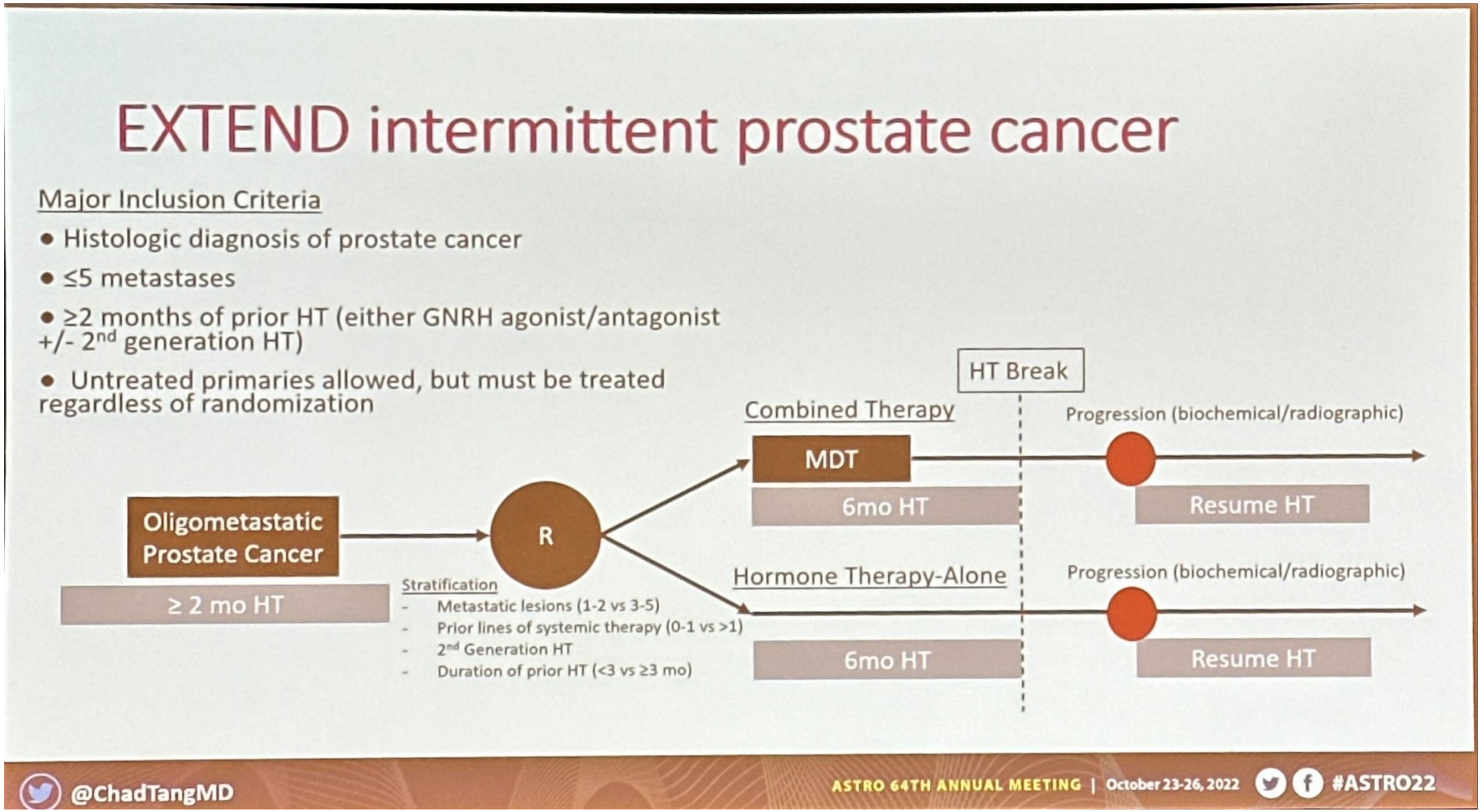
Clinical Genitourinary Cancer Month 2020

118 oligometastases in 88 patients treated with **upfront SBRT for oligorecurrence without ADT**

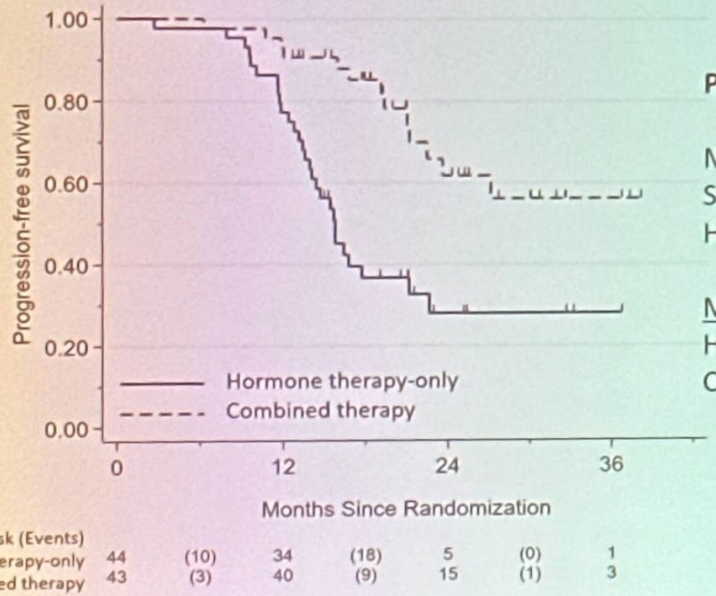
44 patients with Choline-PET

44 patients with PSMA-PET




EXTEND intermittent prostate cancer
Major Inclusion Criteria
• Histologic diagnosis of prostate cancer
• ≤5 metastases
• ≥2 months of prior HT (either GNRH agonist/antagonist +/- 2nd generation HT)
• Untreated primaries allowed, but must be treated regardless of randomization
HT Break
Combined Therapy
MDT
6mo HT
Progression (biochemical/radiographic)
Resume HT
Oligometastatic Prostate Cancer
≥ 2 mo HT
R
Stratification
- Metastatic lesions (1-2 vs 3-5)
- Prior lines of systemic therapy (0-1 vs >1)
- 2nd Generation HT
- Duration of prior HT (<3 vs ≥3 mo)
Hormone Therapy-Alone
6mo HT
Progression (biochemical/radiographic)
Resume HT
@ChadTangMD
ASTRO 64TH ANNUAL MEETING | October 23-26, 2022
#ASTRO22

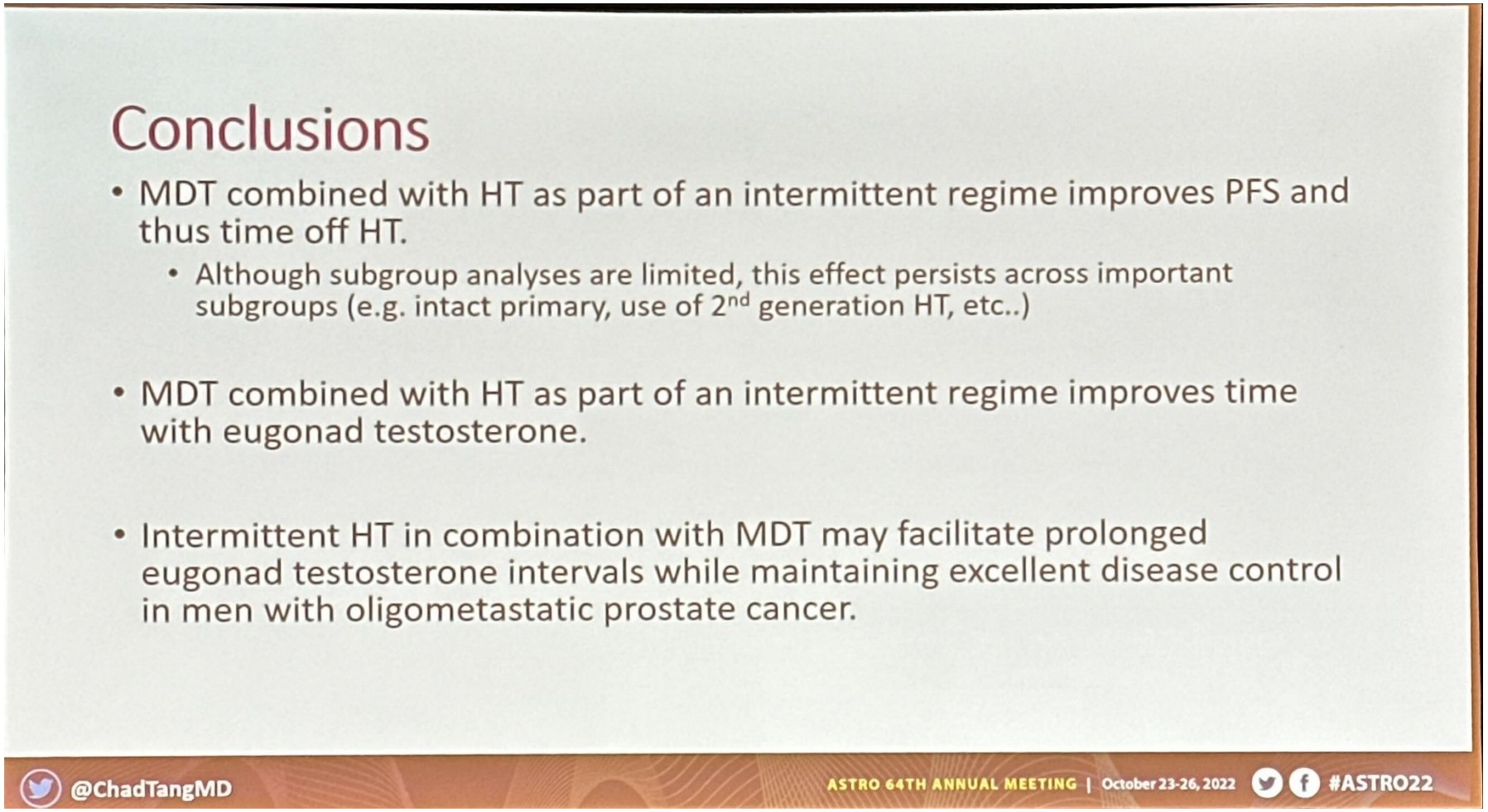
Primary endpoint: progression free survival



Protocol-specified primary analysis at 41 events

Median follow: 22.1 mo
Stratified Log Rank: P<0.001
HR = 0.25 (95% CI: 0.12-0.55)

Median PFS
Hormone therapy-only: 15.8 mo
Combined therapy: not reached


Conclusions
• MDT combined with HT as part of an intermittent regime improves PFS and thus time off HT.
• Although subgroup analyses are limited, this effect persists across important subgroups (e.g. intact primary, use of 2nd generation HT, etc..)
• MDT combined with HT as part of an intermittent regime improves time with eugonad testosterone.
• Intermittent HT in combination with MDT may facilitate prolonged eugonad testosterone intervals while maintaining excellent disease control in men with oligometastatic prostate cancer.
@ChadTangMD
ASTRO 64TH ANNUAL MEETING | October 23-26, 2022
#ASTRO22

EAU - EANM - ESTRO - ESUR - ISUP - SIOG Guidelines on Prostate Cancer

- LIMITED UPDATE MARCH 2022

Offer ADT combined with prostate radiotherapy (RT) (using the doses and template from the STAMPEDE study) to patients whose first presentation is M1 disease and who have low volume of disease by CHAARTED criteria.	Strong
Do not offer ADT combined with any local treatment (RT/surgery) to patients with high-volume (CHAARTED criteria) M1 disease outside of clinical trials (except for symptom control).	Strong
Do not offer ADT combined with surgery to M1 patients outside of clinical trials.	Strong
Only offer metastasis-directed therapy to M1 patients within a clinical trial setting or well-designed prospective cohort study.	Strong

ON-GOING STUDIES

Metastasis Directed Stereotactic Body Radiotherapy for Oligo Metastatic Hormone Sensitive Prostate Cancer (METRO)

Sponsor:
Umeå University

Collaborators:
University Hospital, Umeå
Karolinska University Hospital
Region Örebro County
Region Jönköping County
Stockholm South General Hospital
Region Skane
Vastra Gotaland Region

ClinicalTrials.gov Identifier: NCT04983095

Recruitment Status : Recruiting
First Posted : July 30, 2021
Last Update Posted : May 26, 2022

See **Contacts and Locations**

Prostate-cancer Treatment Using Stereotactic Radiotherapy for Oligometastases Ablation in Hormone-sensitive Patients (PRESTO)

Sponsor:
UNICANCER

Information provided by (Responsible Party):
UNICANCER

ClinicalTrials.gov Identifier: NCT04115007

Recruitment Status : Recruiting
First Posted : October 3, 2019
Last Update Posted : May 12, 2022

See **Contacts and Locations**

Conclusions

The management of patients with metastatic prostate cancer has been evolving rapidly in recent years.

The early start of new generation systemic treatments already in the hormone sensitive phase allows to improve the survival of these patients.

The choice of the drug to use should be mainly based on its impact on patient's quality of life as well as on the efficacy of the treatment.

While the role of RT on de novo metastatic primary tumor is clear, the treatment of metastases in these new scenarios still needs to be prospectively investigated.

@CiroFranzese1

THANK YOU !