74th Annual Meeting
June 29 – July 1
74e Congrès annuel
29 juin – 1 juillet
QUÉBEC 2019

Clearing the Path:

Untangling advanced prostate cancer management

Introduction

Dr. Fred Saad

The scientific content of this program was developed in collaboration with the Canadian Urological Association.

Disclosure of Commercial Support

This program has received financial support from Astellas Pharma Canada, Inc. in the form of an educational grant.

Program Faculty

Fred Saad, MD, FRCS

Chief of Urology, Professor of Surgery
Raymond Garneau Chair in Prostate Cancer
University of Montreal Hospital Centre (CHUM)
Montreal, Quebec

Scott North, MD, FRCPC, MHPE

Medical Oncologist, Professor
Department of Medical Oncology
University of Alberta, Cross Cancer Institute
Edmonton, Alberta

Kim Chi, MD, FRCPC

Medical Oncologist, BC Cancer
Professor of Medicine, UBC
Regional Medical Director, Vancouver Cancer Centre
Vancouver, British Columbia

Program Faculty (cont'd)

Dr. Saad and Dr. North are CUA Members and Dr. Chi is an Associate CUA Member, all in good standing and have adhered to the:

- CMA Code of Ethics (Update 2004)
- CMA Guidelines for Physician Interactions with Industry (2007)
- Innovative Medicines Canada Code of Ethical Practices (2016)

Disclosure of Commercial Support

Potential conflict(s) of interest:

Astellas Pharma Canada Inc. benefits from the sale of a product that will be discussed in this program:

- enzalutamide

Janssen Inc. benefits from the sale of a product that will be discussed in this program:

- apalutamide
- abiraterone

Disclosures

Dr. Fred Saad

- Received honoraria as a consultant and funding for research (institution)
- Amgen, Astellas Pharma, AstraZeneca, BMS, Bayer, Janssen, Sanofi

Dr. Kim Chi

- Grant support, consulting fees, and lecture fees from Janssen, Astellas Pharma, and Sanofi
- Grant support and consulting fees from Essa Pharma, Bayer, Pfizer, Roche, and AstraZeneca

Dr. Scott North

Honoraria and Advisory Board Fees

- Astellas, Janssen, Merck, AstraZeneca, Roche, Pfizer, Ipsen, Eisai, Sanofi
- All clinical trial per case payments made to institution and not to any individual

Before Starting…

If you are an industry member, please act only as a silent observer to avoid commercial bias.

Objectives

By the end of this session, participants can expect to:

- **Review** the results of clinical trials in nmCRPC and how this impacts clinical practice
- **Review** the adverse event profiles of these agents and their impact on QOL in patients with nmCRPC
- **Review** the results of clinical trials in mHSPC and how this impacts clinical practice
- **Navigate** through discussions the treatment options for both nmCRPC and mHSPC

Part 1

Managing nmCRPC:

Reviewing the Benefits and Impacts on Quality of Life

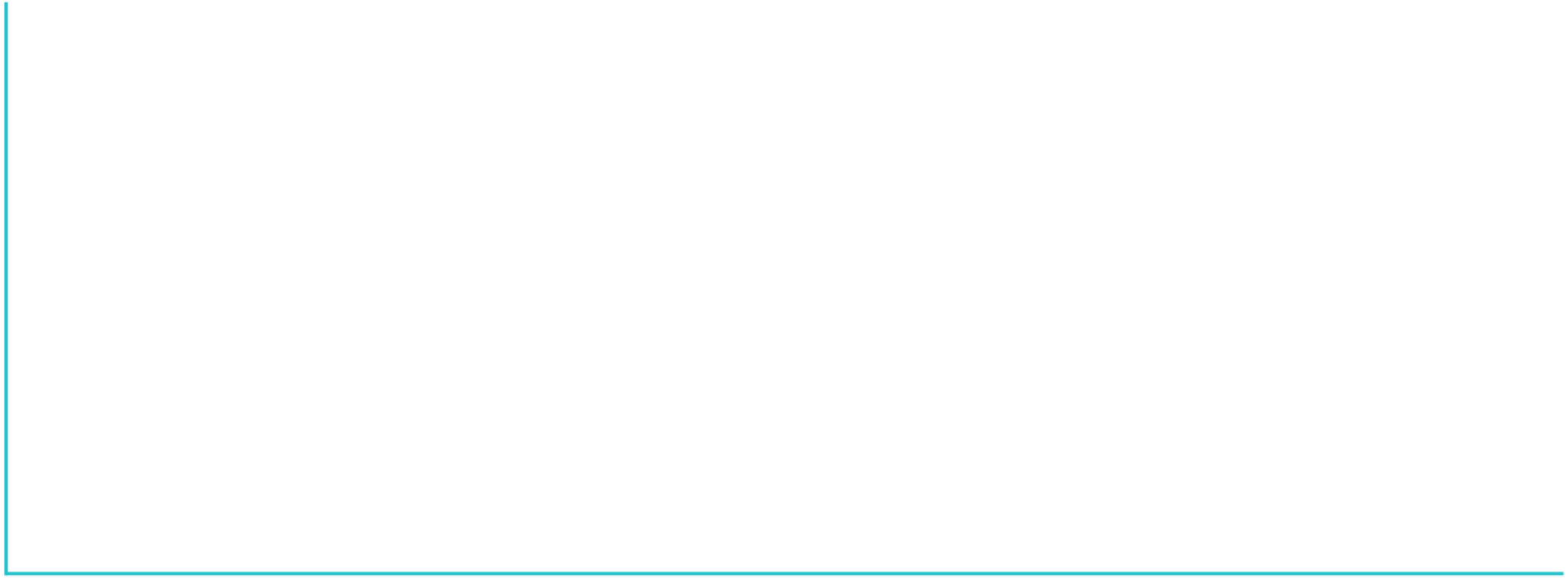
Clinical Patient Case

- 62 year old retired high school professor
- Diagnosed 5 years prior with Gleason 4+4 = 8 prostate cancer treated with EBRT + 2 years of ADT
- PSA Nadir 1
- PSA rise to 8, 12 months after stopping ADT
- ADT restarted
- 6 months after starting ADT PSA nadir of 1.5 but then started to rise again on ADT
- PSA now 13 while on ADT (PSADT 5.8 months)
- Imaging remains negative

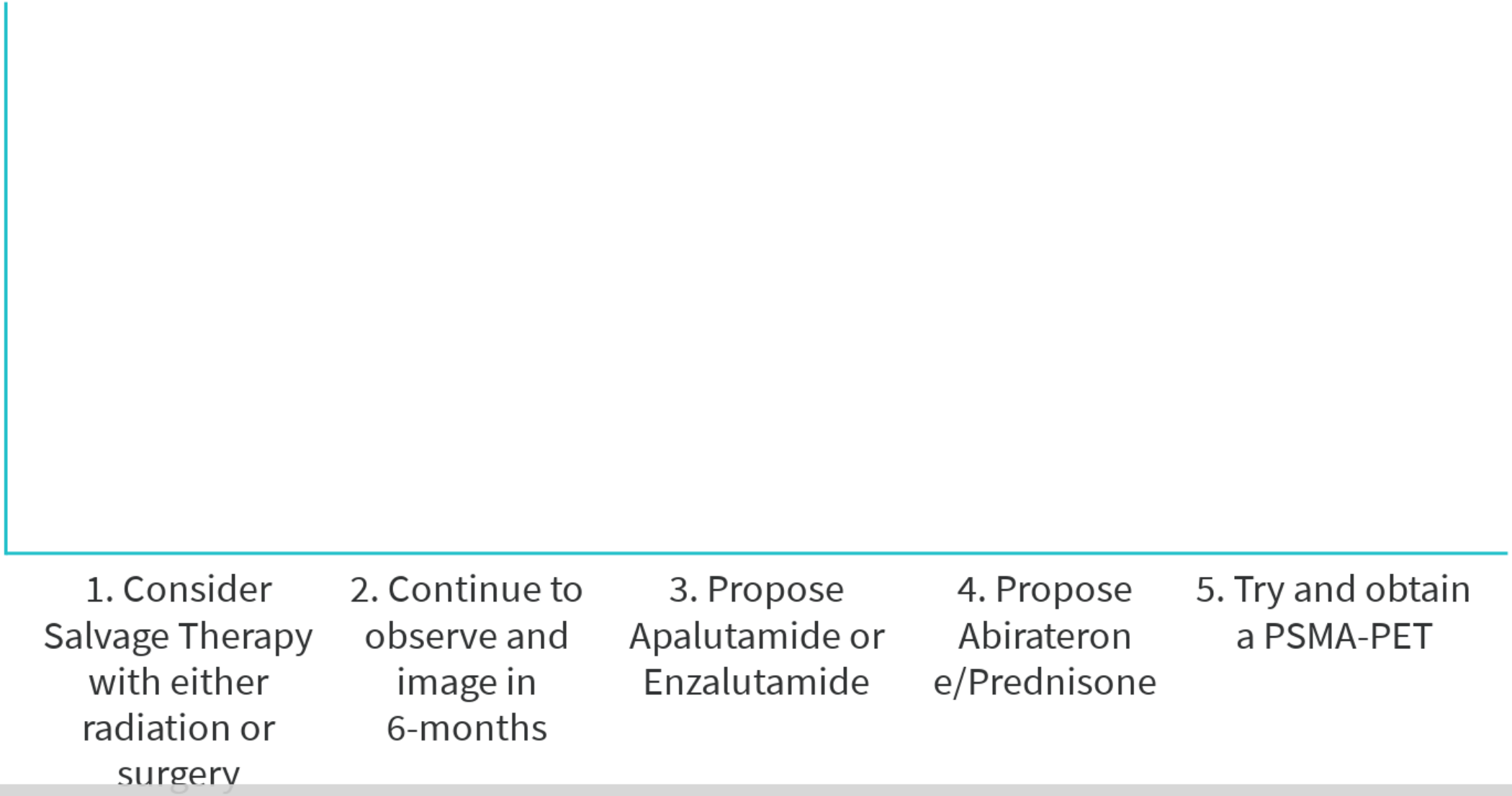
Question 1 : How would you manage this patient with nmCRPC (PSADT 5.8-months)?

1. Consider Salvage Therapy with either radiation or surgery
2. Continue to observe and image in 6-months
3. Propose Apalutamide or Enzalutamide
4. Propose Abiraterone/Prednisone
5. Try and obtain a PSMA-PET

Question 1 : How would you manage this patient with nmCRPC (PSADT 5.8-months)?



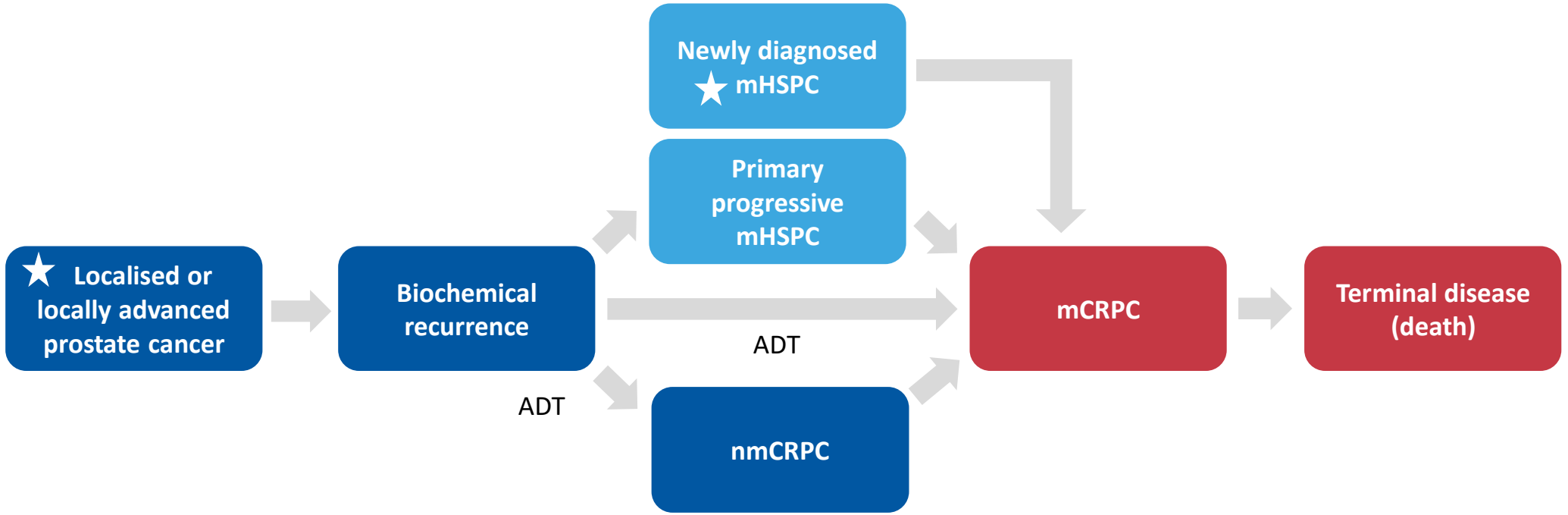
Question 1 : How would you manage this patient with nmCRPC (PSADT 5.8-months)?



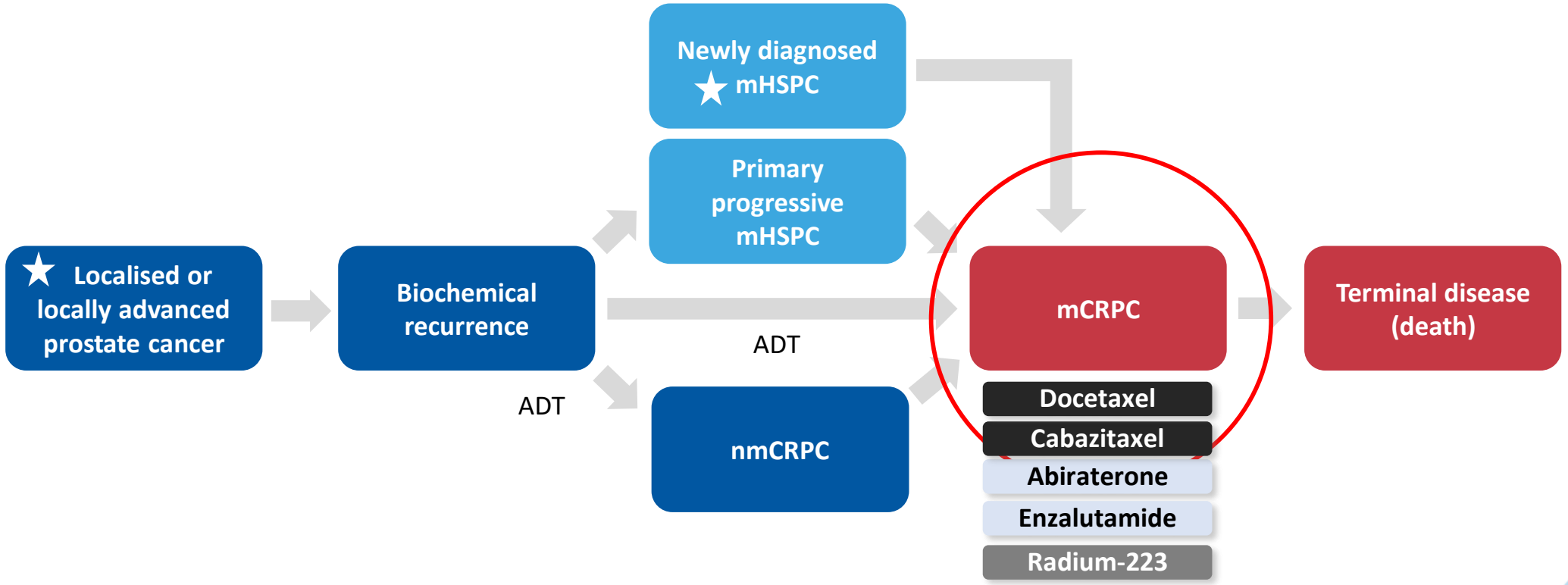
Why treat non metastatic CRPC?

Fred Saad MD FRCS
Professor and Chairman of Urology
Director of GU Oncology
Raymond Garneau Chair in Prostate Cancer
University of Montreal Hospital Center
Montreal, Quebec

The Prostate Cancer Landscape



The Prostate Cancer Landscape



Does earlier treatment improve outcome?

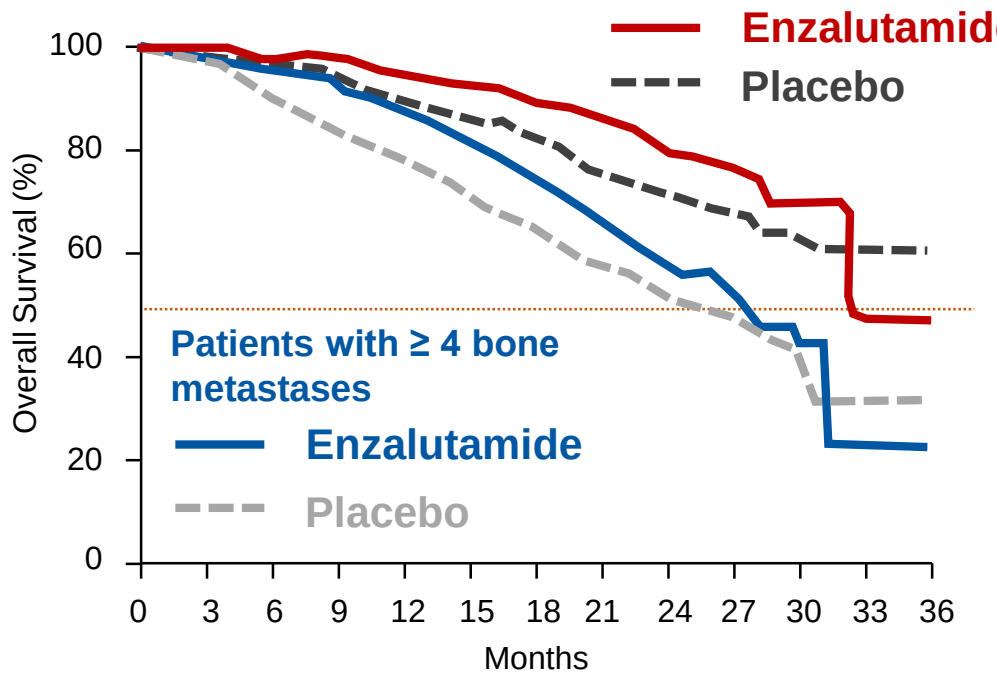
Better Outcomes for Patients Treated Early with mCRPC

Quartile	Q1	Q2	Q3	Q4
Baseline PSA (ng/mL)	<15.6	15.6 to <39.5	39.5 to <106.2	≥106.2
		OS		
HR (95% CI) *P* value	0.53 (0.39–0.72) <0.001	0.71 (0.54–0.93) 0.014	0.87 (0.67–1.11) 0.257	1.00 (reference) -

The lower the baseline PSA, the greater the impact of abiraterone +P on overall survival

Ryan C et al. Lancet Oncol 2015;16:152-60

Better Outcomes for Patients Treated Early with mCRPC



Patients with < 4 bone metastases													
Enzalutamide	441	439	435	428	419	399	311	223	145	80	21	1	0
Placebo	426	422	407	398	380	359	275	187	122	59	18	2	0
Patients with ≥ 4 bone metastases													
Enzalutamide	431	424	415	396	378	346	255	172	99	48	12	1	0
Placebo	419	413	374	346	321	285	209	141	91	43	9	0	0

Patients with < 4 bone metastases

Enzalutamide reduces risk of death by **38 %**

HR : 0,62 (IC 95 % ; 0,47-0,84)

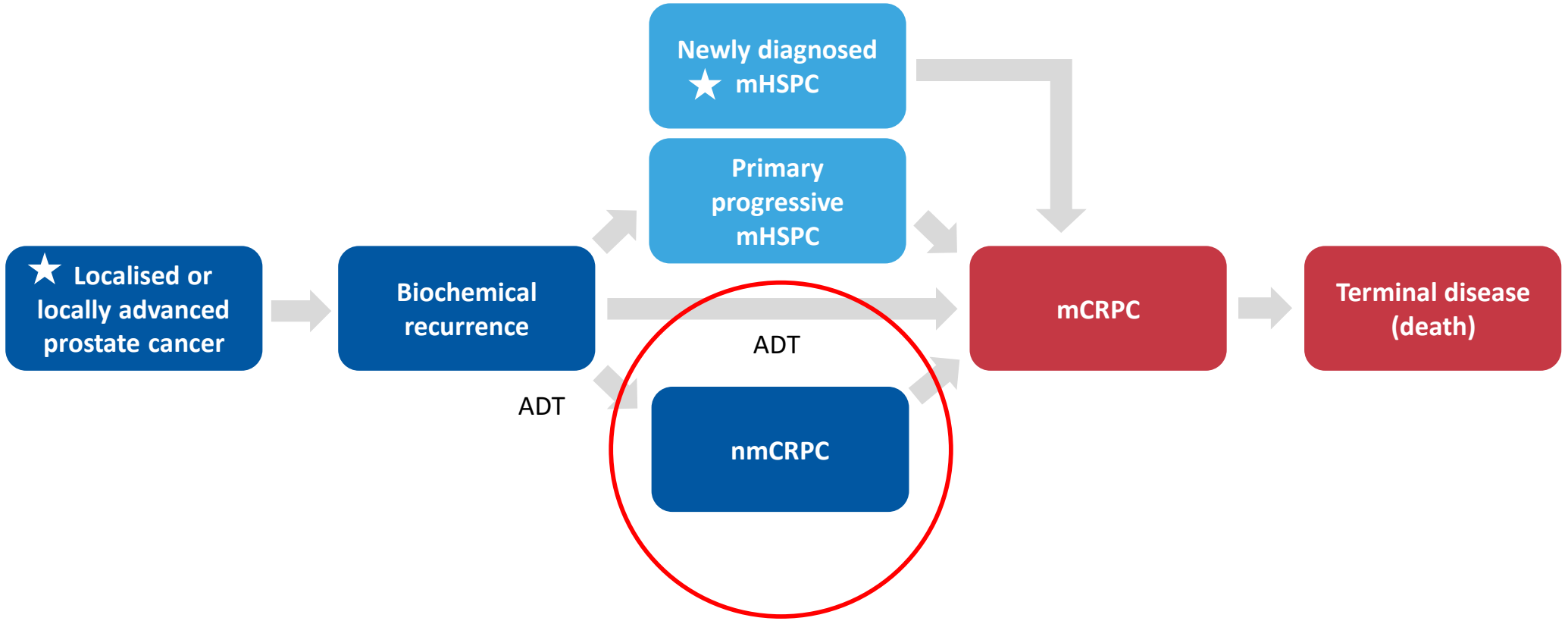
Patients with ≥ 4 bone metastases

Enzalutamide reduces risk of death by **25 %**

HR : 0,75 (IC 95 % ; 0,67-0,92)

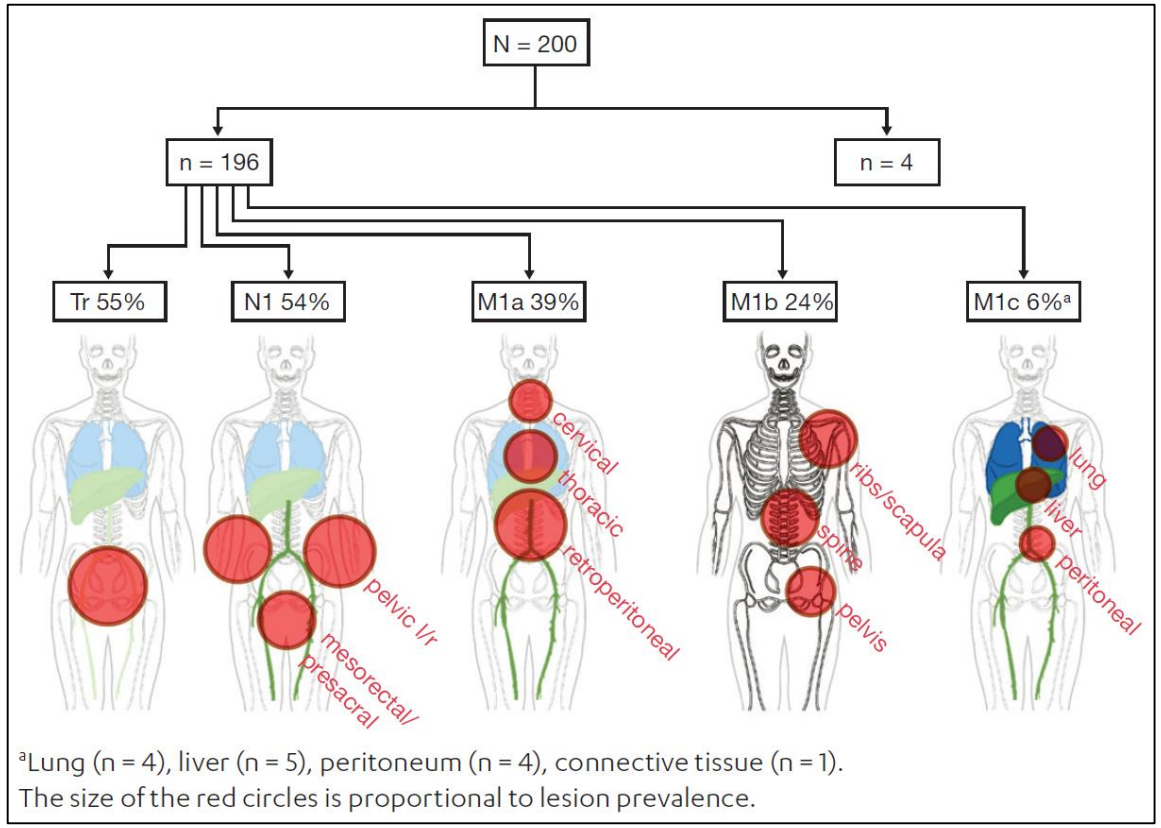
Evans et al, Eur Urol 2016;70(4):675-83.

The Prostate Cancer Landscape



Probably low volume metastatic CRPC

PSMA-PET in a High Risk nmCRPC Matched Cohort



[a]Lung (n = 4), liver (n = 5), peritoneum (n = 4), connective tissue (n = 1).
The size of the red circles is proportional to lesion prevalence.

Category based on miTNM stage, n (%)	All patients N = 200
M0	**91 (46)**
T0N0M0 (no prostate cancer lesion)	4 (2)
TrN0M0	48 (24)
T0N1M0	13 (7)
TrN1M0	26 (13)
Any M1	**109 (55)**
T0N0M1	31 (16)
T0N1M1	42 (21)
TrN0M1	9 (5)
TrN1M1	27 (14)
N/M disease extent	
Unifocal (1 lesion)	29 (15)
Oligometastatic (2-3 lesions)	28 (14)
Multiple/disseminated (≥ 4 lesions)	91 (46)

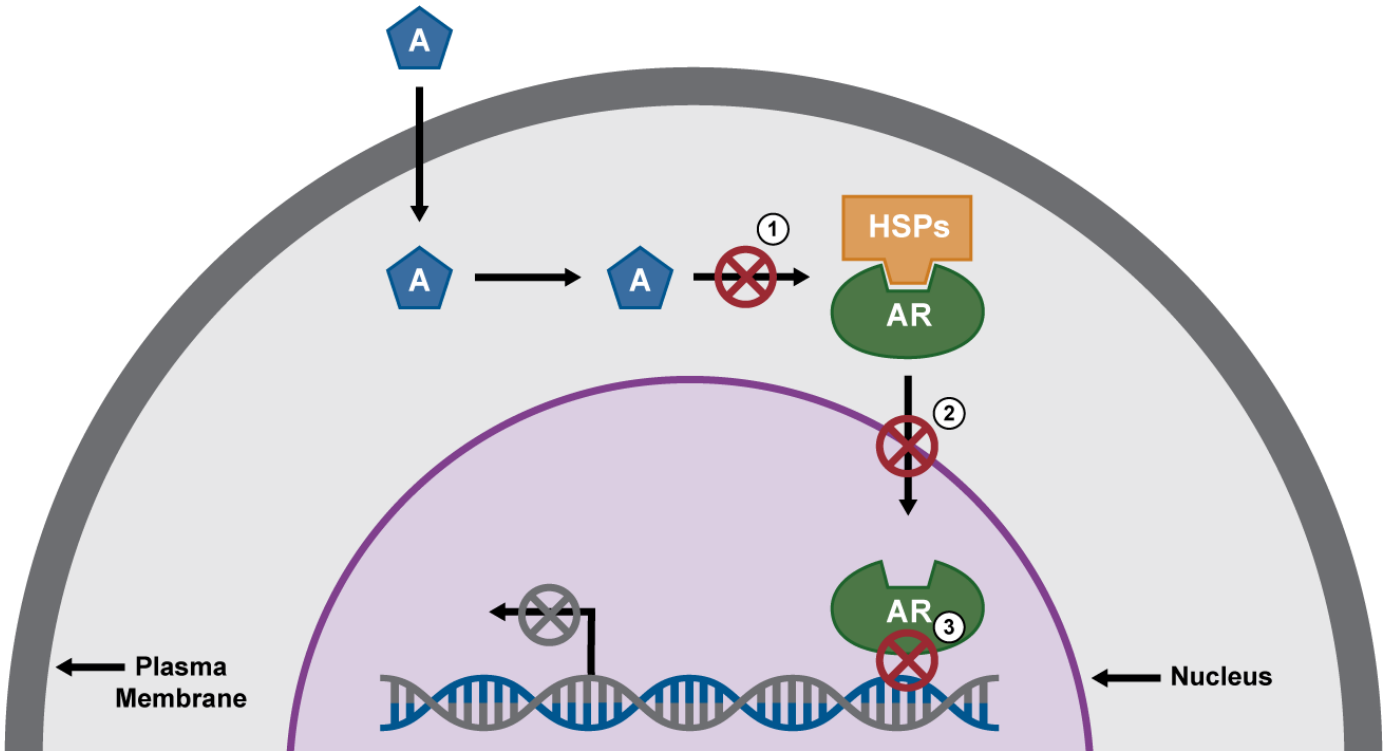
PSMA-PET was positive in 196 of 200 (98%) study patients overall

75% of patients had metastatic (55% distant, 20% regional) disease despite negative conventional imaging

Hadaschik B, et al. Oral presentation at EAU 2019. Mar 15-19. Barcelona, Spain. Abstract 523.

AR-Targeted Therapy

- The most effective target in treating advanced prostate cancer



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 27, 2012 VOL. 367 NO. 13

Increased Survival with Enzalutamide in Prostate Cancer after Chemotherapy

Howard I. Scher, M.D., Karim Fizazi, M.D., Ph.D., Fred Saad, M.D., Mary-Ellen Taplin, M.D., Cora N. Sternberg, M.D., Kurt Miller, M.D., Ronald de Wit, M.D., Peter Mulders, M.D., Ph.D., Kim N. Chi, M.D., Neal D. Shore, M.D., Andrew J. Armstrong, M.D., Thomas W. Flaig, M.D., Aude Fléchon, M.D., Ph.D., Paul Mainwaring, M.D., Mark Fleming, M.D., John D. Hainsworth, M.D., Mohammad Hirmand, M.D., Bryan Selby, M.S., Lynn Seely, M.D., and Johann S. de Bono, M.B., Ch.B., Ph.D., for the AFFIRM Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

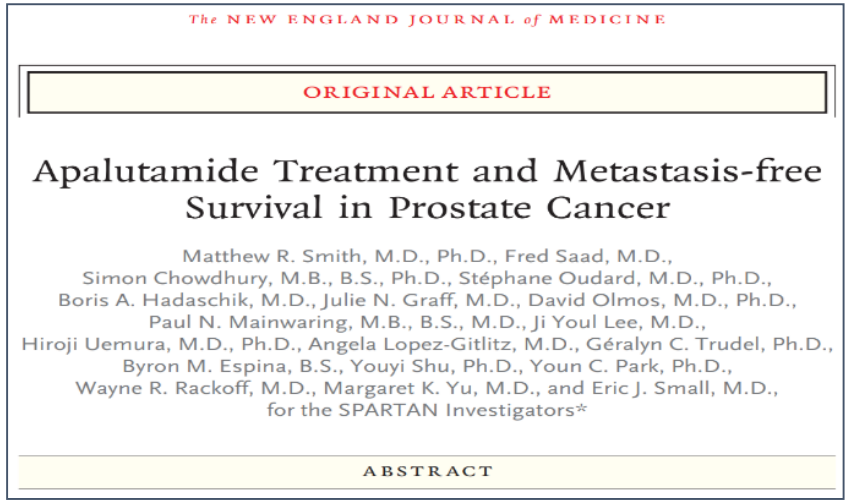
Enzalutamide in Metastatic Prostate Cancer before Chemotherapy

T.M. Beer, A.J. Armstrong, D.E. Rathkopf, Y. Loriot, C.N. Sternberg, C.S. Higano, P. Iversen, S. Bhattacharya, J. Carles, S. Chowdhury, I.D. Davis, J.S. de Bono, C.P. Evans, K. Fizazi, A.M. Joshua, C.-S. Kim, G. Kimura, P. Mainwaring, H. Mansbach, K. Miller, S.B. Noonberg, F. Perabo, D. Phung, F. Saad, H.I. Scher, M.-E. Taplin, P.M. Venner, and B. Tombal, for the PREVAIL Investigators*

Does it work?

YES!

APA[1]



The NEW ENGLAND JOURNAL of MEDICINE

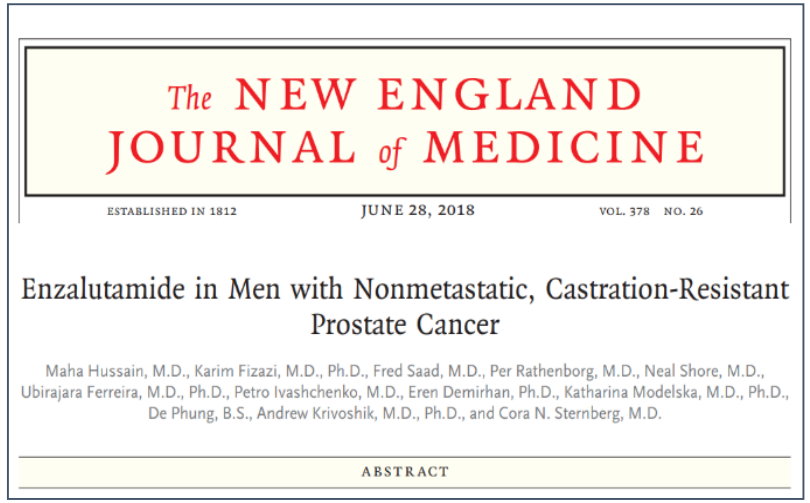
ORIGINAL ARTICLE

Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer

Matthew R. Smith, M.D., Ph.D., Fred Saad, M.D., Simon Chowdhury, M.B., B.S., Ph.D., Stéphane Oudard, M.D., Ph.D., Boris A. Hadaschik, M.D., Julie N. Graff, M.D., David Olmos, M.D., Ph.D., Paul N. Mainwaring, M.B., B.S., M.D., Ji Youl Lee, M.D., Hiroji Uemura, M.D., Ph.D., Angela Lopez-Gitlitz, M.D., Géralyn C. Trudel, Ph.D., Byron M. Espina, B.S., Youyi Shu, Ph.D., Youn C. Park, Ph.D., Wayne R. Rackoff, M.D., Margaret K. Yu, M.D., and Eric J. Small, M.D., for the SPARTAN Investigators*

ABSTRACT

ENZA[2]



The NEW ENGLAND JOURNAL of MEDICINE

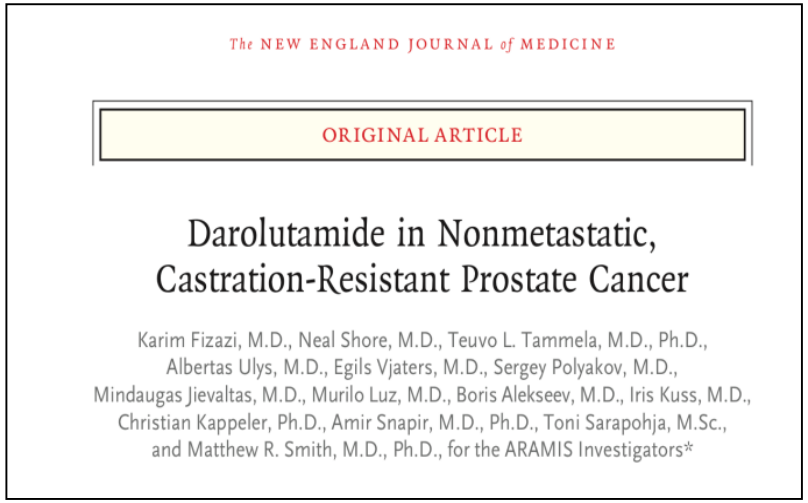
ESTABLISHED IN 1812 JUNE 28, 2018 VOL. 378 NO. 26

Enzalutamide in Men with Nonmetastatic, Castration-Resistant Prostate Cancer

Maha Hussain, M.D., Karim Fizazi, M.D., Ph.D., Fred Saad, M.D., Per Rathenborg, M.D., Neal Shore, M.D., Ubirajara Ferreira, M.D., Ph.D., Petro Ivashchenko, M.D., Eren Demirhan, Ph.D., Katharina Modelska, M.D., Ph.D., De Phung, B.S., Andrew Krivoshik, M.D., Ph.D., and Cora N. Sternberg, M.D.

ABSTRACT

DARO[3]



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

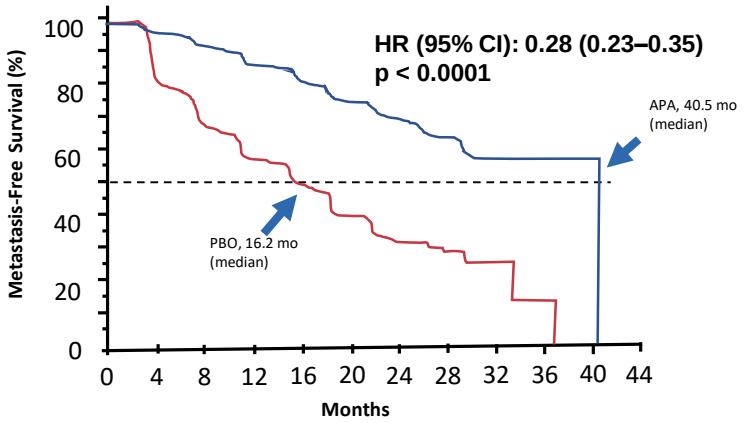
Darolutamide in Nonmetastatic, Castration-Resistant Prostate Cancer

Karim Fizazi, M.D., Neal Shore, M.D., Teuvo L. Tammela, M.D., Ph.D., Albertas Ulys, M.D., Egils Vjaters, M.D., Sergey Polyakov, M.D., Mindaugas Jievaltas, M.D., Murilo Luz, M.D., Boris Alekseev, M.D., Iris Kuss, M.D., Christian Kappeler, Ph.D., Amir Snapir, M.D., Ph.D., Toni Sarapohja, M.Sc., and Matthew R. Smith, M.D., Ph.D., for the ARAMIS Investigators*

1. Smith MR, et al. N Engl J Med. 2018;378:1408-18.
2. Hussain M, et al. N Engl J Med. 2018;378:2465-74.
3. Fizazi K, et al. N Engl J Med. 2019 Feb 14 [Epub ahead of print].

MFS in nmCRPC Patients with PSADT ≤ 10-Months

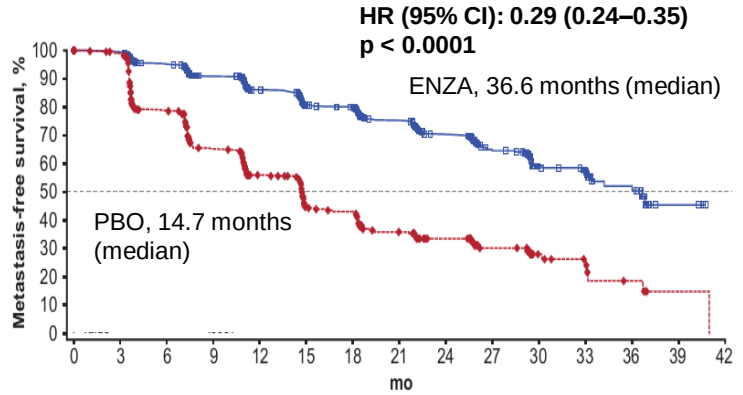
SPARTAN[1] (APA)



Number at risk												
APA	806	713	652	514	398	282	180	96	36	16	3	0
PBO	401	291	220	153	91	58	34	13	5	1	0	0

- 72% reduction of metastases or death
- Median MFS: APA 40.5 vs PBO 16.2 months

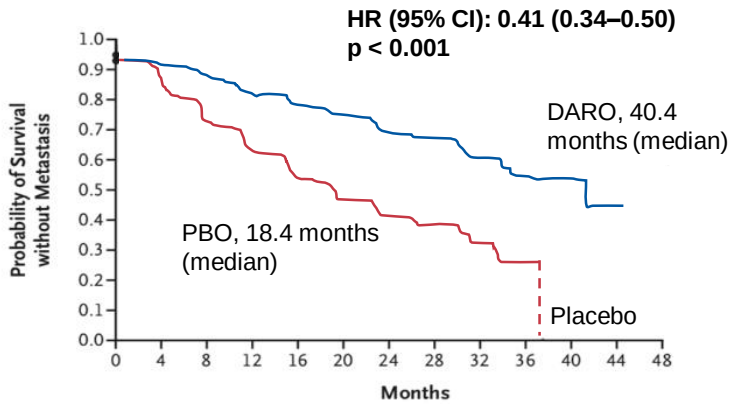
PROSPER[2] (ENZA)



Number at risk															
ENZA + ADT	933	865	759	637	528	431	418	328	237	159	87	77	31	4	0
PBO + ADT	468	420	296	212	157	105	98	64	49	31	16	11	5	1	0

- 71% reduction of metastases or death
- Median MFS: ENZA 36.6 vs PBO 14.7 months

ARAMIS[3] (DARO)



Number at risk													
Darolutaminde	955	817	675	506	377	262	189	116	68	37	18	2	0
Placebo	554	368	275	180	117	75	50	29	12	4	0	0	0

- 59% reduction of metastases or death
- Median MFS: DARO 40.4 vs PBO 18.4 months

~ 2 year delay in appearance of metastases

CI, confidence interval; mo, months.

1. Smith MR, et al. N Engl J Med. 2018;378:1408-18.
2. Hussain M, et al. N Engl J Med. 2018;378:2465-74.
3. Fizazi K, et al. N Engl J Med. 2019 Feb 14 [Epub ahead of print].

Predictors of MFS

Multivariate Analysis of Individual Predictors of MFS		
Covariate	**HR (95% CI)**	**P Value**
Treatment, APA vs PBO	0.26 (0.21-0.32)	< 0.0001
Baseline PSA, ≤ 7.8 ng/mL vs > 7.8 ng/mL	0.59 (0.47-0.73)	< 0.0001
PSADT, > 6 months vs ≤ 6 months	0.65 (0.51-0.84)	0.0007
Loco-regional disease, N0 vs N1	0.68 (0.52-0.89)	0.0055
Gleason score at diagnoses, ≤ 7 vs ≥ 8	0.75 (0.61-0.92)	0.0063
Age per 10 years	0.88 (0.77-1.01)	0.0784
ECOG PS at baseline, 0 vs 1	0.84 (0.66-1.07)	0.154
Use of bone-sparing agent, yes vs no	0.78 (0.55-1.12)	0.174
Prior hormonal therapies, n, ≥ 2 vs 1	0.90 (0.69-1.16)	0.406

Smith et al. ASCO 2018

Summary of Site and Number of Mets

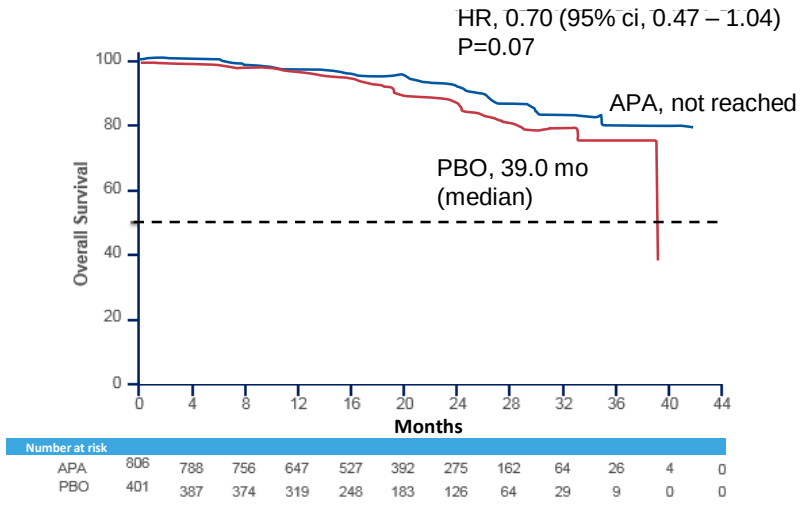
Summary of Metastasis Sites in Patients With nmCRPC From the SPARTAN Study		
	APA (N=806)	**PBO (N=401)**
Total patients with metastases, n(%)	175 (22)	191 (48)
	APA (n=175)	**PBO (n=191)**
Type of metastasis[a], n (%)		
Bone	100 (57)	100 (52)
Nodal	52 (30)	76 (40)
Any visceral	23 (13)	15 (8)
Number of sites[b], n (%)		
Single	161 (92)	165 (86)
Multiple	14 (8)	26 (14)

[a] Bone (bone ± M1 nodes), nodal (M1 nodes + soft tissues), and visceral (visceral regardless of other sites).
[b] Single, metastases occurring in a single type (bone, nodal, or visceral; multiple, metastases occurring in more than 1 type.

Smith et al. ASCO 2018

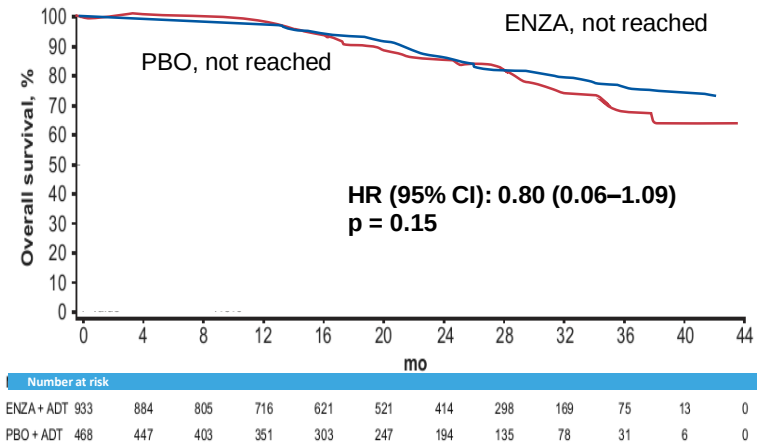
OS: Still too few deaths
Positive trend but not yet significant

SPARTAN[1]



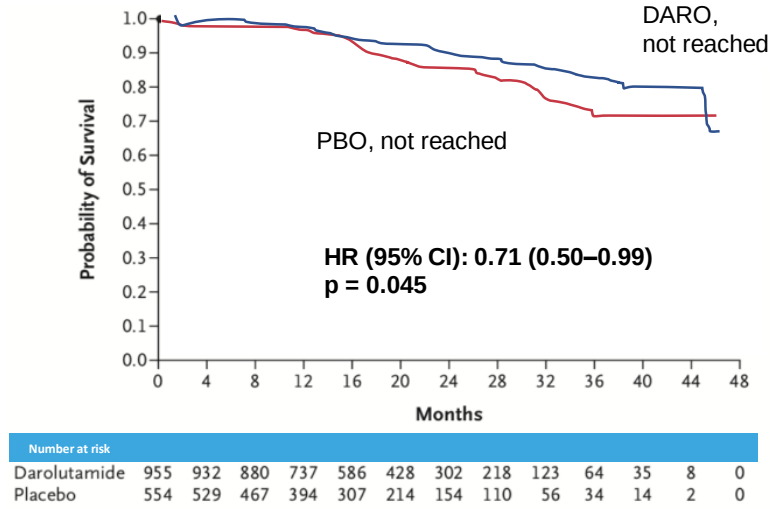
30% risk reduction of death

PROSPER[2]



20% risk reduction of death

ARAMIS[3]



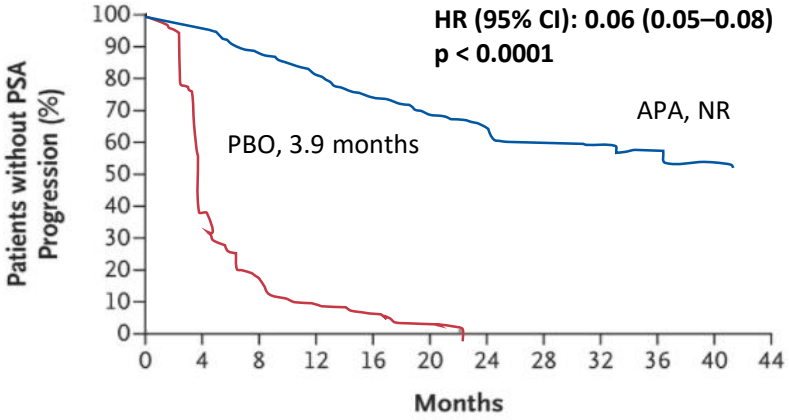
29% risk reduction of death

Patients in placebo arms treated very early

1. Smith MR, et al. N Engl J Med. 2018;378:1408-18.
2. Hussain M, et al. N Engl J Med. 2018;378:2465-74.
3. Fizazi K, et al. N Engl J Med. 2019 Feb 14 [Epub ahead of print].

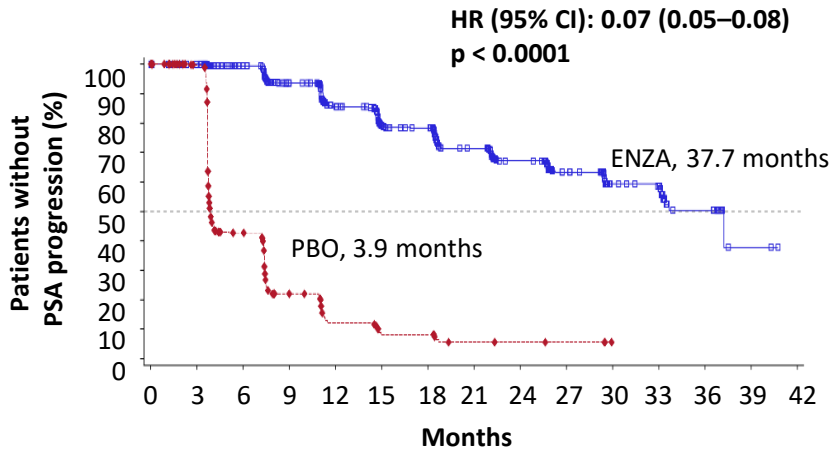
Time to PSA Progression

SPARTAN[1] (APA)



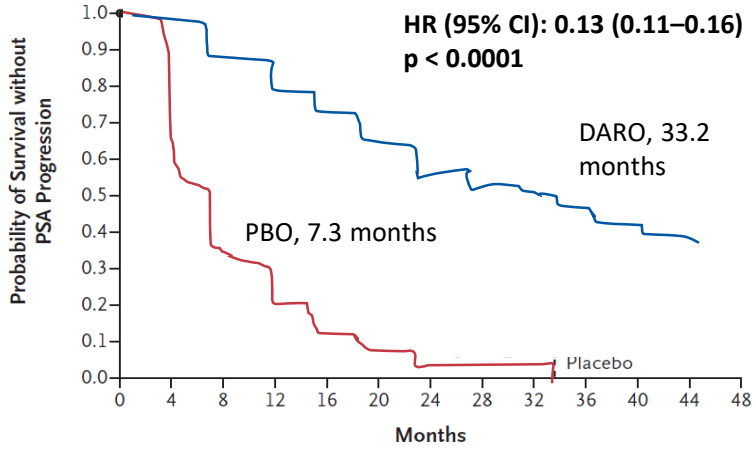
- 94% risk reduction in PSA progression
- TTPP: PBO 3.9 vs APA NR months

PROSPER[2] (ENZA)



- 93% risk reduction in PSA progression
- TTPP: PBO 3.9 vs ENZA 37.7 months

ARAMIS[3] (DARO)



- 87% risk reduction in PSA progression
- TTPP: PBO 7.3 vs DARO 33.2 months

Resistance to therapy much longer than in mCRPC

1. Smith MR, et al. N Engl J Med. 2018;378:1408-18.
2. Hussain M, et al. N Engl J Med. 2018;378:2465-74.
3. Fizazi K, et al. N Engl J Med. 2019 Feb 14 [Epub ahead of print].

How well are these treatments tolerated in asymptomatic patients?

Adverse Events ≠ Side effects

- Adverse events are what patients complained about to our nurses regardless of cause

- Risk factors for AEs:
  - Time on therapy
  - Frequency of visits
  - Looking for AEs

AE, Adverse event

AEs of Interest

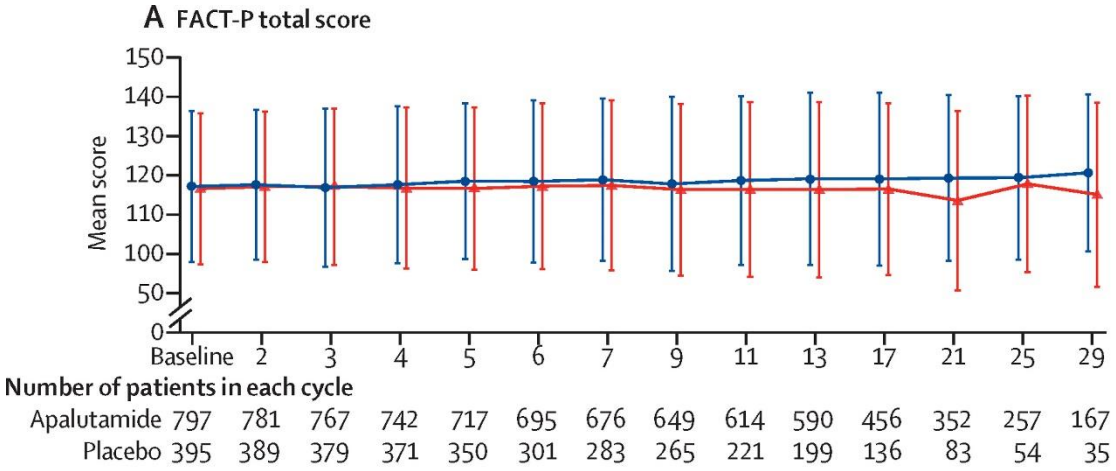
	SPARTAN[1]		PROSPER[2]		ARAMIS[3]	
Monitoring schedule[a]	Every 4 weeks		Every 16 weeks		Every 16 weeks	
	APA (n = 803)	**PBO (n = 398)**	**ENZA (n = 930)**	**PBO (n = 465)**	**DARO (n = 954)**	**PBO (n = 554)**
Median duration of trial regimen (months)	16.9	11.2	18.4	11.1	14.8	11
Any AEs, n (%)	775 (96.5)	371 (93.2)	808 (87)	360 (77)	794 (83.2)	426 (76.9)
Any serious AEs, n (%)	199 (24.8)	92 (23.1)	226 (24)	85 (18)	237 (24.8)	111 (20.0)
AEs (all grades), %						
Fatigue	30.4	21.1	33.0	14.0	12.1	8.7
Hypertension	24.8	19.8	12.0	5.0	6.6	5.2
Rash	23.8	5.5	NR	NR	2.9	0.9
Falls	15.6	9.0	11.0	4.0	4.2	4.7
Fractures	11.7	6.5	NR	NR	4.2	3.6
Mental/ cognitive impairment	5.1	3.0	5.0	2.0	0.4	0.2

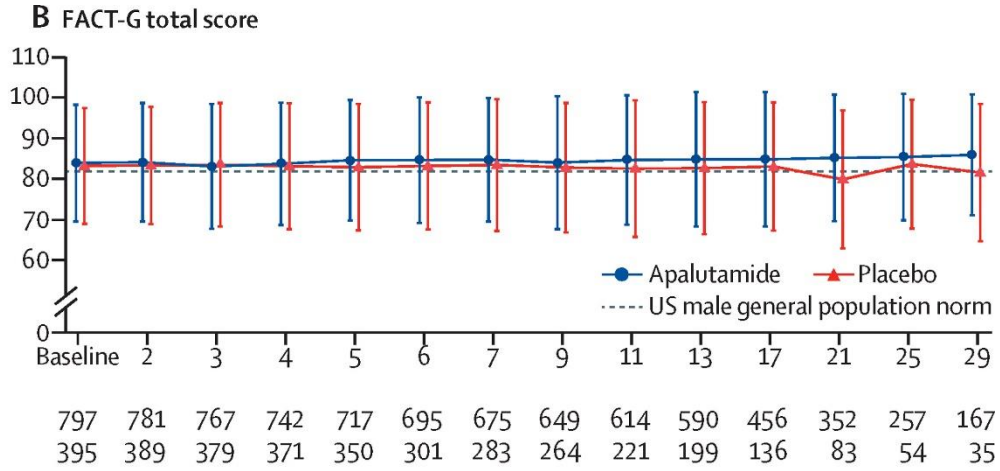
NR, not reported.

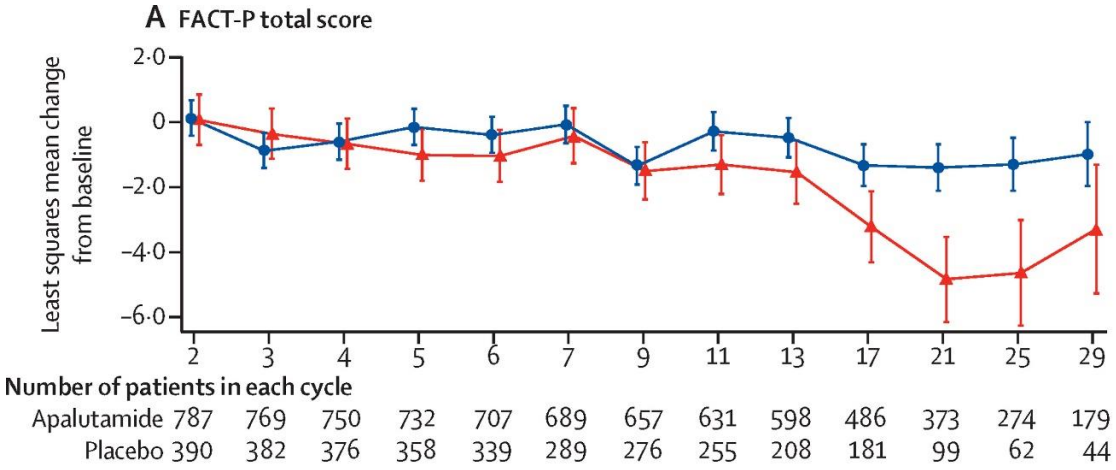
1. Smith MR, et al. N Engl J Med. 2018;378:1408-18.
2. Hussain M, et al. N Engl J Med. 2018;378:2465-74.
3. Fizazi K, et al. N Engl J Med. 2019 Feb 14 [Epub ahead of print].

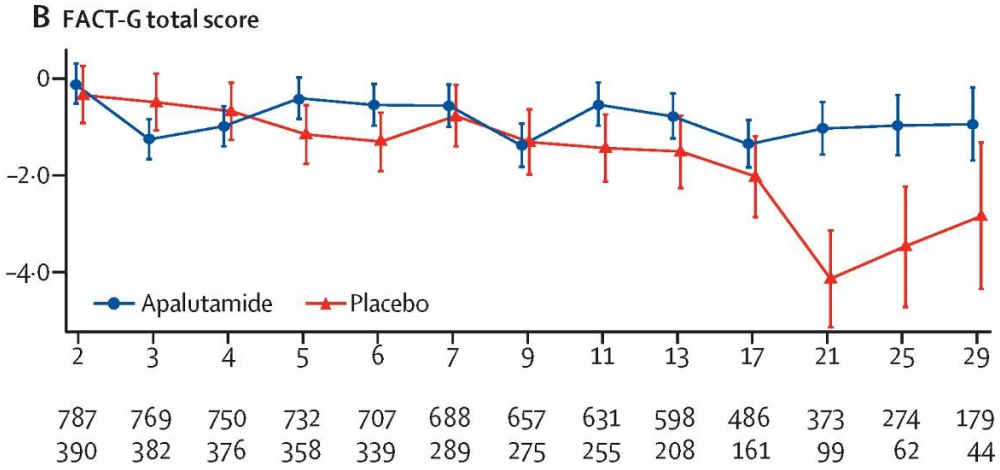
So how does this affect patients' quality of life?

SPARTAN: QoL

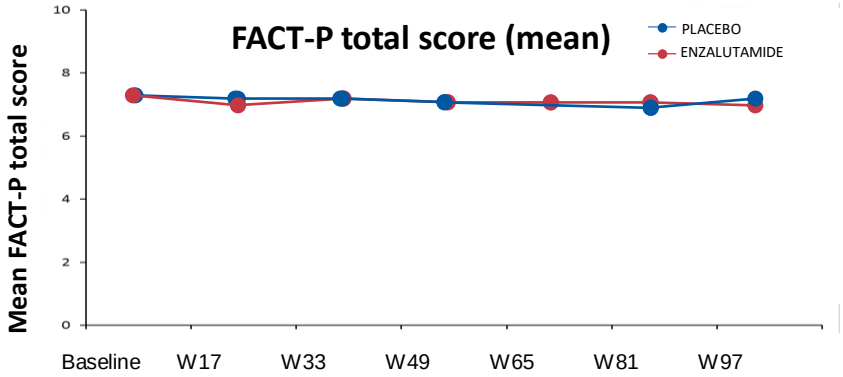

A FACT-P total score
Mean score
150
140
130
120
110
100
50
0
Baseline 2 3 4 5 6 7 9 11 13 17 21 25 29
Number of patients in each cycle
Apalutamide 797 781 767 742 717 695 676 649 614 590 456 352 257 167
Placebo 395 389 379 371 350 301 283 265 221 199 136 83 54 35

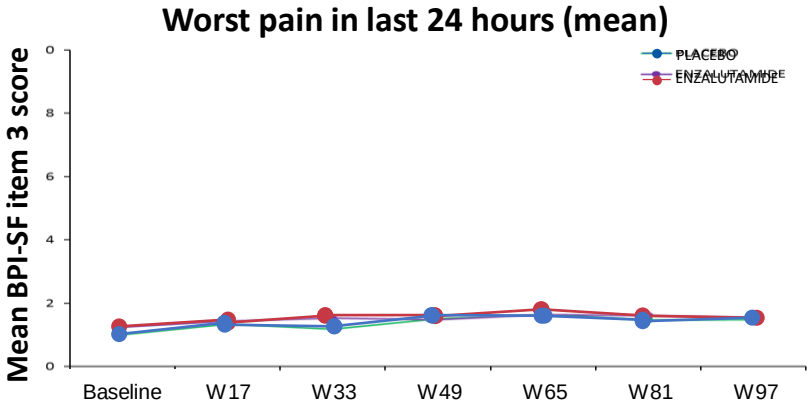

B FACT-G total score
110
100
90
80
70
60
0
Apalutamide
Placebo
US male general population norm
Baseline 2 3 4 5 6 7 9 11 13 17 21 25 29
797 781 767 742 717 695 675 649 614 590 456 352 257 167
395 389 379 371 350 301 283 264 221 199 136 83 54 35

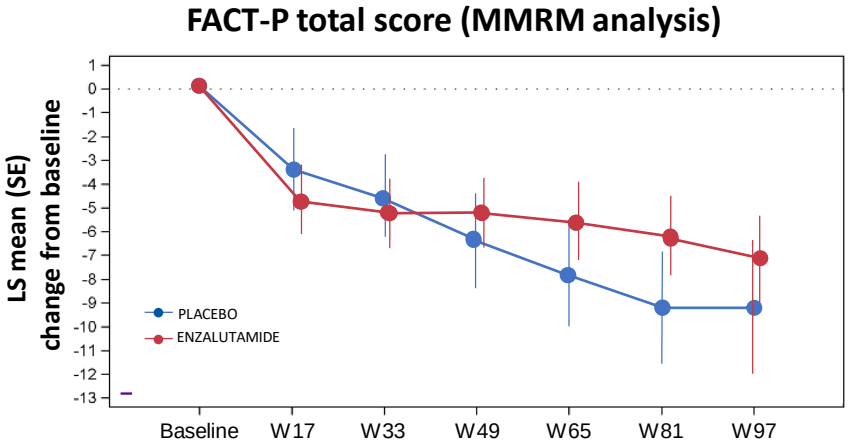

A FACT-P total score
Least squares mean change from baseline
2·0
0
−2·0
−4·0
−6·0
2 3 4 5 6 7 9 11 13 17 21 25 29
Number of patients in each cycle
Apalutamide 787 769 750 732 707 689 657 631 598 486 373 274 179
Placebo 390 382 376 358 339 289 276 255 208 181 99 62 44

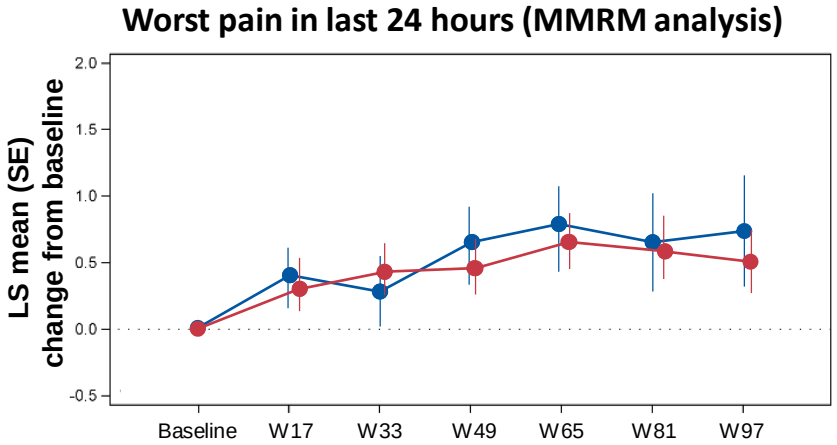

B FACT-G total score
0
−2·0
−4·0
Apalutamide
Placebo
2 3 4 5 6 7 9 11 13 17 21 25 29
787 769 750 732 707 688 657 631 598 486 373 274 179
390 382 376 358 339 289 275 255 208 161 99 62 44

PROSPER: QoL





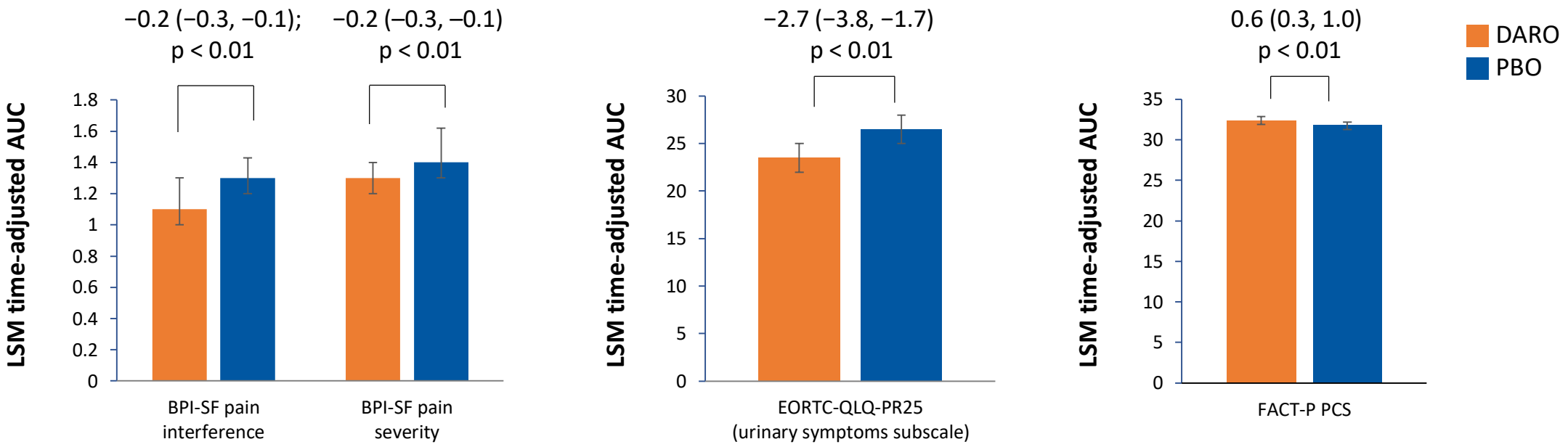




No statistical or clinically meaningful change in FACT-P total score or worsening pain observed over 97 weeks*

Tombal B, et al. Lancet Oncol. 2019 Feb 12 [Epub ahead of print].

ARAMIS: QoL



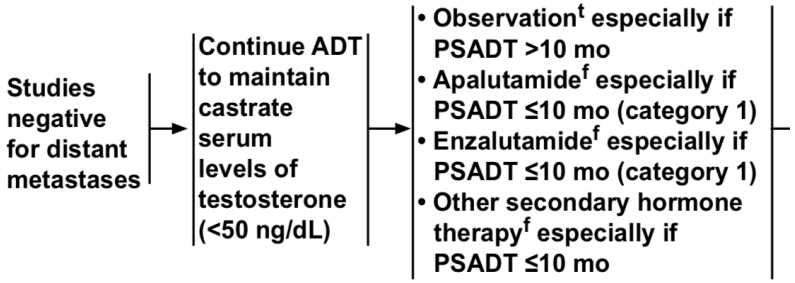
Fizazi K, et al. N Engl J Med. 2019 Feb 14 [Epub ahead of print].

Guidelines

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2018
Prostate Cancer

SYSTEMIC THERAPY FOR M0 CASTRATION–RESISTANT PROSTATE CANCER (CRPC)[gg]



American Urological Association (AUA) Guideline

Clinicians should offer apalutamide or enzalutamide with continued androgen deprivation to patients with nonmetastatic CRPC at high risk for developing metastatic disease (Standard; Evidence Level Grade A).

EAU guidelines for 2019

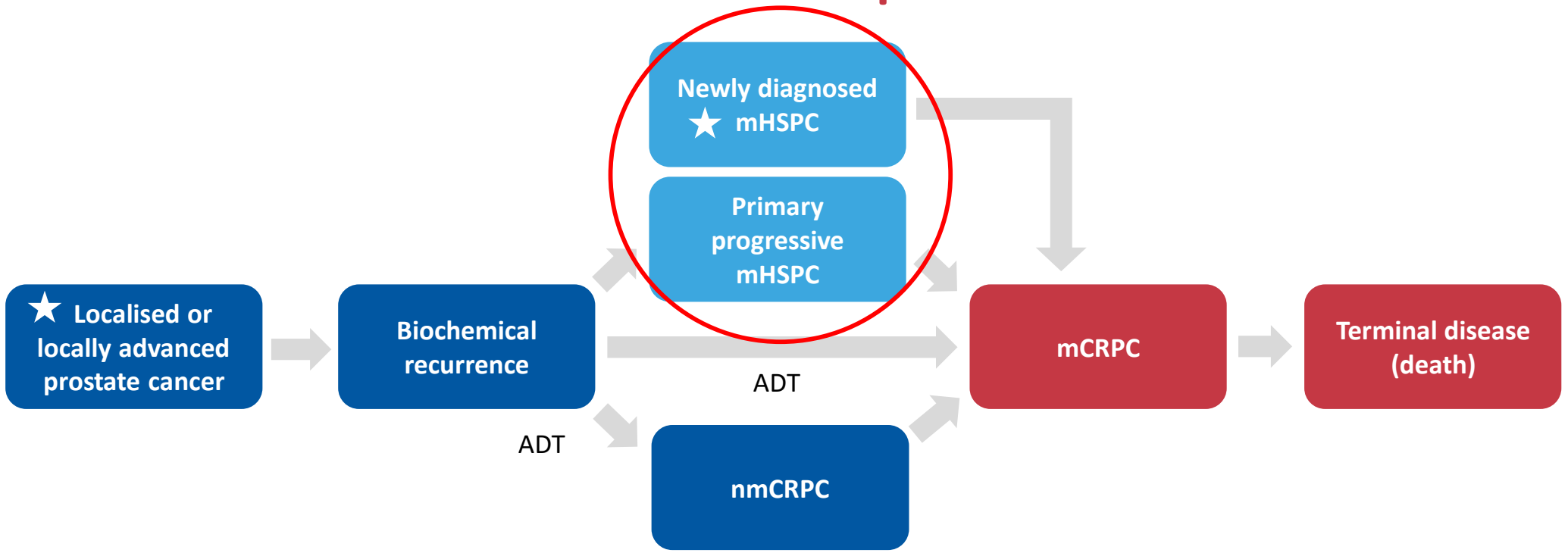
nmCRPC	Offer apalutamide or enzalutamide to patients with M0 CRPC and a high risk of developing metastasis (PSA-DT < 10 months) to prolong time to metastases	Strong

CUA guidelines for 2019

Conclusions

1. Patients in the mCRPC state live fewer than 3 years on average
2. Patients begin to fail therapy and progress within about 12 months
3. High-risk nmCRPC progresses rapidly to mCRPC
    - Opportunity to delay a lethal form of prostate cancer
4. AR inhibition is one of the most effective therapeutic options for mCRPC
5. Studies and RWE suggest that patients respond better and for longer when ARAT therapy is given early
6. APA, ENZA, and soon DARO, will fulfil an important, unmet need and maintain QoL in patients with high-risk nmCRPC

The Prostate Cancer Landscape



Probably low volume metastatic CRPC

Part 2

Reviewing the options for patients with mHSPC

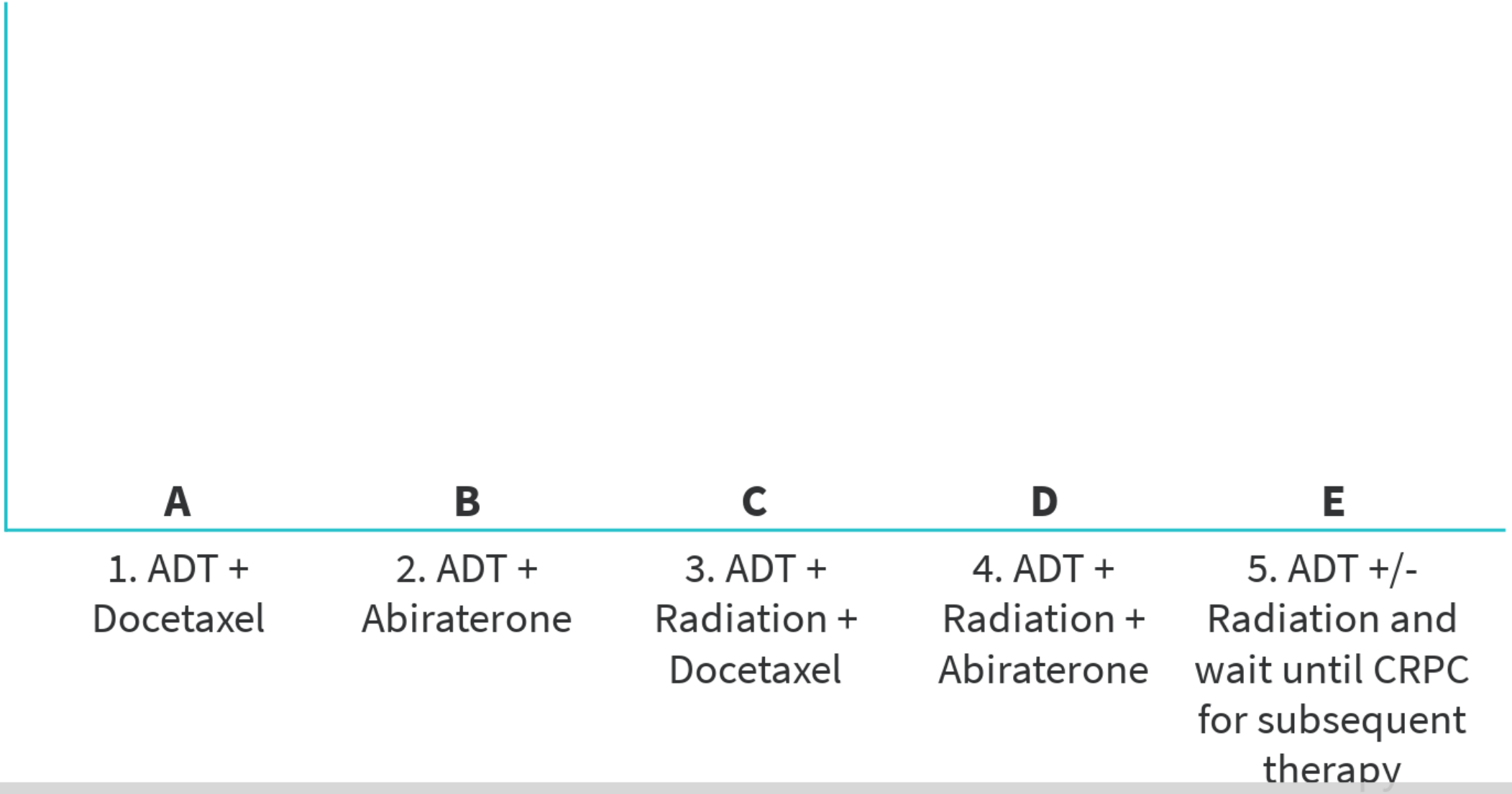
Patient Case: mCSPC

- 70 year old male presenting to physician with concerns about urgency, frequency and mild back pain
- Physical examination is notable for an irregularly enlarged prostate, palpable firm nodule on the right side. Clinically, rectal exam reveals T3 disease
- Biopsy reveals Gleason 4,4 = 8 and serum PSA is 150ng/mL
- Bone scan shows multifocal bone disease with >10 lesions in the axial and appendicular skeleton; CT shows retroperitoneal and pelvic lymphadenopathy but no visceral involvement
- Otherwise well; mild HTN managed with amlodipine

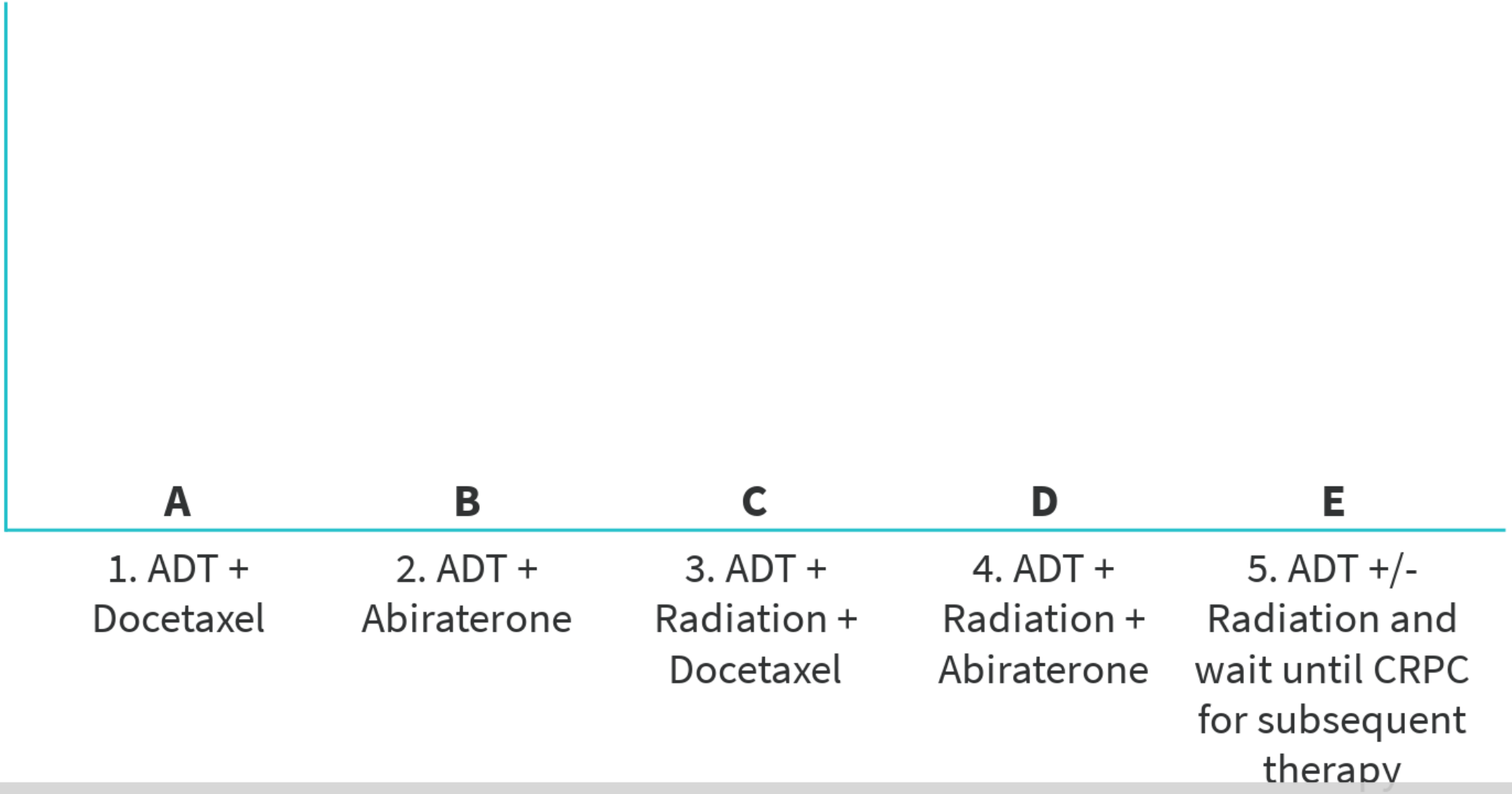
Question 2 : How would you treat?

1. ADT + Docetaxel	**A**
2. ADT + Abiraterone	**B**
3. ADT + Radiation + Docetaxel	**C**
4. ADT + Radiation + Abiraterone	**D**
5. ADT +/- Radiation and wait until CRPC for subsequent therapy	**E**

Question 2 : How would you treat?



Question 2 : How would you treat?



Intensifying ADT for Metastatic Castration Sensitive Prostate Cancer: "Maximum androgen blockade" revisited

Kim N. Chi, MD FRCPC
Professor of Medicine
University of British Columbia
Vancouver, British Columbia

VANCOUVER PROSTATE CENTRE
A UBC & VGH Centre of Excellence

BC Cancer Agency
CARE & RESEARCH
An agency of the Provincial Health Services Authority

74th Annual Meeting
June 29 – July 1
74e Congrès annuel
29 juin – 1 juillet
QUÉBEC 2019

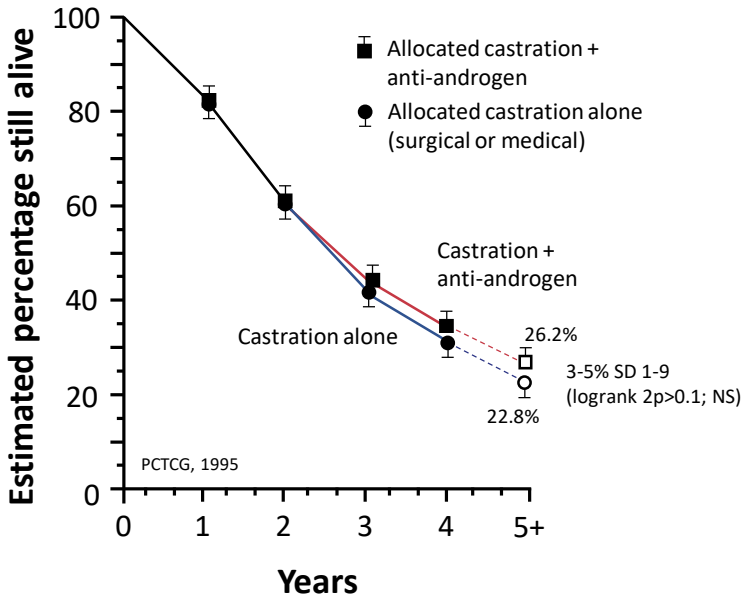
The Effects of Castration on Advanced Carcinoma of the Prostate Gland

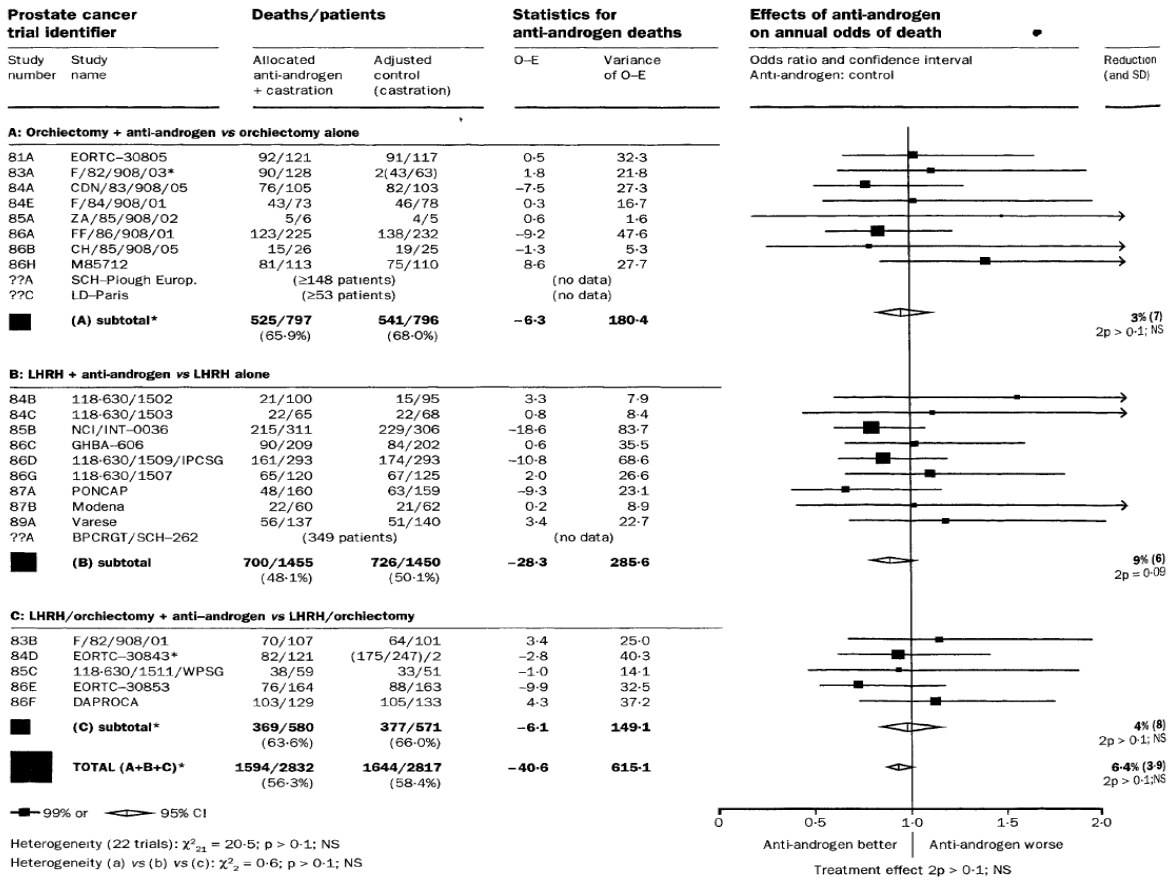
CHARLES HUGGINS, M.D.; R. E. STEVENS, Jr., M.D.; CLARENCE V. HODGES, M.D.
Arch Surg. 1941;43(2):209-223.

In this paper, evidence is presented that significant improvement often occurs in the clinical condition of patients with far advanced cancer of the prostate after they have been subjected to castration. Conversely, the symptoms are aggravated when androgens are injected. We believe that this work provides a new concept of prostatic carcinoma.

Charles B. Huggins
Nobel Prize in Physiology or Medicine 1966

“Old School” Maximum Androgen Blockade





Prostate cancer trial identifier		Deaths/patients		Statistics for anti-androgen deaths		Effects of anti-androgen on annual odds of death
Study number	Study name	Allocated anti-androgen + castration	Adjusted control (castration)	O–E	Variance of O–E	Odds ratio and confidence interval Anti-androgen: control
A: Orchiectomy + anti-androgen *vs* orchiectomy alone						Reduction (and SD)
81A	EORTC–30805	92/121	91/117	0·5	32·3	
83A	F/82/908/03*	90/128	2(43/63)	1·8	21·8	
84A	CDN/83/908/05	76/105	82/103	–7·5	27·3	
84E	F/84/908/01	43/73	46/78	0·3	16·7	
85A	ZA/85/908/02	5/6	4/5	0·6	1·6	
86A	FF/86/908/01	123/225	138/232	–9·2	47·6	
86B	CH/85/908/05	15/26	19/25	–1·3	5·3	
86H	M85712	81/113	75/110	8·6	27·7	
??A	SCH–Plough Europ.	(≥148 patients)		(no data)		
??C	LD–Paris	(≥53 patients)		(no data)		
	(A) subtotal*	**525/797** (65·9%)	**541/796** (68·0%)	**–6·3**	**180·4**	3% (7) 2p > 0·1; NS
B: LHRH + anti-androgen *vs* LHRH alone						
84B	118·630/1502	21/100	15/95	3·3	7·9	
84C	118·630/1503	22/65	22/68	0·8	8·4	
85B	NCI/INT–0036	215/311	229/306	–18·6	83·7	
86C	GHBA–606	90/209	84/202	0·6	35·5	
86D	118·630/1509/IPCSG	161/293	174/293	–10·8	68·6	
86G	118·630/1507	65/120	67/125	2·0	26·6	
87A	PONCAP	48/160	63/159	–9·3	23·1	
87B	Modena	22/60	21/62	0·2	8·9	
89A	Varese	56/137	51/140	3·4	22·7	
??A	BPCRGT/SCH–262	(349 patients)		(no data)		
	(B) subtotal	**700/1455** (48·1%)	**726/1450** (50·1%)	**–28·3**	**285·6**	9% (6) 2p = 0·09
C: LHRH/orchiectomy + anti–androgen *vs* LHRH/orchiectomy						
83B	F/82/908/01	70/107	64/101	3·4	25·0	
84D	EORTC–30843*	82/121	(175/247)/2	–2·8	40·3	
85C	118·630/1511/WPSG	38/59	33/51	–1·0	14·1	
86E	EORTC–30853	76/164	88/163	–9·9	32·5	
86F	DAPROCA	103/129	105/133	4·3	37·2	
	(C) subtotal*	**369/580** (63·6%)	**377/571** (66·0%)	**–6·1**	**149·1**	4% (8) 2p > 0·1; NS
	TOTAL (A+B+C)*	**1594/2832** (56·3%)	**1644/2817** (58·4%)	**–40·6**	**615·1**	6·4% (3·9) 2p > 0·1; NS

99% or 95% CI

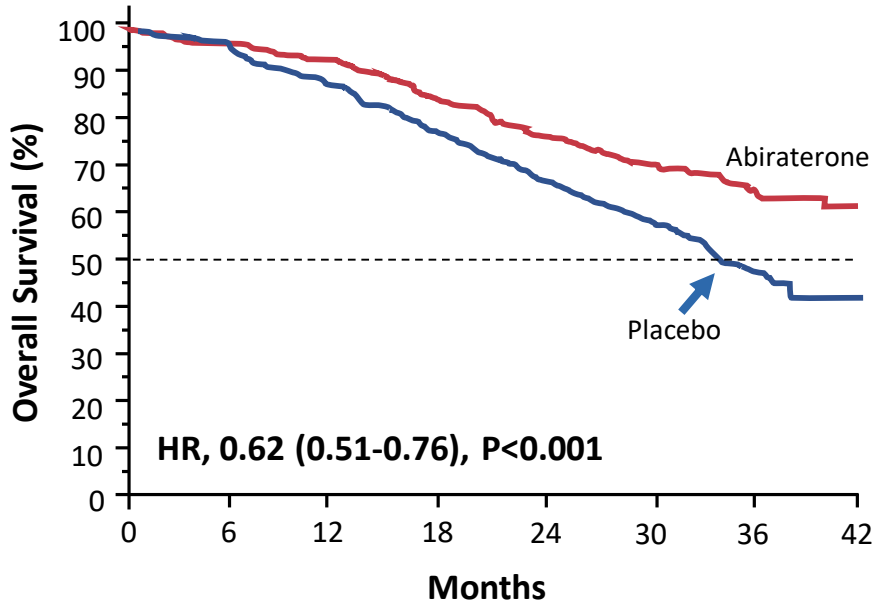
Heterogeneity (22 trials): $\chi^2_{21} = 20·5$; p > 0·1; NS
Heterogeneity (a) *vs* (b) *vs* (c): $\chi^2_2 = 0·6$; p > 0·1; NS

0 0·5 1·0 1·5 2·0
Anti-androgen better | Anti-androgen worse
Treatment effect 2p > 0·1; NS

Prostate Cancer Trialists Collaborative Group, Lancet, 346:265, 1995

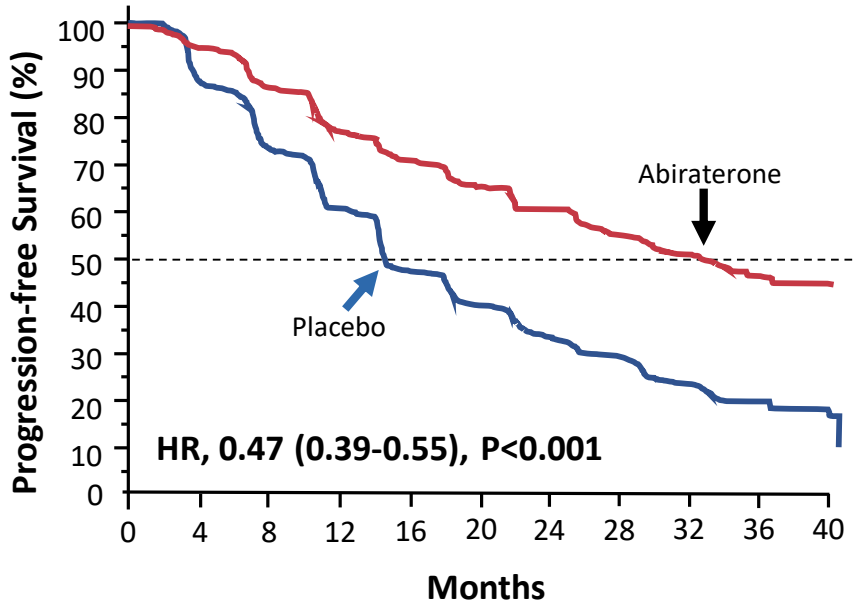
LATITUDE: ADT + abiraterone + prednisone in high risk patients improves OS

A Overall Survival



Number at risk								
Abiraterone	597	565	529	479	388	233	93	9
Placebo	602	564	504	432	332	172	57	2

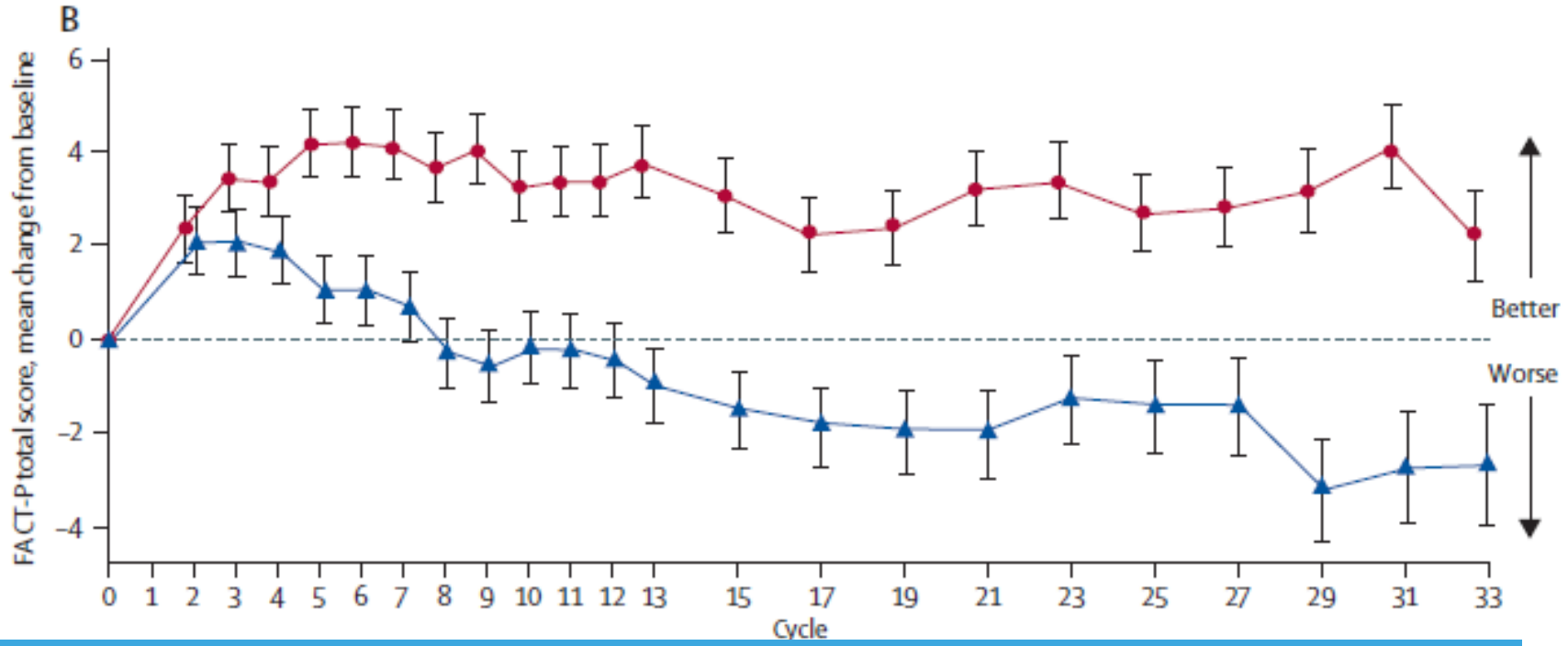
B Radiographic Progression-free Survival



Number at risk											
Abiraterone	597	533	464	400	353	316	251	177	102	51	21
Placebo	602	488	367	289	214	168	127	81	41	17	7

K. Fizazi, N Engl J Med 2017;377:352-60.

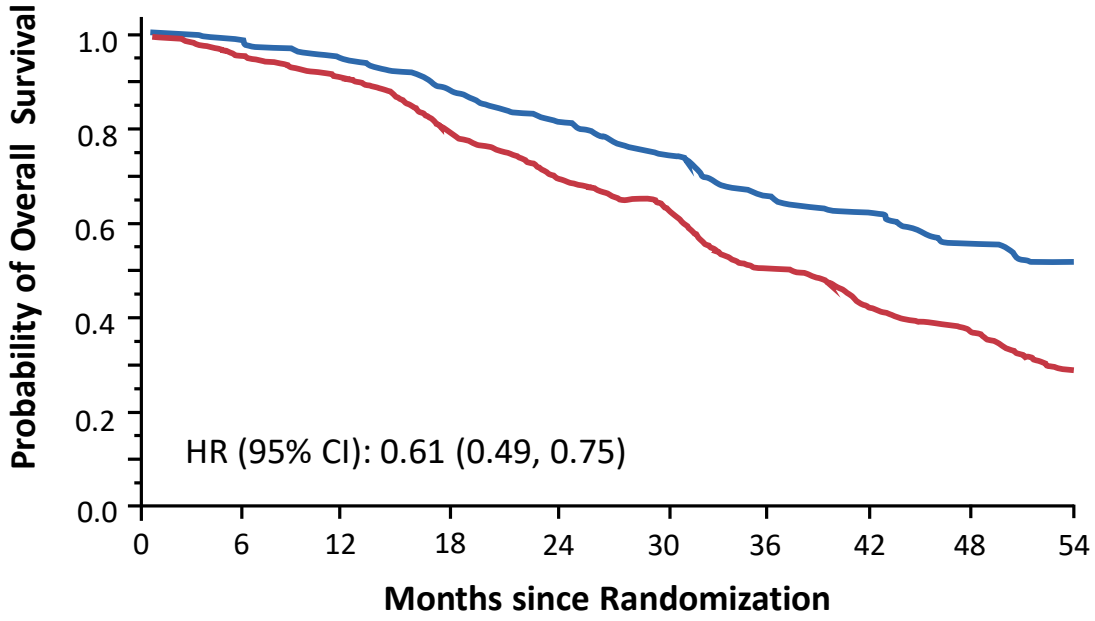
LATITUDE: ADT + abiraterone
Quality of life is improved vs placebo



Number of patients at each cycle																							
ADT plus abiraterone acetate and prednisone	597	597	557	543	542	527	517	503	494	476	462	461	449	438	409	387	373	342	325	309	277	250	219	181
ADT plus placebos	602	602	569	555	542	526	488	479	451	431	394	370	357	345	303	270	237	209	185	168	142	124	100	76

KN Chi, et al. Lancet Oncol 19(2):194-206, 2018

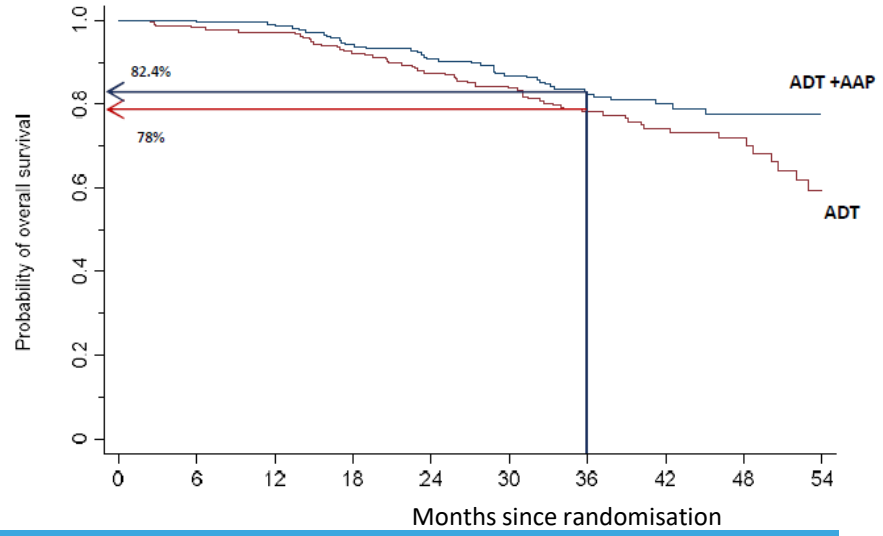
STAMPEDE: ADT + abiraterone in M1 patients improves overall survival



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

STAMPEDE: Abiraterone improves OS in high and low risk subgroups

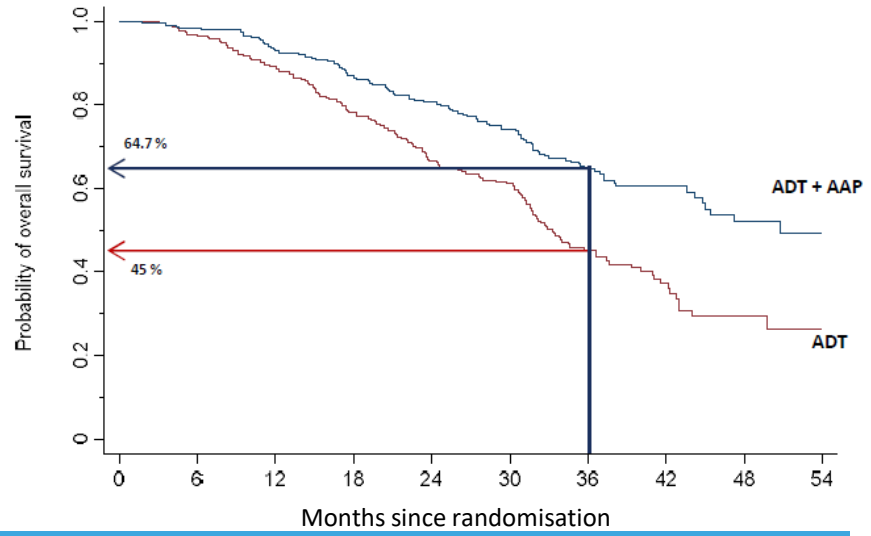
Low Risk



Number at patients (Events)									
AAP	208	(2)	205	(17)	186	(16)	131	(5)	45
ADT alone	220	(6)	210	(21)	186	(19)	125	(7)	43

OS – 4.4%
HR 0.66 (0.44-0.98)
P=0.041

High Risk

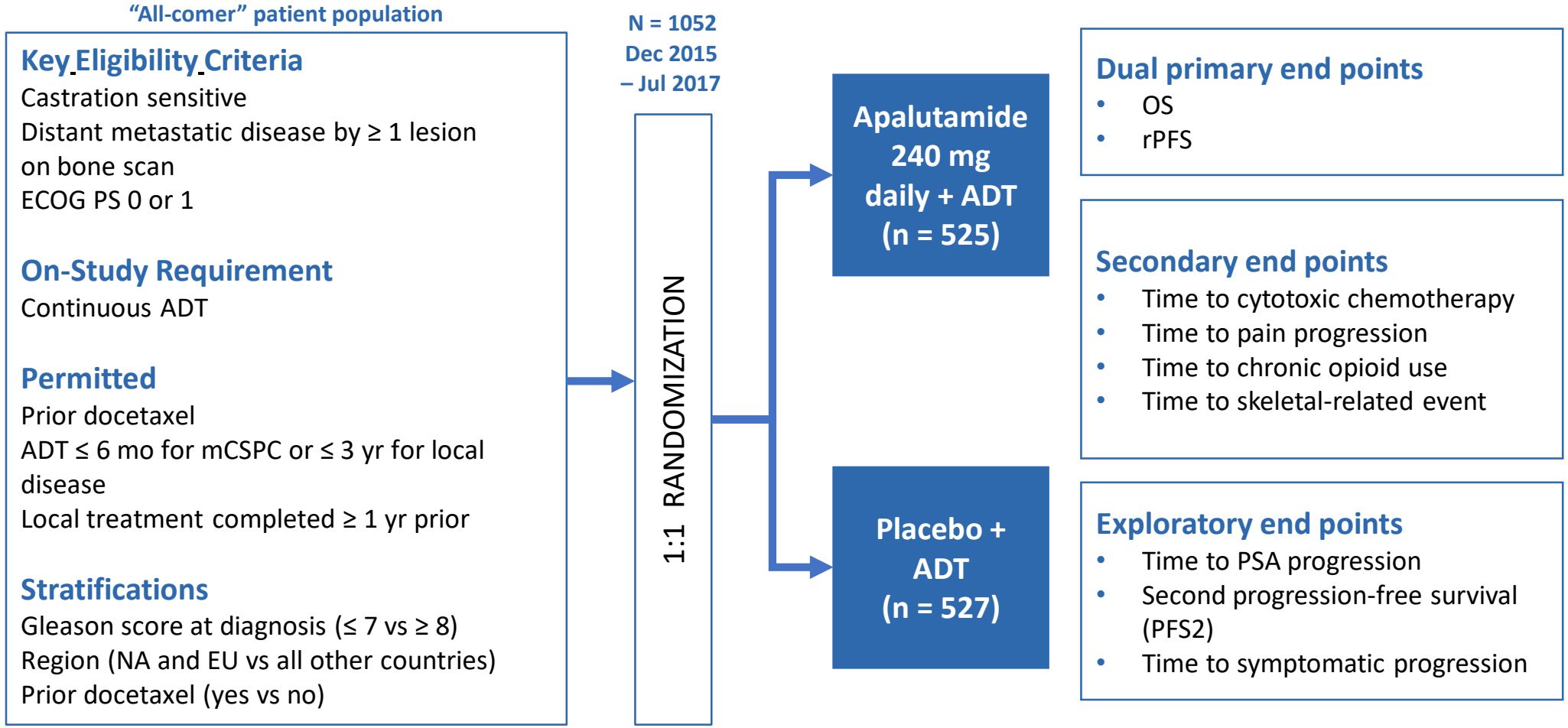


Number at patients (Events)									
AAP	241	(17)	220	(29)	190	(35)	106	(12)	28
ADT alone	232	(25)	204	(51)	148	(44)	71	(15)	13

OS – 19.7%
HR 0.54 (0.41-0.70)
P<0.001

A Hoyle, et al. ESMO 2018

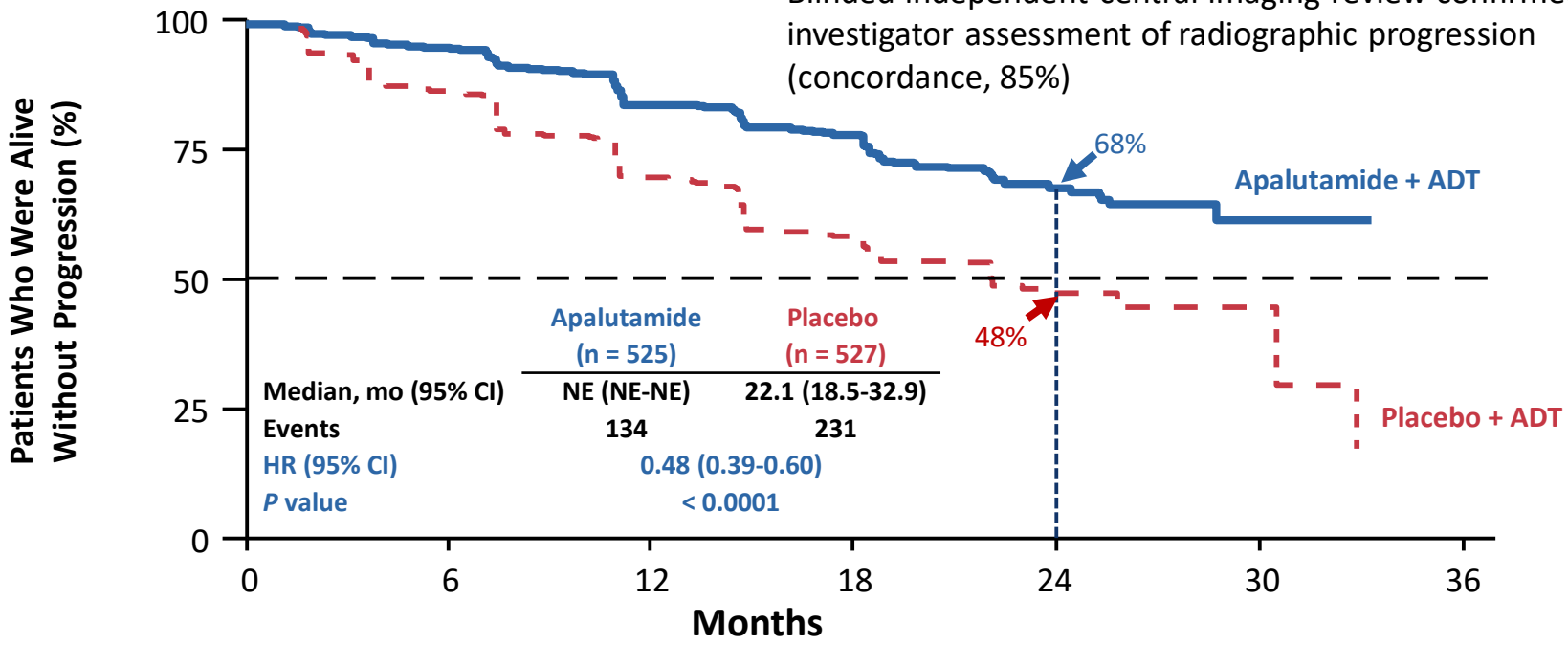
TITAN: Phase 3 double-blind, randomized study of apalutamide versus placebo in patients with metastatic castration-sensitive prostate cancer receiving androgen deprivation therapy



ECOG PS, Eastern Cooperative Oncology Group performance status;
NA, North America; PSA, prostate-specific antigen; rPFS, radiographic progression-free survival

TITAN: rPFS apalutamide significantly reduced risk of radiographic progression or death by 52%

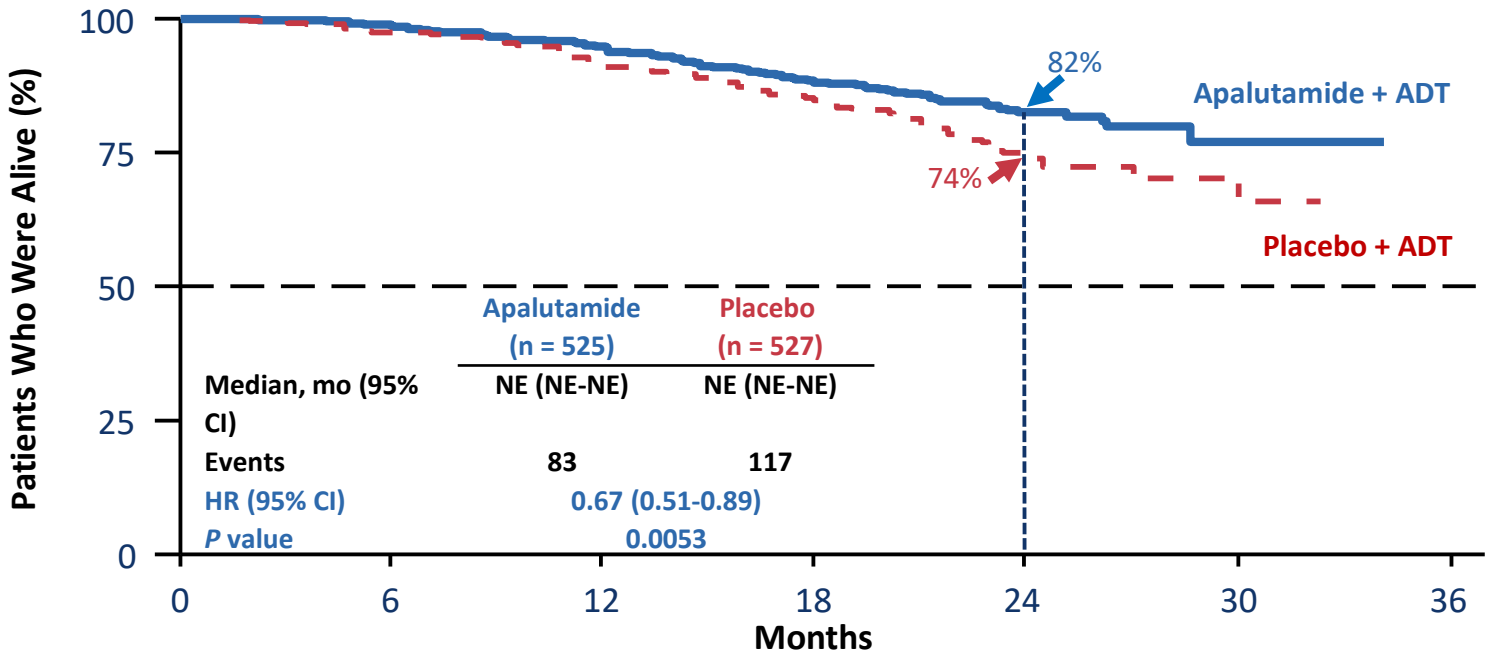
- Blinded independent central imaging review confirmed investigator assessment of radiographic progression (concordance, 85%)



Number at risk							
Apalutamide	525	469	389	315	89	2	0
Placebo	527	437	325	229	57	3	0

CI, confidence interval; NE, not evaluable.

TITAN OS: Apalutamide significantly reduced the risk of death by 33%



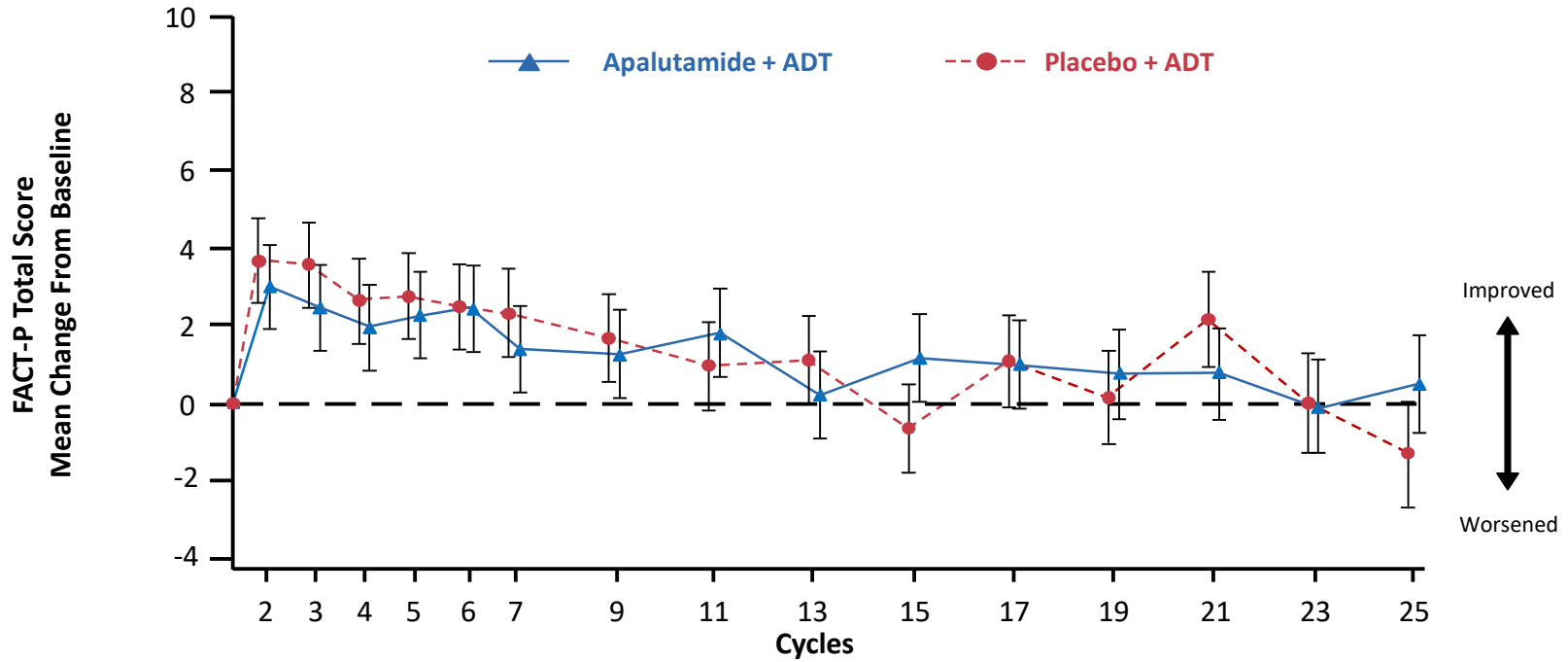
Number at risk							
Apalutamide	525	513	490	410	165	14	0
Placebo	527	509	473	387	142	16	0

TITAN: Adverse events of special interest

	Apalutamide + ADT (n = 524)		Placebo + ADT (n = 527)	
Adverse Event, n (%)	**All Grades**	**Grade ≥ 3**	**All Grades**	**Grade ≥ 3**
Rash[a]	142 (27.1)	33 (6.3)	45 (8.5)	3 (0.6)
Fatigue	103 (19.7)	8 (1.5)	88 (16.7)	6 (1.1)
Fall	39 (7.4)	4 (0.8)	37 (7.0)	4 (0.8)
Hypothyroidism[b]	34 (6.5)	0	6 (1.1)	0
Fracture[c]	33 (6.3)	7 (1.3)	24 (4.6)	4 (0.8)
Seizure[d]	3 (0.6)	1 (0.2)	2 (0.4)	0

[a]Rash was a grouped term including rash, butterfly rash, erythematous rash, exfoliative rash, follicular rash, generalized rash, macular rash, maculo-papular rash, papules, papular rash, pruritic rash, pustular rash, genital rash, blister, skin exfoliation, exfoliative dermatitis, skin reaction, systemic lupus erythematosus rash, toxic skin eruption, mouth ulceration, drug eruption, conjunctivitis, erythema multiforme, stomatitis, and urticaria.
[b]Hypothyroidism was a grouped term including autoimmune thyroiditis, blood thyroid-stimulating hormone increased, and hypothyroidism.
[c]Fracture was a grouped term including acetabulum fracture, ankle fracture, clavicle fracture, femoral neck fracture, femur fracture, fibula fracture, foot fracture, forearm fracture, fracture, fractured ischium, fracture pain, hand fracture, hip fracture, lower limb fracture, patella fracture, radius fracture, rib fracture, skull fracture, spinal compression fracture, spinal fracture, sternal fracture, thoracic vertebral fracture, tibia fracture, traumatic fracture, ulna fracture, upper limb fracture, and wrist fracture.
[d]Seizure was a grouped term including seizure and tongue biting.

TITAN: Health-related quality of life was preserved with Apalutamide + ADT and not different from placebo + ADT



Number at risck															
Apalutamide	358	350	349	342	333	315	305	302	298	278	265	252	225	188	147
Placebo	366	359	355	348	334	300	310	298	262	245	214	193	271	130	103

Error bars are standard errors of the mean. Raw FACT-P scores range from 0 to 156, with higher scores indicating more favorable health-related quality of life; a 6- to 10-point change in FACT-P total score would be the minimally important difference. However, this figure presents mean changes in total scores compared with baseline rather than raw total scores.
FACT-P, Functional Assessment of Cancer Therapy-Prostate.

ARCHES: Phase 3 study of androgen deprivation therapy with enzalutamide (ENZA) or placebo (PBO) in metastatic hormone-sensitive prostate cancer

Key eligibility criteria

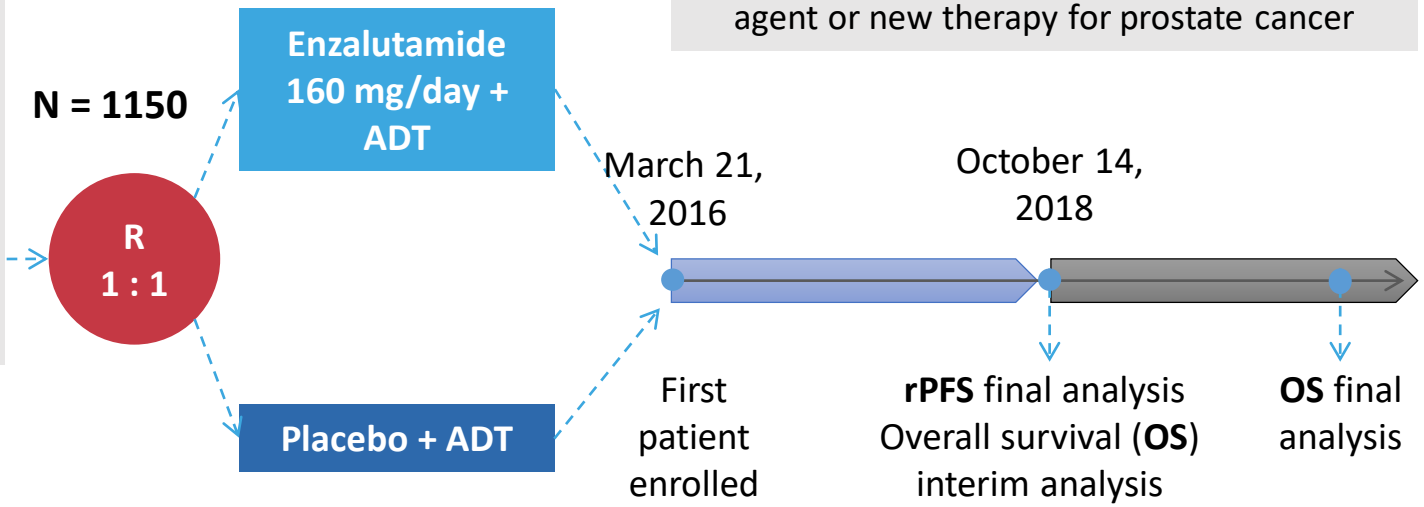
- mHSPC (confirmed by bone scan, CT, or MRI), histologically confirmed adenocarcinoma
- ECOG Performance Status 0 to 1
- Current ADT duration ≤3 months unless prior docetaxel, then ≤6 months

Stratification factors

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

Key discontinuation criteria

Radiographic progression, unacceptable toxicity, or initiation of an investigational agent or new therapy for prostate cancer

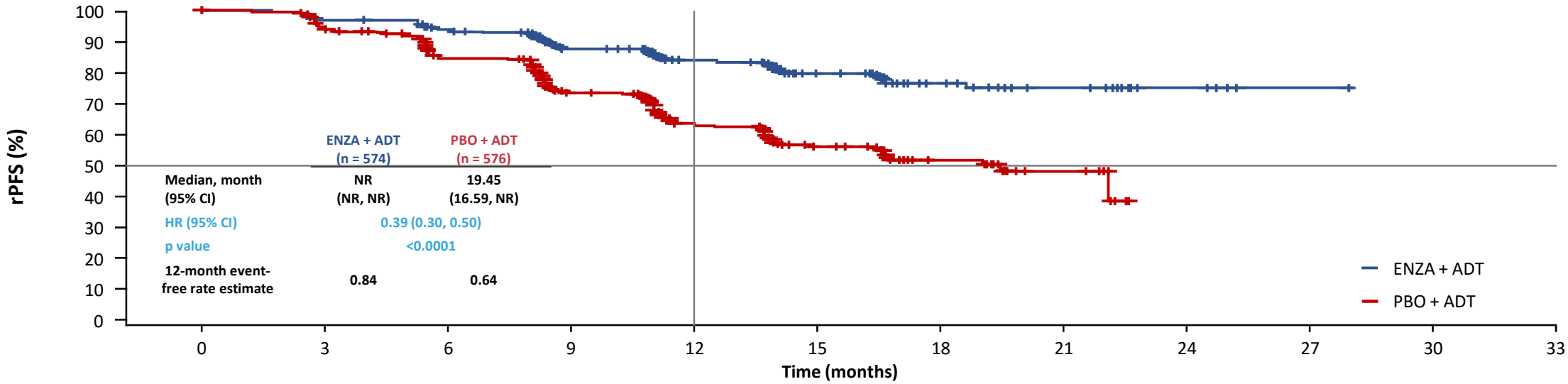


Primary endpoint

- rPFS: time from randomization to first objective evidence of radiographic progression assessed centrally, or death from any cause within 24 weeks of treatment discontinuation, whichever occurs first
  - Radiographic disease progression was defined by RECIST 1.1 criteria for soft tissue disease or by appearance of ≥2 new lesions on bone scan compared to baseline (at week 13) or vs. best response on treatment (week 25 or later). New bone scan lesions observed at week 13 required confirmation of ≥2 additional new bone lesions on subsequent scans

*Defined as metastases involving the viscera or, in the absence of visceral lesions, ≥4 bone lesions, ≥1 of which must be in a bony structure beyond the vertebral column and pelvic bone

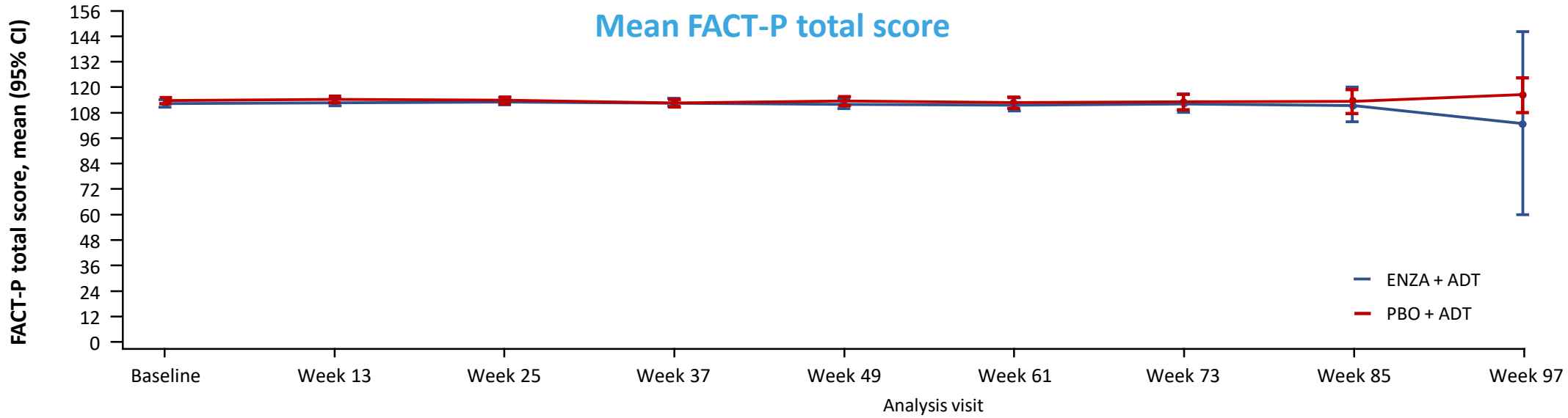
ARCHES Primary endpoint: rPFS



Number at risk						
ENZA + ADT	574	493	257	63	5	0
PBO + ADT	576	445	192	39	0	0

- At data cut-off, there were 262 events of radiographic progression (enzalutamide + ADT, 77; placebo + ADT, 185) and 25 deaths without radiographic progression (enzalutamide + ADT, 12; placebo + ADT, 13)
- 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
- As of October 14, 2018 (cut-off date), 769 patients were still on treatment, 437 (76%) for enzalutamide + ADT and 332 (58%) for placebo + ADT

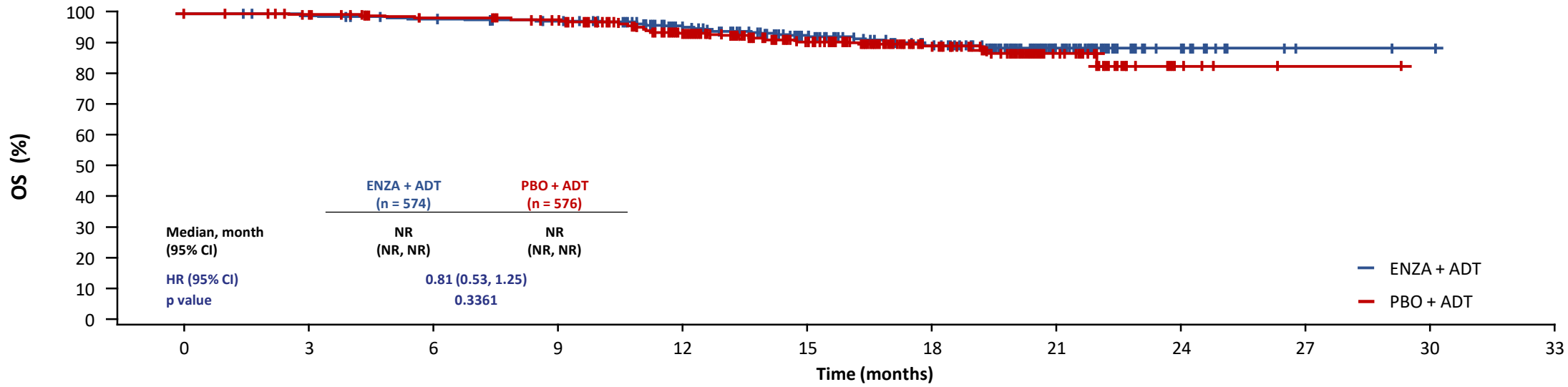
ARCHES: Quality of life over time



Number of patients									
PBO + ADT	553	529	487	429	298	191	101	36	6
ENZA + ADT	550	533	499	474	349	236	128	51	18

- As of data cut-off with a median follow up of 14.4 months, addition of enzalutamide to ADT did not have a significant impact on time to deterioration in urinary symptoms (HR 0.88, 95% CI 0.72, 1.08; p=0.2162) or FACT-P total score compared with placebo plus ADT

ARCHES: Overall survival interim analysis (84 deaths)

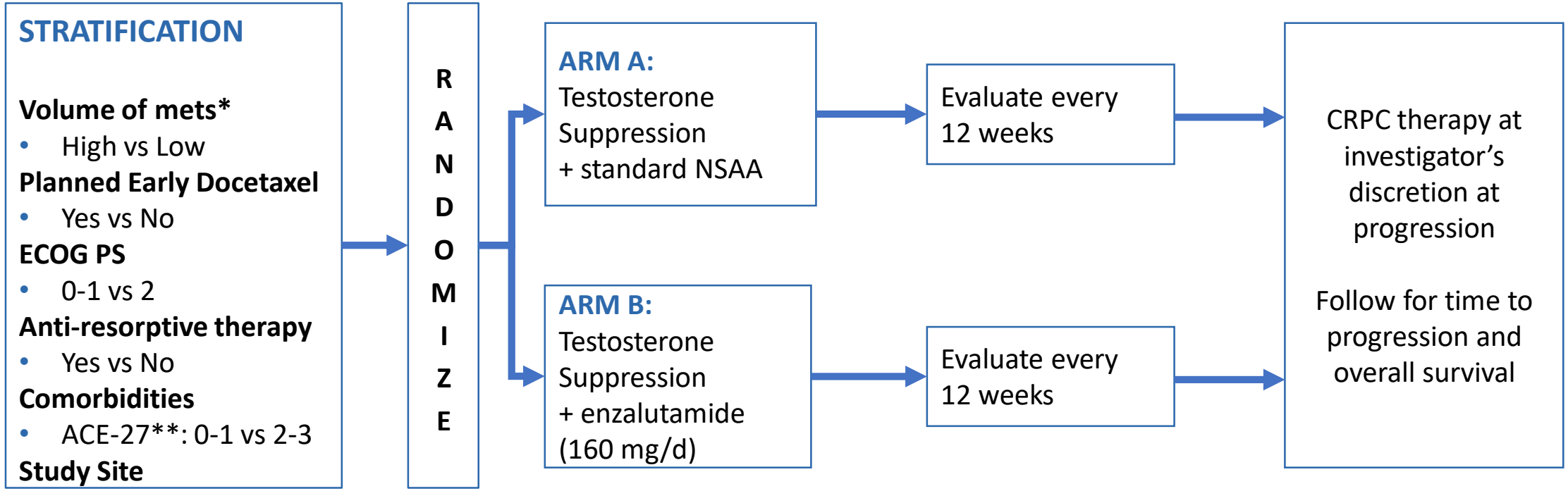


Number at risk						
ENZA + ADT	574	559	379	130	13	1
PBO + ADT	576	548	353	116	5	0

- At the time of interim analysis, OS data are not mature, with 25% of 342 events required for final analysis (enzalutamide plus ADT, 39; placebo plus ADT, 45) and 19% reduction in risk of death that is not statistically significant
- Final OS analysis will be conducted with ~342 deaths at 4% significance level

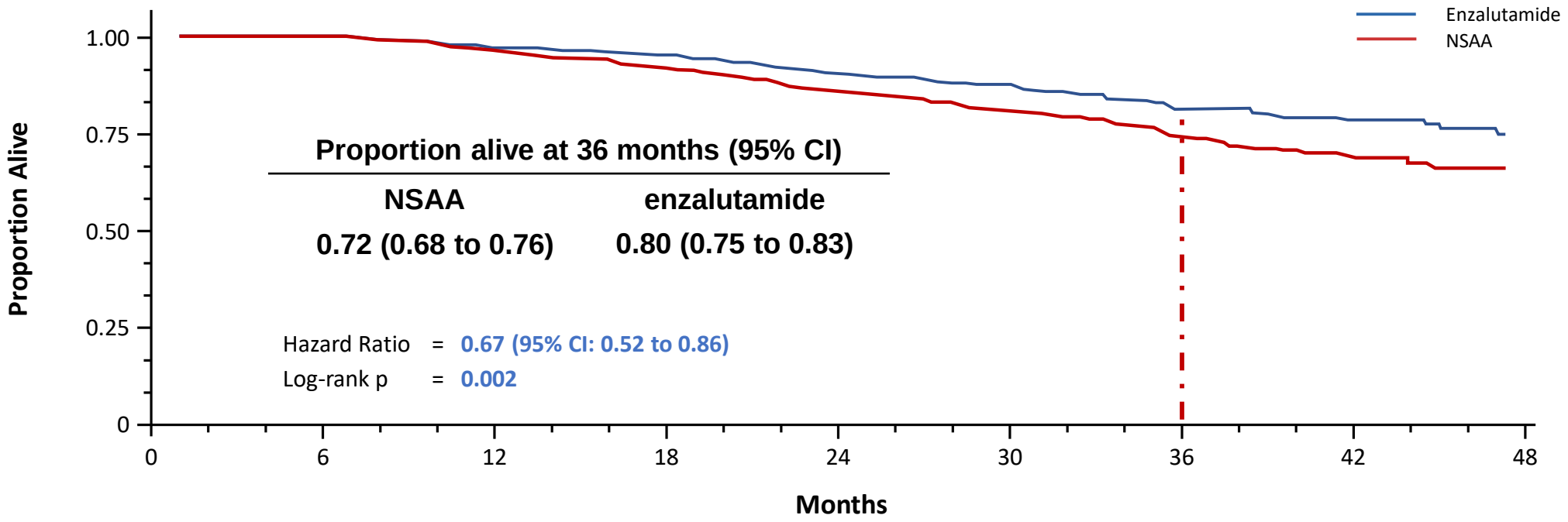
ENZAMET (ANZUP 1304)

AN ANZUP-LED INTERNATIONAL CO-OPERATIVE GROUP TRIAL (NHMRC CTC, CCTG, CTI, DFCI)



- Prior to randomization testosterone suppression up to 12 weeks and 2 cycles of docetaxel was allowed.
- Intermittent ADT and cyproterone were not allowed
- NSAA: bicalutamide; nilutamide; flutamide
- *High volume: visceral metastases and/or 4 or more bone metastases (at least 1 beyond pelvis and vertebral column)
- **Adult Co-morbidity Evaluation-27

ENZAMET Primary endpoint: Overall survival



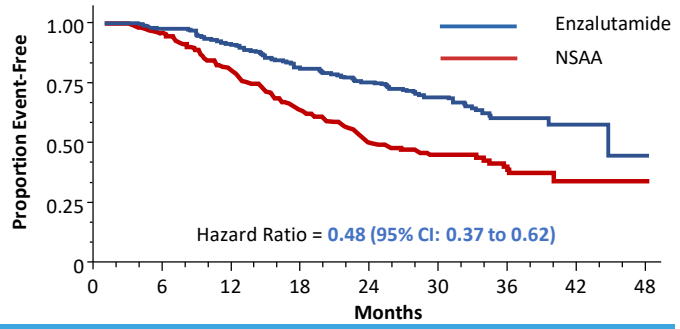
Number at risk									
NSAA	562	551	531	501	452	311	174	86	32
Enzalutamide	563	558	541	527	480	340	189	106	45

ENZAMET: Concurrent docetaxel prespecified subgroup

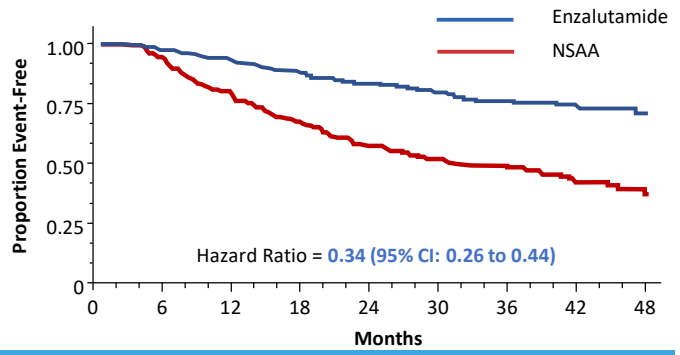
Testosterone Suppression + docetaxel N=503 (71% High Volume)

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

Clinical Progression-Free Survival

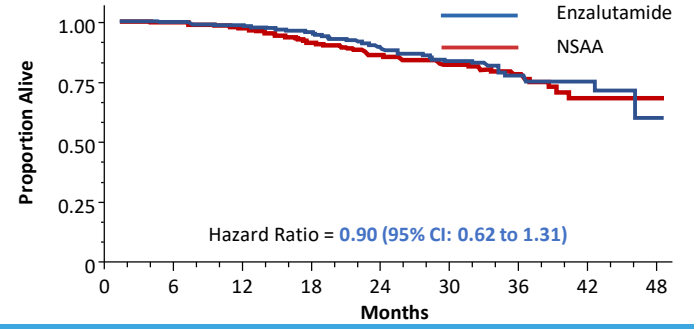


Number at risk									
NSAA	249	230	185	148	112	73	21	6	1
Enzalutamide	254	248	226	202	178	109	35	12	2

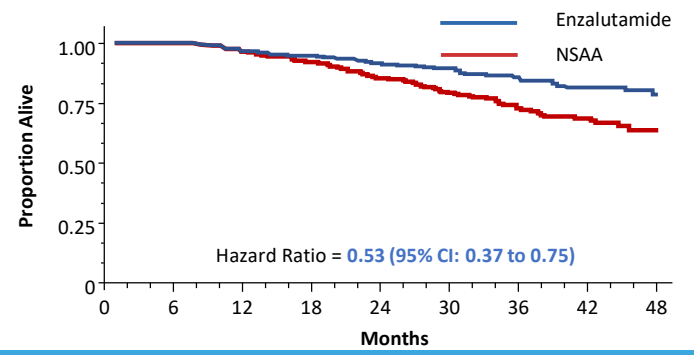


Number at risk									
NSAA	313	282	233	198	160	109	75	44	16
Enzalutamide	309	299	281	266	246	175	121	72	34

Overall Survival



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



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

Duration of study therapy and reasons for discontinuing

	TS + NSAA N=558	TS + ENZA N=563
6 cycles of early docetaxel*	**76% of 238**	**65% of 243**
Proportion on Rx at 36 months (95% CI)	0.34 (0.29 to 0.38)	0.62 (0.57 to 0.66)
Reasons for discontinuing	**N=356**	**N=201**
Discontinue due to adverse event	**14 (4%)**	**33 (16%)**
Imaging	144 (40%)	88 (44%)
Symptoms	55 (15%)	32 (16%)
New anti-cancer Rx	45 (13%)	7 (4%)
Clinician Preference	58 (16%)	13 (6%)
Death	7 (2%)	6 (3%)

*of those who received at least one cycle of docetaxel

Summary

Intensifying ADT with next generation hormonal therapy delays progression and improves overall survival

- ADT + abiraterone + prednisone
  - LATITUDE: Newly diagnosed high risk (Health Canada approval)
  - STAMPEDE: Newly diagnosed metastatic
- New evidence: ADT + apalutamide
  - TITAN: “all comers” M1 had improved rPFS and OS
    - Newly diagnosed high and low risk/volume; prior localized disease/treatment with recurrent M1; Prior docetaxel
- New evidence: ADT + enzalutamide
  - ARCHES and ENZAMET: “all comers” M1 had improved rPFS and OS
    - Don’t combine ADT + enzalutamide + docetaxel

Docetaxel in the mCSPC patient: Everything old is new again

Scott North, MD, FRCPC, MHPE
Medical Oncologist
Cross Cancer Institute
Edmonton, Alberta

Overview

DOCETAXEL	How did we get to the point of using it at all for prostate cancer?
Docetaxel in the CSPC patient	• CHAARTED • STAMPEDE • ENZAMET and concurrent chemo/ARAT use

Docetaxel in Metastatic CRPC

Prior to 2004, the standard chemotherapy for advanced prostate cancer was mitoxantrone

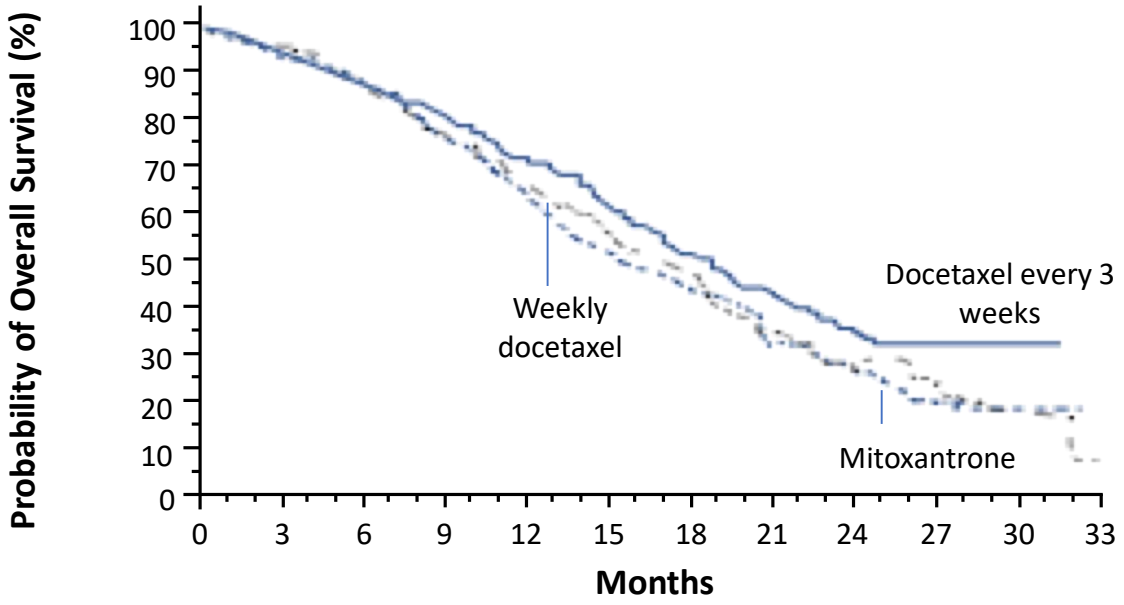
Primary benefit was quality of life but no survival benefit had ever been shown although trials were small and underpowered.

- Two pivotal trials demonstrated that docetaxel could improve survival and QoL for mCRPC patients
  - TAX327[1]
  - SWOG 9916[2]

1. Tannock I et al. N Engl J Med 2004; 351:1502-1512
2. Petrylak D et al. N Engl J Med 2004; 351:1513-1520

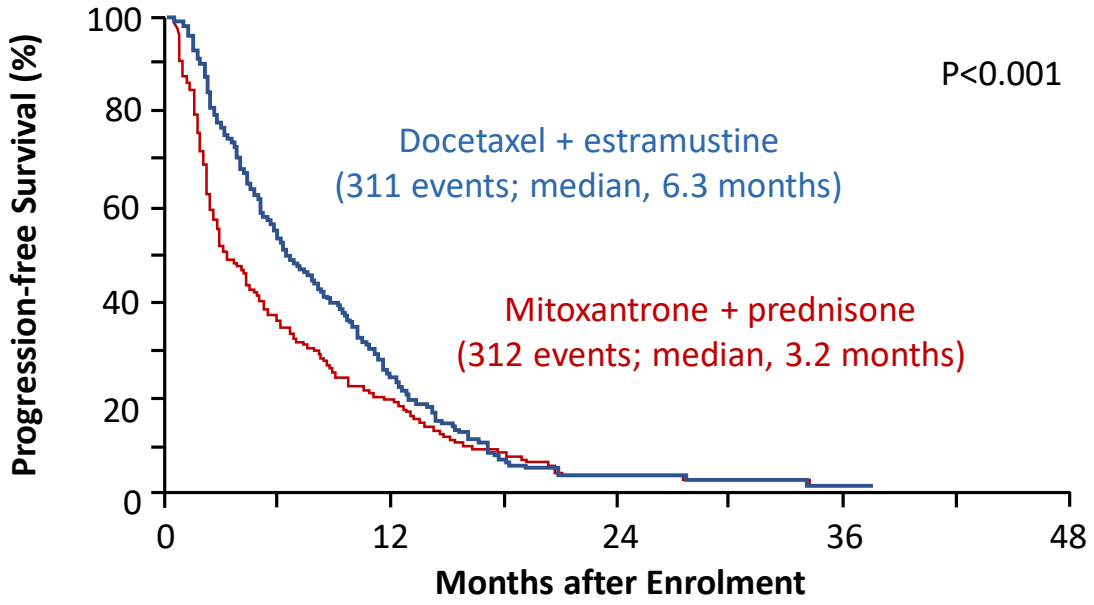
Docetaxel in CRPC

TAX327



Number at risk						
Docetaxel every 3 weeks	335	296	217	104	37	5
Weekly docetaxel	334	297	200	105	29	4
Mitoxantrone	337	297	192	95	29	3

SWOG 9916



Number at risk					
D + E	338	176	75	20	6
M + P	336	116	56	15	6

Fast Forward to 2014: Docetaxel moves into the CSPC space

Remember that in the mCSPC discussions, we speak about patients with high/low volume disease and high/low risk of disease

VOLUME

Defined by the CHAARTED trial

- High volume is visceral disease OR >4 bone mets with at least one outside the spine/pelvis
- Everyone else is low volume

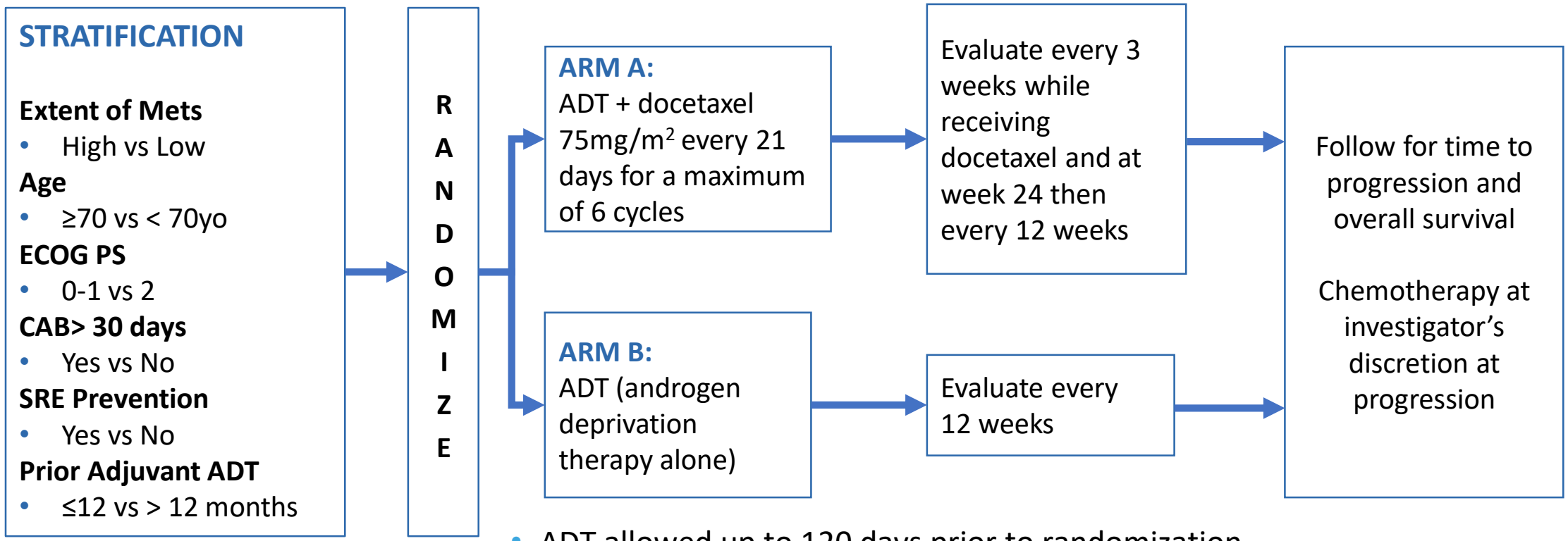
RISK

Defined by the LATITUDE trial

- Presence of at least 2 of the 3 risk factors:
  - Gleason 8-10
  - visceral disease
  - >3 bone mets

Other trials do not necessarily stratify by these volume and risk definitions

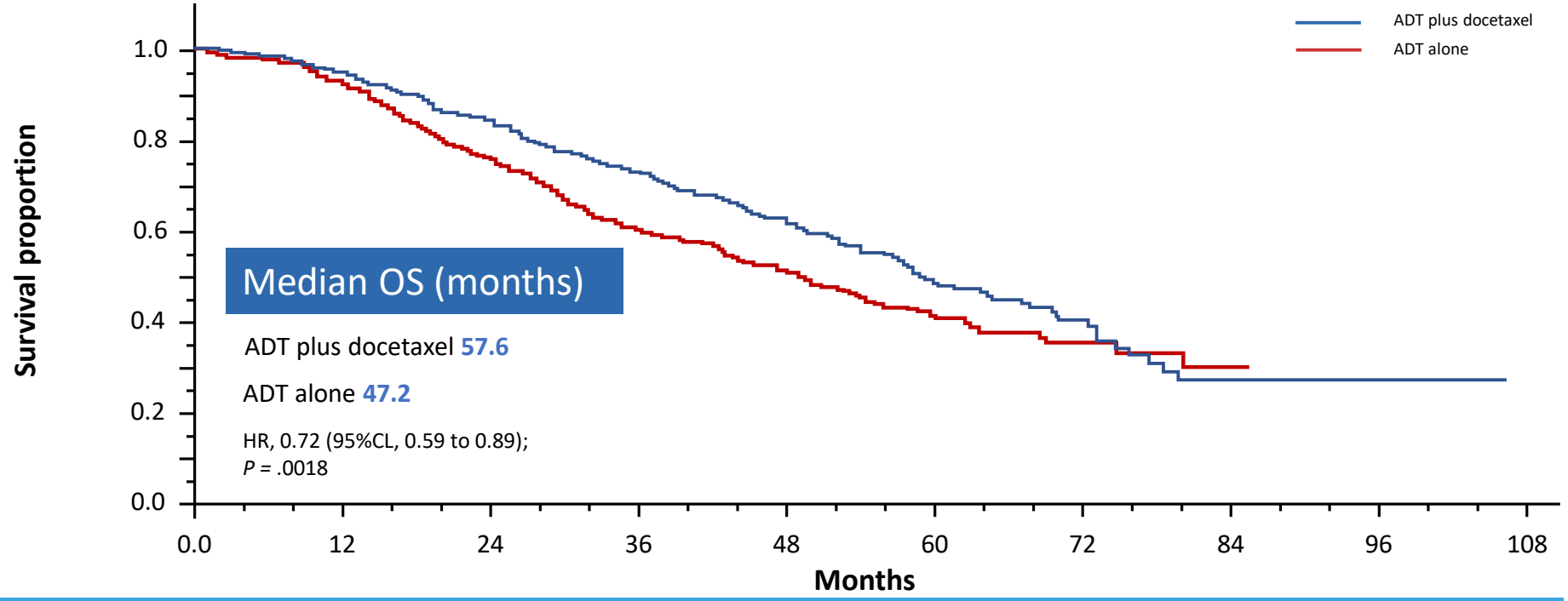
E3805 – CHAARTED Treatment



- ADT allowed up to 120 days prior to randomization
- Intermittent ADT dosing was not allowed
- Standard dexamethasone premedication but no daily prednisone

Updated OS

J Clin Oncol. 2018 Apr 10; 36(11): 1080–1087

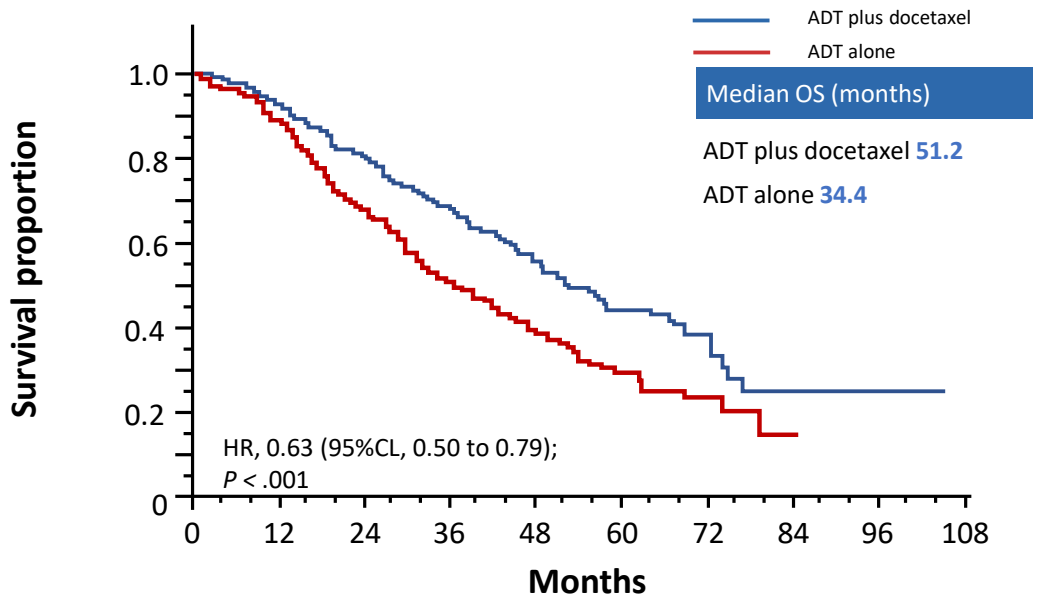


Number at risk										
ADT plus docetaxel	397	366	314	245	155	67	28	7	2	0
ADT alone	393	352	278	198	126	45	21	2	0	0

OS by Volume Stratification

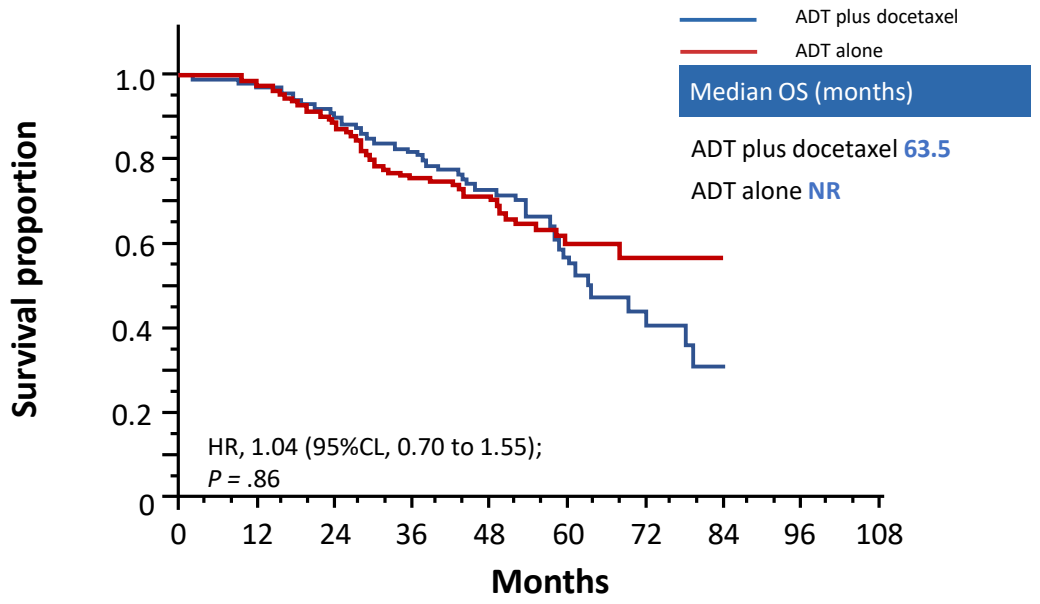
J Clin Oncol. 2018 Apr 10; 36(11): 1080–1087

High Volume



Number at risk										
ADT plus docetaxel	263	239	202	151	91	41	16	5	2	0
ADT alone	250	215	156	104	59	19	9	1	0	0

Low Volume



Number at risk										
ADT plus docetaxel	134	127	112	94	64	26	12	2	0	0
ADT alone	143	137	122	94	67	26	12	1	0	0

Results shown are for de novo metastatic patients; results similar for patients recurring after prior local therapy

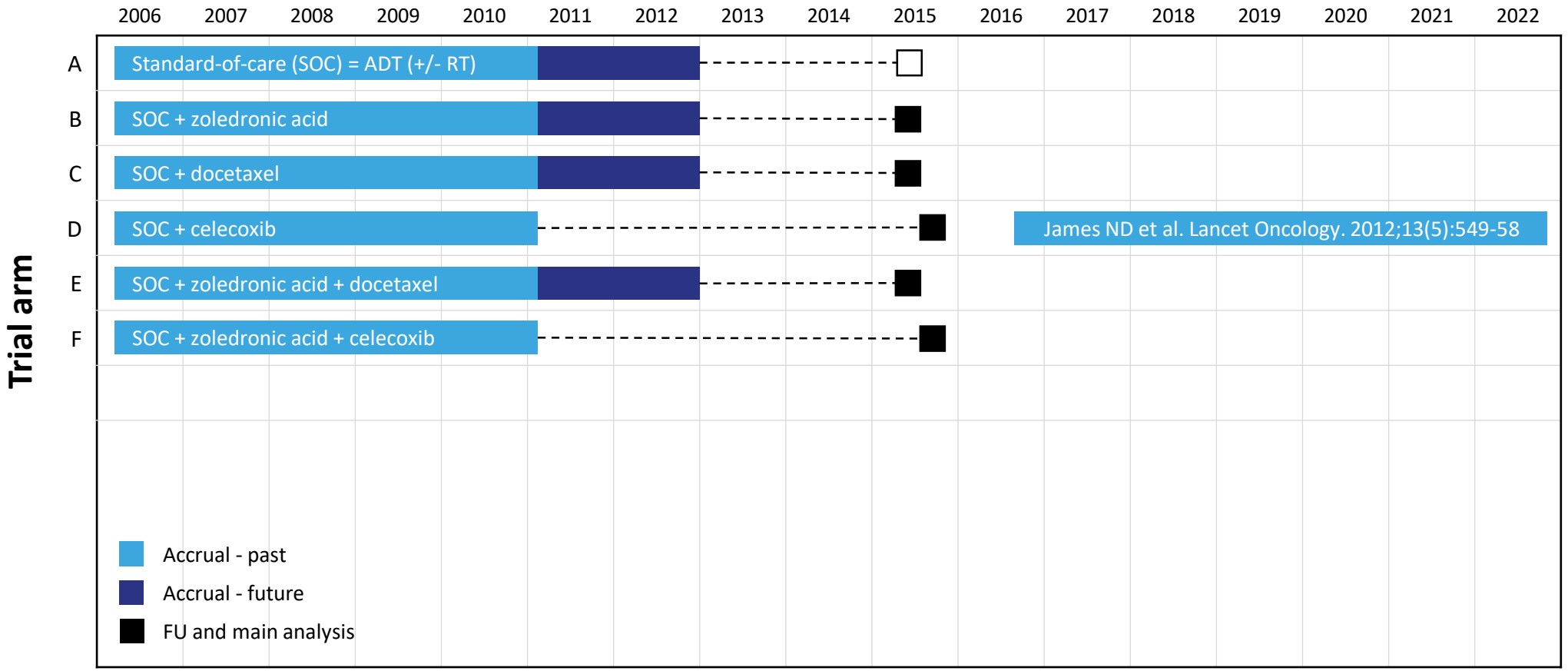
Docetaxel and/or zoledronic acid for hormone-naïve prostate cancer: First survival results from STAMPEDE

Nicholas James
University of Warwick and Queen Elizabeth Hospital Birmingham
on behalf of

Matthew Sydes, Malcolm Mason, Noel Clarke, David Dearnaley, Melissa Spears, Robin Millman, Chris Parker, Alastair Ritchie, J. Martin Russell, John Staffurth, Robert Jones, Shaun Tolan, John Wagstaff, Andrew Protheroe, Rajaguru Srinivasan, Alison Birtle, Joe O'Sullivan, Richard Cathomas, Mahesh Parmar and the STAMPEDE Investigators

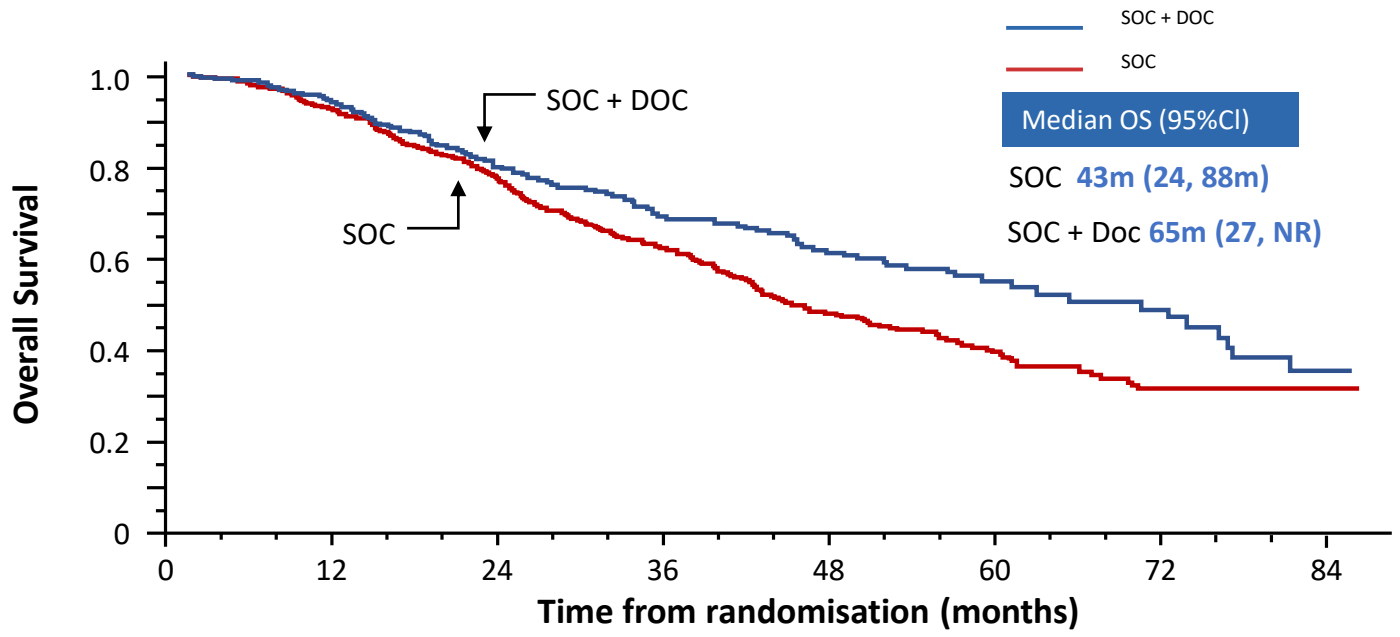
STAMPEDE: Activity stage 2

Celecoxib stops accrual



Docetaxel: Survival – M1 Patients

Docetaxel: Survival – M1 Patients



Group at Risk (events)															
SOC	725	(66)	645	(117)	469	(75)	254	(52)	134	(21)	58	(10)	24	(0)	10
SOC + Doc	362	(27)	326	(49)	242	(27)	151	(13)	91	(8)	37	(5)	24	(5)	9

SOC	**343 deaths**
SOC + Doc	**134 deaths**
HR (95%CI)	**0.73** (0.59, 0.89)
P-value	**0.002**

Non-PH p-value 0.23

Restricted mean OS time

SOC	49.3m
SOC + Doc	56.1m
Diff (95%CI)	6.8m (2.8,11.0m)

STAMPEDE

Supports the use of docetaxel in improving survival for hormone sensitive prostate cancer across a spectrum of patients.

Majority of the benefits observed in the M1 patient population but this trial does not stratify by volume of disease.

OVERALL SURVIVAL (OS) RESULTS OF A PHASE III RANDOMIZED TRIAL OF STANDARD OF CARE THERAPY WITH OR WITHOUT ENZALUTAMIDE FOR METASTATIC HORMONE SENSITIVE PROSTATE CANCER (mHSPC)

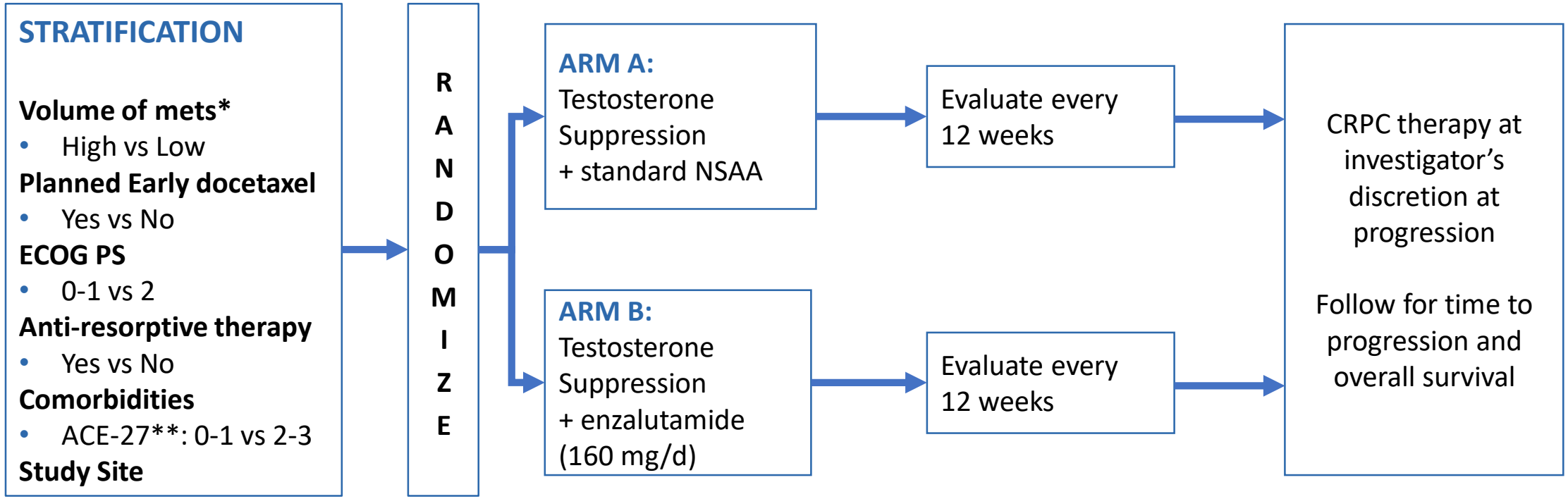
ENZAMET (ANZUP 1304):

AN ANZUP-LED INTERNATIONAL CO-OPERATIVE GROUP TRIAL (NHMRC CTC, CCTG, CTI, DFCI)

Christopher Sweeney, Andrew Martin, Robert Zielinski, Alastair Thomson, Thean Hsiang Tan, Shahneen Sandhu, M. Neil Reaume, David Pook, Francis Parnis, Scott North, Gavin Marx, John McCaffrey, Ray McDermott, Nicola Lawrence, Lisa Horvath, Mark Frydenberg, Simon Chowdhury, Kim Chi, Martin Stockler, Ian Davis

Christopher Sweeney, MBBS

ENZAMET Treatment



- Prior to randomization testosterone suppression up to 12 weeks and 2 cycles of docetaxel was allowed.
- Intermittent ADT and cyproterone were not allowed
- NSAA: bicalutamide; nilutamide; flutamide
- *High volume: visceral metastases and/or 4 or more bone metastases (at least 1 beyond pelvis and vertebral column)
- **Adult Co-morbidity Evaluation-27

Patient Characteristics

	TS + NSAA (N=562)		TS + enzalutamide (N=563)	
	N	%	N	%
Planned Early Docetaxel				
Yes	249	44%	254	45%
No	313	56%	309	55%
Volume of Metastases				
High	297	53%	291	52%
Low	265	47%	272	48%
ACE-27 Stratum				
0-1	419	75%	422	75%
2-3	143	25%	141	25%
Prostate Cancer Related Therapies				
Planned SRE Rx	58	10%	55	10%
Prior Local Rx**	235	42%	238	42%
Prior Adjuvant ADT	40	7%	58	10%

Early docetaxel

- 61% high volume; 27% of low volume

ADT: androgen deprivation therapy

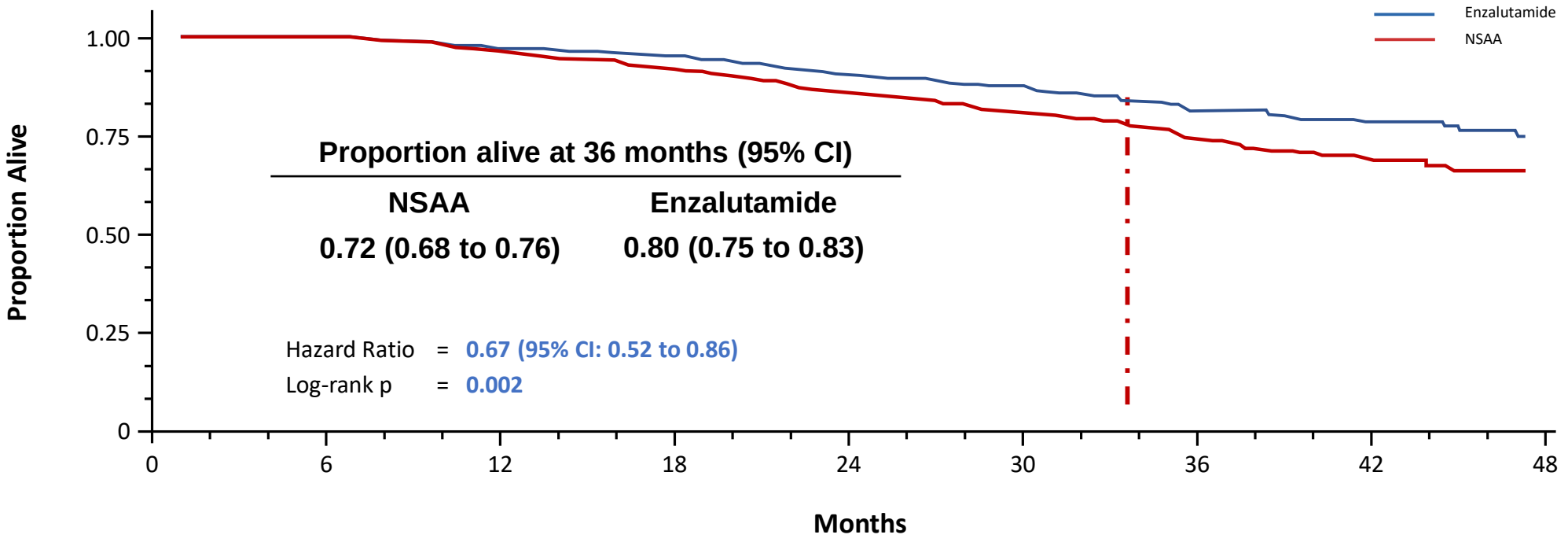
ACE: Adult Comorbidity Evaluation-27

SRE Rx: Skeletal related event

- Antiresorptive bone therapy

****Prostatectomy or radiation**

Primary Endpoint: Overall survival

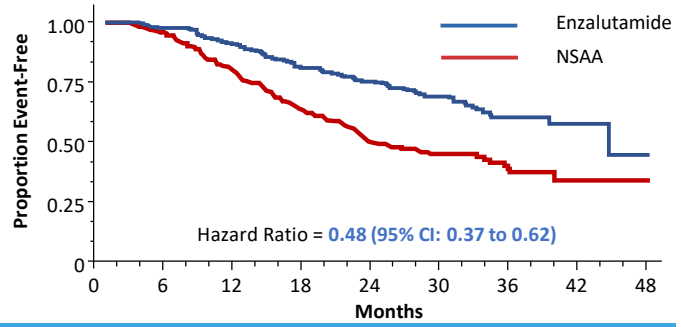


Number at risk									
NSAA	562	551	531	501	452	331	174	86	32
Enzalutamide	563	558	541	527	480	340	189	106	45

Concurrent Docetaxel: Prespecified subgroup of interest (biology and treatment implications)

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

Clinical Progression-Free Survival



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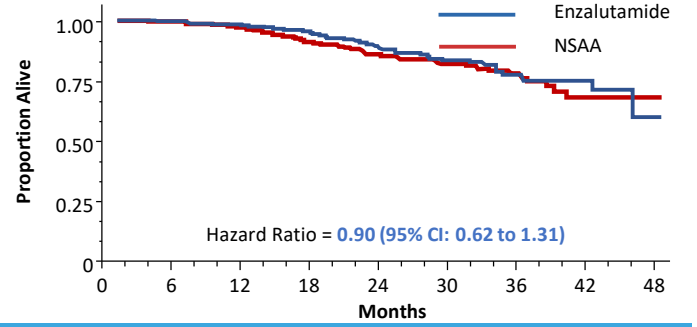
Overall Survival



Number at risk									
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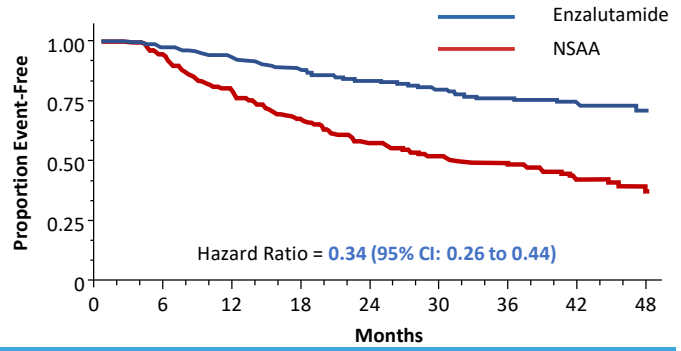
Enzalutamide	254	252	246	238	210	139	54	19	3

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



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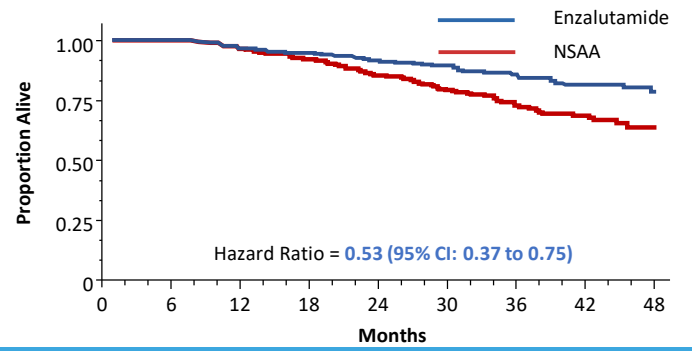


Number at risk									
NSAA	313	310	296	281	249	176	118	73	30
Enzalutamide	309	306	295	289	270	201	135	87	42

ENZAMET Conclusions

1. Enzalutamide added to ADT improves OS irrespective of volume of disease
2. There is no conclusive proof at this time that concurrent use of enzalutamide + docetaxel followed by enzalutamide "maintenance" improves OS compared to enzalutamide alone
   - Pick either chemotherapy or AR targeted treatment
3. Further follow up will be needed
4. Combination therapy with enzalutamide and docetaxel has more toxicity

Conclusions

1. Docetaxel provides a survival advantage for men with mCSPC but predominantly in those with high volume disease

2. Low volume patients (by conventional definitions) do not benefit from the addition of docetaxel

3. Concurrent/ sequential docetaxel and AR targeted therapies do not appear to have additive benefit; ongoing follow-ups are needed

Polling Questions

Question 3

A 47 year old man presents with screening PSA of 6.6 and a prostate nodule on DRE. Biopsy reveals Gleason score 10/10 adenocarcinoma. CT/Bone Scan/PSMA-PET imaging reveals 2 pelvic lymph node metastases and 3 bone metastases (T and L-spine).

Question 3 : What management would you offer?

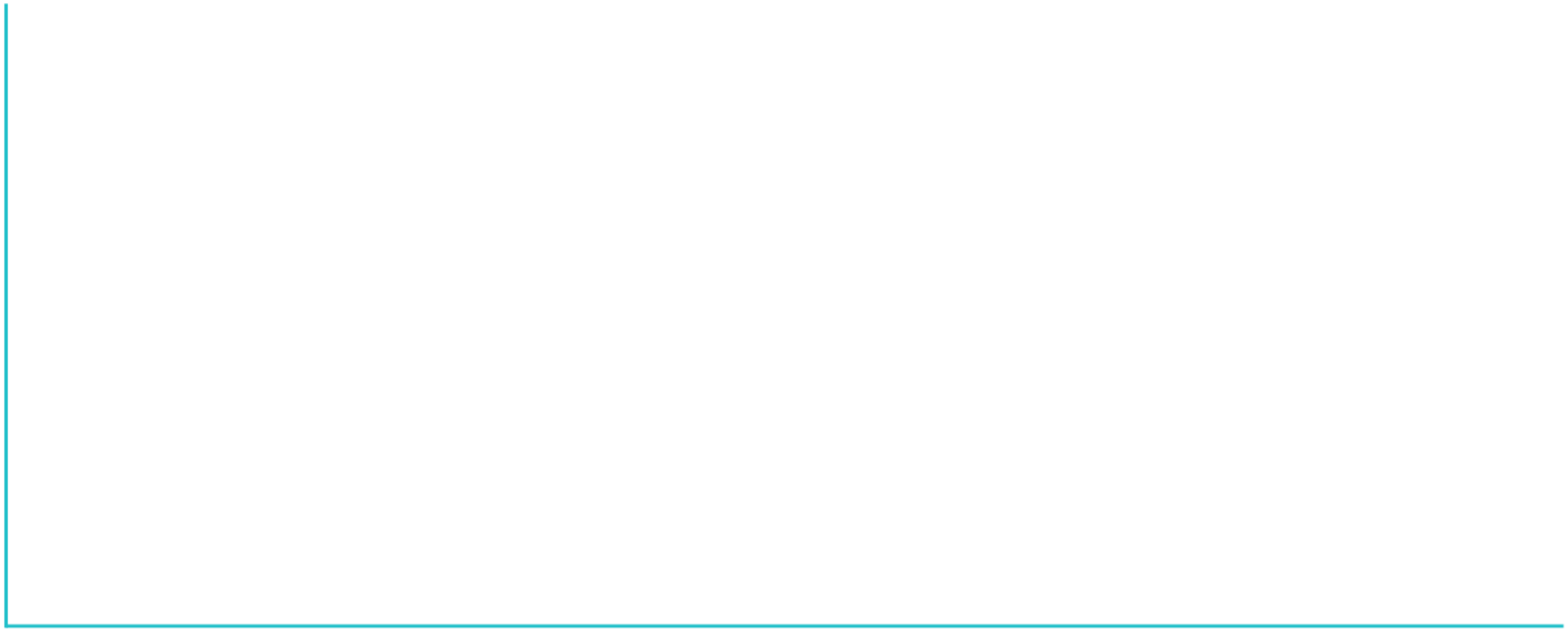
1. ADT alone: he has low volume disease

2. ADT + abiraterone: he has high risk disease

3. ADT + apalutamide or enzalutamide: he has metastatic disease

4. ADT + docetaxel + apalutamide: he has nasty metastatic prostate cancer

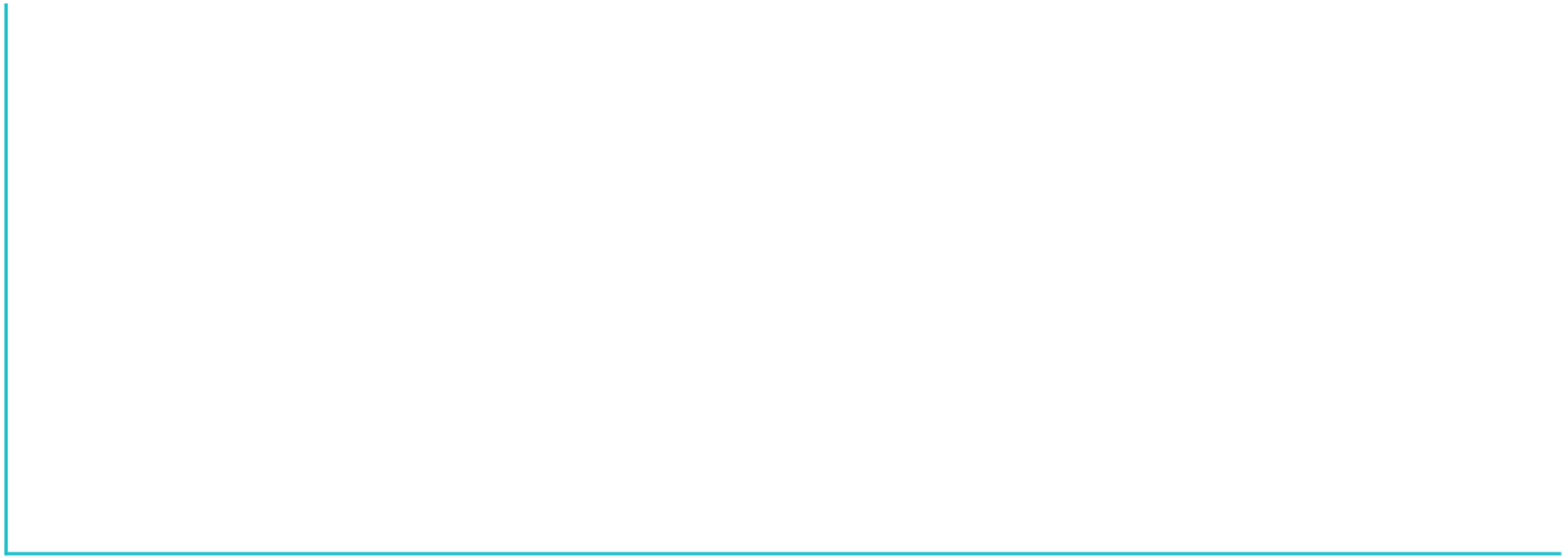
Question 3 : What management would you offer?



1. ADT alone: he has low volume disease
2. ADT + abiraterone: he has high risk disease
3. ADT + apalutamide or enzalutamide: he has metastatic disease
4. ADT + docetaxel + apalutamide: he has nasty metastatic prostate cancer

Question 3 : What management would you offer?

Poll locked. Responses not accepted.



Question 4

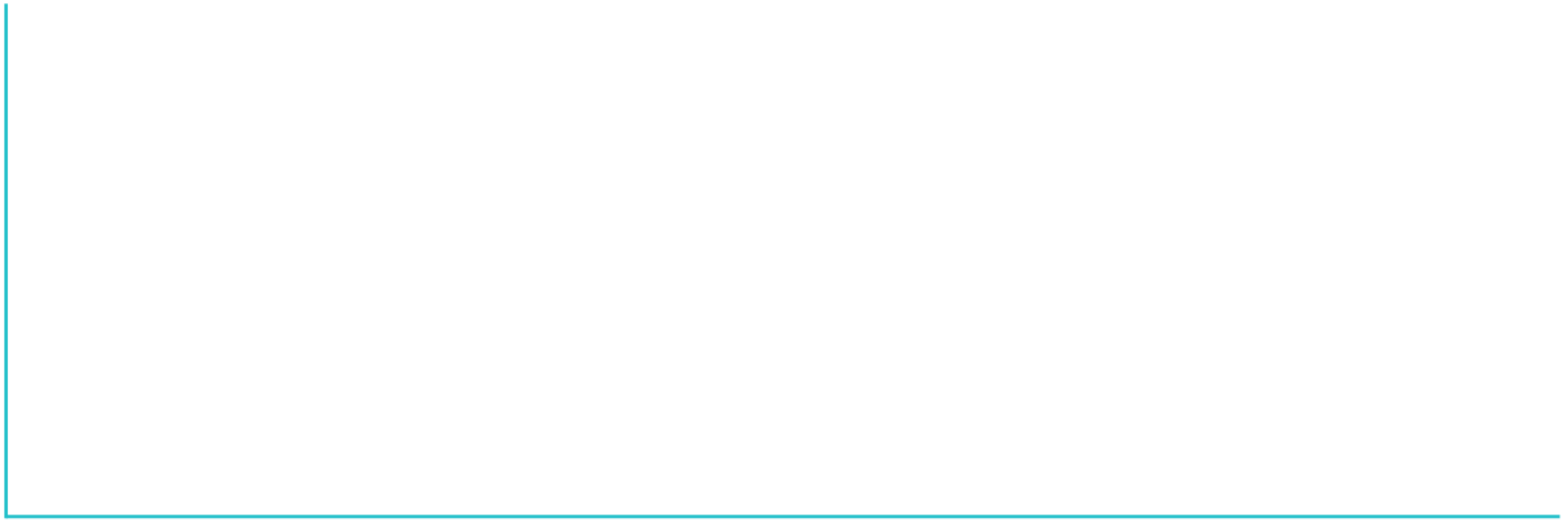
A 69 year old previously healthy man presents with bone pain and is found to have a large hard nodule in his prostate on DRE, 6 bone metastases throughout his skeleton and a PSA of 150. A biopsy of his prostate reveals adenocarcinoma

Gleason score 5 + 4 = 9 in 8/8 cores.

Question 4 : The most appropriate therapy for him would be :

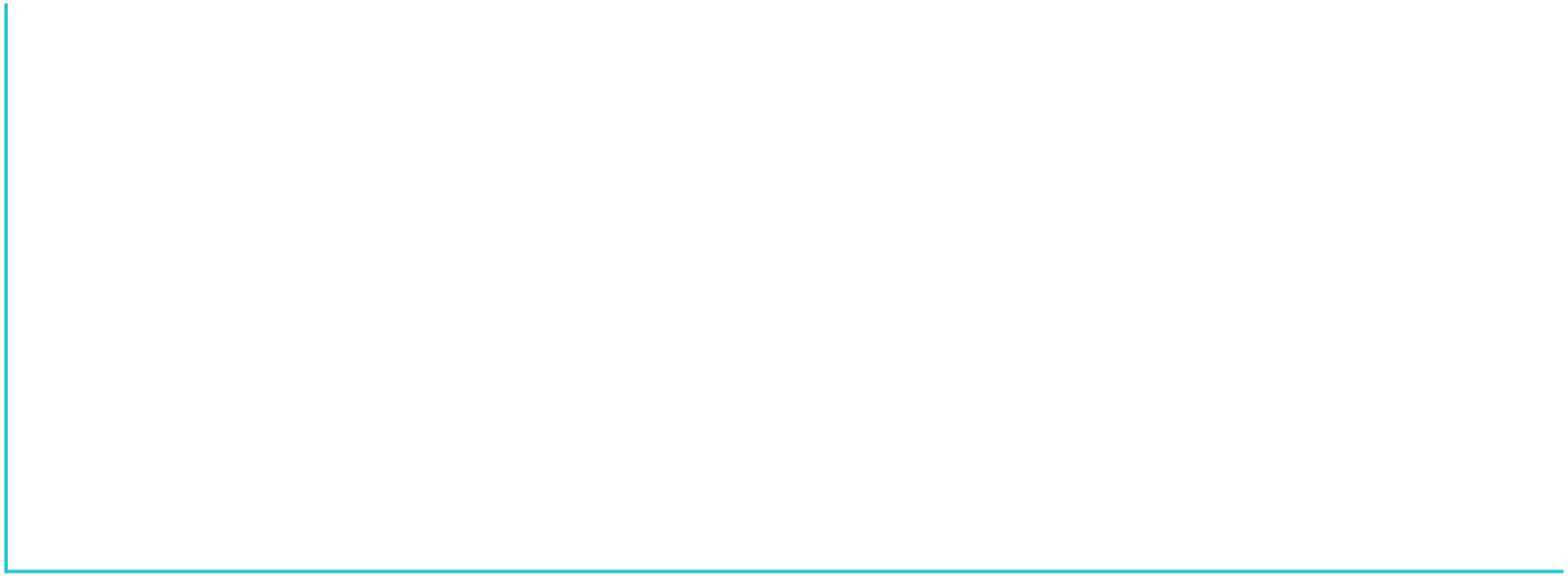
1. Androgen deprivation therapy (ADT) with medical or surgical castration
2. ADT + abiraterone
3. ADT + docetaxel + denosumab every 4 weeks
4. ADT + docetaxel + abiraterone
5. ADT + docetaxel or abiraterone + radiation to the prostate
6. I don't know

Question 4 : The most appropriate therapy for him would be :



Question 4 : The most appropriate therapy for him would be :

Poll locked. Responses not accepted.



Q&A


74th Annual Meeting
June 29 – July 1
74e Congrès annuel
29 juin – 1 juillet
QUÉBEC
2019

Final Disclosure

- The CUA is committed to providing high-quality CPD programs that are fair and balanced. If you have perceived any bias in this presentation or have any feedback, please contact:

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