MOVEMBER

NUOVE PROSPETTIVE DI CURA PER IL PAZIENTE CON CARCINOMA PROSTATICO AVANZATO

22-23 NOVEMBRE 2018

MILANO

HILTON MILAN
via L. Galvani 12

SIU
Società Italiana di Urologia
dal 1908

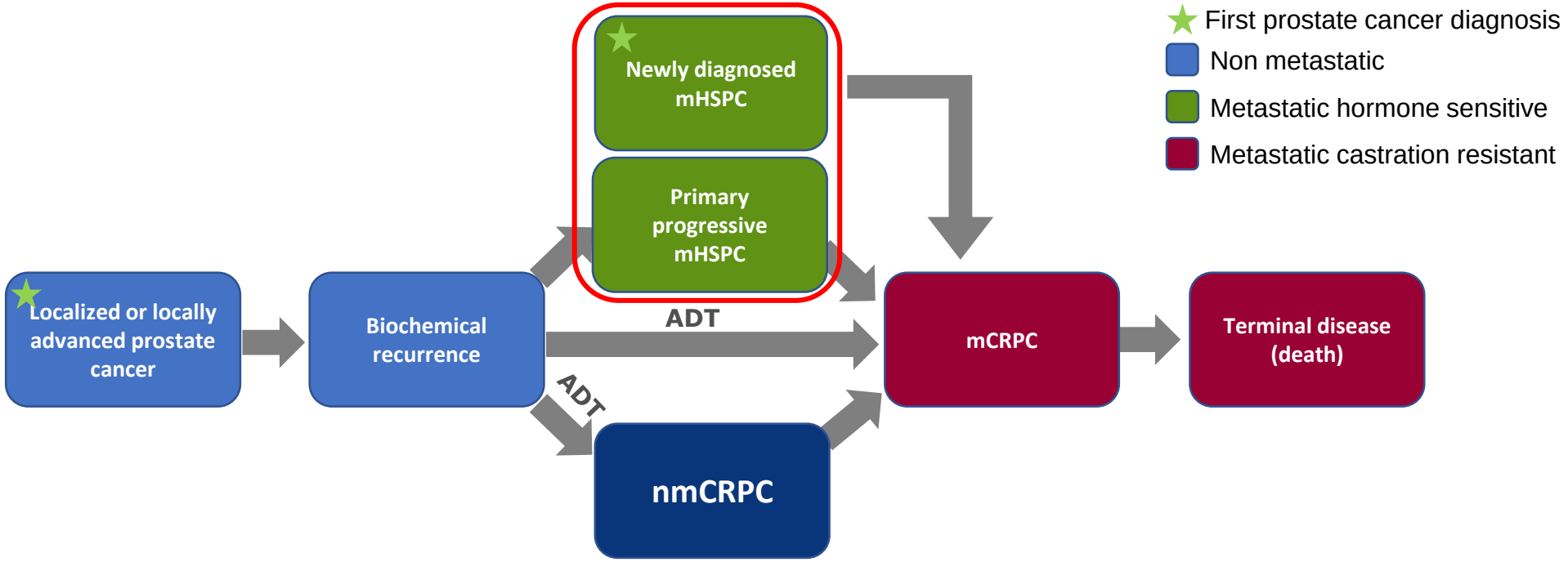
AZIENDA OSPEDALIERA SANT' ANDREA
FACOLTÀ DI MEDICINA E PSICOLOGIA

La malattia metastatica ormonosensibile

Cosimo De Nunzio

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

The different stages of prostate cancer



Adapted from: Scher HI, et al. J Clin Oncol. 2016;34:1402-18. Mottet, N, et al. EAU/ESTRO/ESUR/SIOG Guidelines on Prostate Cancer 2018. Available from: http://uroweb.org/guideline/prostate-cancer. Accessed April 2018.

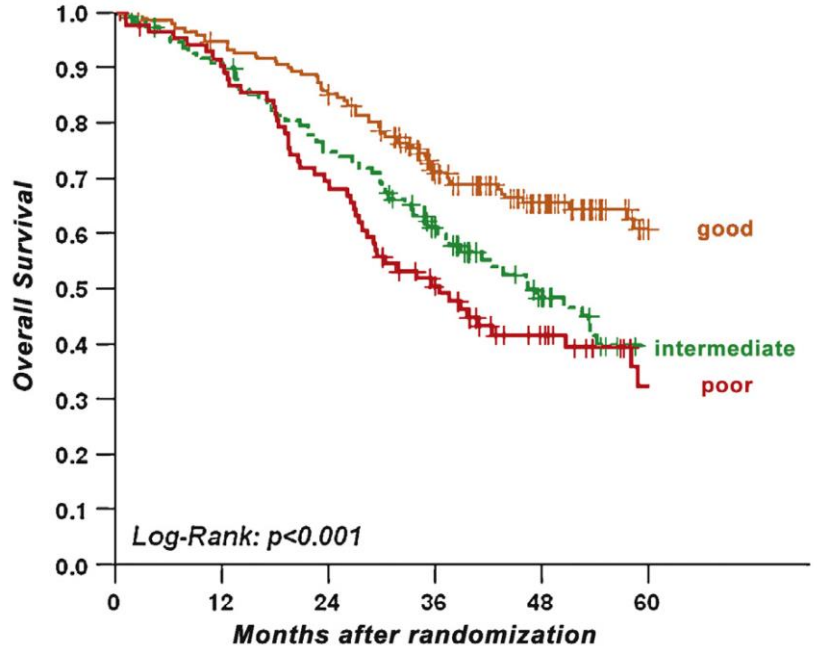
mCRPC, metastatic castration-resistant prostate cancer; nmCRPC, non-metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer.

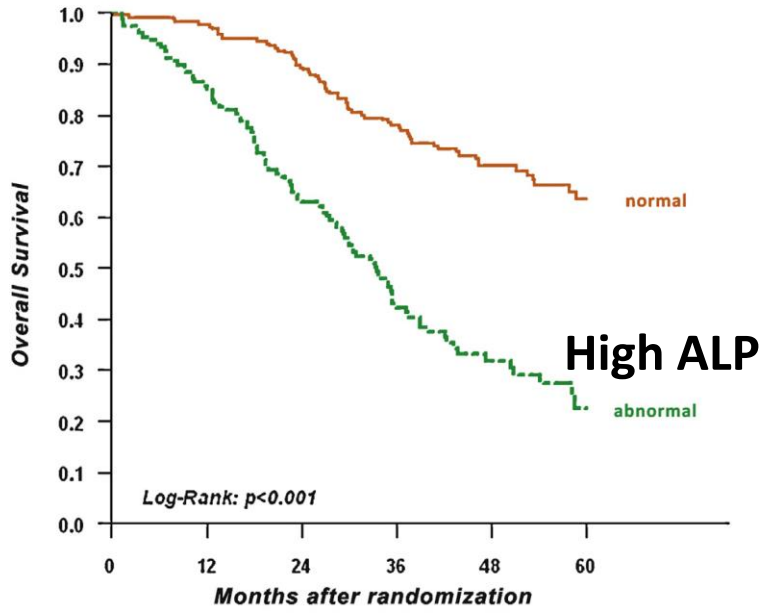
M+ HSPC: Historical prognostic group

Table 1 – Definition of Glass risk groups

Prognosis	Patient characteristics
Good	Without appendicular disease[a] and without visceral involvement **OR** With appendicular disease and/or visceral involvement and performance status of 0 and Gleason <8
Intermediate	With appendicular disease and/or visceral involvement and performance status of 0 and Gleason ≥8 **OR** With appendicular disease and/or visceral involvement and performance status ≥1 and PSA <65 ng/ml
Poor	With appendicular disease and/or visceral involvement and performance status ≥1 and PSA ≥65 ng/ml

[a] Appendicular: bone lesions in the chest, head and/or extremities.

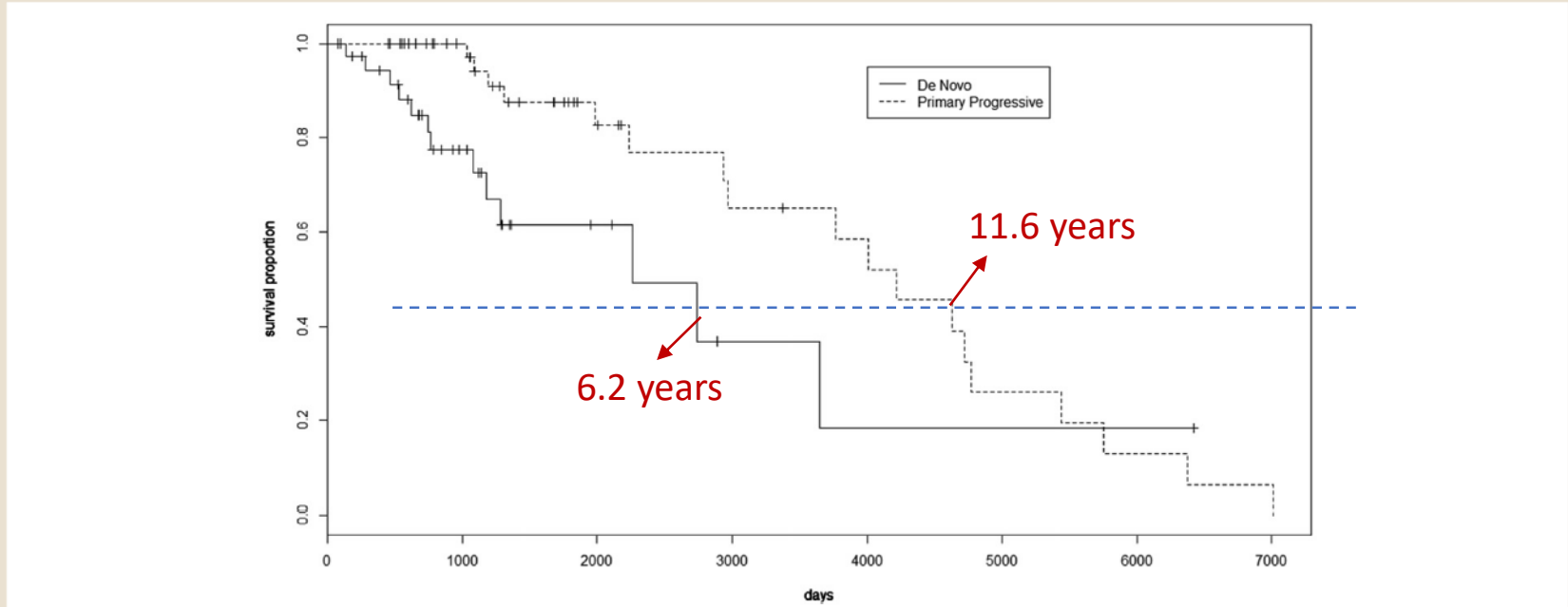




Gravis G et al Eur Urol 2015

Parameters with an impact on prognosis: De novo vs primary progressing metastatic PCa

Figure 1 Overall Survival for De Novo Versus Primary Progressive Disease From Time of Metastases



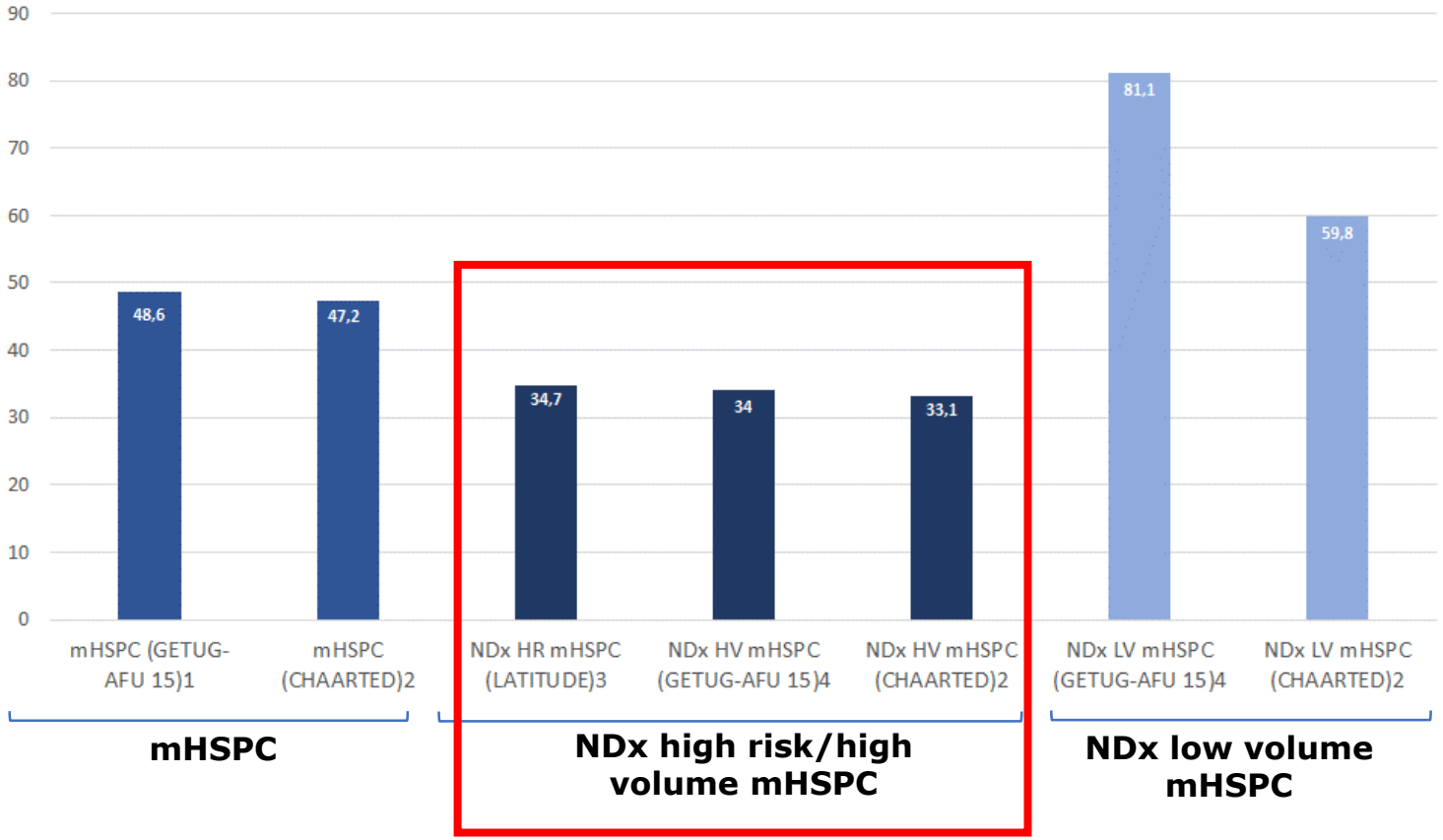
Finianos, Antoine, et al. Clinical Genitourinary Cancer,2017.

Parameters with an impact on prognosis: High Risk/Volume vs Low Risk/Volume

Median OS in patients with De Novo HR/HV mHSPC receiving ADT is less than 3 years

Median OS

Data from the control arm (ADT) of phase III trials in pts with mHSPC



HIGH RISK (HR)

At least 2 of 3:

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

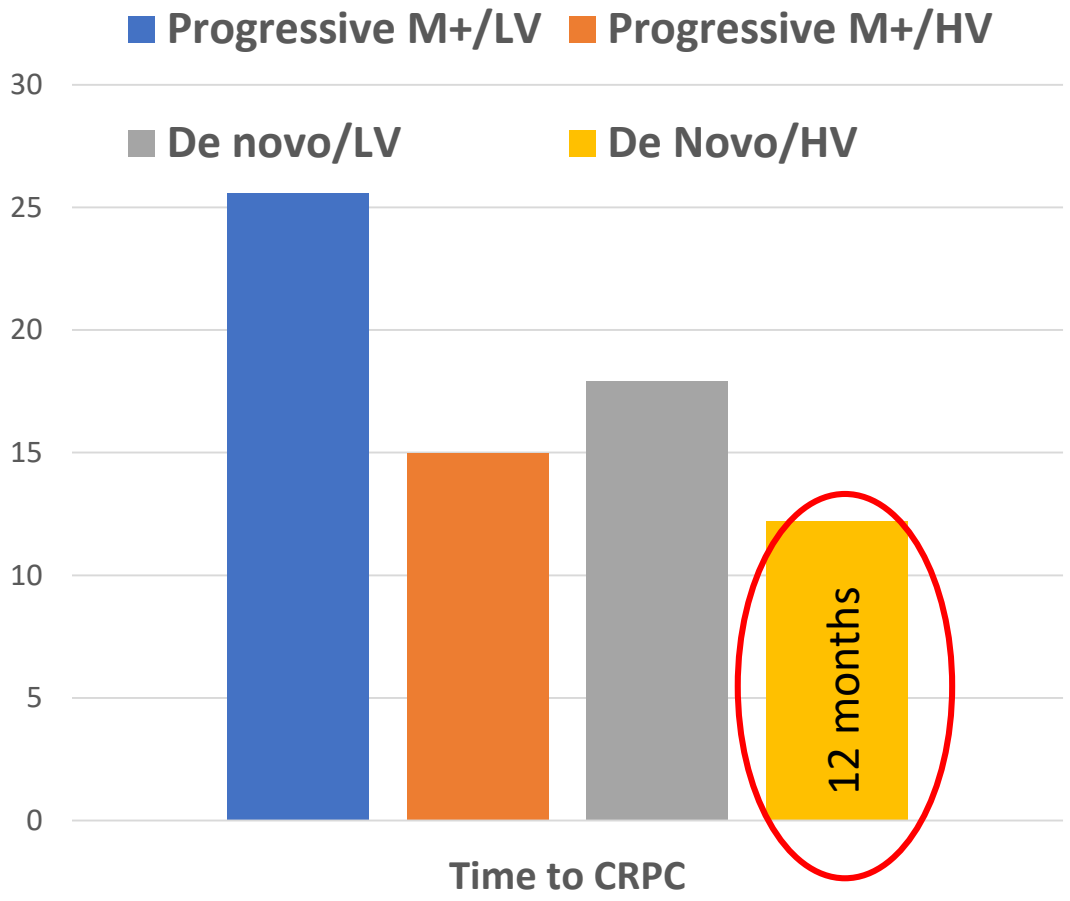
HIGH VOLUME (HV)

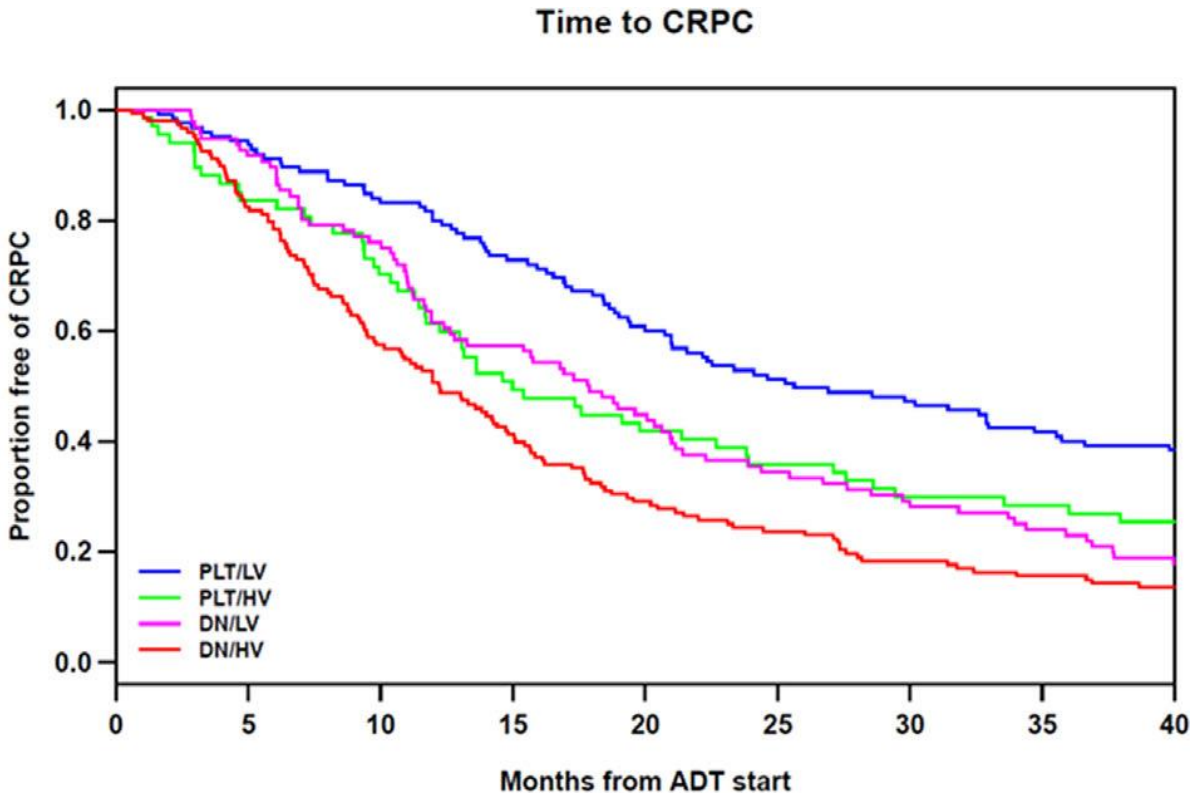
At least 1 of 2:

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

1. Gravis G, et al. Eur Urol. 2016 Aug;70(2):256-62; 2. Sweeney C, et al. Ann Oncol 2016;27(suppl 6):Abstract (and poster) 720PD; 3. Fizazi K, et al. N Engl J Med. 2017 Jul 27;377(4):352-360; 4. Gravis G, et al. ASCO-GU 2017. Abstract 136 (and poster)

mHSPC time to CRPC status: time of presentation and disease volume





Francini E et al. Prostate 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	62.1	48.6	0.88 (0.68-1.14)	0.3
CHAARTED+	57.6	47.2	0.73 (0.59-0.89)	0.0018
STAMPEDE	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***

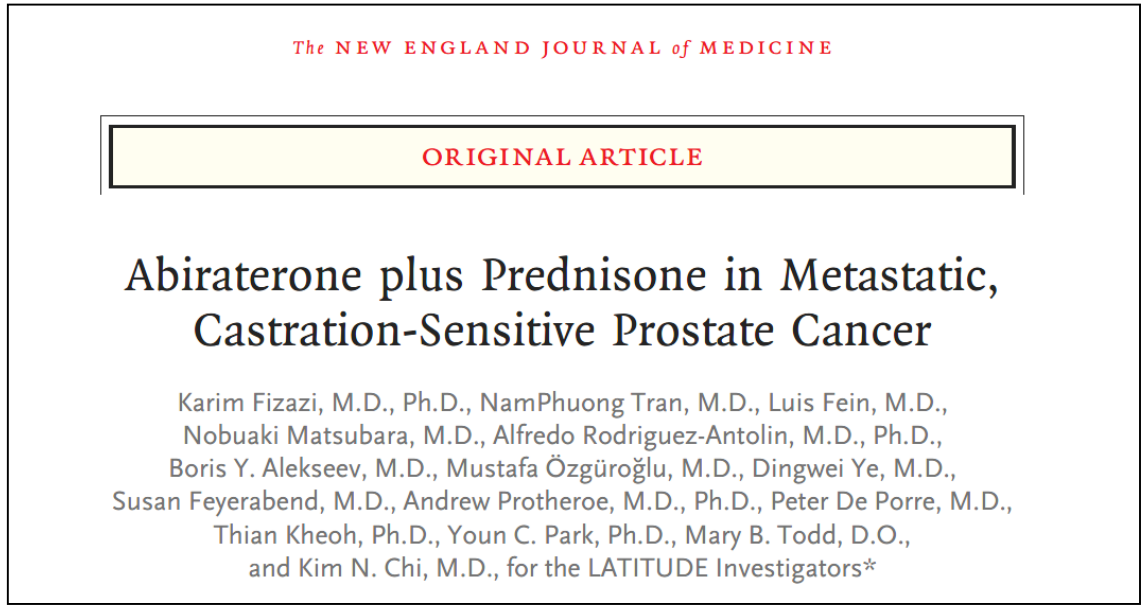
Recommendations	LE	GR
In M1 symptomatic patients, offer immediate castration to palliate symptoms and reduce the risk for potentially catastrophic sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction, extra-skeletal metastasis).	1b	A
In M1 asymptomatic patients, 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



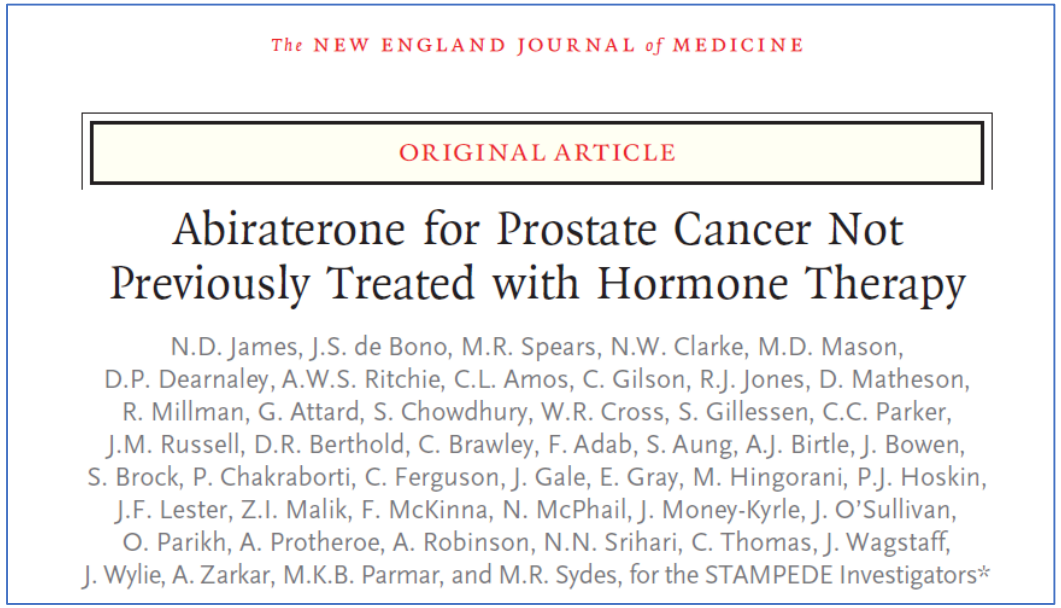
The NEW ENGLAND JOURNAL of MEDICINE

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

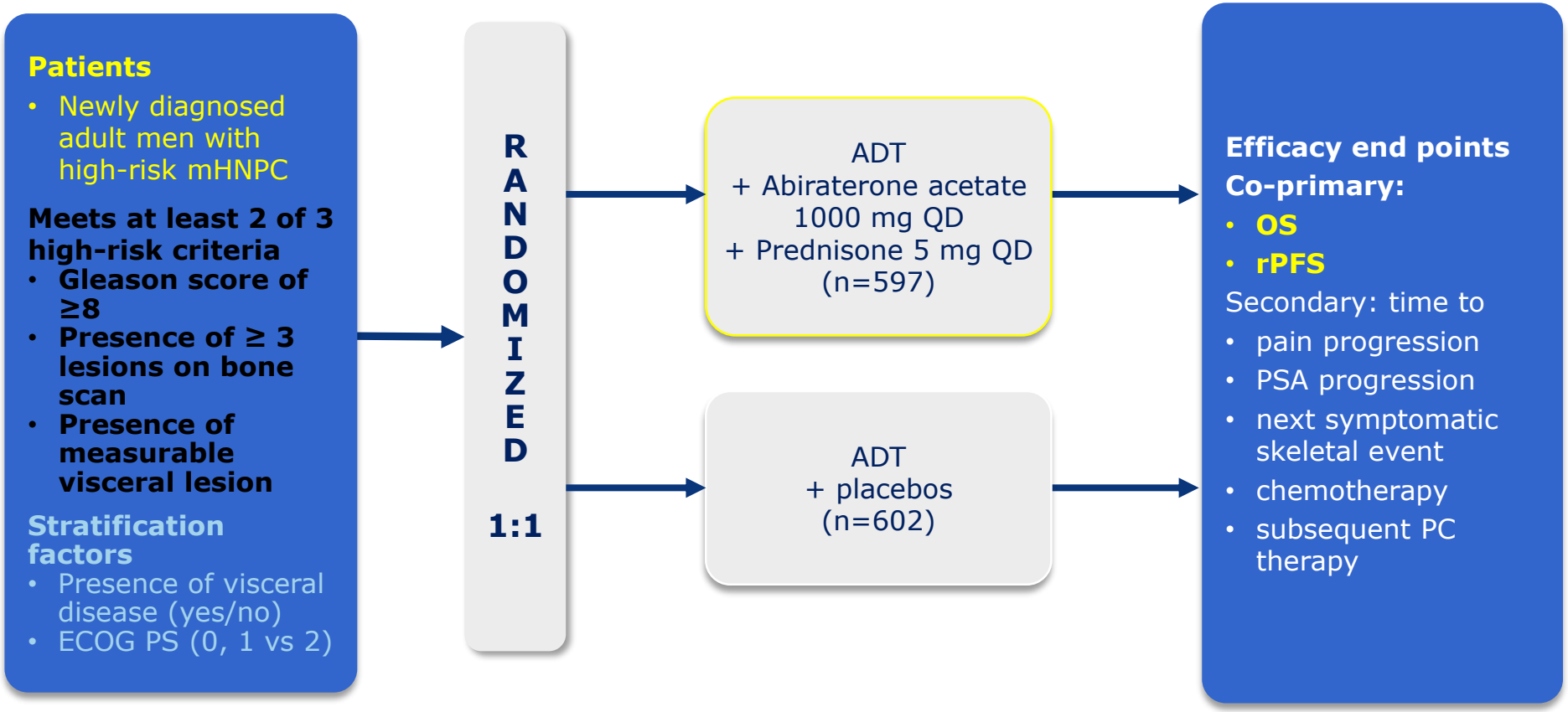
ORIGINAL ARTICLE

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

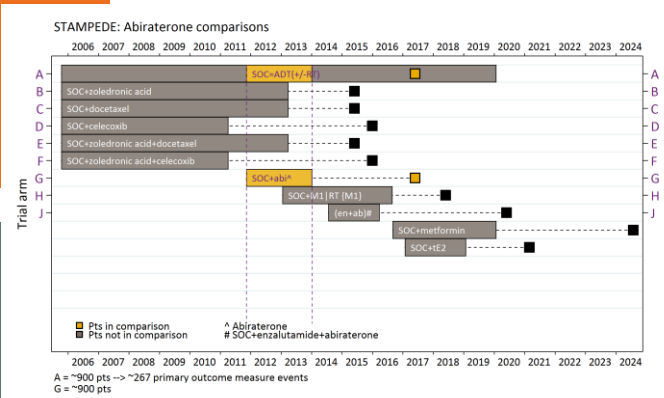
Failure-free survival (FFS)

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

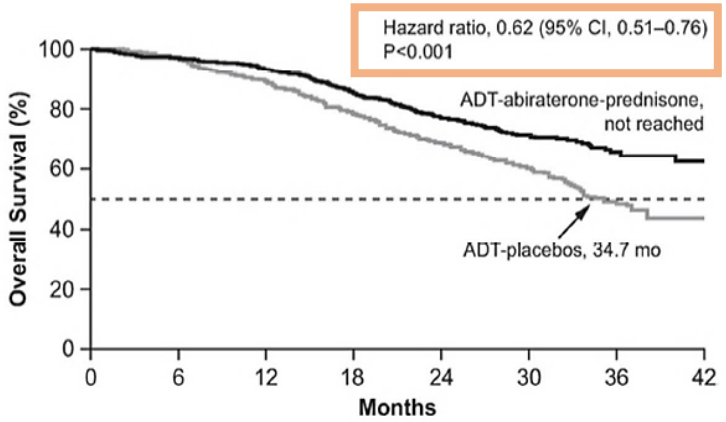
James N, et al. ASCO 2017. LBA5003 and Oral Abstract Session

Demographics and Baseline Disease Characteristics: LATITUDE

	ADT + AA + P (n = 597)	ADT + Placebos (n = 602)
Median age, years (range)	68.0 (38-89)	67.0 (33-92)
Gleason score ≥ 8 at initial diagnosis	98%	97%
Patients with ≥ 3 bone metastases at screening	98%	97%
Extent of disease		
Bone	97%	98%
Liver	5%	5%
Lungs	12%	12%
Node	47%	48%
Baseline pain score (BPI-SF Item 3)		
0-1	50%	50%
2-3	22%	24%
≥ 4	29%	27%

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

LATITUDE[1]

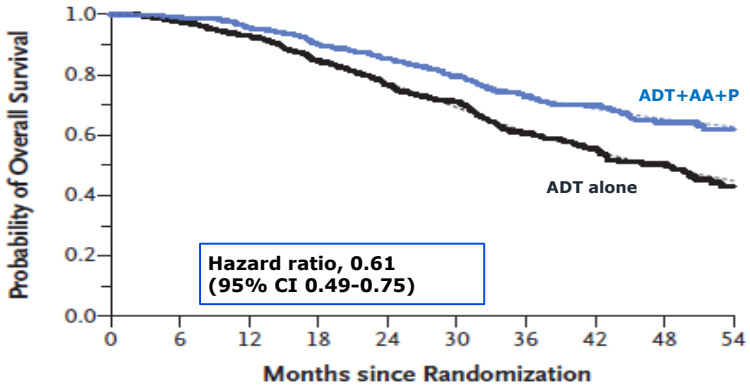


No. at Risk								
ADT-abiraterone-prednisone	597	565	529	479	388	233	93	9
ADT-placebos	602	564	504	432	332	172	57	2

ASCO 2018
36% risk reduction confirmed at 41 months FU

- **…in the risk of death** in …x HR mHSPC

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

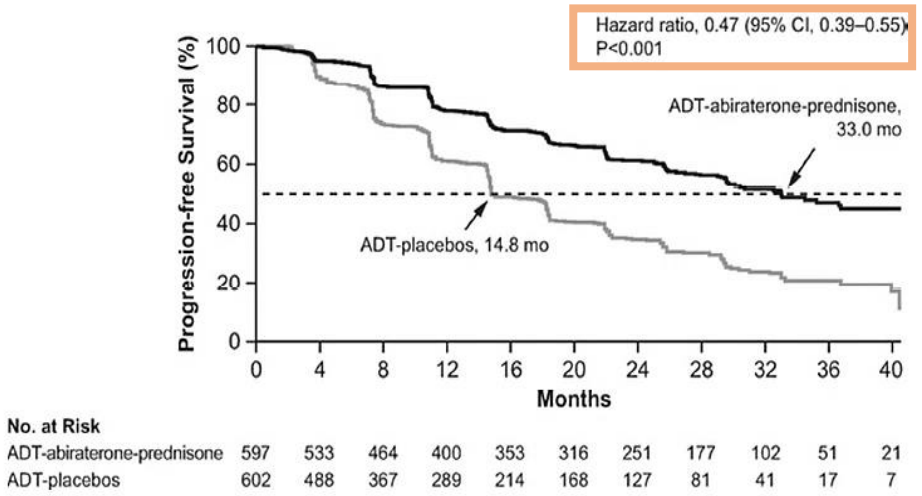
Combination therapy by Kaplan–Meier estimates — Combination therapy by flexible parametric model
ADT alone by Kaplan–Meier estimates — ADT alone by flexible parametric model

- 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. ASCO 2017. LBA5003 and Oral Abstract Session; 3. 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

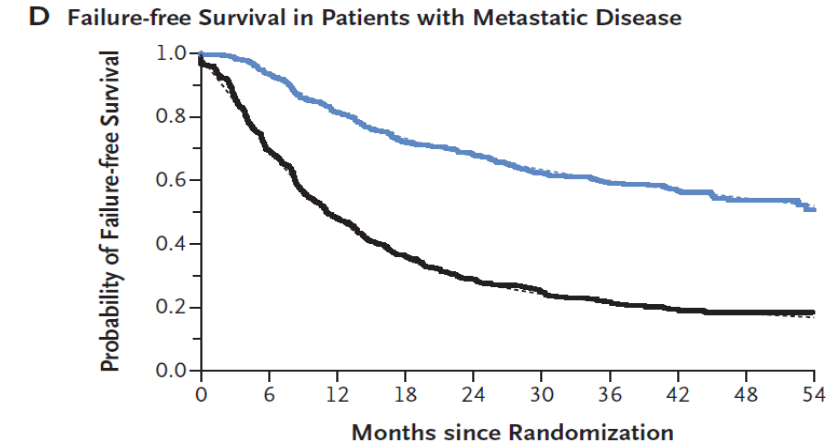
LATITUDE - rPFS[1]



No. at Risk

ADT-abiraterone-prednisone	597	533	464	400	353	316	251	177	102	51	21
ADT-placebos	602	488	367	289	214	168	127	81	41	17	7

STAMPEDE – FFS [2,3]



No. of Patients (no. of treatment-failure events)

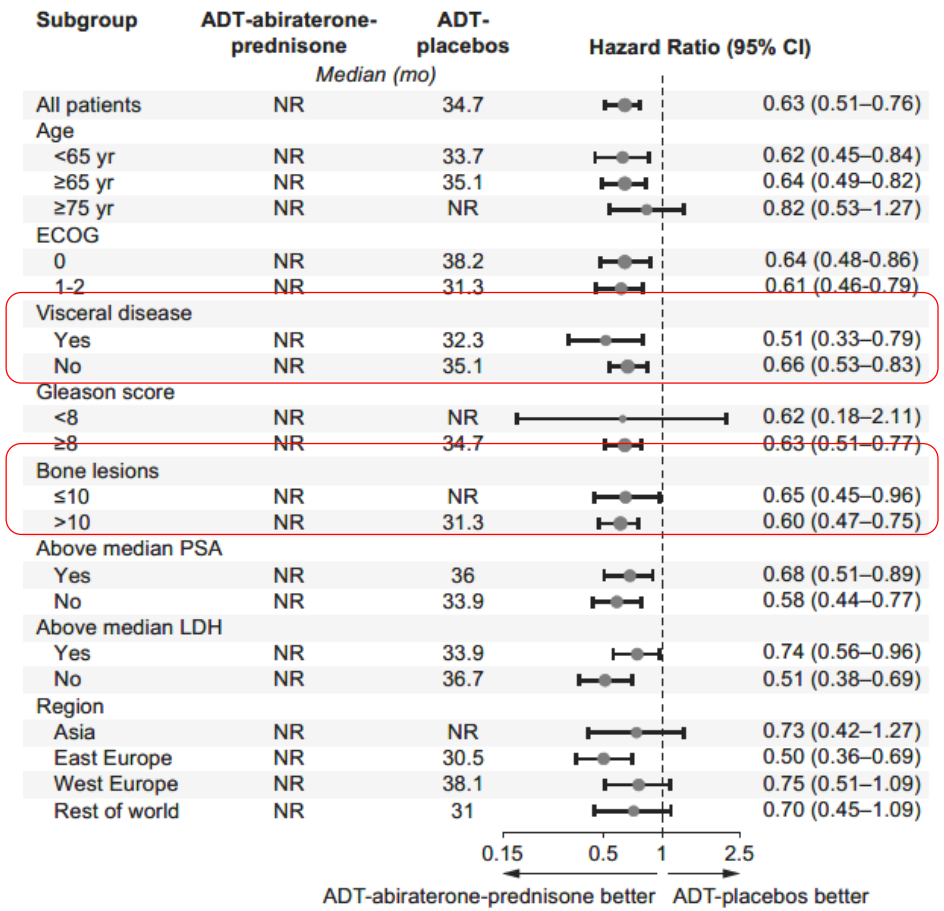
Combination therapy	500	(92)	399	(65)	326	(40)	202	(11)	63
ADT alone	502	(258)	236	(93)	139	(33)	83	(9)	23

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

- 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

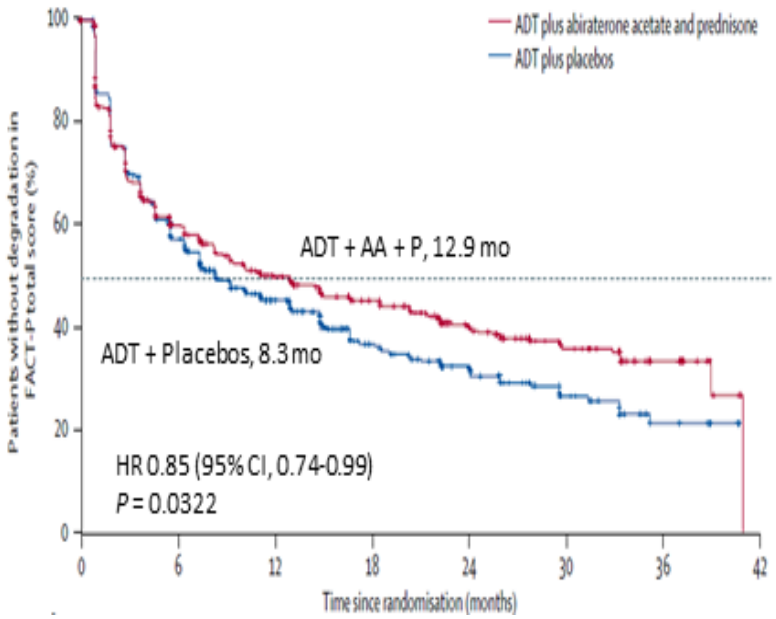


The treatment effect of ADT-abiraterone-prednisone on OS was consistently favorable across nearly all prespecified subgroups

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

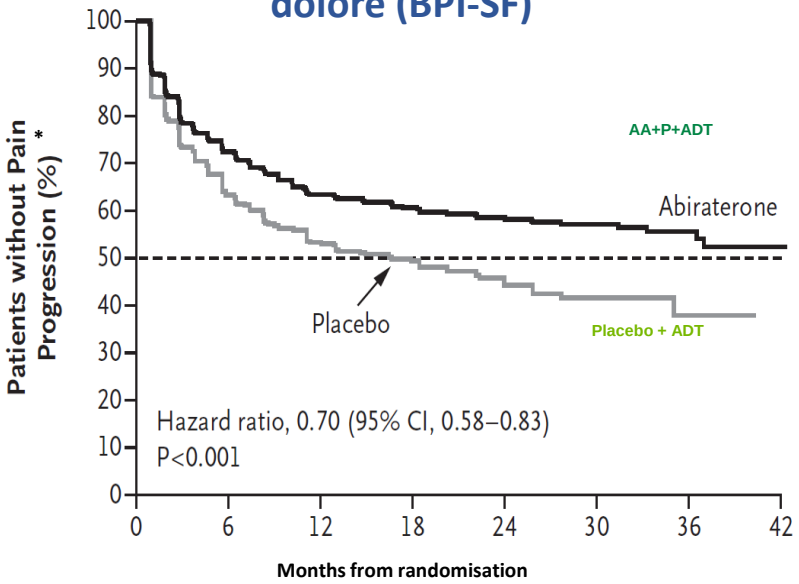
PRO: statistically significant and clinically relevant benefits

Tempo al peggioramento della QoL (FACT-P)



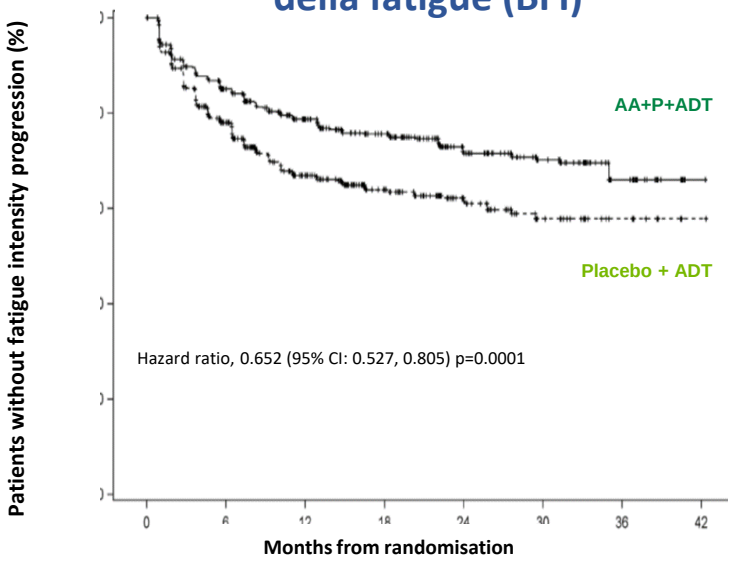
Riduzione significativa nel rischio di peggioramento della QoL

Tempo all'evento di intensità peggiore del dolore (BPI-SF)



Riduzione significativa nel rischio di progressione del dolore

Tempo all'evento di intensità peggiore della fatigue (BFI)



Riduzione significativa nel rischio di progressione della fatigue

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

LATITUDE: Summary of Adverse Events

Adverse Event	ADT-Abiraterone-Prednisone (n = 597)	ADT-Placebos (n = 602)
	no of patients (%)	
Any adverse event	558 (93)	557 (93)
Grade 3 or 4 adverse event	374 (63)	287 (48)
Any serious adverse event	165 (28)	146 (24)
Any adverse event leading to treatment discontinuation	73 (12)	61 (10)
Adverse event leading to death	28 (5)	24 (4)

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

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What patient populations were included?
Poorer prognosis in Latitude

	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%

HIGH RISK (HR)[1]

At least 2 of 3:
- ≥3 bone lesions
- Visceral metastasis
- Gleason score ≥8

HIGH VOLUME (HV)[4,5]

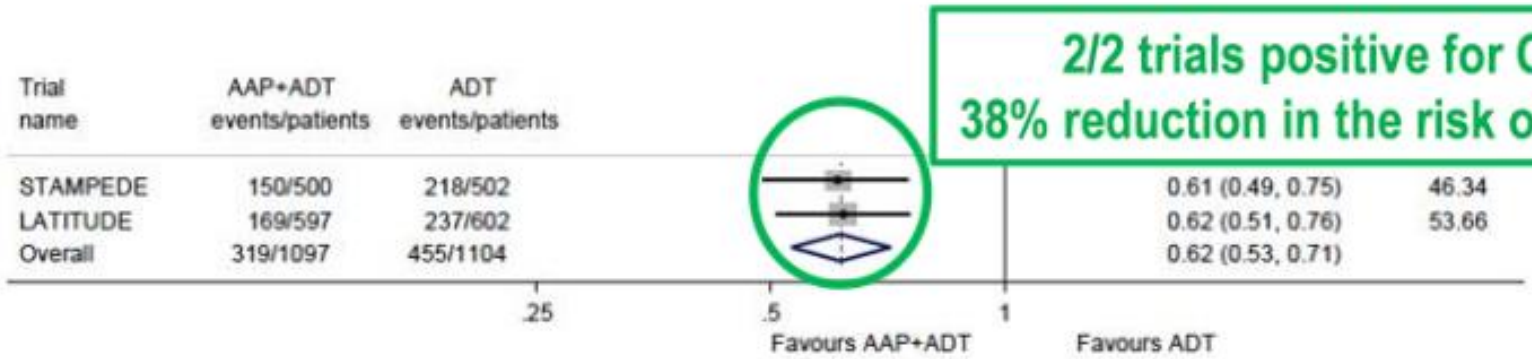
At least 1 of 2:
- ≥4 bone lesions with ≥1 beyond the vertebral bodies/pelvis
- Visceral metastasis

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

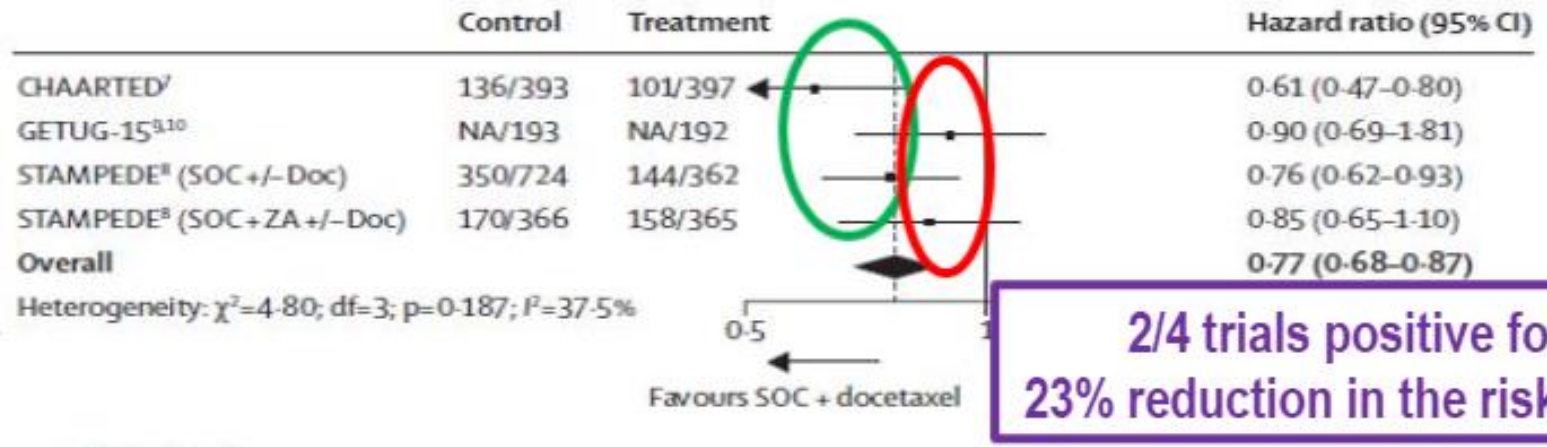
Meta-analysis of new agents for M1 (OS)

Abiraterone



2/2 trials positive for OS
38% reduction in the risk of death

Docetaxel



2/4 trials positive for OS
23% reduction in the risk of death

MUNICH 2018 ESMO congress

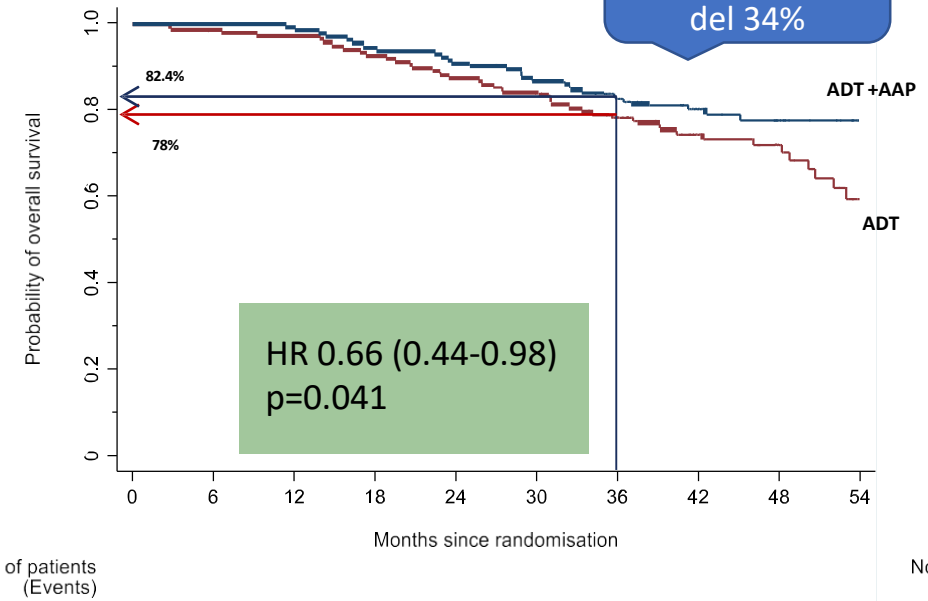
Vale C, Lancet Oncol 2016;17:243-56
Rydzewska L, Eur J Cancer 2017; 84: 88-101

Feyerabend S, Eur J Cancer 2018; 103: 78-87
Vale C, Ann Oncol 2018; 29: 1249-1257

Overall Survival nello studio Stampede: vantaggio per abiraterone nei pazienti a basso ed alto rischio

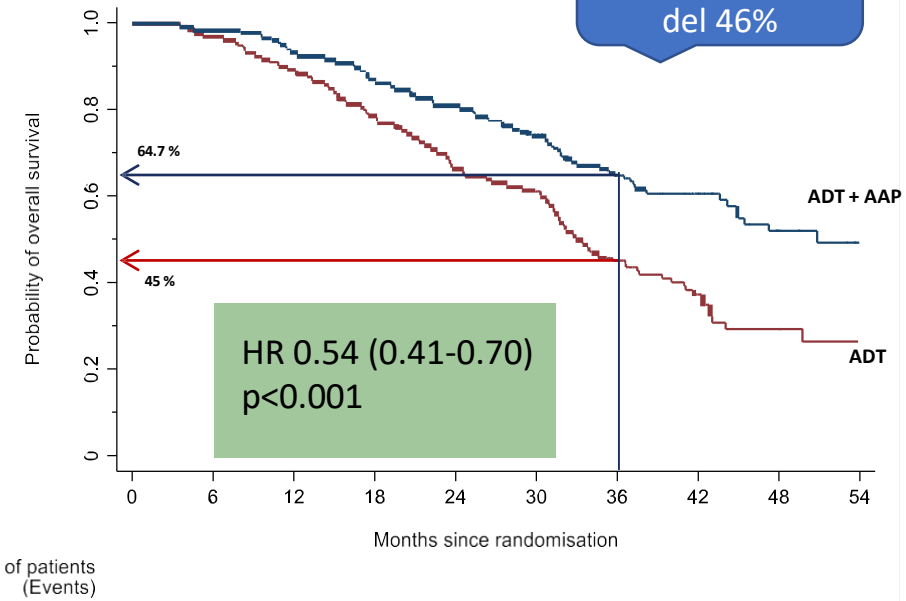
Low Risk

Riduzione del rischio di morte del 34%



High Risk

Riduzione del rischio di morte del 46%

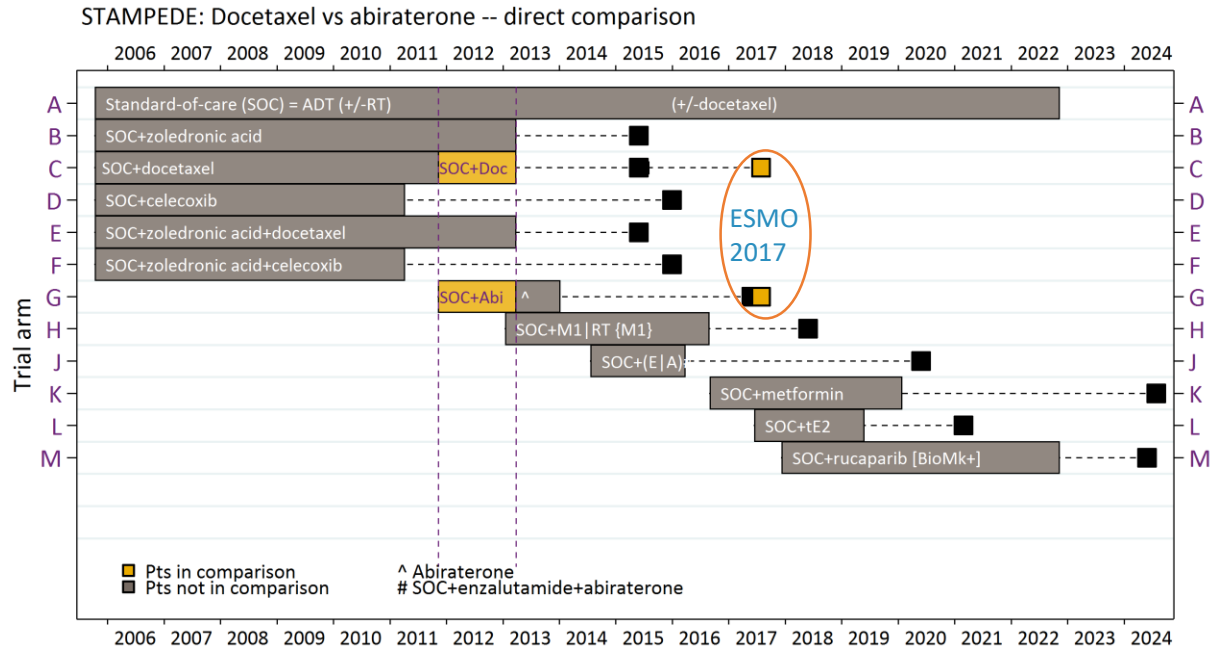


Hoyle, Presidential Symposium at ESMO 2018

Sydes M, et al.

Direct randomized comparison from

STAMPEDE: ADT+AA+P vs ADT+DOC



Recruitment: Nov-2011 to Mar-2013

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

Reported: ESMO 2017

Published: (paper in development)

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)

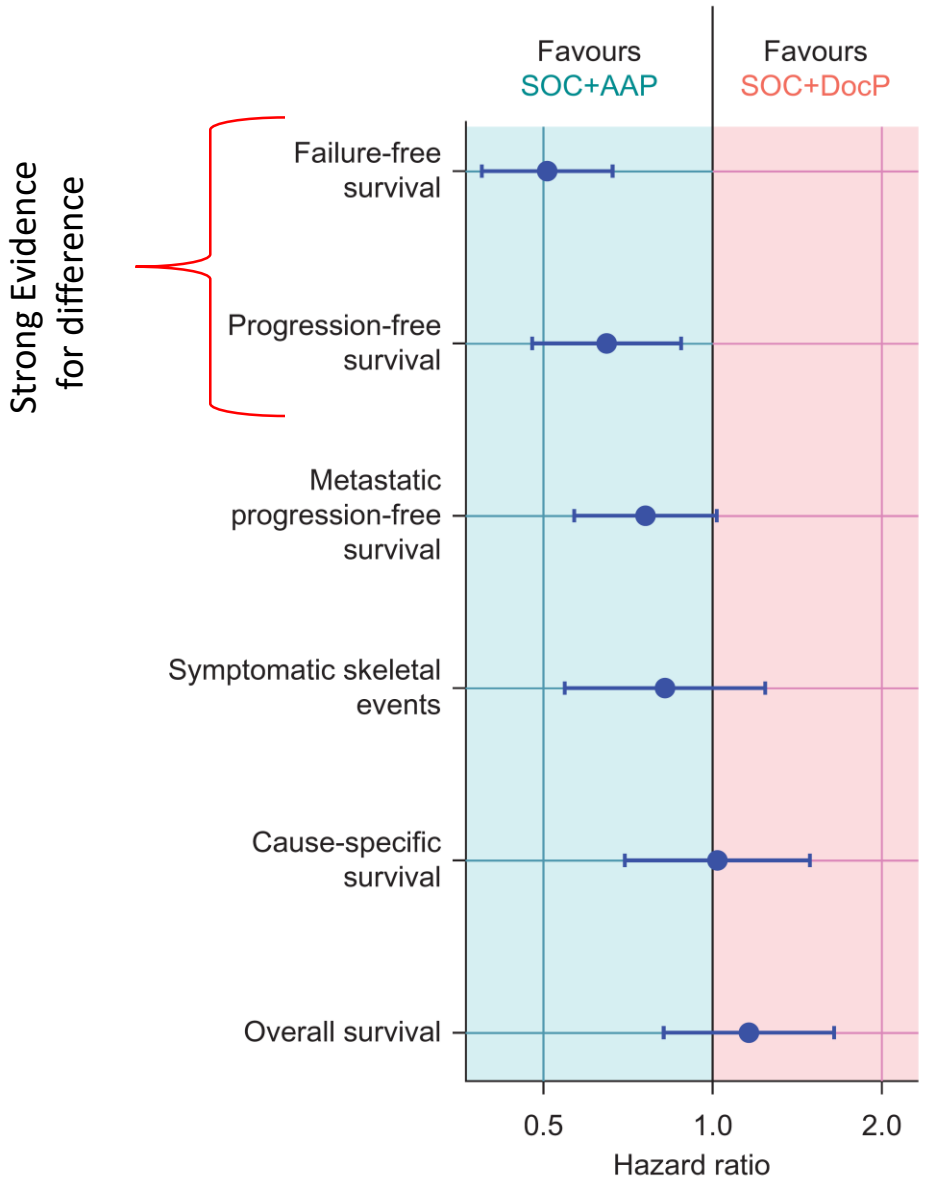


Figure 4. Depiction of disease state over time.

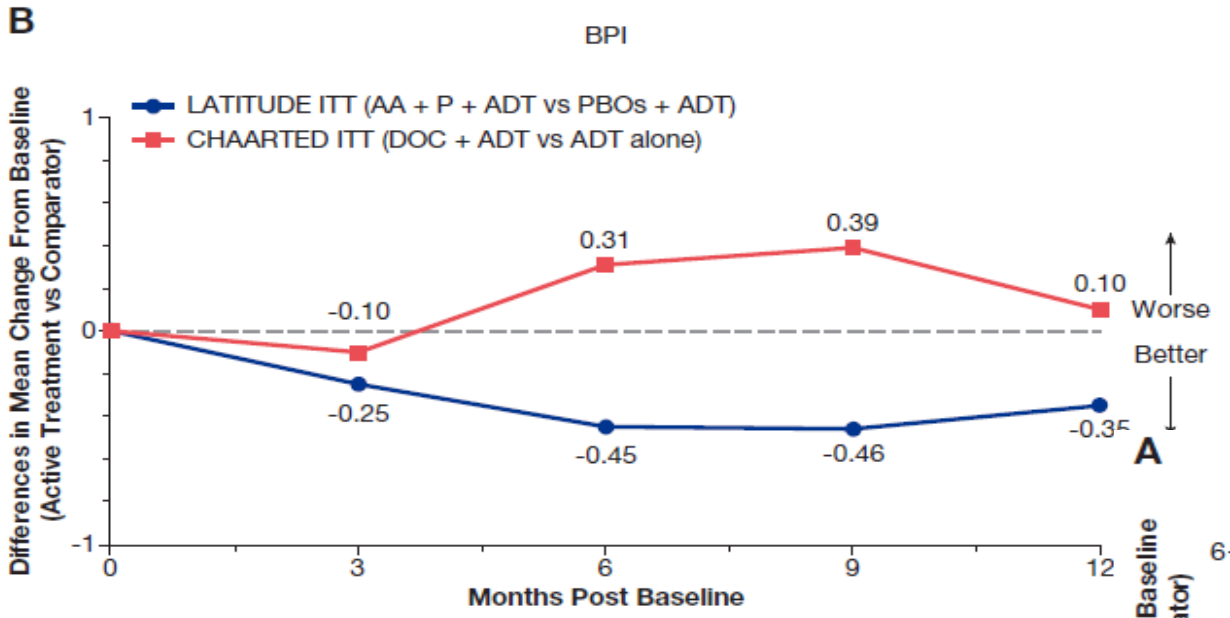
Table 3. Worst adverse event (grade) reported over entire time on trial

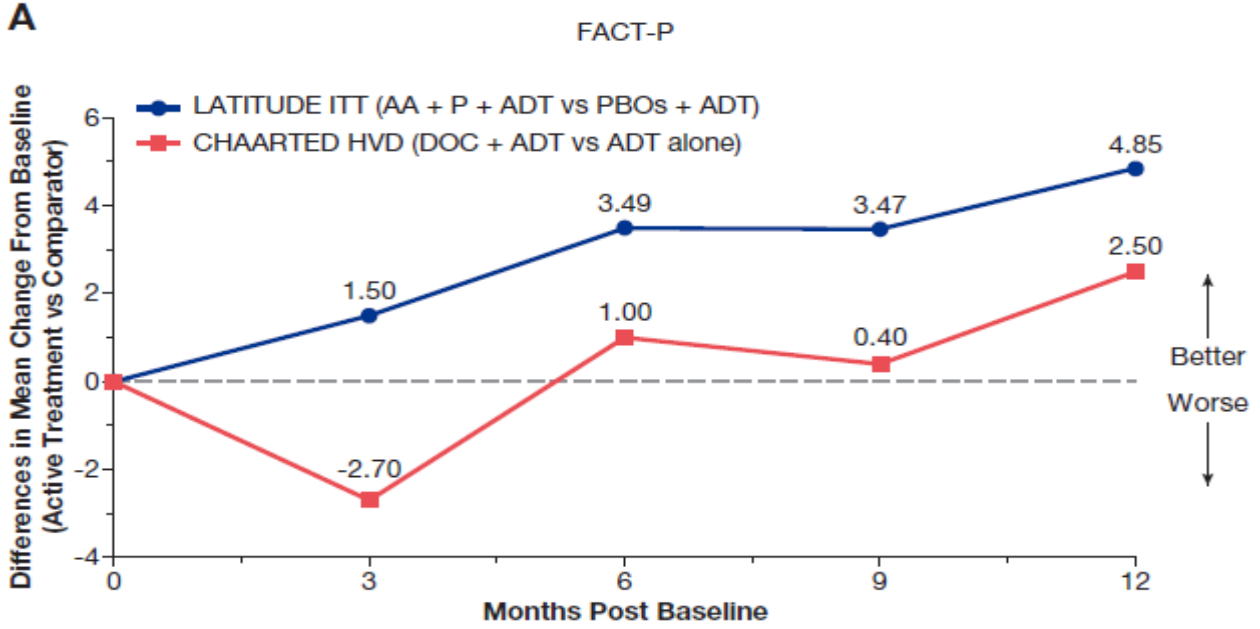
	SOC + Doc (*n* = 189)	SOC + AAP (*n* = 377)
Safety population		
Number of patients included in analysis[a]	**172**	**373**
Patients with an adverse event—no. (%)		
Grade 1–5 adverse event	172 (100)	370 (99)
Grade 3–5 adverse event	86 (50)	180 (48)
Grade 3–5 adverse events—no. (%)		
Endocrine disorder	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: QoL 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!!!