CARCINOMA PROSTATICO METASTATICO

LA CARTA D'IDENTITÀ DEL PAZIENTE CANDIDABILE AI NUOVI TRATTAMENTI

14 OTTOBRE 2018

Palazzo dei Congressi di Riccione

Il paziente metastatico ormonosensibile: identificazione e trattamento

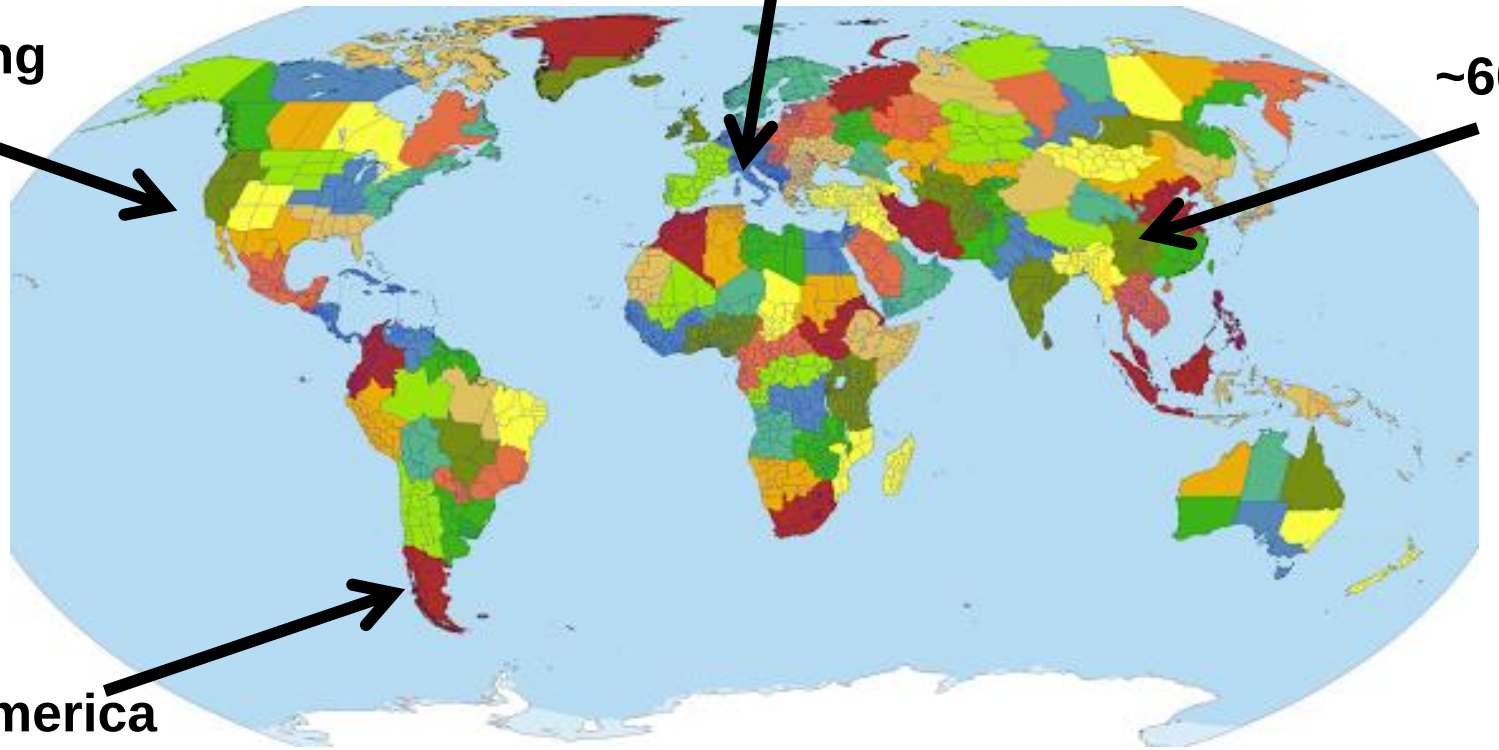
Cosimo De Nunzio
UOC Urologia, Ospedale Sant'Andrea
Sapienza - Università di Roma

De Novo Metastatic Prostate Cancer incidence

~6 % across Europe

~3% in US and rising

~60% in Asia Pacific



~4-10% in Latin America

Historically, androgen deprivation therapy (ADT) has been the standard of care

1. Weiner AB, et al. *Prostate Cancer Prostatic Dis*. 2016;19:395-397. 2. Buzzoni C, et al. *Eur Urol*. 2015;68:885-890. 3. Chen R, et al. *Asian J Urol*. 2014;1:15-29. 4. Ito K. *Nat Rev Urol*. 2014;11:15-29. 5. Nardi AC. *Int Braz J Urol*. 2012;38:155-166. 6. Yamaoka M, et al. *Clin Cancer Res*. 2010;16:4319-4324

Current diagnostic paradigm is evolving:

Intermediate-risk PCa	LE	Strength rating
In predominantly Gleason pattern 4 (≥ ISUP 3), use prostate multiparametric magnetic resonance imaging (mpMRI) for local staging.	2b	Weak
In predominantly Gleason pattern 4, include at least a cross-sectional abdominopelvic imaging and bone-scan for metastatic screening.	2a	Weak

High-risk localised PCa/locally advanced PCa	LE	Strength rating
Use prostate mpMRI for local staging.	2b	Strong
Perform metastatic screening including at least cross-sectional abdominopelvic imaging and a bone-scan.	2a	Strong

TC PET PSMA can change management in about 21% of patients

EAU guidelines 2018

ADT + docetaxel: a new standard of care for men with mHNPC (high metastatic burden)

Overall Survival	ADT + DOC	ADT		
	Median (mos)	Median (mos)	HR (95% CI)	*P* Value
GETUG-15[1]	62.1	48.6	0.88 (0.68-1.14)	0.3
CHAARTED[2*] +	57.6	47.2	0.73 (0.59-0.89)	0.0018
STAMPEDE[3]	60	45	0.76 (0.62-0.92)	0.005

Gravis G, et al. *Eur Urol*. 2016 ;
Sweeney C, et al. *N Engl J Med*. 2015;
James N, et al. *Lancet*. 2016;.

* HVD as presence of visceral metastasis or ≥4 bone metastases with ≥1 beyond the vertebral bodies and pelvis

M+ Hormone Naive Prostate Cancer

6.6.10. ***Guidelines for hormonal treatment of metastatic prostate cancer***

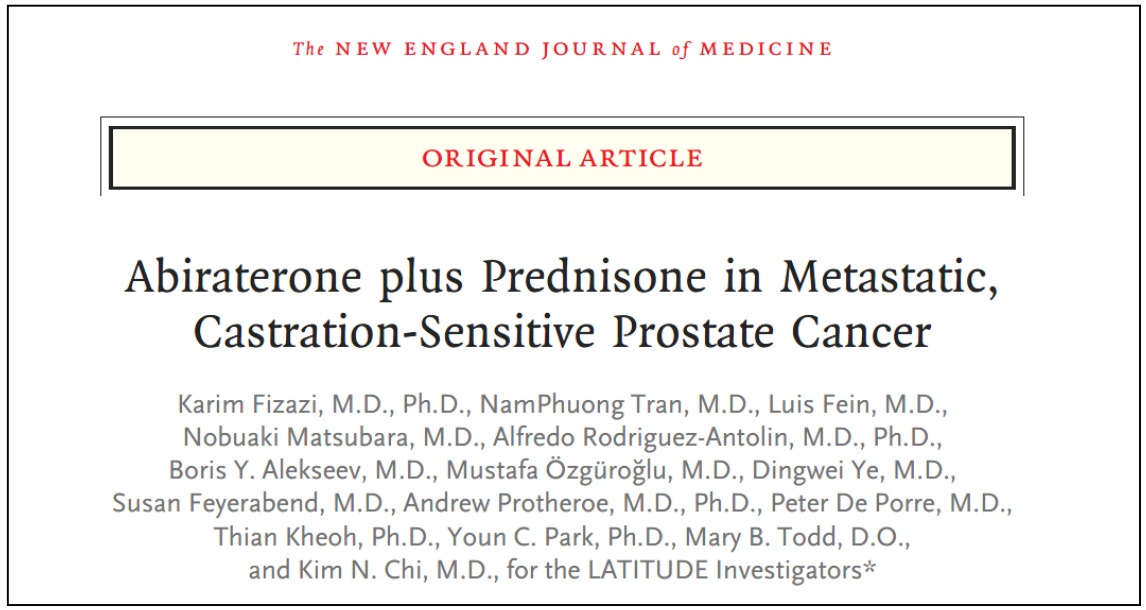
Recommendations	LE	GR
In M1 symptomatic patients, offer immediate castration to palliate symptoms and reduce the risk for potentially catastrophic sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction, extra-skeletal metastasis).	1b	A
In M1 asymptomatic patients, offer immediate castration to defer progression to a symptomatic stage and prevent serious disease progression-related complications.	1b	A
Offer castration combined with abiraterone acetate plus prednisone to all patients whose first presentation is M1 disease and who are fit enough for the regimen.		Strong
In M1 asymptomatic patients, discuss deferred castration with a well-informed patient since it lowers the treatment side effects, provided the patient is closely monitored.	2b	B

EAU Guidelines 2018

EAU Guidelines 2017

Hormone Sensitive Prostate Cancer

Latitude study
N Engl J Med. 2017 June 4



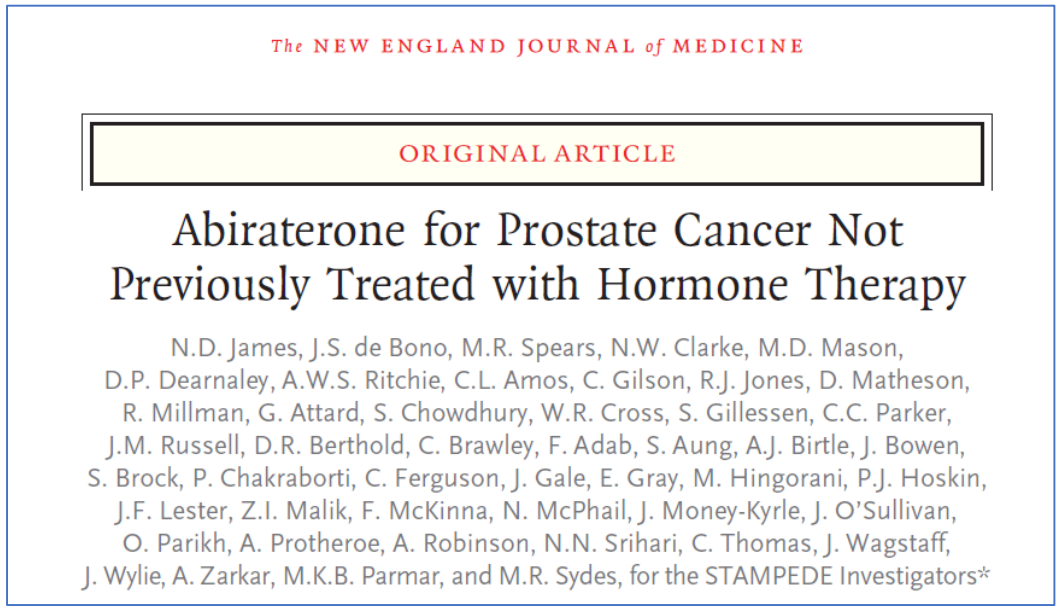
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer

Karim Fizazi, M.D., Ph.D., NamPhuong Tran, M.D., Luis Fein, M.D., Nobuaki Matsubara, M.D., Alfredo Rodriguez-Antolin, M.D., Ph.D., Boris Y. Alekseev, M.D., Mustafa Özgüroğlu, M.D., Dingwei Ye, M.D., Susan Feyerabend, M.D., Andrew Protheroe, M.D., Ph.D., Peter De Porre, M.D., Thian Kheoh, Ph.D., Youn C. Park, Ph.D., Mary B. Todd, D.O., and Kim N. Chi, M.D., for the LATITUDE Investigators*

Stampede study
N Engl J Med. 2017 June 3



The NEW ENGLAND JOURNAL of MEDICINE

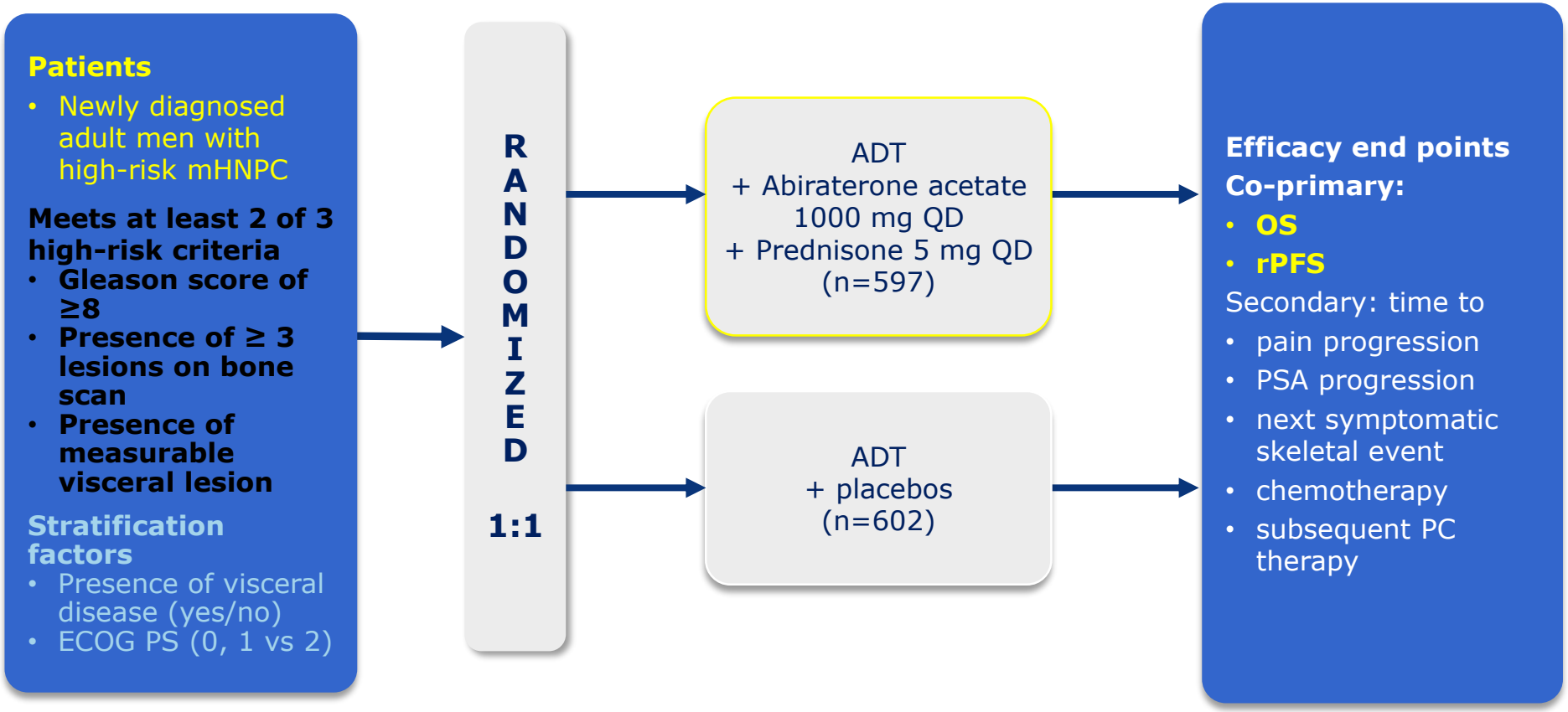
ORIGINAL ARTICLE

Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy

N.D. James, J.S. de Bono, M.R. Spears, N.W. Clarke, M.D. Mason, D.P. Dearnaley, A.W.S. Ritchie, C.L. Amos, C. Gilson, R.J. Jones, D. Matheson, R. Millman, G. Attard, S. Chowdhury, W.R. Cross, S. Gillessen, C.C. Parker, J.M. Russell, D.R. Berthold, C. Brawley, F. Adab, S. Aung, A.J. Birtle, J. Bowen, S. Brock, P. Chakraborti, C. Ferguson, J. Gale, E. Gray, M. Hingorani, P.J. Hoskin, J.F. Lester, Z.I. Malik, F. McKinna, N. McPhail, J. Money-Kyrle, J. O'Sullivan, O. Parikh, A. Protheroe, A. Robinson, N.N. Srihari, C. Thomas, J. Wagstaff, J. Wylie, A. Zarkar, M.K.B. Parmar, and M.R. Sydes, for the STAMPEDE Investigators*

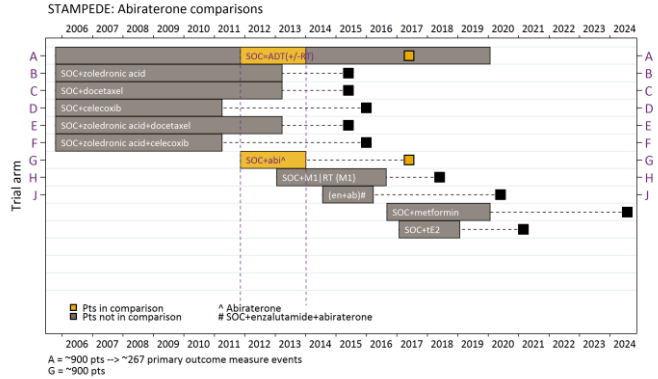
- **Abiraterone ha ricevuto l'approvazione EMA (Nov 2017)**

LATITUDE: Study Design



- **Conducted at 235 sites in 34 countries in Europe, Asia-Pacific, Latin America, and Canada**
- **Designed and fully enrolled prior to publication of CHAARTED/STAMPEDE results**

STAMPEDE Outcome measures



Primary outcome measure

Overall survival

Secondary outcome measures

Failure-free survival (FFS)

Toxicity

Quality of life

Skeletal-related events

Cost effectiveness

FFS definition

First of:

- PSA failure
- Local failure
- Lymph node failure
- Distant metastases
- Prostate cancer death

PSA failure definition

PSA fall >= 50%

→ 24wk nadir + 50% **and**

→ >4ng/ml

PSA fall of <50%

→ failure at t=0

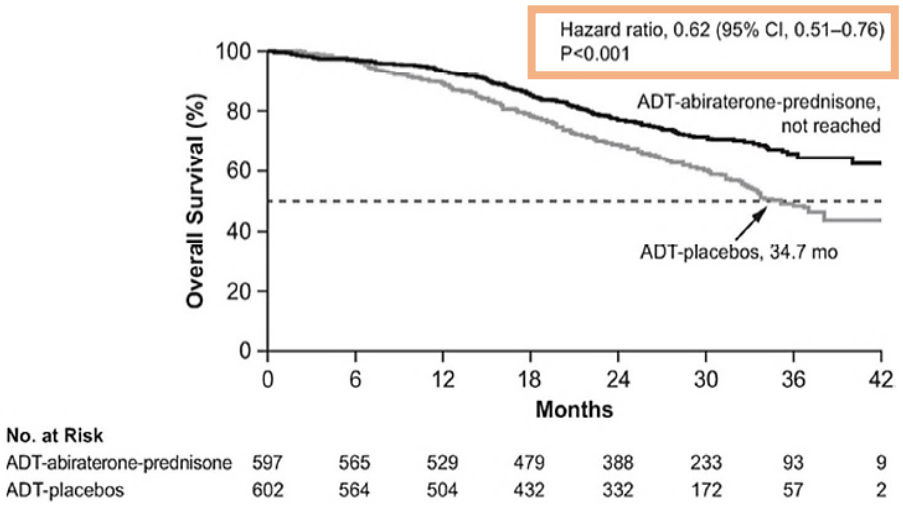
James N, et al. ASCO 2017. LBA5003 and Oral Abstract Session

Demographics and Baseline Disease Characteristics: LATITUDE

	ADT-Abiraterone-Prednisone (n = 597)	ADT-Placebos (n = 602)
Age (yr), n (%)		
< 65	221 (37)	233 (39)
65–69	112 (19)	134 (22)
70–74	141 (24)	115 (19)
≥ 75	123 (21)	120 (20)
Median (range)	68.0 (38-89)	67.0 (33-92)
Gleason score at initial diagnosis, n (%)		
< 7	4 (0.7)	1 (0.2)
7	9 (2)	15 (2)
≥ 8	584 (98)	586 (97)
Baseline pain score (BPI-SF Item 3), n (%)		
0–1	284 (50)	288 (50)
2–3	123 (22)	137 (24)
≥ 4	163 (29)	154 (27)
Patients with ≥ 3 bone metastases at screening, n/N (%)	586/597 (98.2)	585/602 (97.2)
Patients with high risk at screening, n (%)		
n	597	601
Gleason score ≥ 8 + ≥ 3 bone lesions	573 (96)	569 (95)
Gleason score ≥ 8 + measurable visceral disease	82 (14)	87 (14)
≥ 3 bone lesions + measurable visceral disease	84 (14)	85 (14)
Gleason score ≥ 8 + ≥ 3 bone lesions + measurable visceral disease	71 (12)	70 (12)

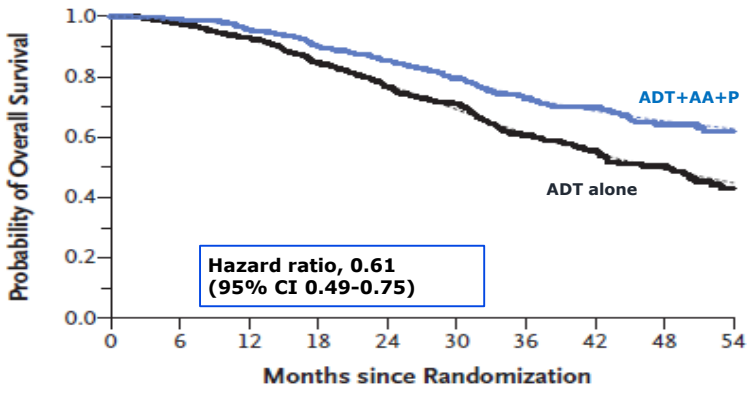
In LATITUDE and STAMPEDE addition of AA+P to ADT significantly improved OS

LATITUDE[1]



No. at Risk								
ADT-abiraterone-prednisone	597	565	529	479	388	233	93	9
ADT-placebos	602	564	504	432	332	172	57	2

STAMPEDE - M1 Disease[2,3]



No. of Patients (no. of deaths)									
Combination therapy	500	(22)	469	(50)	415	(57)	256	(18)	81
ADT alone	502	(35)	460	(80)	371	(73)	215	(23)	60

Combination therapy by Kaplan–Meier estimates
ADT alone by Kaplan–Meier estimates
Combination therapy by flexible parametric model
ADT alone by flexible parametric model

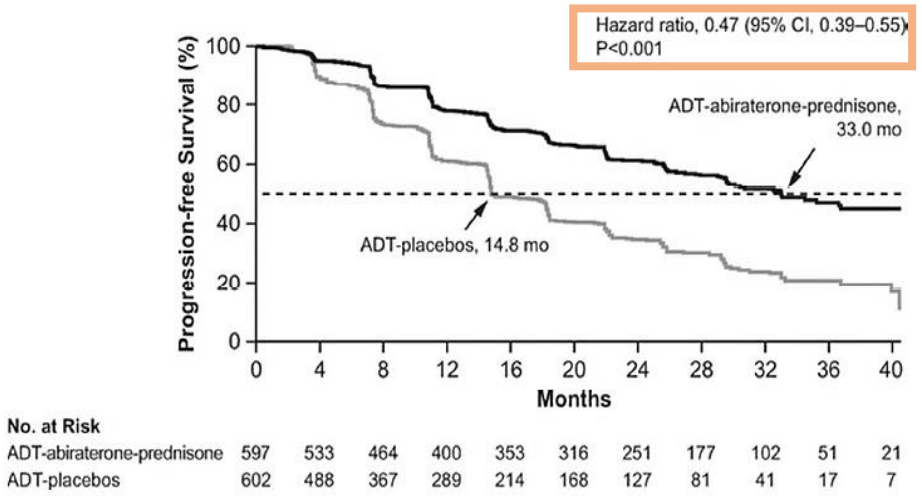
- LATITUDE: **38% reduction in the risk of death** in patients with NDx HR mHSPC

- STAMPEDE: **39% reduction in the risk of death** in patients with mHSPC

1. Fizazi K, et al. N Engl J Med. 2017 Jul 27;377(4):352-360;
2. James N, et al. N Engl J Med. 2017 Jul 27;377(4):338-351

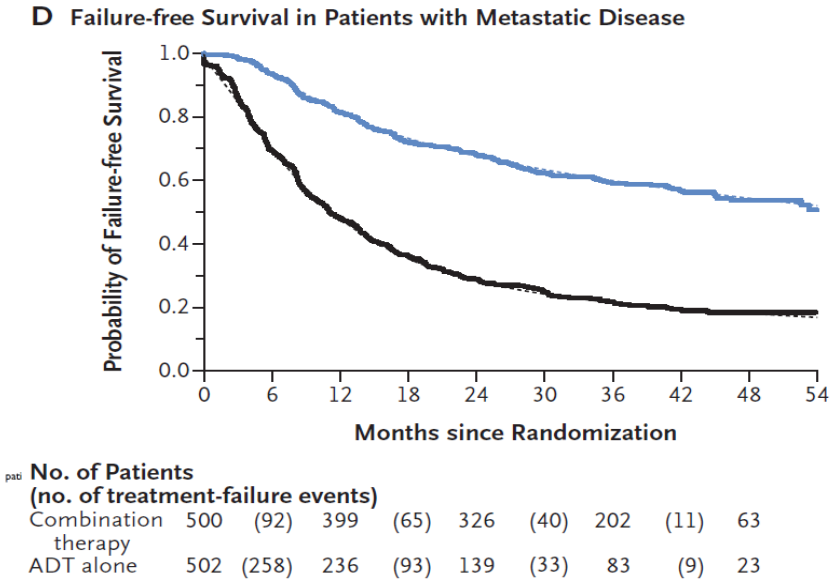
In LATITUDE and STAMPEDE addition of AA+P to ADT significantly delayed progression

LATITUDE - rPFS[1]



- LATITUDE: **53% reduction in the risk** of radiographic progression or death in patients with NDx HR mHSPC

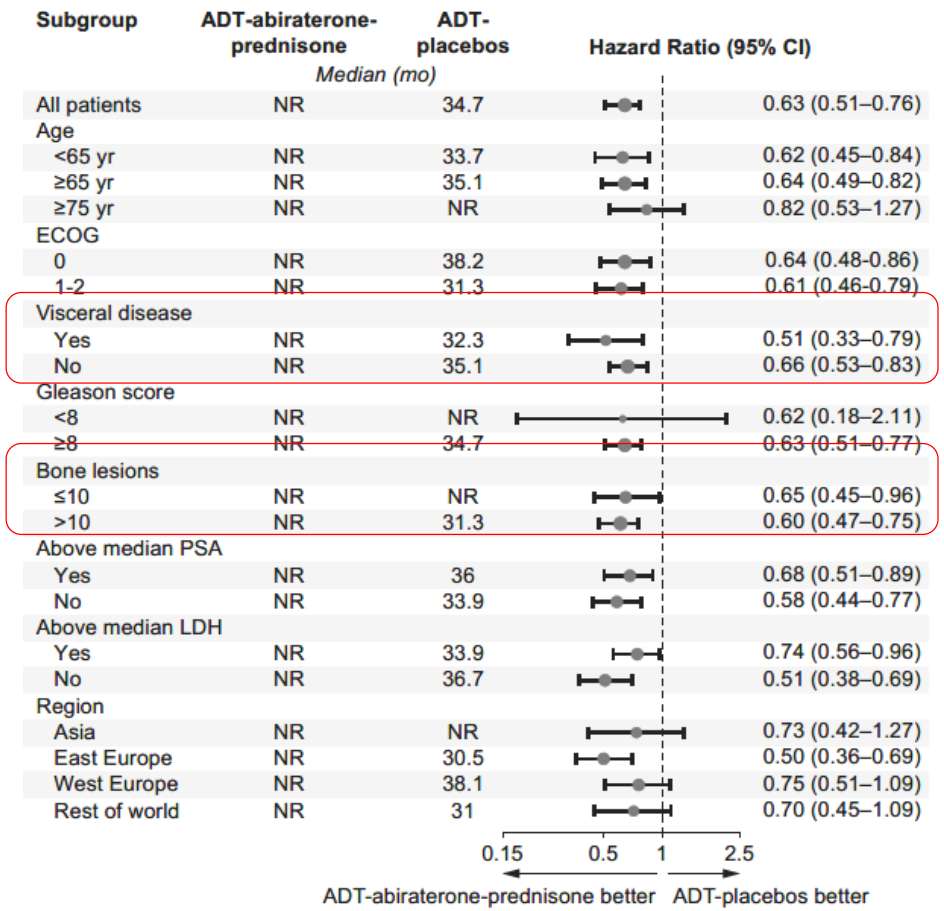
STAMPEDE – FFS [2,3]



- STAMPEDE: **69% reduction in the risk** of FFS in patients with mHSPC

1. Fizazi K, et al. N Engl J Med. 2017 Jul 27;377(4):352-360
2. James N, et al. N Engl J Med. 2017 Jul 27;377(4):338-351

LATITUDE: Overall Survival by Subgroup



The treatment effect of ADT-abiraterone-prednisone on OS was consistently favorable across nearly all prespecified subgroups

Fizazi, Karim, et al. New England Journal of Medicine 377.4 (2017): 352-360

LATITUDE: Summary of Most Common Adverse Events and Adverse Events of Special Interest

Adverse Event	ADT-Abiraterone-Prednisone (n = 597)			ADT-Placebos (n = 602)		
	All	Gr 3	Gr 4	All	Gr 3	Gr 4
	no of patients (%)					
Hypertension	37	20	0	22	10	0.2
Hypokalemia	20	10	0.8	4	1	0.2
ALT increased	16	5	0.3	13	1	0
Hyperglycemia	13	4	0.2	11	3	0
AST increased	15	4	0.2	11	1	0
Bone pain	12	3	0	15	3	0
Cardiac disorder Atrial fibrillation	12 1	3 0.3	0.8 0	8 0.3	1 0.2	0 0
Anemia	9	2	0.5	14	4	0.2
Back pain	18	2	0	20	3	0
Fatigue	13	2	0	14	2	0
Spinal cord compression	2	2	0	2	1	0.5

Abiraterone vs Docetaxel in M+HNPCa

Doce+ADT vs ADT

Articles

Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial

Gwenaelle Gravis, Karim Fizazi, Florence Joly, Stéphane Oudard, Franck Priou, Benjamin Esterni, Igor Latorzeff, Remy Delva, Ivan Krakowski,

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

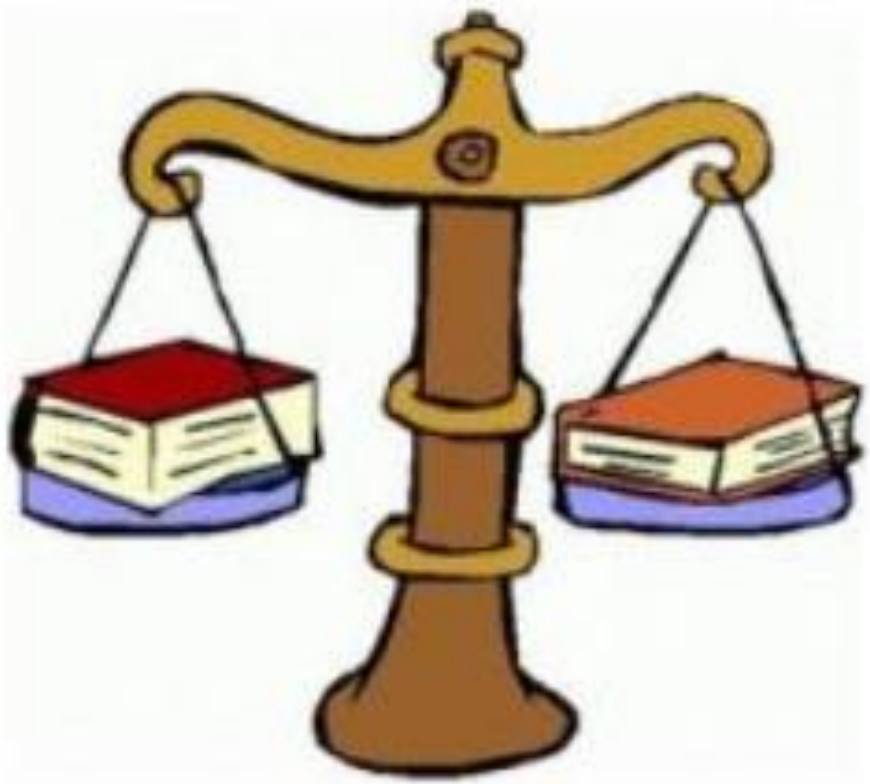
Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer

Christopher J. Sweeney, M.B., B.S., Yu-Hui Chen, M.S., M.P.H.,

Articles

Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial

Nicholas D James, Matthew R Sydes, Noel W Clarke, Malcolm D Mason, David P Dearnaley, Melissa R Spears, Alastair W S Ritchie,



AA+P+ADT vs ADT

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Karim Fizazi, M.D., Ph.D., NamPhuong Tran, M.D., Luis Fein, M.D.,

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Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy

N.D. James, J.S. de Bono, M.R. Spears, N.W. Clarke, M.D. Mason,

What patient populations were included?

	ADT+AA+P vs ADT		ADT+Doce vs ADT		
	LATITUDE*[1]	STAMPEDE (Arm G)[2,3]	GETUG-AFU 15[4]	CHAARTED[5,6]	STAMPEDE (Arm C)[7]
Total sample size, n	1199	1917	385	790	1776
Patients with mHSPC	100%	52%	100%	100%	61%
Patients with high-risk/high volume mHSPC	100%	NE	47.5% (183)	65 % (513)	NE
Patients with *de novo* M1	100%	49%	71%	72.8%	58%
Patients with visceral metastasis	17.3%	3%	14.5%	15.6%	3.8%
Patients with Gleason Score ≥8	98%	74.9%	56.1%	61.3%	70.1%

* All LATITUDE patients had high-risk and newly diagnosed metastatic disease
NE, not evaluated

HIGH RISK (HR)[1]

At least 2 of 3:

- **≥3 bone lesions**
- **Visceral metastasis**
- **Gleason score ≥8**

HIGH VOLUME (HV)[4,5]

At least 1 of 2:

- **≥4 bone lesions with ≥1 beyond the vertebral bodies/pelvis**
- **Visceral metastasis**

Not head-to-head comparison studies

1. Fizazi K, et al. New England J Med. 2017 Jul 27;377(4):352-360; 2. James N, et al. ASCO 2017. LBA5003 and Oral Abstract Session; 3. James N, et al. New England J Med. 2017 Jul 27;377(4):338-351; 4. Gravis G, et al. Eur Urol. 2016 Aug;70(2):256-62; 5. Sweeney et al. N Eng J Med 2015; 378(8): 737-746; 6. Sweeney C, et al. Ann Oncol 2016;27(suppl 6):Abstract (and poster) 720PD; 7. James et al. Lancet 2016; 387(10024):1163-77

AA + P 5 mg QD in mHNPC: Detailed Safety Analyses From the LATITUDE Phase 3 Trial

The Majority of LATITUDE Patients Met the CHAARTED Definition for HV Disease

	AA + P + ADT	PBOs + ADT	Total
Overall population, n	597	602	1199
Patients with high-volume disease,[a] n (%)	487 (82)	468 (78)	955 (80)
Patients with low-volume disease, n (%)	110 (18)	133 (22)	243 (20)
Unknown,[b] n (%)	0	1 (<1)	1 (<1)

[a]Defined as the presence of visceral metastases and/or ≥4 bone lesions with ≥1 outside of the vertebral column and pelvis. [b]Due to missing baseline scan.

Post hoc analyses

- General population
- High volume sec CHAARTED

Clinical Benefits in Patients With HV Disease Were Similar to Those Seen in the Overall Population

	Patients with high-volume disease		Patients with low-volume disease		Overall population	
Clinical outcomes	**AA + P + ADT n = 487**	**PBOs + ADT n = 468**	**AA + P + ADT n = 110**	**PBOs + ADT n = 133**	**AA + P + ADT n = 597**	**PBOs + ADT n = 602[a]**
Overall survival						
Median, months	NR	33.1	NR	NR	NR	34.7
HR (95% CI)	0.57 (0.46-0.71)[b]		0.81 (0.48-1.34)[c]		0.62 (0.51-0.76)[d]	
rPFS[e]						
Median, months	30.7	14.7	NR	22.4	33.0	14.8
HR (95% CI)	0.43 (0.36-0.52)[b]		0.53 (0.35-0.80)[f]		0.47 (0.39-0.55)[d]	

[a]Includes 1 patient with missing baseline scan. [b]$p < 0.0001$. [c]$p = 0.4052$. [d]$p < 0.001$. [e]Sequential radiographic imaging to assess rPFS (CT or MRI and bone scanning) was performed every 4 months, starting at Week 16. [f]$p = 0.0024$.
NR, not reached.

CHAARTED HV long term data

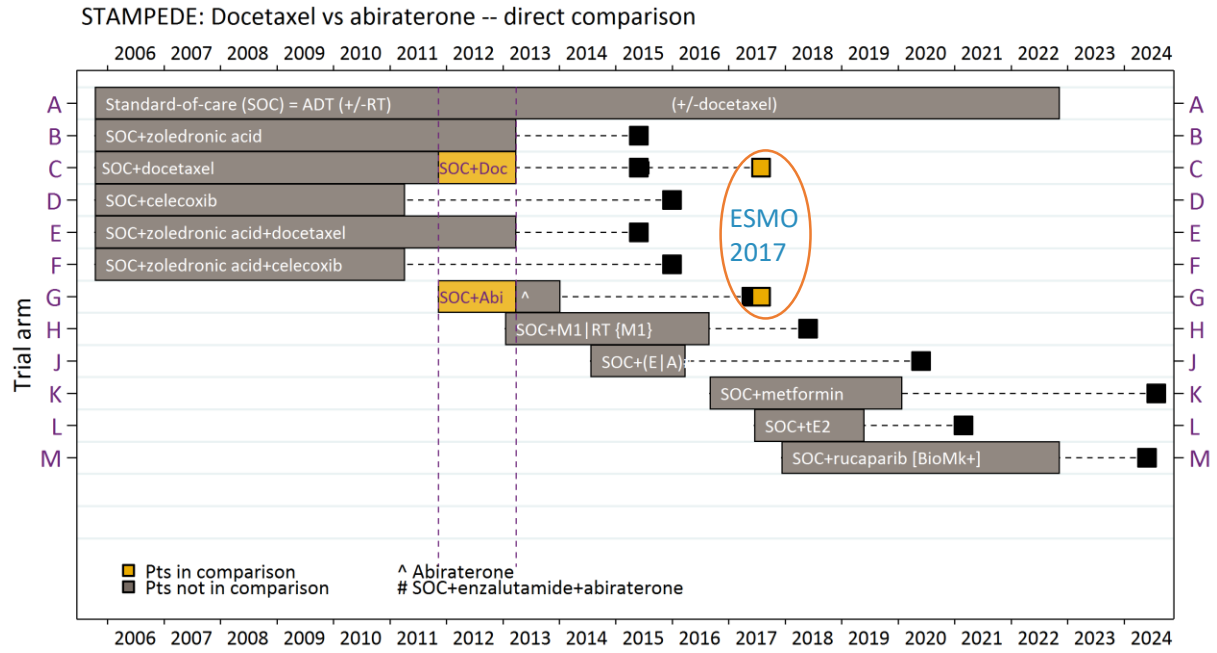
P value HR (95% CI)
0.0004 **0.63** (0.49 - 0.81)

Fizazi K, et al. Poster presented at ASCO-GU 2018; abstract 182.

Sydes M, et al.

Direct randomized comparison from

STAMPEDE: ADT+AA+P vs ADT+DOC



Recruitment: Nov-2011 to Mar-2013

Reported: ESMO 2017

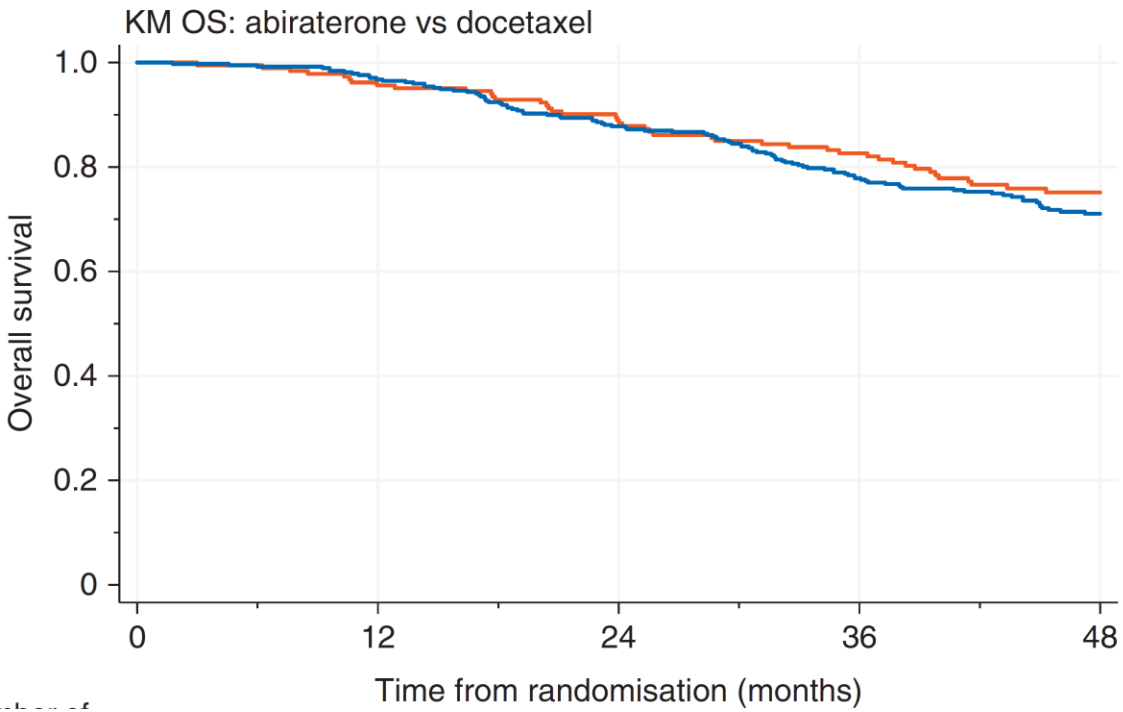
Published: (paper in development)

Patients: 189 ADT+DOC
377 ADT+AA+P

566 patients randomised contemporaneously to either research arm

AA+P = abiraterone acetate plus prednisone/prednisolone; ADT = androgen-deprivation therapy; DOC = docetaxel;
SOC = standard of care (STAMPEDE terminology for ADT)

STAMPEDE: ADT+AA+P vs ADT+DOC



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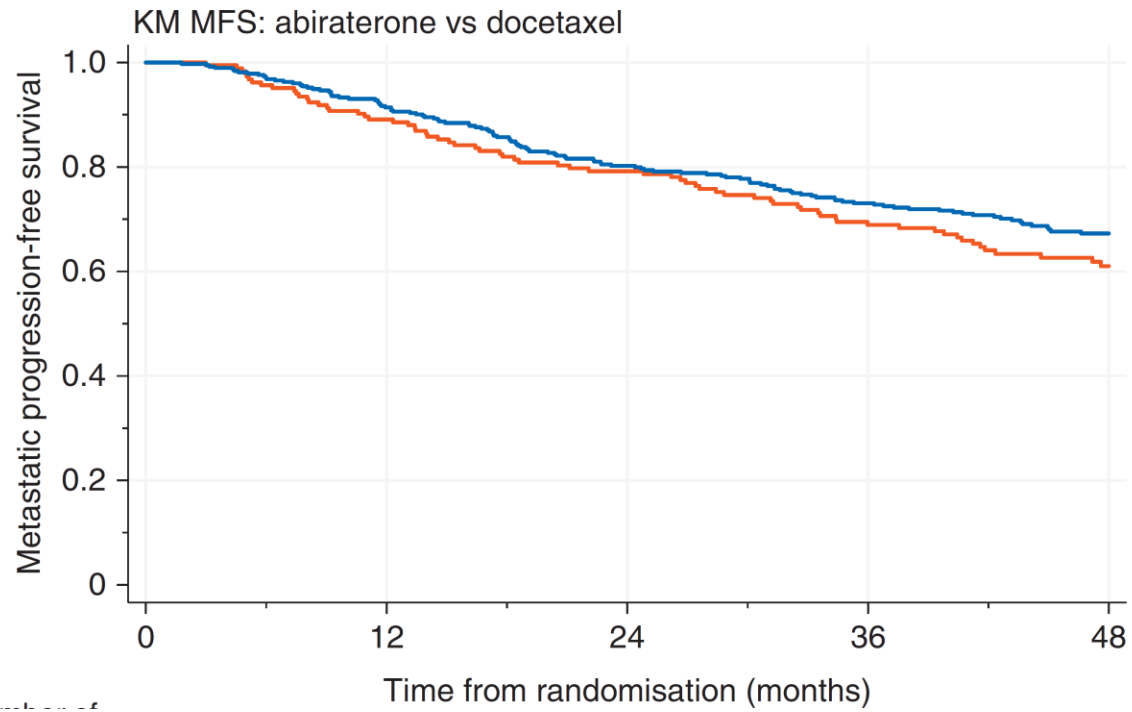


Sydes et al Annals Oncology 2018

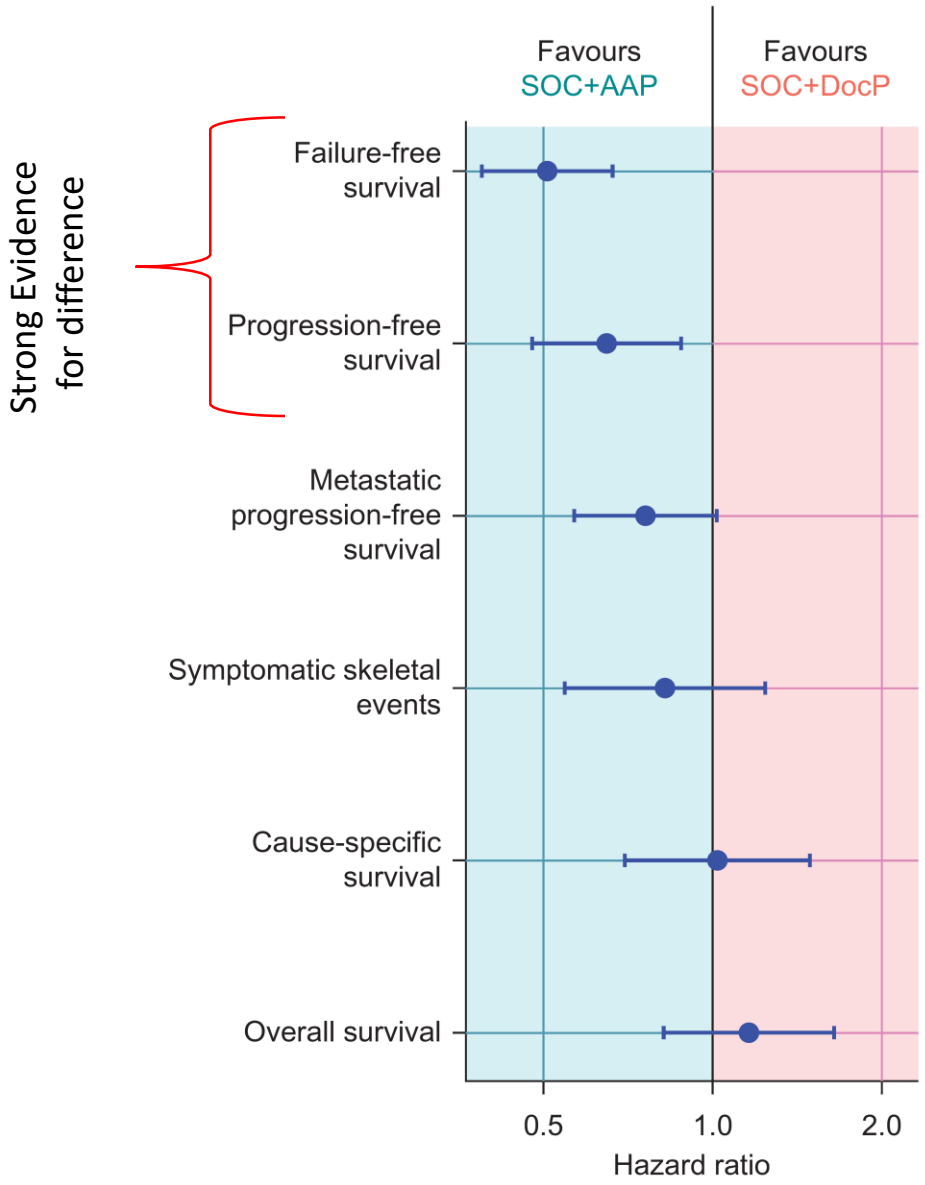


Figure 4. Depiction of disease state over time.

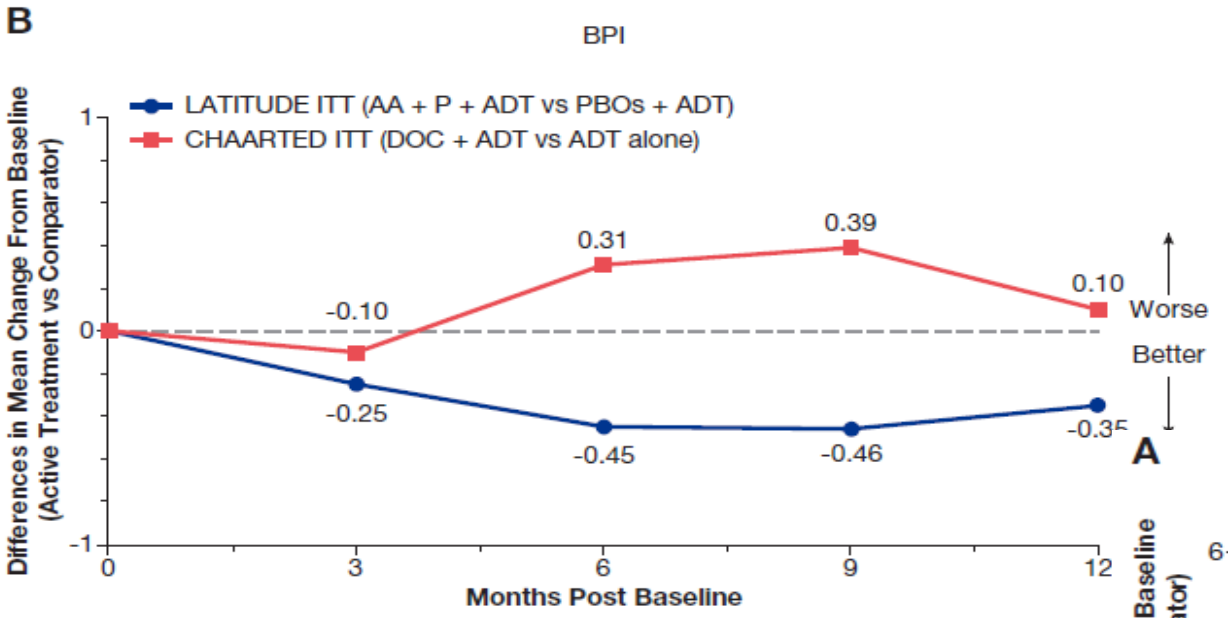
Table 3. Worst adverse event (grade) reported over entire time on trial

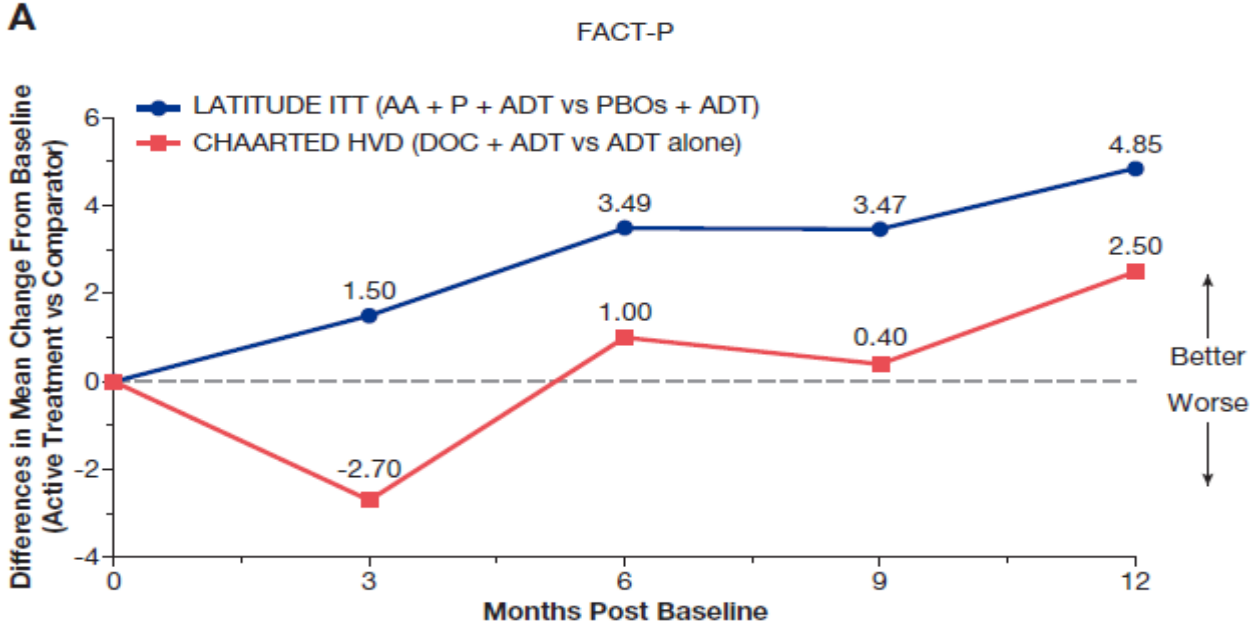
	SOC + Doc (*n* = 189)	SOC + AAP (*n* = 377)
Safety population		
Number of patients included in analysis[a]	**172**	**373**
Patients with an adverse event—no. (%)		
Grade 1–5 adverse event	172 (100)	370 (99)
Grade 3–5 adverse event	86 (50)	180 (48)
Grade 3–5 adverse events—no. (%)		
Endocrine disorder	15 (9)	49 (13)
Febrile neutropenia	29 (17)	3 (1)
Neutropenia (neutrophils)	22 (13)	4 (1)
General disorder	18 (10)	21 (6)
Fatigue	7 (4)	8 (2)
Oedema	1 (1)	2 (1)
Musculoskeletal disorder	9 (5)	33 (9)
Cardiovascular disorder	6 (3)	32 (9)
Hypertension	0 (0)	12 (3)
Myocardial infarction	2 (1)	4 (1)
Cardiac dysrhythmia	1 (1)	5 (1)
Gastrointestinal disorder	9 (5)	28 (8)
Hepatic disorder	1 (1)	32 (9)
Increased AST	0 (0)	6 (2)
Increased ALT	1 (1)	23 (6)
Respiratory disorder	12 (7)	11 (3)
Dyspnoea	4 (2)	1 (1)
Renal disorder	5 (3)	20 (5)
Lab abnormalities	9 (5)	11 (3)
Hypokalaemia	0 (0)	3 (1)

Sydes et al Annals Oncology 2018

LATITUDE vs CHARTEED: QL analysis

Mean Change in PRO Scores from Baseline for FACT-P (A) and BPI (B) from LATITUDE and CHAARTED





- Continuative vs short term treatment is effective in term of QoL and pain control

Feyerabend S, et al. Poster presented at ASCO-GU 2018; abstract 200.

Conclusion

- ✓ The LATITUDE and STAMPEDE trials open a new era in the management of M+ hormone naïve PCa
- ✓ Abiraterone + P add to ADT led to:
  - ✓ Significantly improved OS with a 37-38% reduction in the risk of death
  - ✓ More than 51% of study population is alive after 41 months
  - ✓ Significantly prolonged rPFS (53% reduction) and all secondary end points
  - ✓ Improve QoL, pain and fatigue as reported by patients
- ✓ Abiraterone is at least effective as Doc in management of patients with M+ Hormone naïve PCA

Take Home messages

- ✓ M+ Hormone naïve PCA:
  - ✓ Poor prognosis
  - ✓ High-risk/high volume (at least 2 of the following: visceral metastases/≥ 3 bone mets/ ≥ GS8)
- ✓ Early treatment in M+ Hormone naïve PCa (within 3 months of ADT) is a new opportunity
- ✓ Further studies and real life data should confirm the best strategy to manage M+ Hormone naïve PCA according to patients 'preference and characteristics

Thank you!!!