Therapeutic Options for Patients with Metastatic Hormone-Sensitive Prostate Cancer (mHSPC)

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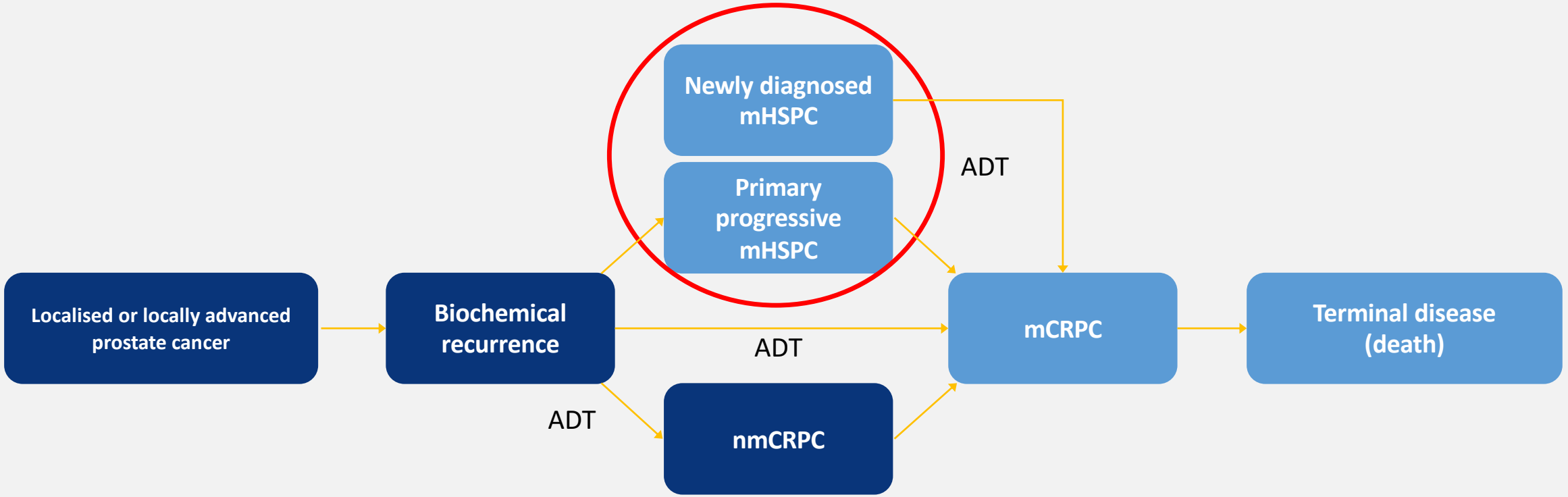
The prostate cancer landscape

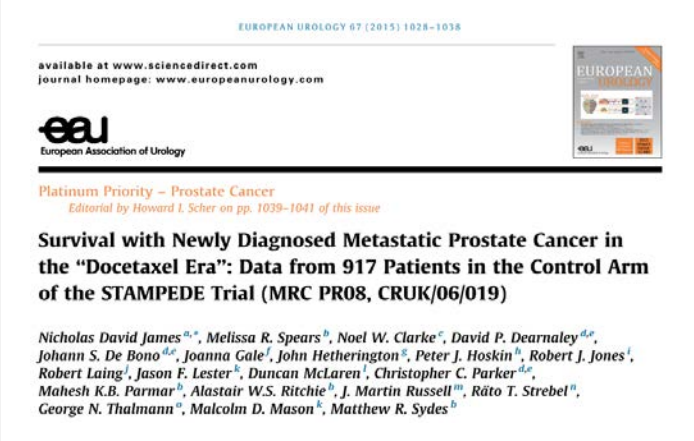


Almost all will progress to mCRPC and die of prostate cancer

Courtesy of Fred Saad, MD CHUM

STAMPEDE control arm (ADT)

FFS and OS



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European Association of Urology

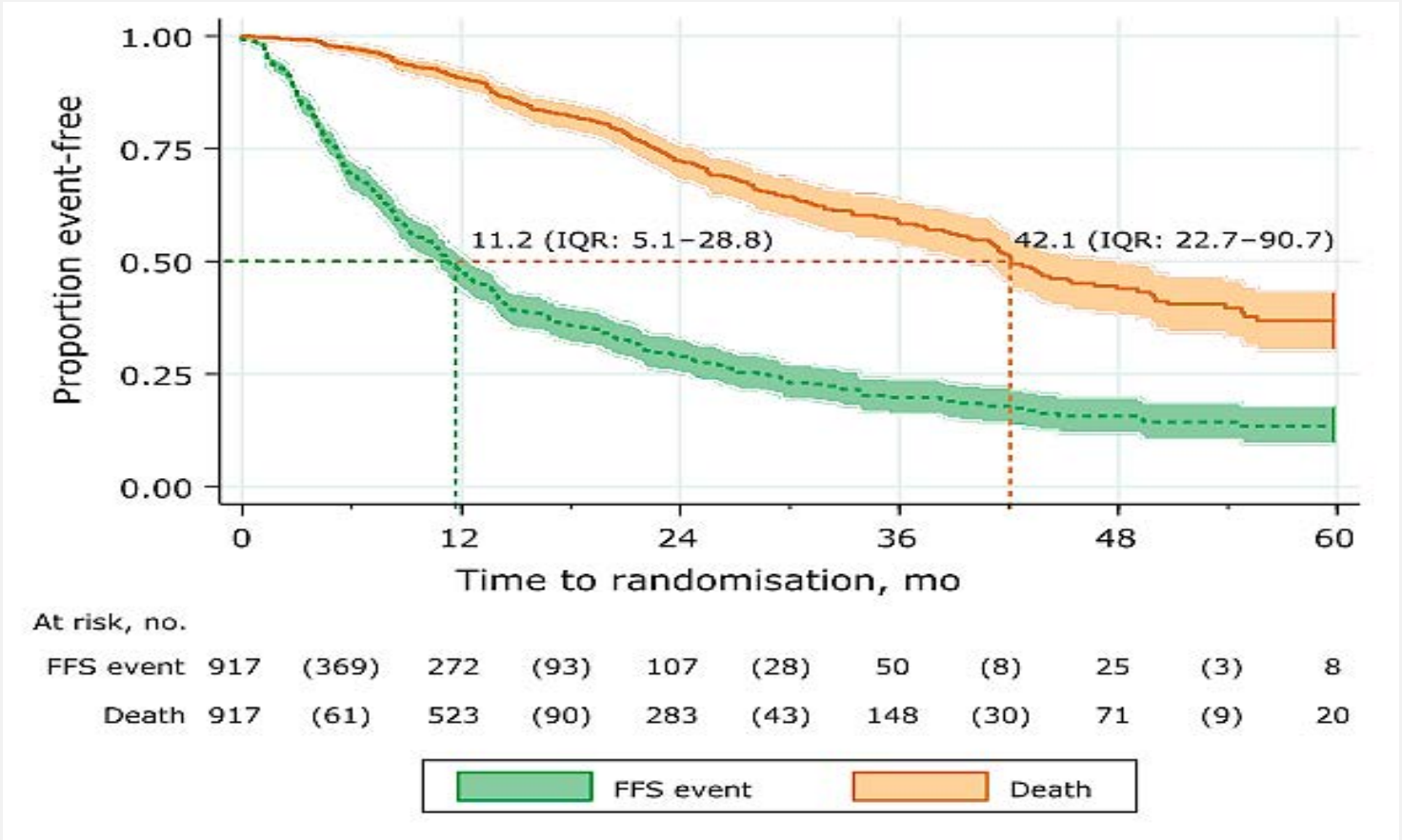
Platinum Priority – Prostate Cancer

Editorial by Howard I. Scher on pp. 1039–1041 of this issue

Survival with Newly Diagnosed Metastatic Prostate Cancer in the "Docetaxel Era": Data from 917 Patients in the Control Arm of the STAMPEDE Trial (MRC PR08, CRUK/06/019)

Nicholas David James[a,], Melissa R. Spears[b], Noel W. Clarke[c], David P. Dearnaley[d,e], Johann S. De Bono[d,e], Joanna Gale[f], John Hetherington[g], Peter J. Hoskin[h], Robert J. Jones[i], Robert Laing[j], Jason F. Lester[k], Duncan McLaren[l], Christopher C. Parker[d,e], Mahesh K.B. Parmar[b], Alastair W.S. Ritchie[b], J. Martin Russell[m], Răto T. Strebel[n], George N. Thalmann[o], Malcolm D. Mason[k], Matthew R. Sydes[b]*

- 917 men with newly diagnosed metastatic PCa treated with ADT only (control arm)



FFS, failure-free survival; **OS**: overall survival ; **ADT**: androgen deprivation therapy; **IQR**, interquartile range.

James ND et al. *Eur Urol*. 2015;67:1028-38.

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Can we do better?

Courtesy of Fred Saad, MD

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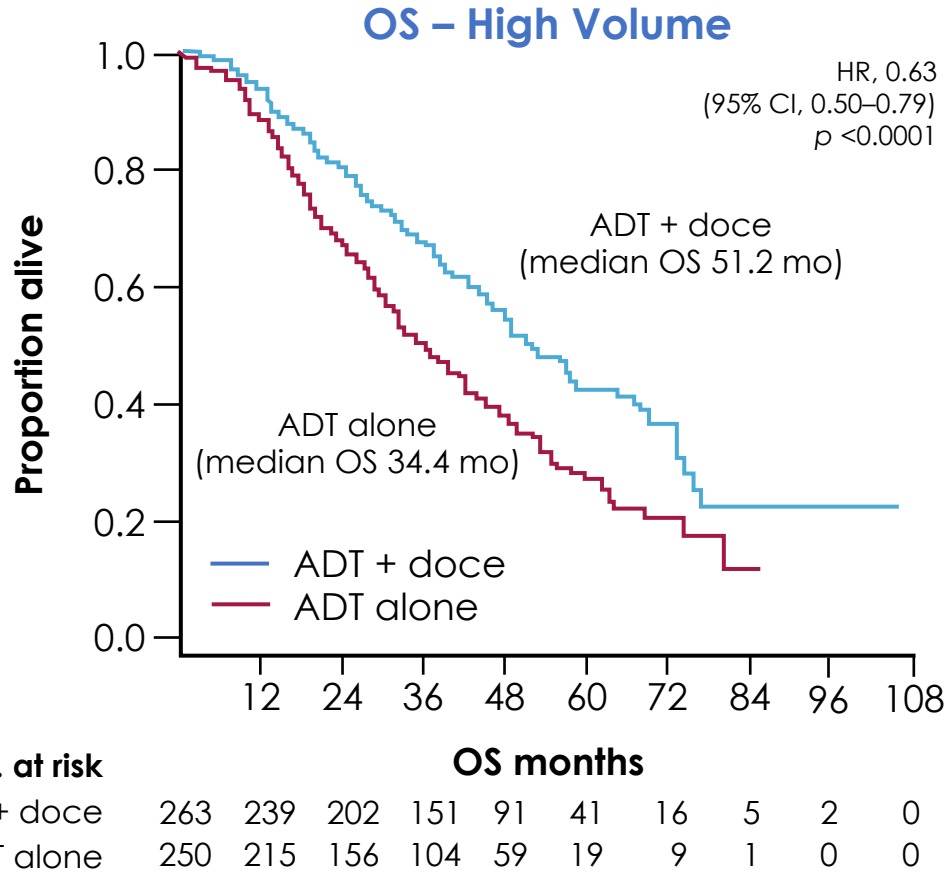
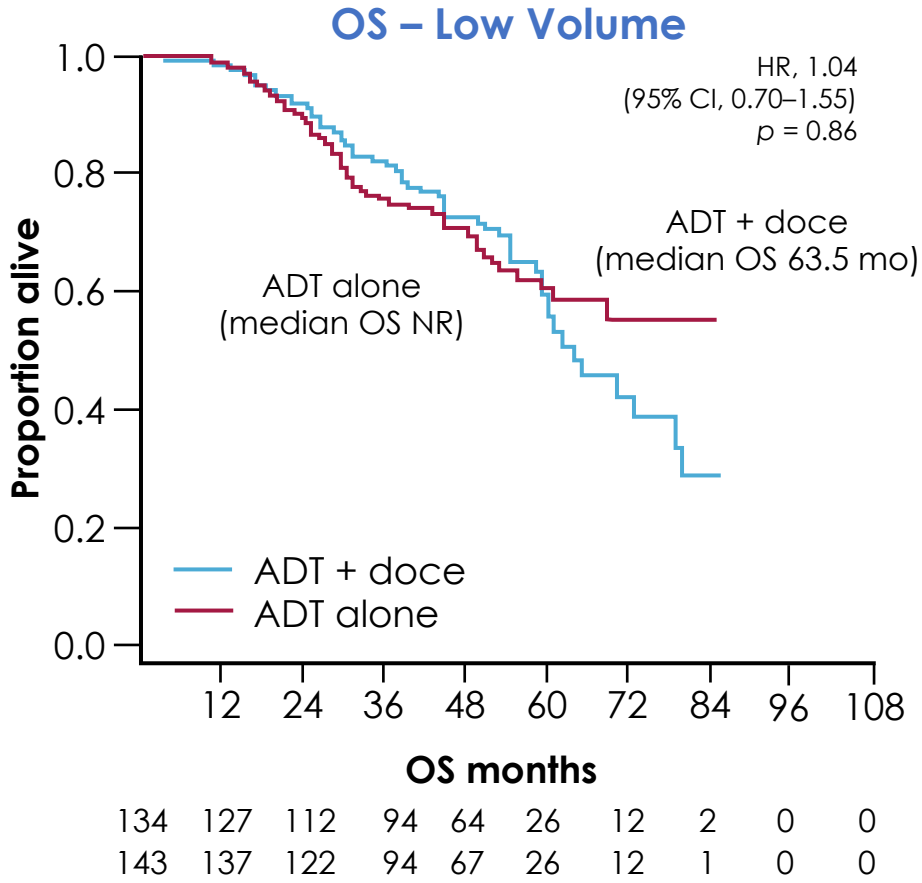
CHAARTED: Docetaxel in High vs Low volume HSPC



16.8 months



0 months

Kyriakopoulos CE, et al. *J Clin Oncol* 2018;36:1080-1087.

Courtesy of Fred Saad, MD

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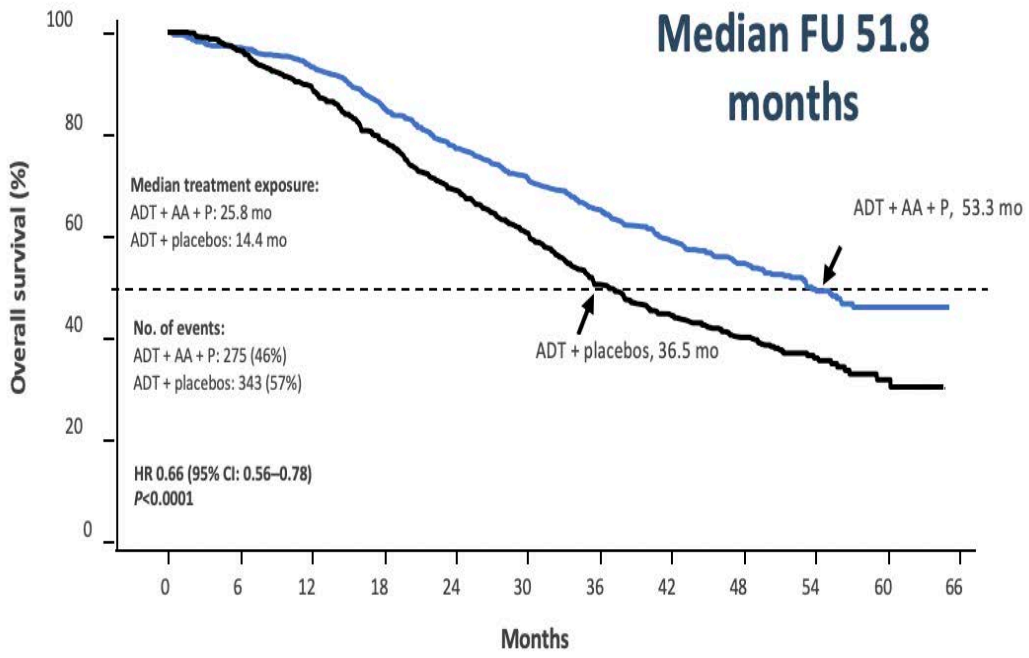
LATITUDE: Abiraterone in high risk mHSPC

Survival



Overall results

	Abiraterone acetate and prednisone plus ADT (n=597)		Placebos plus ADT (n=602)		Hazard ratio (95% CI)	p value
	Events	Median, months	Events	Median, months		
Primary endpoint						
Overall survival	275 (46%)	53·3 (48·2–NR)	343 (57%)	36·5 (33·5–40·0)	0·66 (0·56–0·78)	<0·0001
Secondary endpoints						
Pain progression	245 (41%)	47·4 (33·2–NR)	292 (49%)	16·6 (11·1–24·0)	0·72 (0·61–0·86)	0·00024
Skeletal-related event*	132 (22%)	NR (NR–NR)	150 (25%)	NR (NR–NR)	0·75 (0·60–0·95)	0·0181
Chemotherapy initiation†	150 (25%)	NR (62·6–NR)	218 (36%)	57·6 (38·2–NR)	0·51 (0·41–0·63)	<0·0001
Subsequent prostate cancer therapy	248 (42%)	54·9 (45·4–NR)	355 (59%)	21·2 (18·6–23·5)	0·45 (0·38–0·53)	<0·0001
Prostate-specific antigen progression	273 (46%)	33·3 (29·4–46·1)	448 (74%)	7·4 (7·2–9·2)	0·31 (0·27–0·36)	<0·0001
Exploratory endpoint						
Secondary progression-free survival‡	267 (45%)	53·3 (44·7–58·1)	336 (56%)	30·1 (26·2–33·4)	0·58 (0·49–0·68)	<0·0001

Fizazi et al. Lancet Onc Published online April 12, 2019

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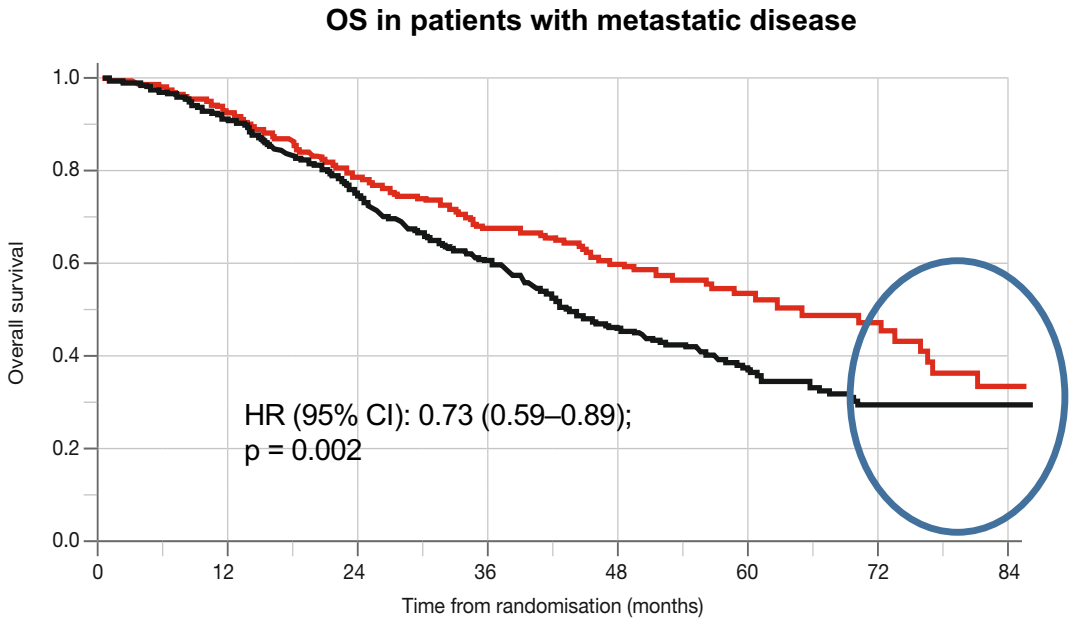
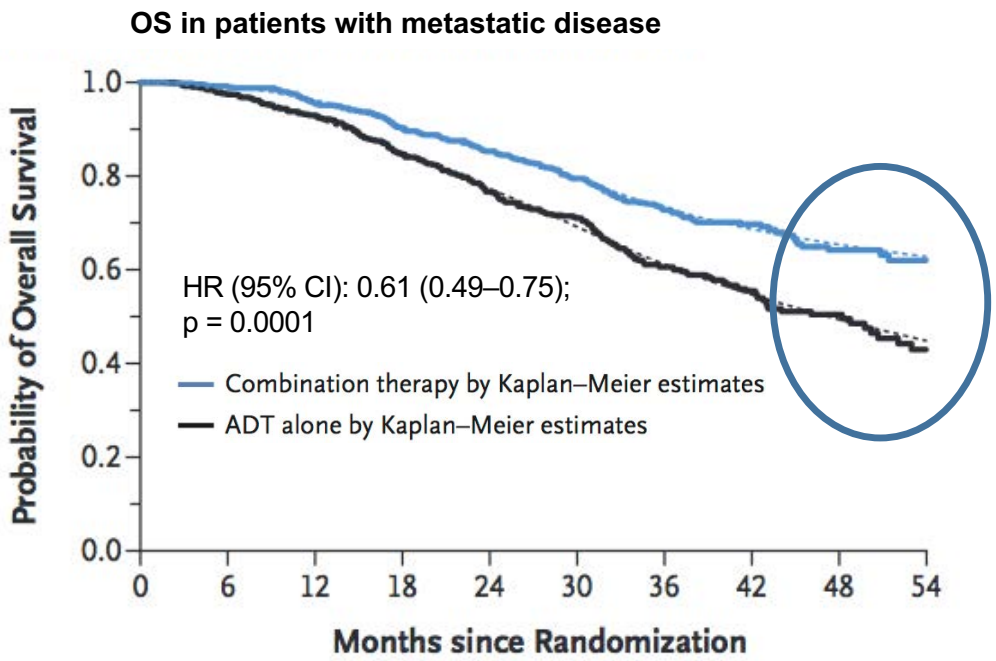
STAMPEDE:
Same results with Docetaxel and Abiraterone

ADT + Docetaxel M1[1]
27% risk reduction



SOC + Abiraterone M1[2]
39% risk reduction



1. James ND, et al. Eur Urol. 2015;67:1028-38.

2. James ND, et al. N Engl J Med. 2017;377:338-51.

Courtesy of Fred Saad, MD

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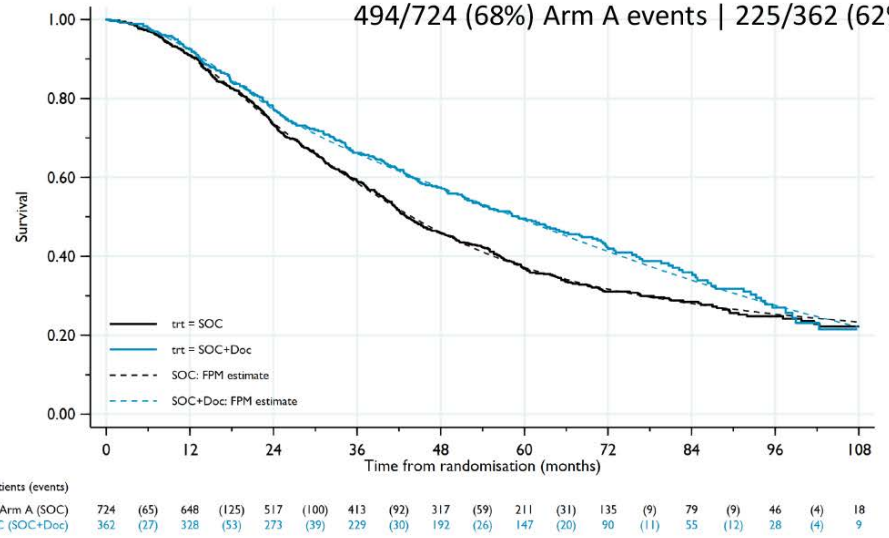
STAMPEDE: Doce + SOC vs SOC — Overall Survival

Overall Survival: All Patients[1]

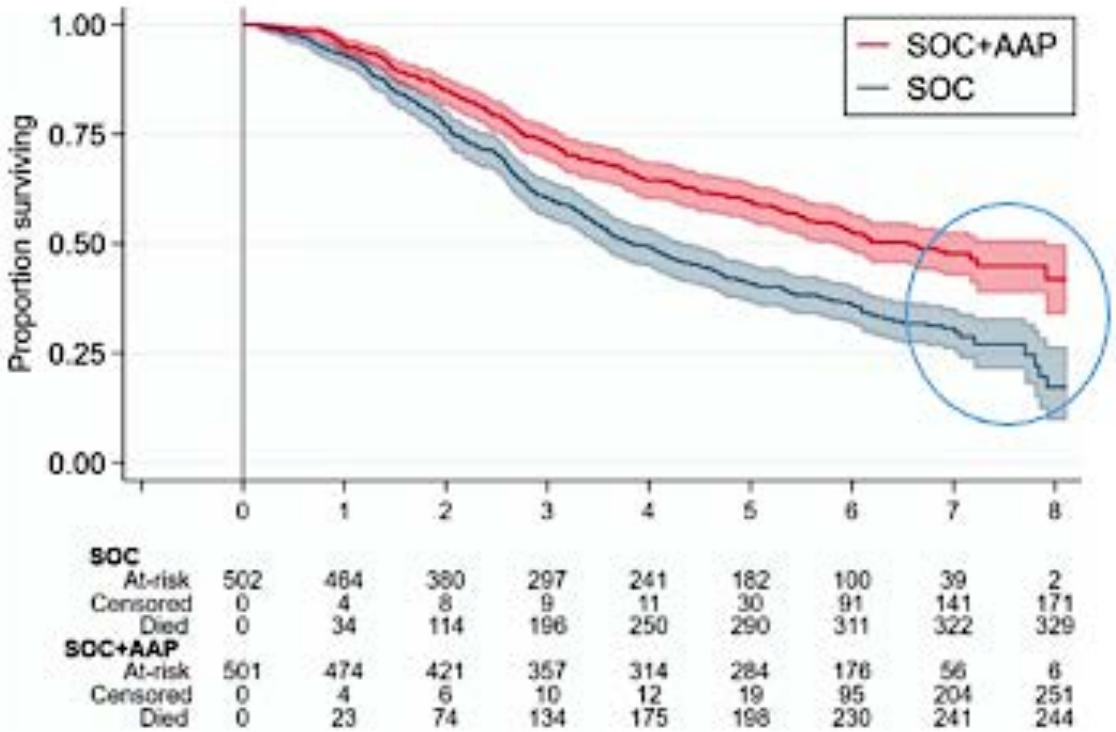
494/724 (68%) Arm A events | 225/362 (62%) Arm C events



HR 0.81
95% CI 0.69 – 0.95
P = 0.009
Non-PH 0.016

5-yr survival:
A 37%
C 49%

RMST difference at 120 months:
6.0 months
95% CI (0.7-11.4)
P = 0.028



BARCELONA 2019 ESMO congress

[1] Clarke NW et al. ESMO 2019;Abstract 2348.

Courtesy of Fred Saad, MD

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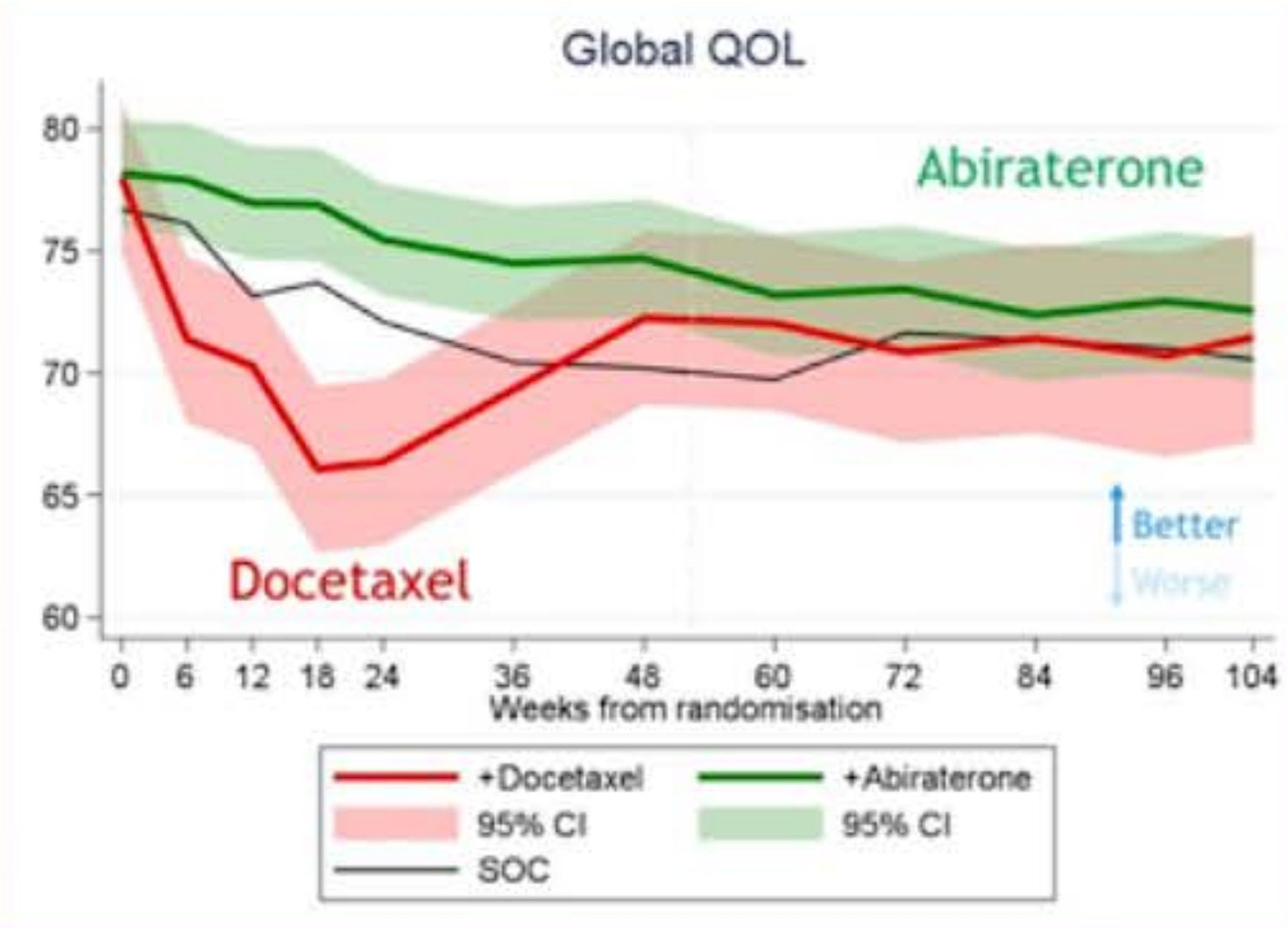
Comparative QOL randomized contemporaneously to docetaxel or abiraterone in the STAMPEDE trial



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TITAN: Apalutamide in all-comers mHSPC

"All-comer" patient population

Key Eligibility Criteria
Castration sensitive
Distant metastatic disease by ≥1 lesion on BS
ECOG PS 0 or 1

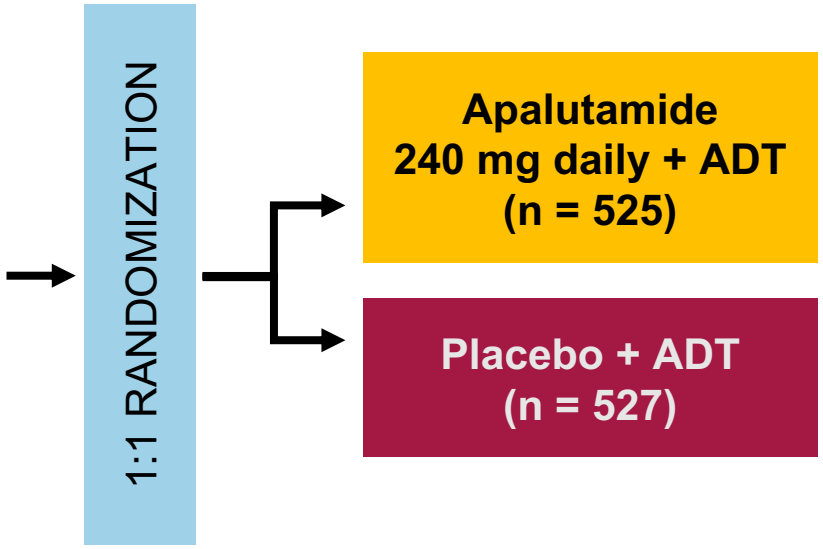
On-Study Requirement
Continuous ADT

Permitted
Prior docetaxel
ADT ≤6 mo for mHSPC or ≤3 yr for local disease
Local treatment completed ≥1 yr prior

Stratifications
Gleason score at diagnosis (≤7 vs. ≥8)
Region (NA and EU vs. all other countries)
Prior docetaxel (yes vs. no)

N = 1052

Dec 2015 – July 2017



Dual primary endpoints
- OS
- rPFS

Secondary endpoints
- Time to cytotoxic chemotherapy
- Time to pain progression
- Time to chronic opioid use
- Time to skeletal-related event

Exploratory endpoints
- Time to PSA progression
- PFS2
- Time to symptomatic progression

Chi K et al. N Engl J Med. 2019 Jul 4;381(1):13-24.

Courtesy of Fred Saad, MD

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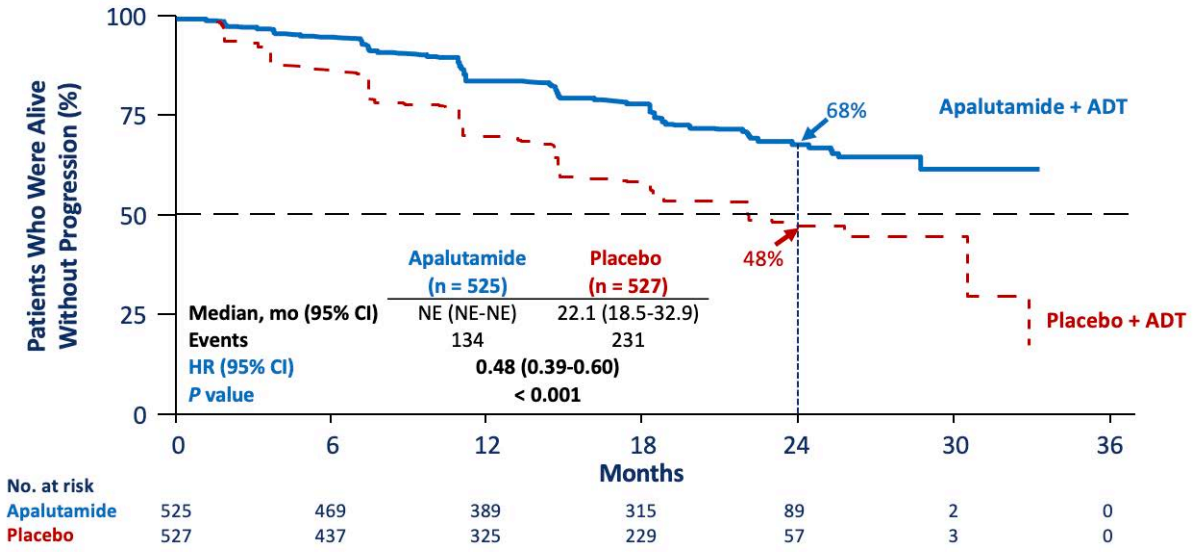
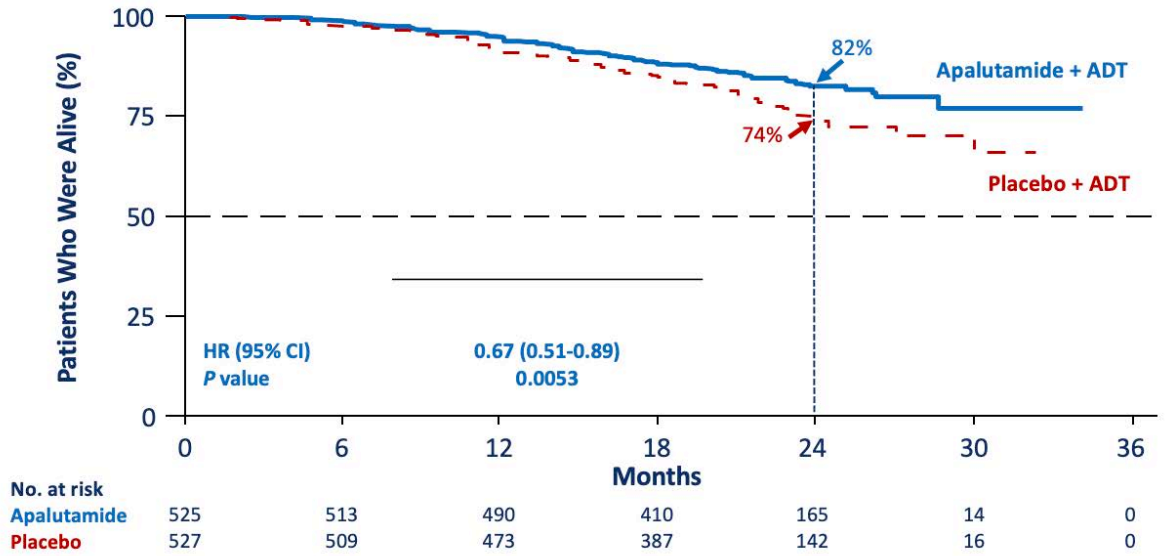
TITAN: Apalutamide in all-comer mHSPC

Progression free survival



Overall survival



Chi K et al. N Engl J Med. 2019 Jul 4;381(1):13-24.

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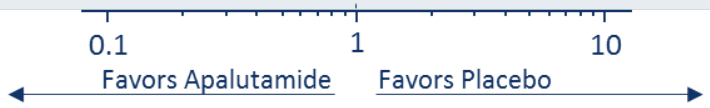
TITAN: Sub-group analysis of overall survival

Variable		Hazard Ratio (95% CI)	Events (n/n) Apalutamide + ADT	Events (n/n) Placebo + ADT
All patients		0.68 (0.51-0.90)	83/525	117/527
Baseline ECOG PS	0	0.71 (0.47-1.05)	41/328	60/348
	1	0.59 (0.40-0.89)	42/197	57/178
Geographic region	EU/NA	0.71 (0.40-1.25)	21/173	29/173
	Other	0.66 (0.48-0.91)	62/352	88/354
Bone metastasis only at baseline	YES	0.47 (0.30-0.75)	28/289	53/269
	NO	0.88 (0.61-1.26)	55/236	64/258
Visceral disease and bone metastasis at baseline	YES	0.99 (0.55-1.77)	20/56	25/72
	NO	0.63 (0.46-0.87)	63/469	92/455
Prior docetaxel use	YES	1.27 (0.52-3.09)	11/58	9/55
	NO	0.63 (0.47-0.85)	72/467	108/472
Age, yr	< 65	0.56 (0.33-0.94)	21/149	43/182
	65-74	0.73 (0.48-1.10)	42/243	51/232
	≥ 75	0.74 (0.41-1.35)	20/133	23/113
Disease volume	High	0.68 (0.50-0.92)	69/325	97/335
	Low	0.67 (0.34-1.32)	14/200	20/192
Metastasis stage at initial diagnosis	M0	0.40 (0.15-1.03)	7/85	11/59
	M1	0.72 (0.53-0.98)	71/411	101/441



Chi K et al. N Engl J Med. 2019 Jul 4;381(1):13-24.

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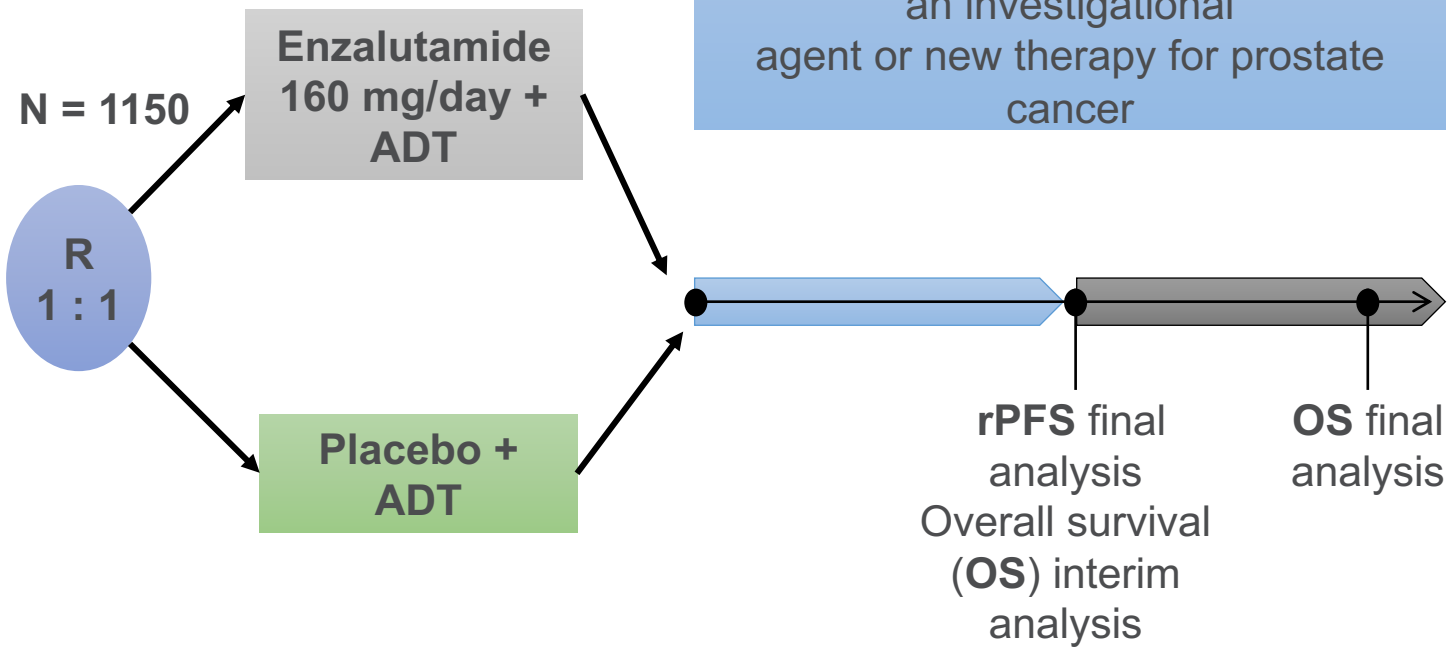
ARCHES Study Design

Key eligibility criteria

- mHSPC (confirmed by bone scan, CT, or MRI), histologically confirmed adenocarcinoma
- ECOG Performance Status 0 to 1
- Current ADT duration ≤3 months unless prior docetaxel, then ≤6 months

Stratification factors

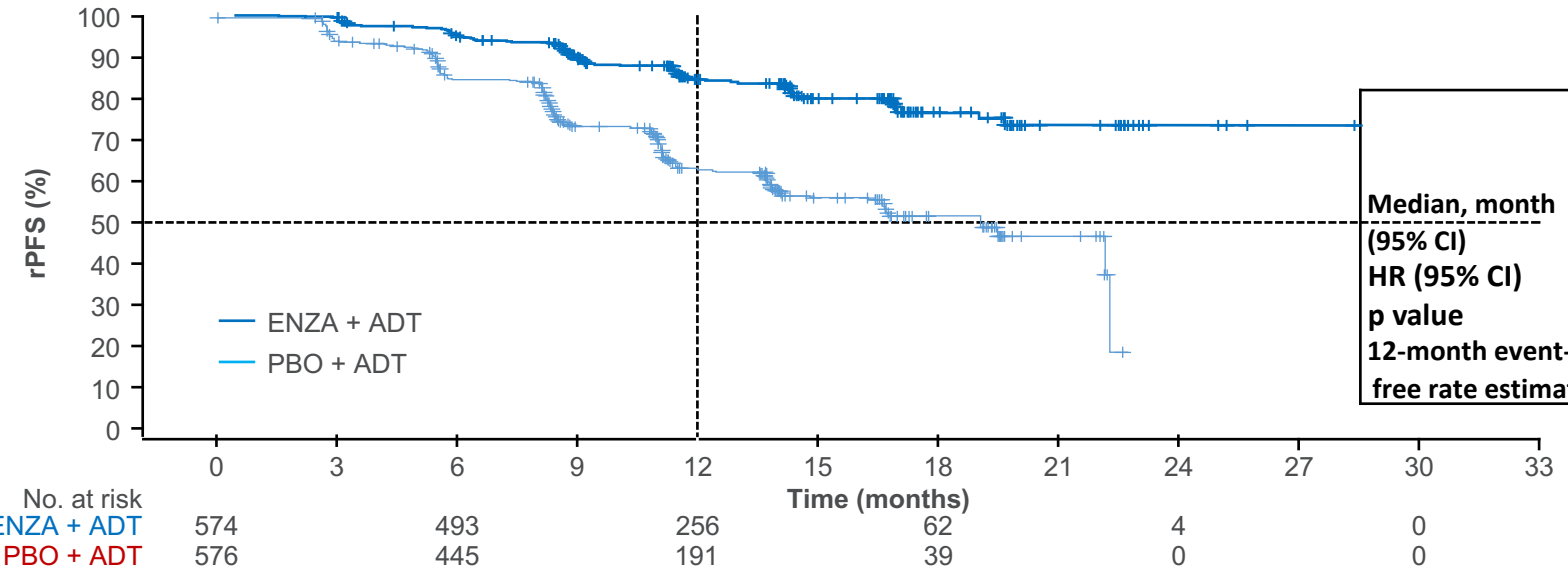
- Volume of disease (low vs. high*)
- Prior docetaxel therapy for mHSPC (none, 1–5, or 6 cycles)



Armstrong, Andrew J., et al. "ARCHES: a randomized, phase III study of androgen deprivation therapy with enzalutamide or placebo in men with metastatic hormone-sensitive prostate cancer." Journal of Clinical Oncology 37.32 (2019): 2974-2986.

Courtesy of Fred Saad, MD CHUM

ARCHES: Primary endpoint — rPFS



	ENZA + ADT (n = 574)	PBO + ADT (n = 576)
Median, month	NR	19.0
(95% CI)	(NR, NR)	(16.59, 22.24)
HR (95% CI)	0.39 (0.30, 0.50)	
p value	<0.001	
12-month event-free rate estimate	0.84	0.63

Enzalutamide with ADT significantly reduced the risk of metastatic progression or death over time versus placebo plus ADT in men with mHSPC

- Median follow-up time is 14.4 months; median duration of therapy was 12.8 (range 0.2–26.6) months for enzalutamide + ADT and 11.6 (range 0.2–24.6) months for placebo + ADT

Armstrong, Andrew J., et al. "ARCHES: a randomized, phase III study of androgen deprivation therapy with enzalutamide or placebo in men with metastatic hormone-sensitive prostate cancer." Journal of Clinical Oncology 37.32 (2019): 2974-2986.

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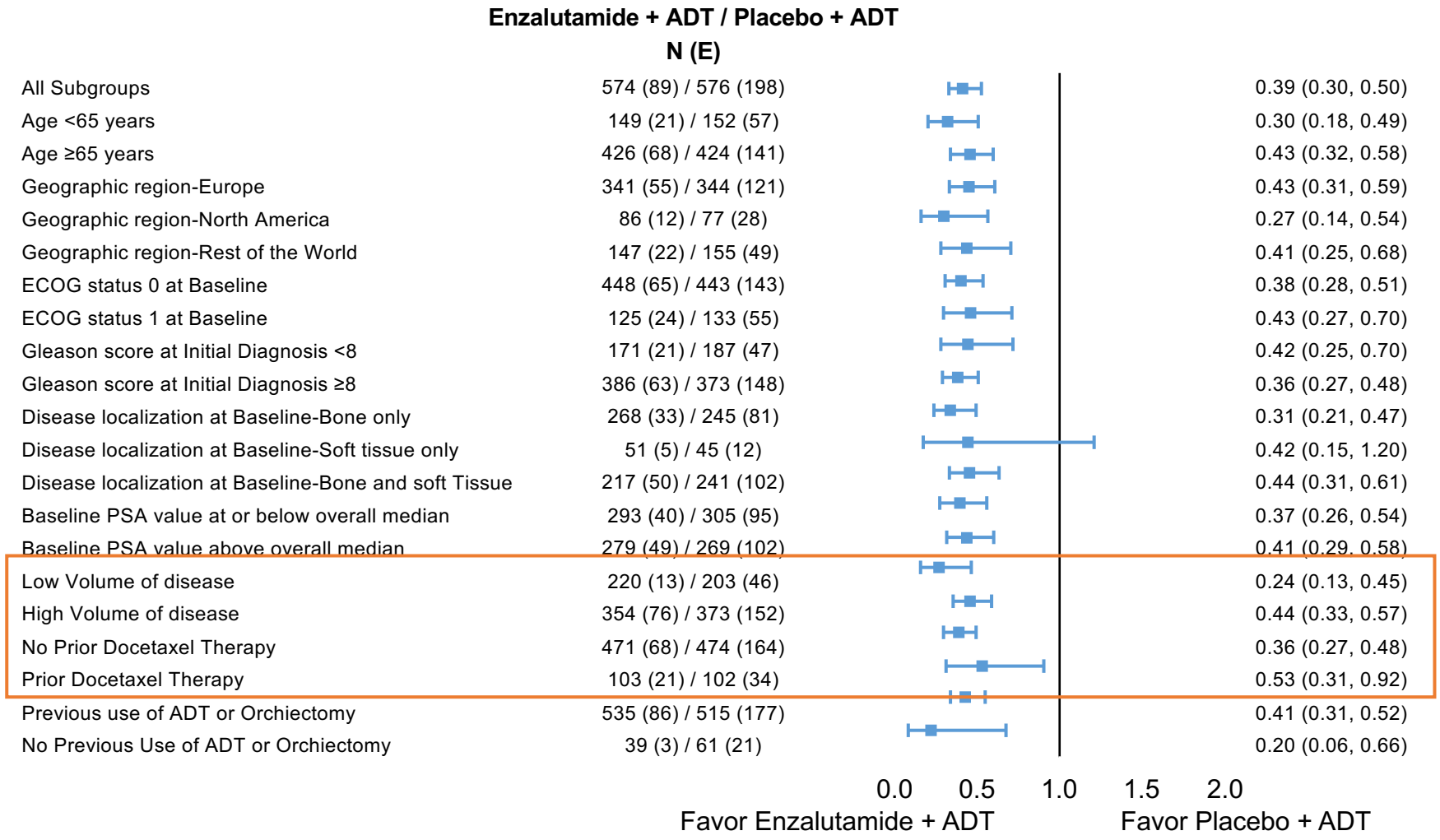
ARCHES: Subgroup analysis of rPFS



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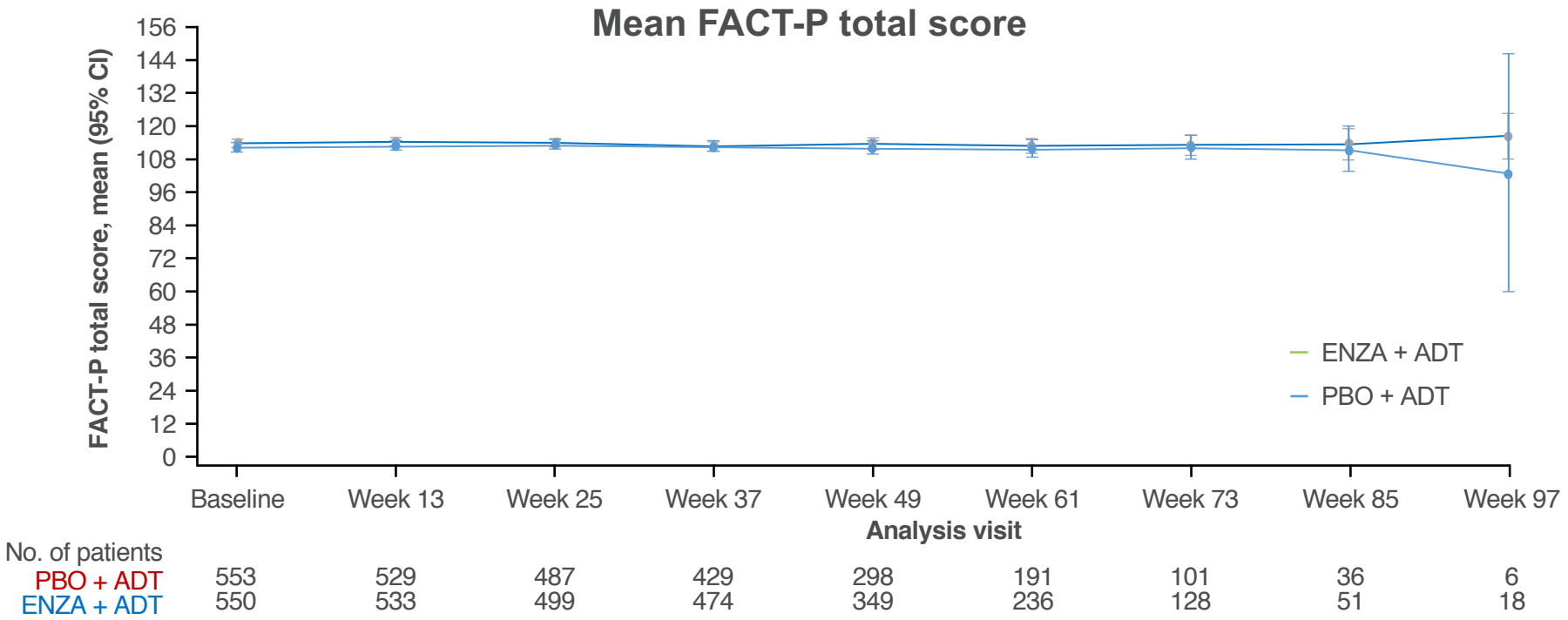
ARCHES: Quality of life over time



Mean Functional Assessment of Cancer Therapy-Prostate (FACT-P) total score (global indicator of quality of life), was high at baseline for both treatment groups, and remained high over time.

Armstrong et al. *ARCHES: A Randomized, Phase III Study of Androgen Deprivation Therapy With Enzalutamide or Placebo in Men With Metastatic Hormone-Sensitive Prostate Cancer (Data Supplement)*; Published online at JCO.org on July 30 2019.

Courtesy of Fred Saad, MD

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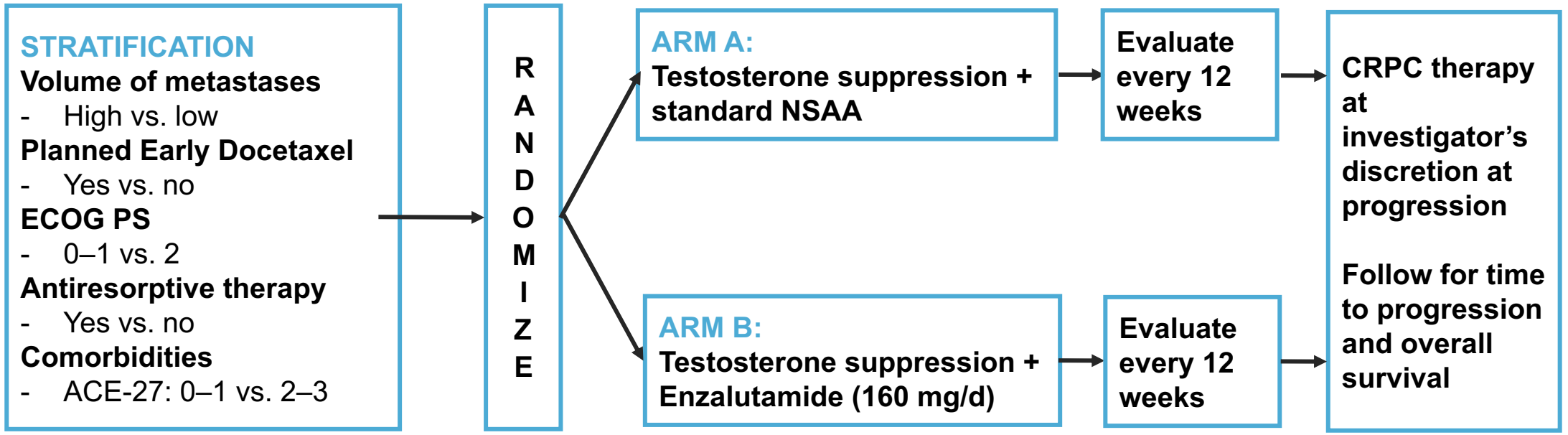
ENZAMET: Enzalutamide in mHSPC

"All-comer" patient population



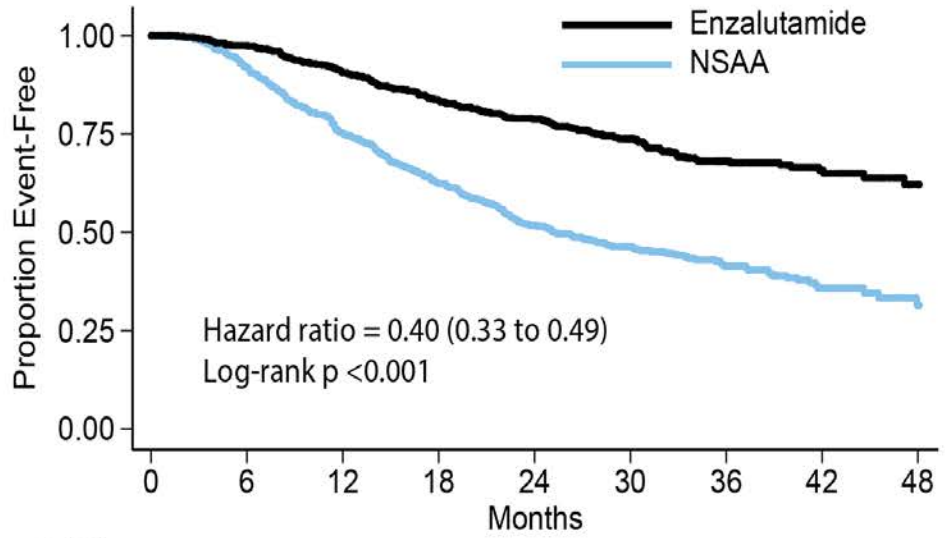
- Prior to randomization, testosterone suppression up to 12 weeks and 2 cycles of docetaxel were allowed
- Intermittent ADT and cyproterone were not allowed
- High volume: visceral metastases and/or 4 or more bone metastases (at least one beyond pelvis and vertebral column)

Davis, I et al. Engl J Med. 2019 Jul 11;381(2):121-131.

Courtesy of Fred Saad, MD CHUM

ENZAMET: Enzalutamide in all-comers

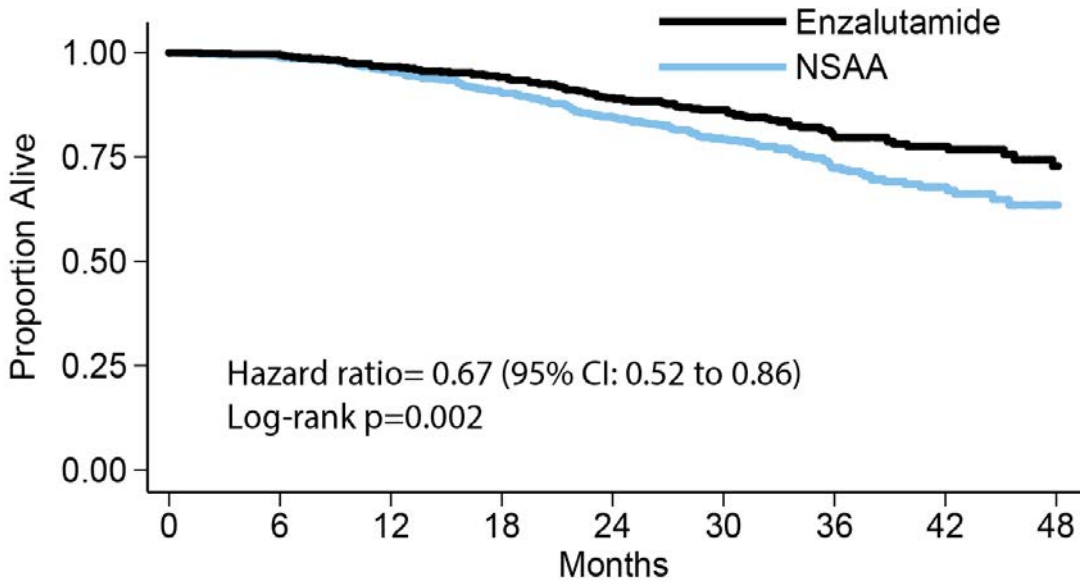
Progression free survival



Number at risk

NSAA	562	512	418	346	272	182	96	50	17
Enzalutamide	563	547	507	468	424	284	156	84	36

Overall survival



Number at risk

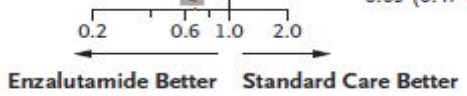
NSAA	562	551	531	501	452	311	174	86	32
Enzalutamide	563	558	541	527	480	340	189	106	45

Davis, I et al. Engl J Med. 2019 Jul 11;381(2):121-131.

Courtesy of Fred Saad, MD CHUM

ENZAMET: Sub-group analysis of overall survival

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)		



Davis, Ian D., et al. "Enzalutamide with standard first-line therapy in metastatic prostate cancer." New England Journal of Medicine 381.2 (2019): 121-131.

Courtesy of Fred Saad, MD

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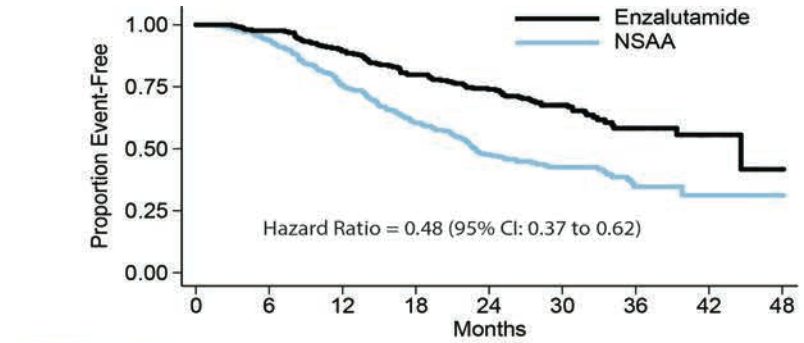
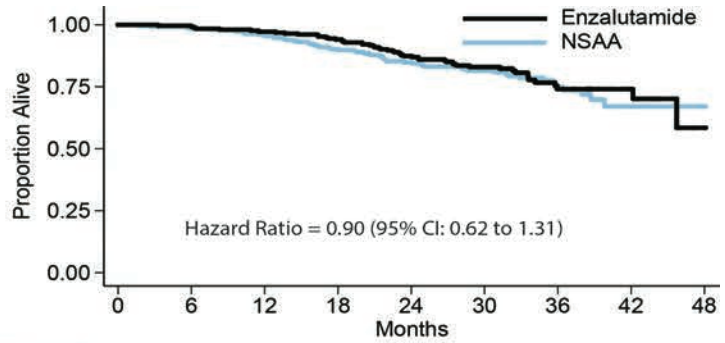
ENZAMET: Concurrent Docetaxel

Testosterone Suppression + Docetaxel N=503 (71% High Volume)



Number at risk

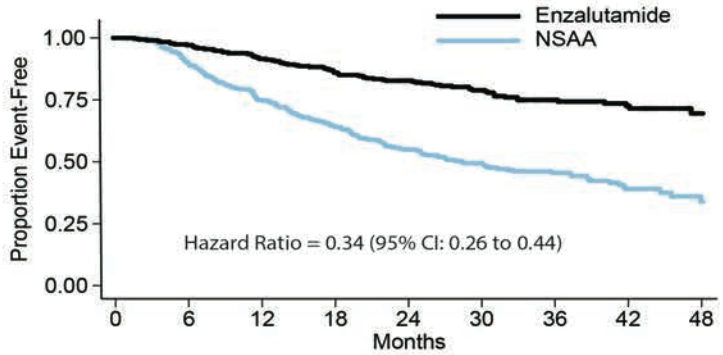
NSAA	249	230	185	148	112	73	21	6	1
Enzalutamide	254	248	226	202	178	109	35	12	2



Number at risk

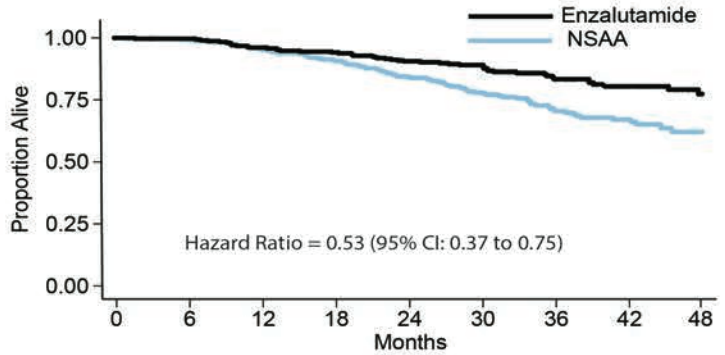
NSAA	249	241	235	220	203	135	56	13	2
Enzalutamide	254	252	246	238	210	139	54	19	3

Testosterone Suppression + No Docetaxel N=622 (37% High Volume)



Number at risk

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



Number at risk

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

Courtesy of Fred Saad, MD

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Adverse events reported with the 4 agents

	CHAARTED
	Docetaxel (n = 390)
Any grade 3–5 AE	29.6%
Completion of 6 cycles	86%
Allergic reaction	2.1%
Fatigue	4.1%
Neutropenia	12.1%
Febrile neutropenia	6.1%
Infection with neutropenia	2.3%
Anemia	1.3%
Neuropathy	0.5%

	ARCHES	
	Enzalutamide (N = 572)	Placebo (N = 574)
Any grade 3–5 AE	24.3%	25.6%
Any AE leading to discontinuation	7.2%	5.2%
Hypertension	3.3%	1.7%
Neutropenia	0.3%	0.3%
Hot flashes	0.3%	0%
Fatigue	0.9%	1%
Convulsion/seizure	0.3%	0.3%
Cognitive/memory impairment or delirium	0.7%	0%

	LATITUDE	
	Abiraterone (N = 597)	Placebo (N = 602)
Any grade 3–5 AE	63%	48%
Any AE leading to discontinuation	12%	10%
Hypertension	20%	~10%
Hypokalemia	11%	~1%
Fatigue	2%	2%
Cardiac disorder (any)	~4%	~1%
Hyperglycemia	~4%	3%
Endocrine disorders	NR	NR
ALT increased	~5%	1%
AST increased	~4%	1%

	Apalutamide (N = 524)	Placebo (N = 527)
Any grade 3–4 AE	42.2%	40.8%
Any AE leading to discontinuation	8%	5.3%
Fatigue	8.4%	9.1%
Rash	6.3%	0.6%
Bone pain	1.1%	1.7%
Anemia	1.7%	3.2%
Back pain	2.3%	2.7%
Anemia	1.1%	1.9%

Kinsey, Emily N. MD*; Zhang, Tian MD, MHS†; Armstrong, Andrew J. MD, ScM, FACP†
Cancer Journal: 1/2 2020 - Volume 26 - Issue 1 - p 64-75

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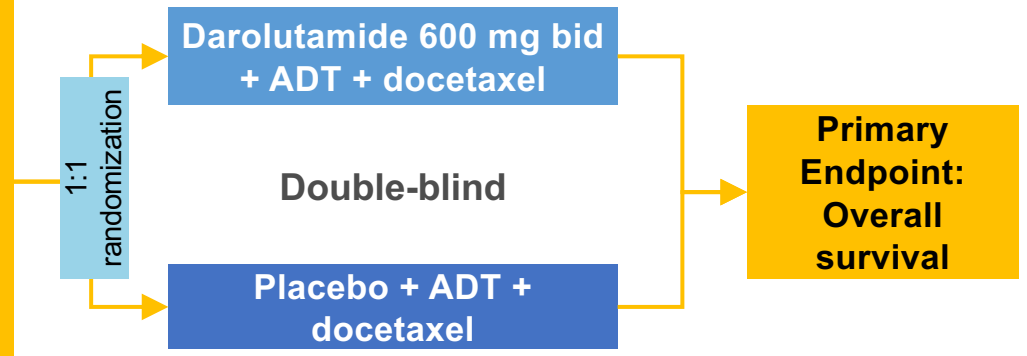
Maximizing therapy for mHSPC

ARASENS Phase III Trial Design

Patients (N=1303)
- mHSPC*
- Histologically or cytologically confirmed adenocarcinoma of the prostate
- ECOG PS ≤1
- Candidates for ADT and docetaxel†

Stratification
- Extent of disease
- Alkaline phosphatase levels



Secondary and additional objectives
- Time to castration-resistant prostate cancer
- Time to initiation of subsequent antineoplastic therapy
- Symptomatic skeletal event–free survival (SSE-FS)
- Time to first symptomatic skeletal event (SSE)
- Time to initiation of opioid use for ≥7 days
- Time to pain progression
- Time to worsening of physical symptoms of disease based on NCCN-FACT FPSI-17
- Safety

Background treatments:
- ADT at investigators' choice (including orchiectomy)
- Docetaxel: 6 cycles (in combination with prednisone/prednisolone at the discretion of the investigator) to be administered after randomization

Enrolment completed in June 2018

Courtesy of Fred Saad, MD CHUM

ADT alone is sub-optimal for mHSPC

	2013	2015	2016	2017	2017	2019	2019	2019
	GETUG-AFU 15[1] (N = 385)	**CHAARTED[2] (N = 790)**	**STAMPEDE[3] (N = 592)**	**STAMPEDE[4] (N = 1,917)**	**LATITUDE[5] (N = 1,199)**	**ARCHES[6] (N = 1,150)**	**TITAN[7] (N = 1,052)**	**ENZAMET[8] (N = 1,125)**
Agent	Doce (vs PBO)	Doce (vs PBO)	Doce (arm C)	AAP (arm G)	AAP (vs PBO)	ENZA (vs PBO)	APA (vs PBO)	ENZA (vs NSAA)
Primary end point: HR (CI)	OS: 1.01 (0.75–1.36) p = 0.955	OS: 0.72 (0.59–0.89) p = 0.0018	OS: 0.78 (0.66–0.93) p = 0.006	OS: 0.61 (0.4–0.75) p < 0.0001	OS: 0.66 (0.56–0.78) p < 0.0001 rPFS: 0.46 (0.39–0.54) p < 0.0001	rPFS: 0.39 (0.30–0.50) p < 0.001	OS: 0.67 (0.51–0.89) p = 0.005 rPFS: 0.48 (0.39–0.60) p < 0.001	OS: 0.67 (0.52–0.86) p = 0.002

Doce, docetaxel; OS, overall survival; rPFS, radiographic progression-free survival; NSAA, nonsteroidal antiandrogen

Not a head-to-head trial comparison

Broad Patient Populations

1. Gravis G, et al. *Lancet Oncol* 2013;14:149;
2. Kyriakopoulos CE, et al. *J Clin Oncol* 2018;36:1080;
3. James ND, et al. *Lancet* 2016;387:1163;
4. James ND, et al. *N Engl J Med* 2017;377:338;
5. Fizazi K, et al. *Lancet Oncol* 2019;20:686;
6. Armstrong AJ, et al. *J Clin Oncol* 2019;37:2974;
1. Chi KN, et al. *N Engl J Med* 2019;381:13;
2. Davis ID, et al. *N Engl J Med* 2019;381:121

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National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2020
Prostate Cancer

NCCN Guidelines Index
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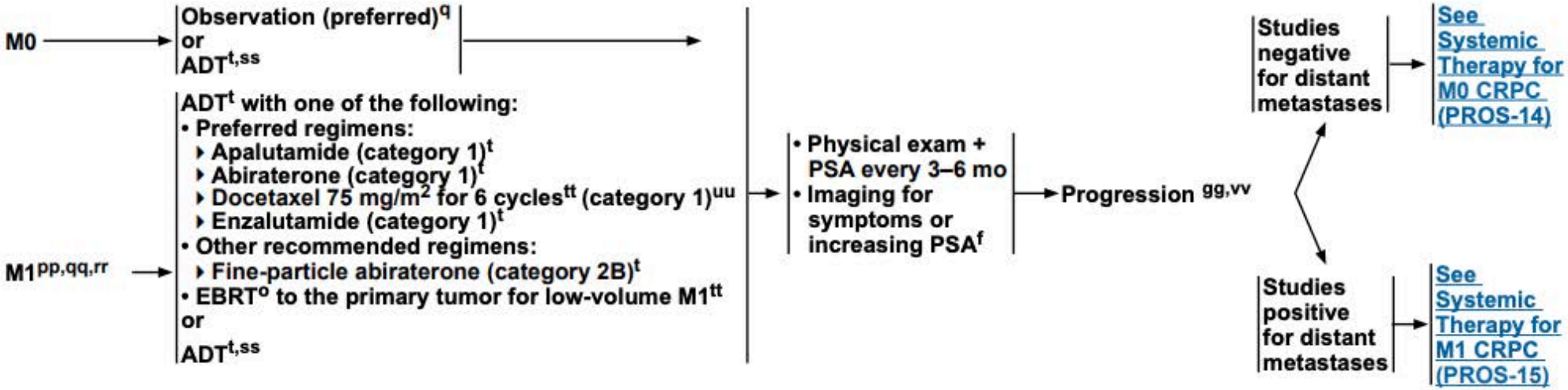
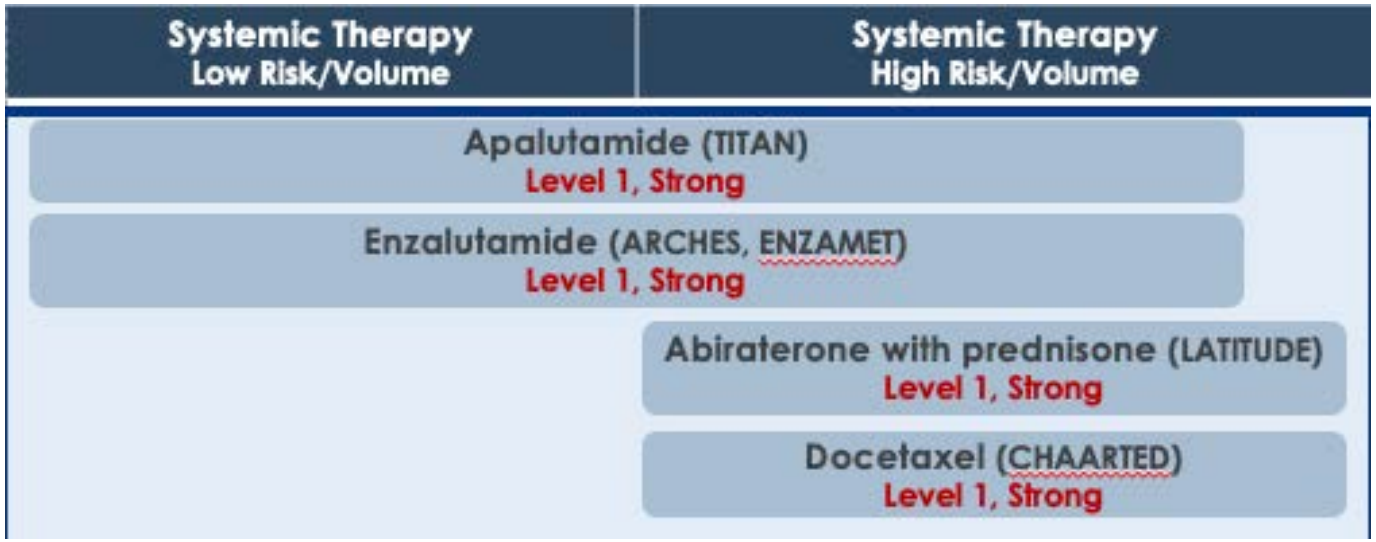
Discussion

SYSTEMIC THERAPY FOR CASTRATION-NAIVE PROSTATE CANCER[oo]



Canadian guidelines

So A et al. *Can Urol Assoc J* 2020



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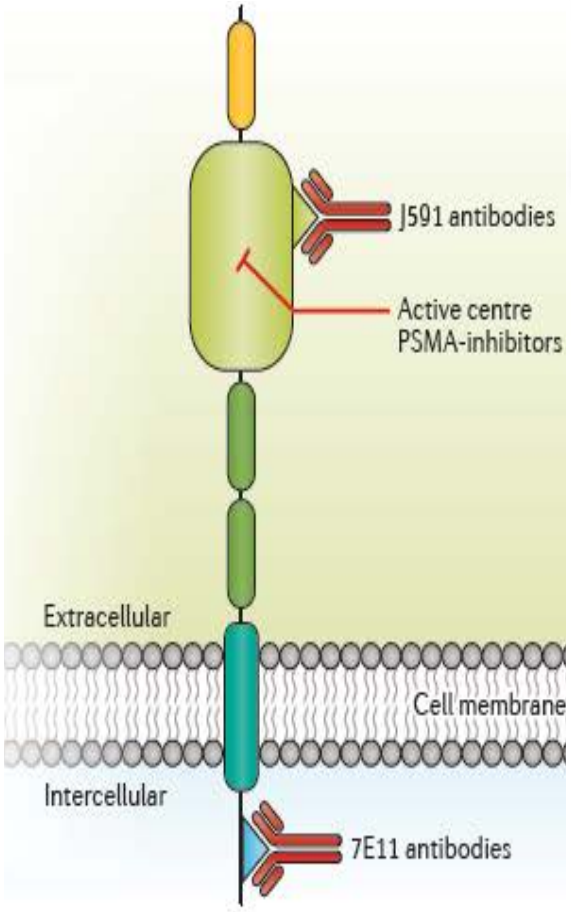
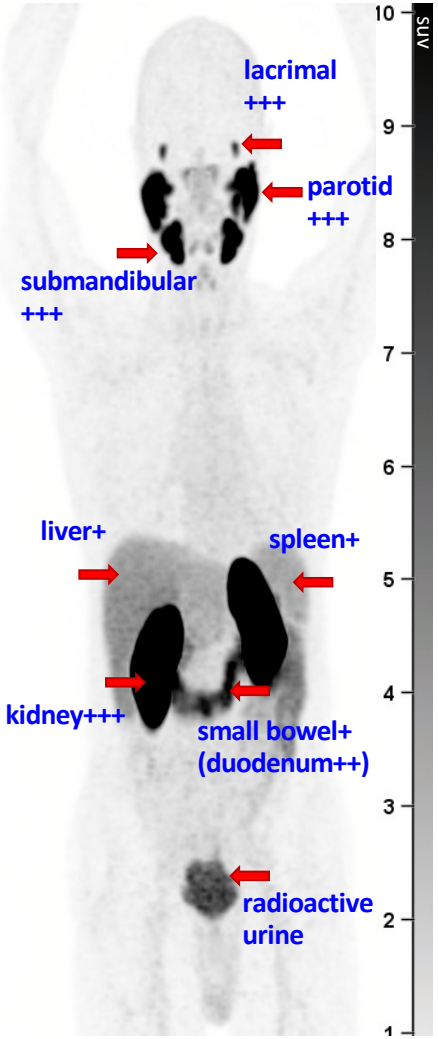
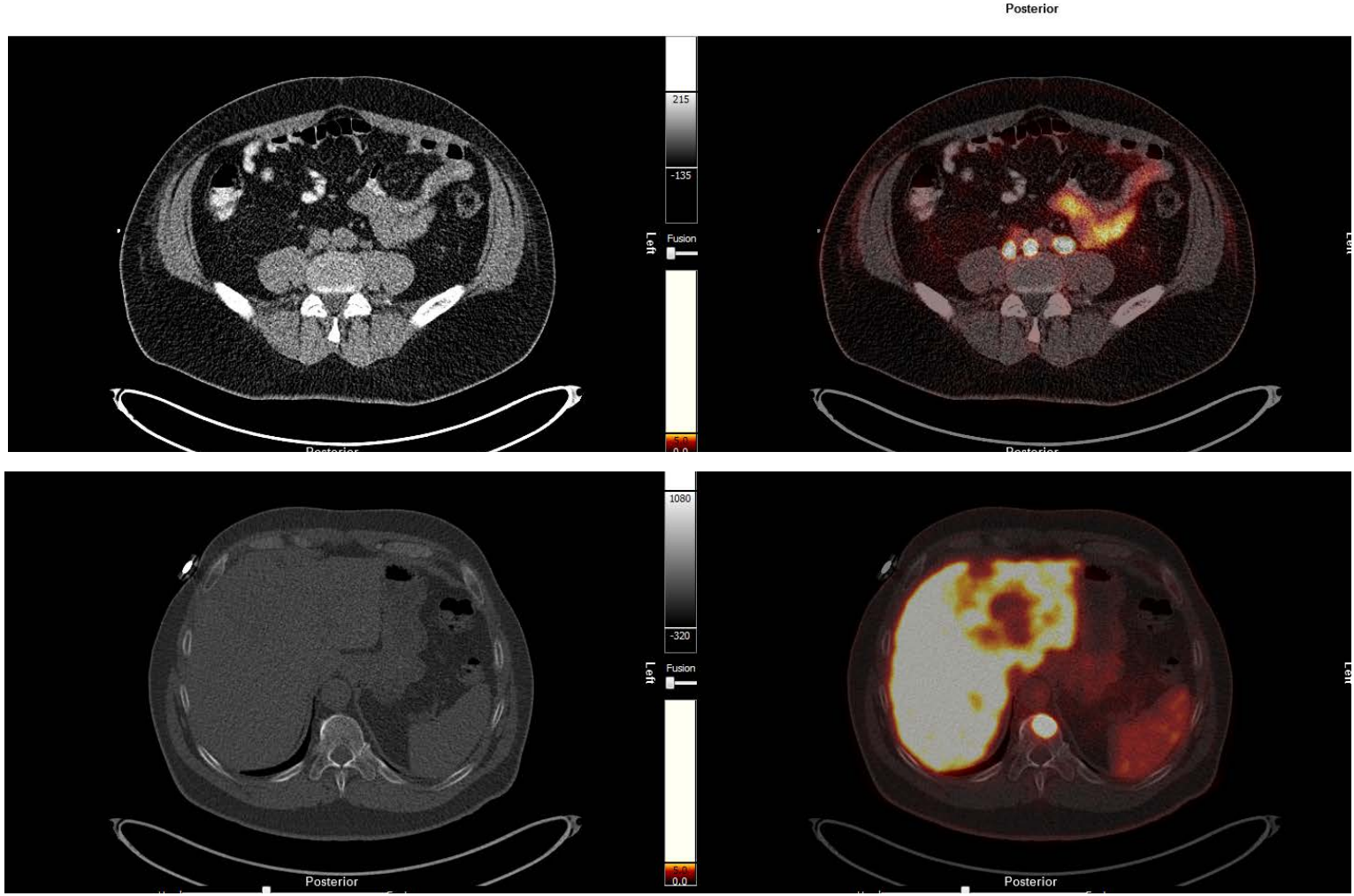
Diagnosing metastases earlier and more precisely
Prostate specific membrane antigen (PSMA)







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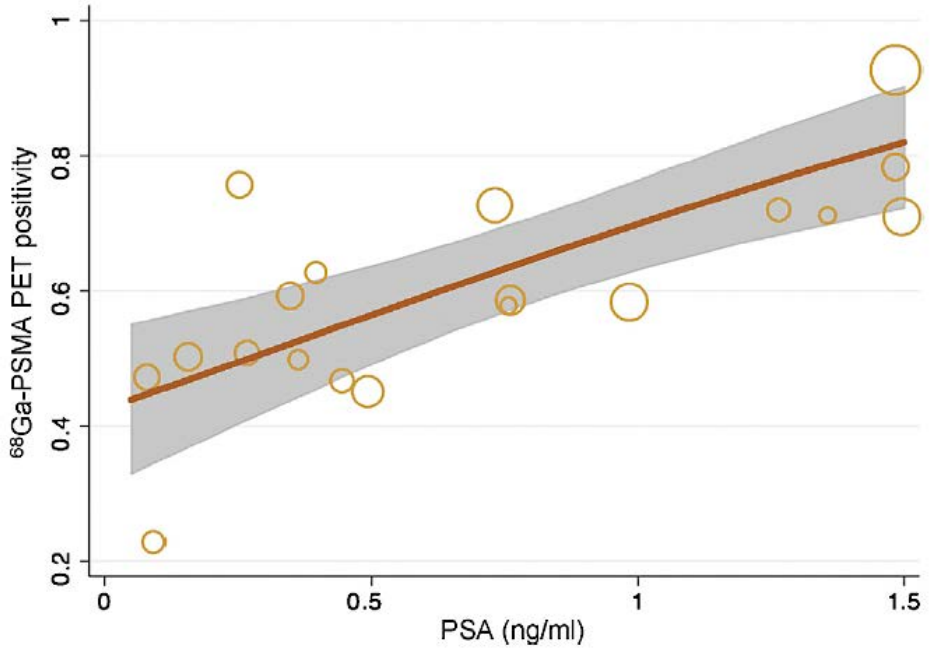
Sensitivity, Specificity, and Predictors of Positive ^{68}Ga–Prostate-specific Membrane Antigen Positron Emission Tomography in Advanced Prostate Cancer: A Systematic Review and Meta-analysis



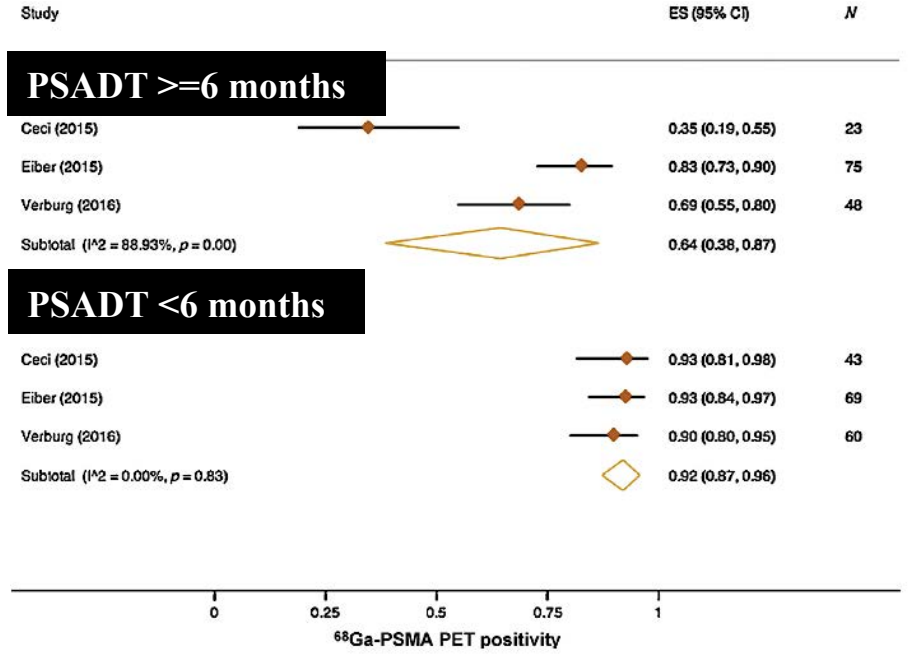


Table 2 – Studies with histopathologic correlation data for ^{68}Ga PSMA PET–positive lesions included in pooled analysis

Study	Study type	Staging setting	HP type	Patients with HP (*n*)	Per patient SS (%)	Per patient SP (%)	Lesions with HP (*n*)	Per lesion SS (%)	Per lesion SP (%)
[29]	Retrospective cohort	Primary	Extended primary LND	30	33	100	608	64	93
[36]	Retrospective analysis	Mixed	Template primary and secondary LND	34	91	67	71	– [a]	– [a]
[38]	Retrospective analysis	Primary	Template primary LND	130	66	99	734	74	99
[41]	Retrospective comparison	Recurrence	Template secondary LND	28	100	0	308	87	93
[43]	Retrospective cohort	Mixed	Template primary and secondary LND	17	– [a]	– [a]	213	94	99

HP = histopathology; LND = lymph node dissection; SS = sensitivity; SP = specificity.
[a] Not included in the pooled analysis as data points did not meet the inclusion criteria.

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The approval was granted to the University of California–San Francisco (UCSF) and UC–Los Angeles (UCLA).

^{68}Ga-PSMA-11 is indicated for

suspected metastatic disease at the time of initial staging prior to definitive therapy,

and for suspected recurrence based on elevated serum prostate-specific antigen (PSA) levels.

Courtesy of Fred Saad, MD CHUM

Conclusions

- Patients with mHSPC are at high risk of rapid progression to mCRPC and early death

- Treating ALL patients beyond ADT is the new standard of care for mHSPC
  - First generation anti-androgens and CAB are not enough

- Effective agents are now available and should be used in patients with mHSPC who are destined to suffer and die **OF** prostate cancer

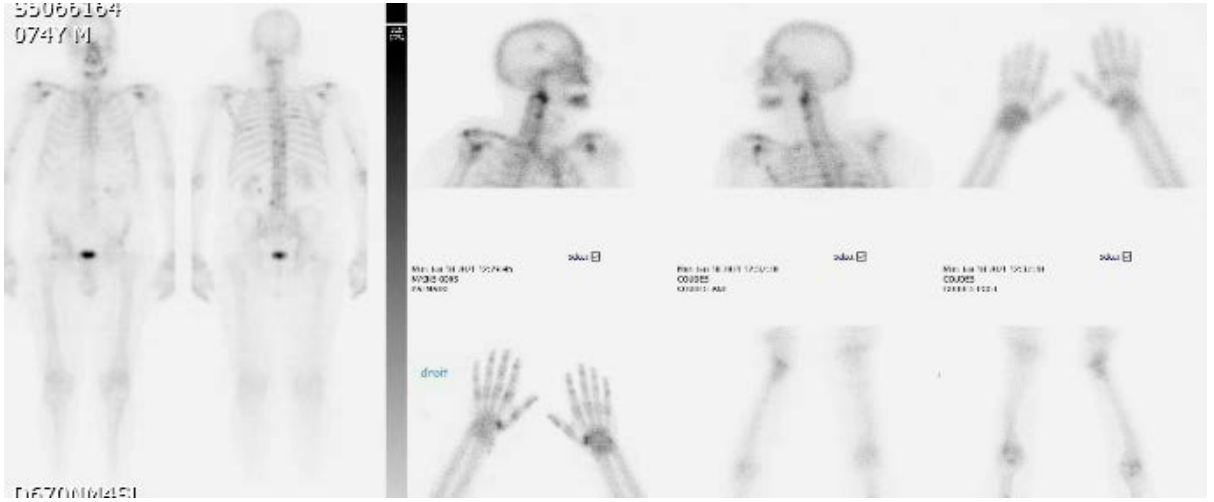
- Work ongoing to determine the benefit of combining NHT with Chemotherapy as well as other agents

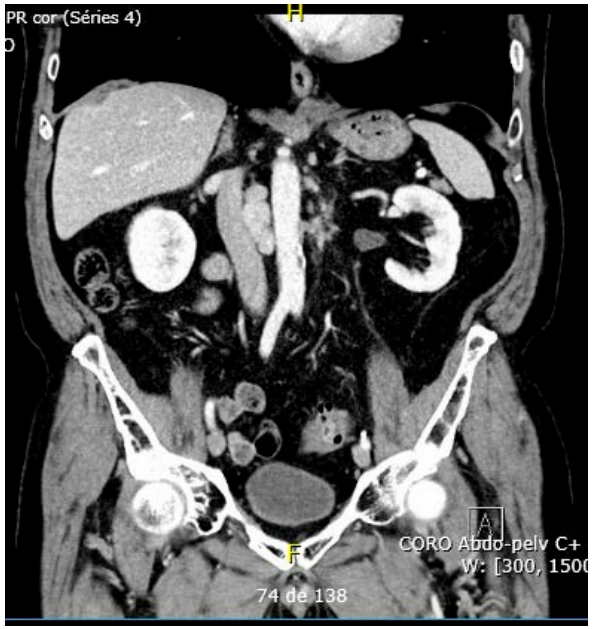
- Improved imaging may further improve outcome

Courtesy of Fred Saad, MD CHUM

Case 1

- 51 year-old musician complains of lower back pain
- Found to have an indurated prostate and PSA of 48
- Biopsy reveals Gleason 4+4 prostate cancer in 12/12 biopsies
- Imaging reveal multiple bone mets
- Abdominal CT reveals enlarged lymph nodes





- Patient seen and options discussed
- Prefers avoiding chemotherapy given international travel plans for concerts
- Patient started on ADT and apalutamide 240 mg/day

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Case 1 continued

- After 6 months PSA is 0.1
- Patient develops a mild rash in his chest treated with topical steroids
- Resolves without change in dosage
- Patient last seen in December 2020 and PSA remains 0.1 1 year after starting therapy

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Case 2

- 68 year old patient treated for cT3, Gleason 4+3 prostate cancer, PSA 18
- Received Radiation therapy + 6 months of ADT 4 years ago
- PSA nadir 0.8 6 months after radiation
- PSA rises to 3.5 2 years later
- Bone scan and CT abdomen and chest within normal limits
- Patient sexually active and declines ADT
- Patient travels 6 months to Florida
- Upon returning PSA is 23

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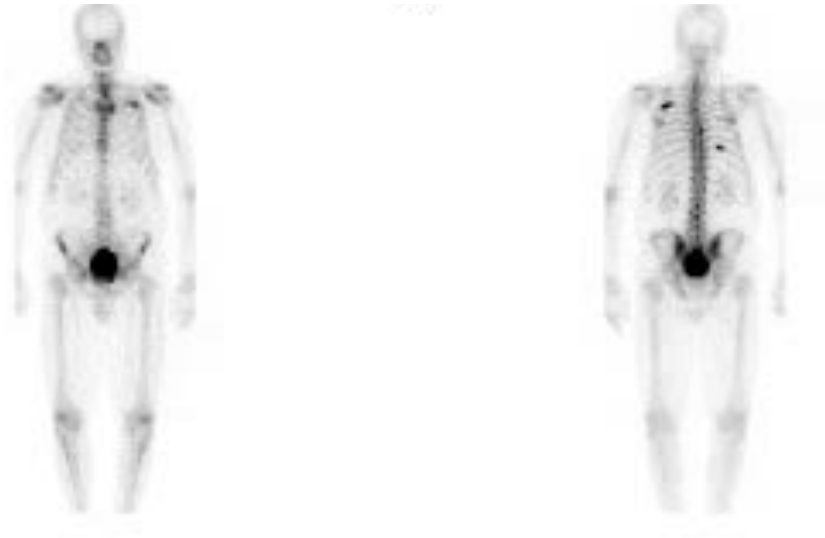
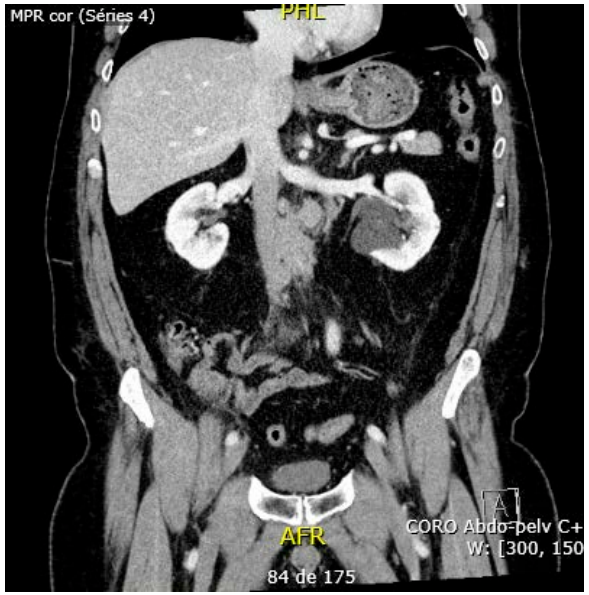
Case 2 continued

- Bone scan reveals multiple new lesions suspicious of mets
- CT abdomen shows multiple retroperitoneal nodes
- Patient started on ADT and enzalutamide 160 mg/day
- PSA declines to 0.4 after 3 months
- Patient complains of fatigue and difficulty in concentrating that interferes with his work
- Enza dose reduced to 120 mg per day and patient feels much better
- PSA continues to decline to 0.2 and remains stable 18 months after starting ADT + Enza





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Thank you!

University of Montreal Hospital center

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