Ente Ecclesiastico Ospedale Reginale «F. Miulli»
Acquaviva delle Fonti
Struttura Complessa di Urologia
Centro di Chirurgia Robotica - Laparoscopica – Mininvasiva
Direttore: Giuseppe Mario Ludovico

“CaP metastatico alla diagnosi: terapia con LHRH e terapie di seconda linea ”

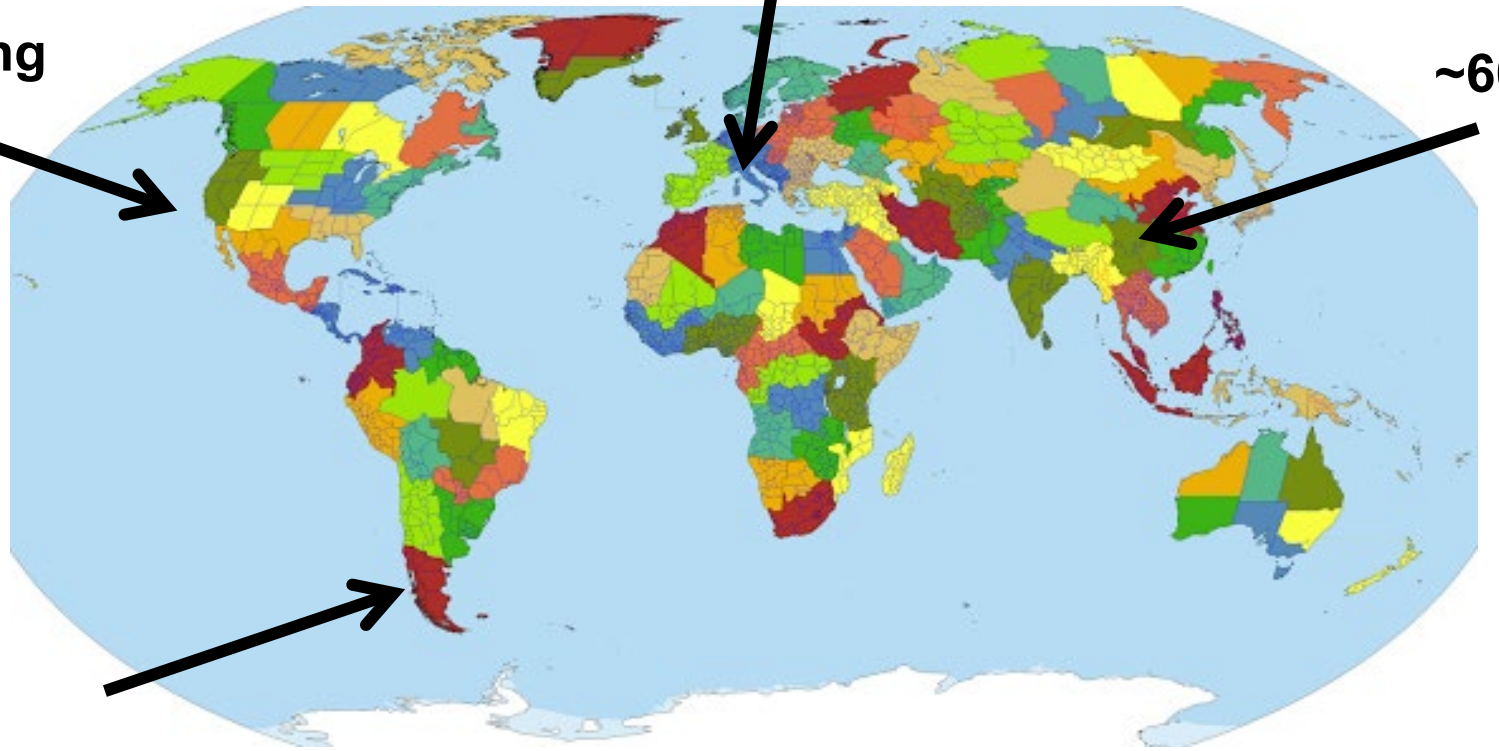
Marcello SCARCIA

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

Median survival of patients with newly diagnosed metastases is about 42 months

Visceral metastases, more than five bone metastases on bone scan, appendicular locations, and ISUP groups > 3 are all independently associated with a decreased survival

Table 6.4.1: Prognostic factors based on the SWOG 9346 study

PSA after 7 months of castration	Median survival
< 0.2 ng/mL	75 months
0.2 < 4 ng/mL	44 month
> 4 ng/mL	13 months

Current diagnostic paradigm is evolving:

EAU guidelines 2018

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 – ESTRO – ESUR – SIOG Guidelines on Prostate Cancer

5.3.3.4 Summary of evidence and practical considerations on initial N/M staging

…Evidence shows that choline PET/CT, MRI and PSMA PET/CT provide a more sensitive detection of LN and bone metastases than the classical work-up associating bone scan and abdominopelvic CT…Yet, the clinical benefit of detecting metastases at an earlier time-point remains unclear...

One prospective multicentre study evaluated changes in planned management before and after PSMA PET/CT in 108 intermediate and high-risk patients

As compared to conventional staging, additional LNs and bone/visceral metastases were detected in 25% and 6% of patients respectively.

Management changes occurred in 21% of patients.

Clearly, this study could not assess whether this changes in management induced better outcome.

EAU – ESTRO – ESUR – SIOG Guidelines on Prostate Cancer

6.4.4.1 Complete androgen blockade

The largest RCT in 1,286 M1b patients found no difference between surgical castration with or without flutamide. However, results with other anti-androgens or castration modalities have differed and ***SRs have shown that CAB using a non-steroidal anti-androgen (NSAA) appears to provide a small survival advantage (< 5%) vs. monotherapy (surgical castration or LHRH agonists)*** beyond five years of survival but this minimal advantage in a small subset of patients must be balanced against **the increased side-effects associated with long-term use of NSAAs**.

6.4.4.2 Non-steroidal anti-androgen monotherapy

Based on a Cochrane SR comparing NSAA monotherapy to castration (either medical or surgical), **NSAA was considered to be less effective in terms of OS, clinical progression,** treatment failure and treatment discontinuation due to adverse events. The evidence quality of the studies included in this review was rated as moderate.

EAU – ESTRO – ESUR – SIOG Guidelines on Prostate Cancer

6.4.4.3 Intermittent versus continuous androgen deprivation therapy

Three independent reviews and two meta-analyses, looked at the clinical efficacy of intermittent androgen deprivation (IAD) therapy. All of these reviews included eight RCTs of which **only three were conducted in patients with exclusively M1 disease**. The five remaining trials included different patient groups, mainly locally advanced and metastatic patients relapsing.

None of the trials that addressed IAD vs. continuous ADT in M1 only patients showed a survival benefit in favour of the latter, but **there was a trend towards better OS and PFS with continuous ADT**. Most of these trials, however, were non- inferiority trials. There is a trend favouring IAD in terms of QoL, especially regarding treatment-related side- effects, such as hot flushes. In some cohorts the negative impact on sexual function was less pronounced with IAD.

These outcomes, as well as the lack of any survival benefit in M1 patients, suggest that this treatment modality should only be considered as an option in a well-informed patient bothered by significant side-effects.

Recent Trials: mHSPC

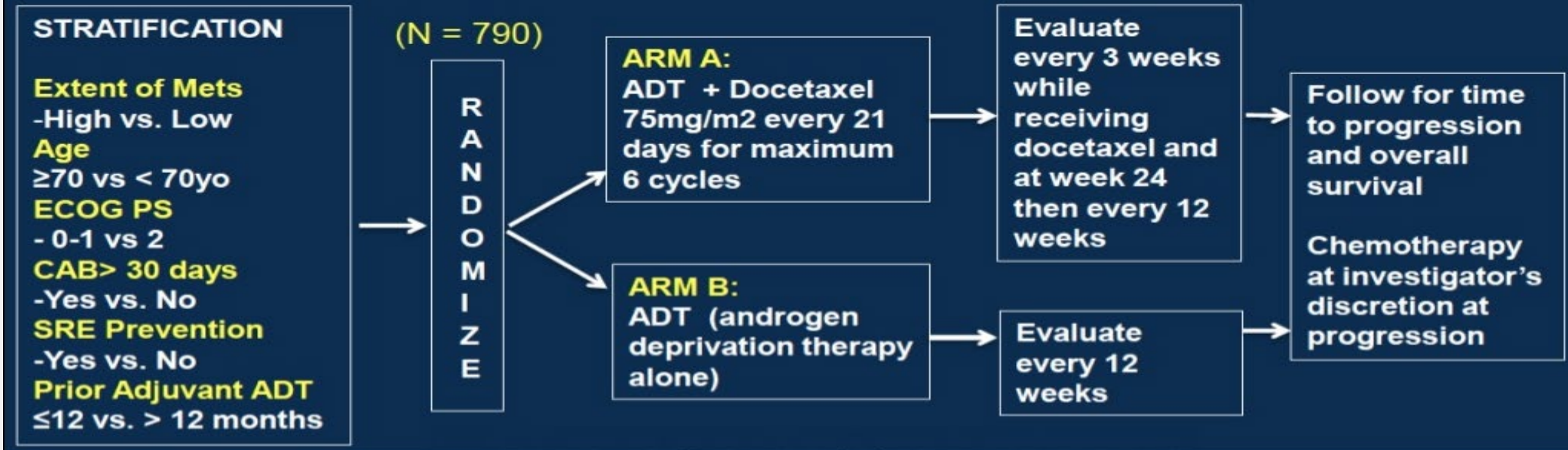
CHAARTED[1]: **C**hemo**H**ormonal Therapy Versus **A**ndrogen **A**blation **R**andomized **T**rial for **E**xtensive **D**isease in Prostate Cancer

STAMPEDE[2]: **S**ystemic **T**herapy in **A**dvancing or **M**etastatic **P**rostate cancer: **E**valuation of **D**rug **E**fficacy: a multi-stage multi-arm randomised controlled trial

LATITUDE[3]: A phase 3, double-blind, randomized trial of androgen deprivation therapy with abiraterone acetate plus prednisone or placebo in newly diagnosed high-risk metastatic hormone-naïve prostate cancer patients

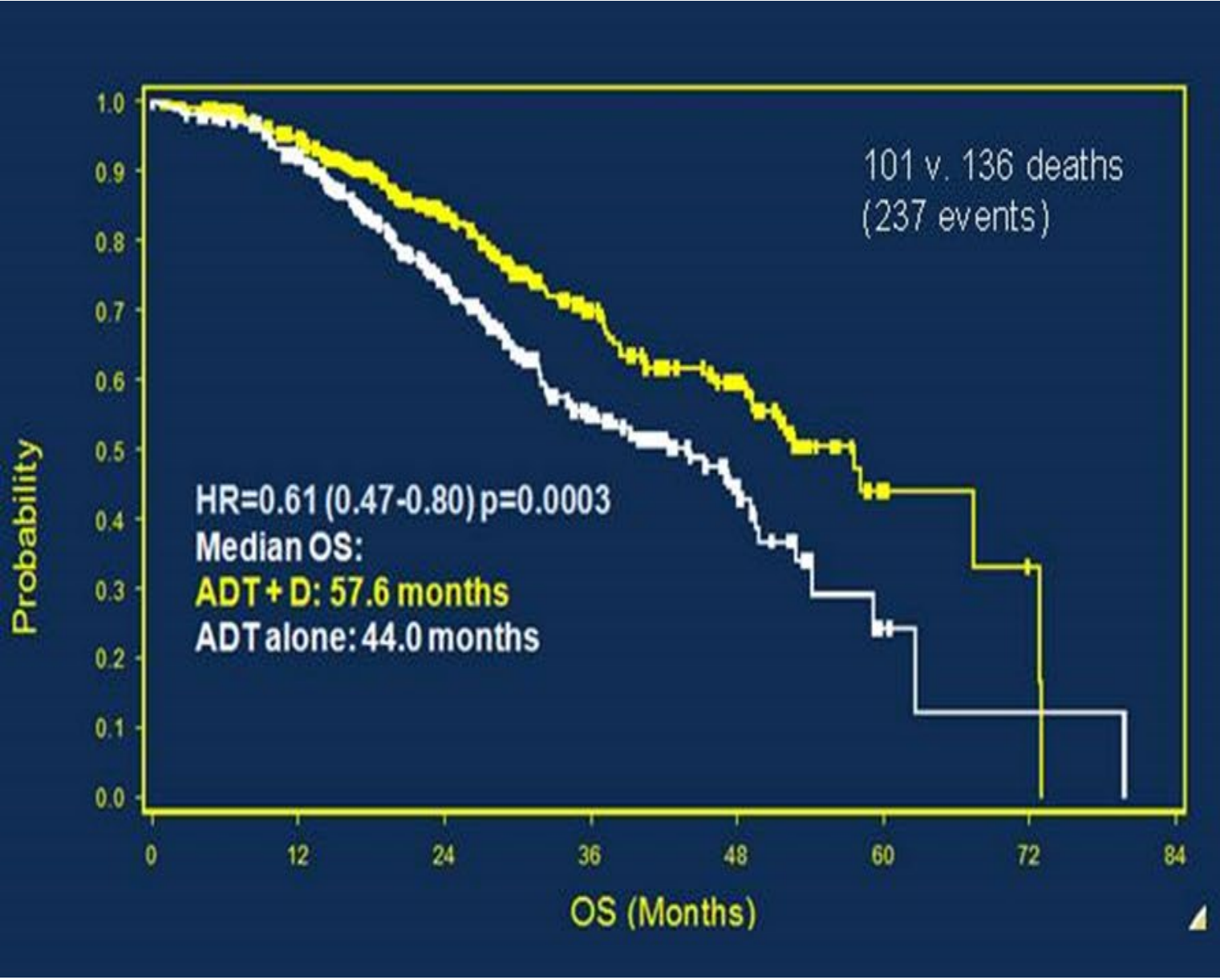
www.clinicaltrials.gov: CHAARTED[1] (NCT00309985); STAMPEDE[2] (NCT00268476); LATITUDE[3] (NCT01715285)

CHAARTED



- ADT Allowed up to 120 days prior Randomization
- Intermitent ADT dosing was not allowed
- Estándar Dexamethasone premedication but no daily PDN

Sweeney CJ, NEJM, 2015

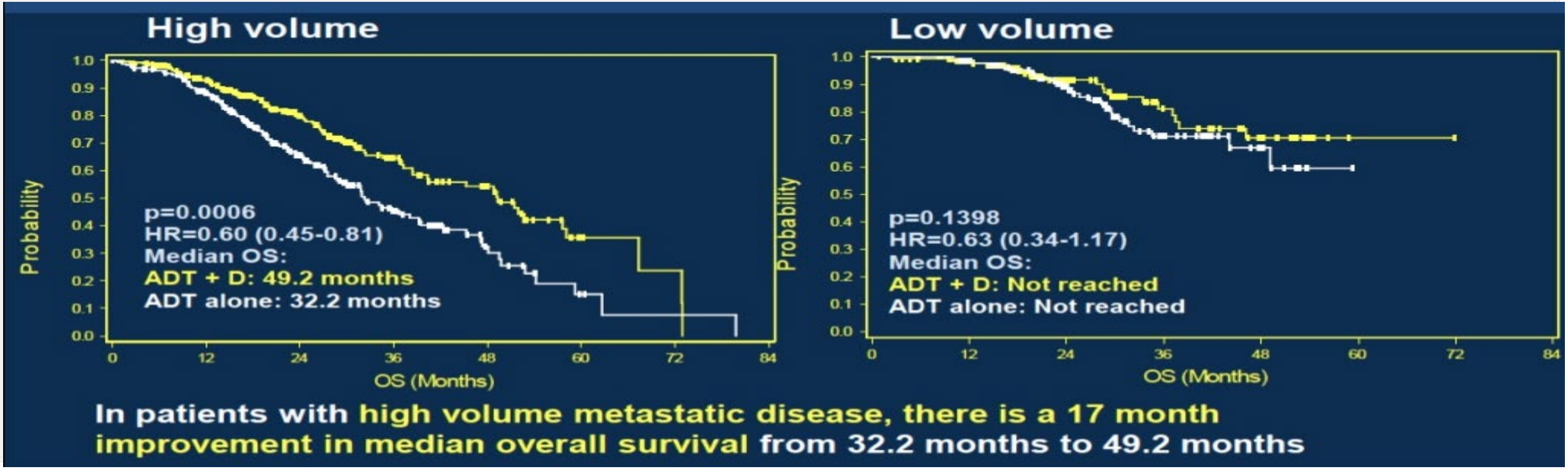


Difference in median:

OS: 13.6 mo's

TTP (clinical or imaging): 12.9 mo's

Time to CRPC: 6 mo's



≥4 bone lesions and ≥1 lesions
beyond the spine/pelvis
or
visceral disease

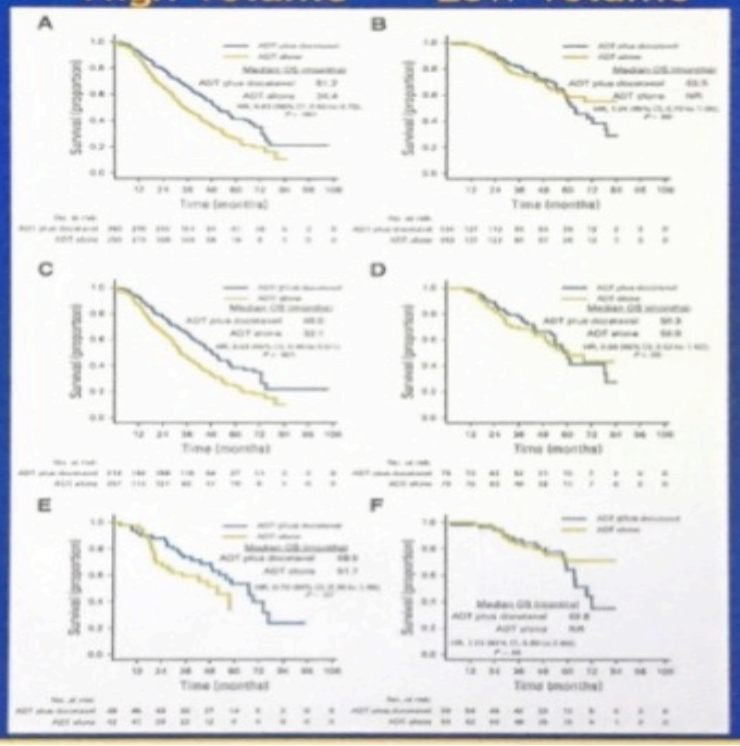
CHAARTED: Updated Analysis on OS Benefit by Disease Volume Status

High Volume Low Volume

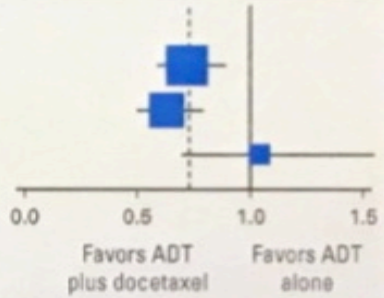
Total Patient Population

De novo Metastatic Patients

Prior Local Therapy



Group	No.	HR	95% CI
Overall	790	0.72	0.59 to 0.89
High-volume disease	513	0.63	0.50 to 0.79
Low-volume disease	277	1.04	0.70 to 1.55



Test of heterogeneity between patients with high- and low-volume disease. The size of the squares is proportional to the inverse of the variance of the log hazard ratio (small squares correspond to large variances).

www.clinicaltrials.gov: CHAARTED (NCT00309985)

Kyriakopoulos CE et al. *J Clin Oncol* 2018 36(11):1080-1087

EUROPEAN UROLOGY 73 (2018) 178–211

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Prostate Cancer
Editorial by Megan E.V. Caram and David C. Miller on pp. 212–214 of this issue

Management of Patients with Advanced Prostate Cancer: The Report of the Advanced Prostate Cancer Consensus Conference APCCC 2017

DEFINITION OF HIGH-VOLUME DISEASE

74% CHAARTED (visceral [lung or liver] and/or 4 bone metastases, at least one beyond pelvis and vertebral column)

6% SWOG (visceral [lung or liver] and/ or any appendicular skeletal involvement)

6% simplified version of high-volume of visceral and/or 4 bone lesions regardless of distribution

14% of the panellists had the opinion that high-volume disease is not a clinically meaningful entity.

M+ Hormone Naive Prostate Cancer

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

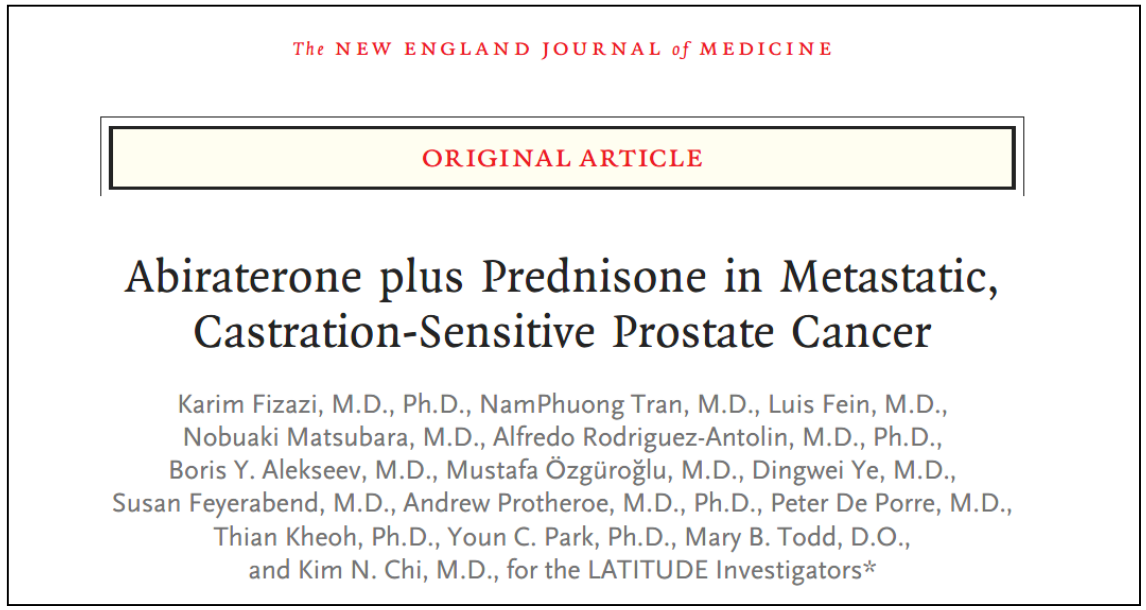
Recommendations	LE	GR
In M1 symptomatic patients, offer immediate castration to palliate symptoms and reduce the risk for potentially catastrophic sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction, extra-skeletal metastasis).	1b	A
In M1 asymptomatic patients, offer immediate castration to defer progression to a symptomatic stage and prevent serious disease progression-related complications.	1b	A
In newly diagnosed M1 patients, offer castration combined with docetaxel, provided patients are fit enough to receive chemotherapy.	1a	A
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 2017

Recommendations	Strength rating
In M1 symptomatic patients, offer immediate systemic treatment to palliate symptoms and reduce the risk for potentially serious sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction, extra-skeletal metastasis).	Strong
Offer luteinizing hormone-releasing hormone (LHRH) antagonists, especially to patients with an impending spinal cord compression or bladder outlet obstruction.	Weak
In M1 asymptomatic patients, offer immediate systemic treatment to improve survival, defer progression to a symptomatic stage and prevent serious disease progression-related complications.	Strong
In M1 asymptomatic patients, discuss deferred castration with a well-informed patient	Weak
Do not offer anti-androgen monotherapy for M1 disease.	Strong
Offer castration combined with chemotherapy (docetaxel) to all patients whose first presentation is M1 disease and who are fit enough for docetaxel.	Strong
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
Offer castration alone, with or without an anti-androgen, to patients unfit for, or unwilling to consider, castration combined with docetaxel or abiraterone acetate plus prednisone.	Strong
Intermittent treatment	
In asymptomatic M1 patients, only offer intermittent treatment to highly motivated men, with a major prostate-specific antigen (PSA) response after the induction period.	Strong
• In M1 patients, follow the schedules used in published clinical trials on timing of intermittent treatment. • Stop treatment when the PSA level is < 4 ng/mL after six to seven months of treatment. • Resume treatment when the PSA level is > 10-20 ng/mL (or returned to the initial level of < 20 ng/mL).	Weak
Do not use castration combined with any local treatment (radiotherapy/surgery) outside an investigational setting except for symptom control.	Strong

Hormone Sensitive Prostate Cancer

Latitude study
N Engl J Med. 2017 June 4



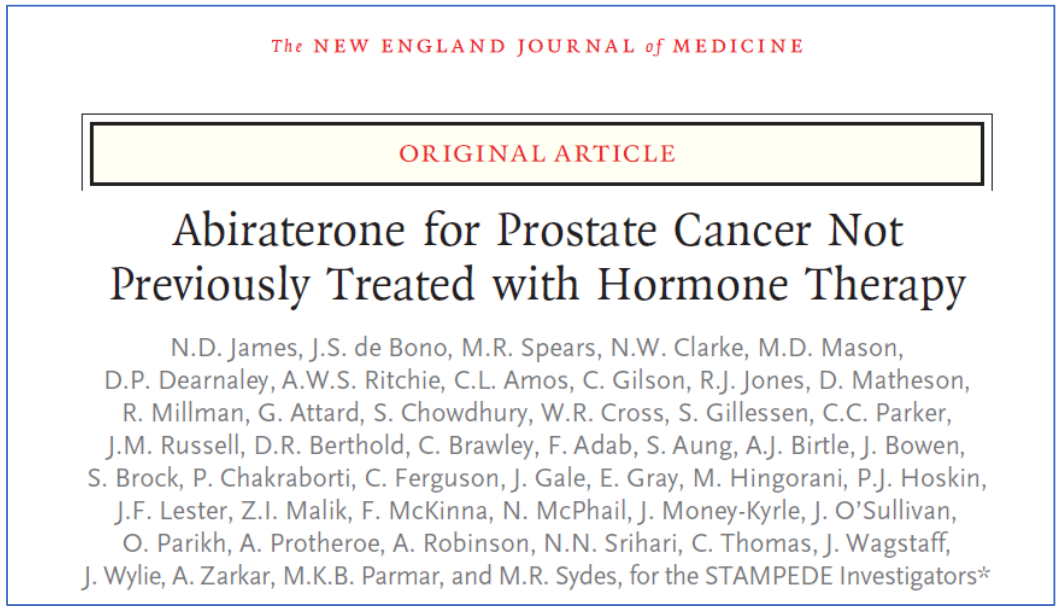
The NEW ENGLAND JOURNAL of MEDICINE

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

Patients

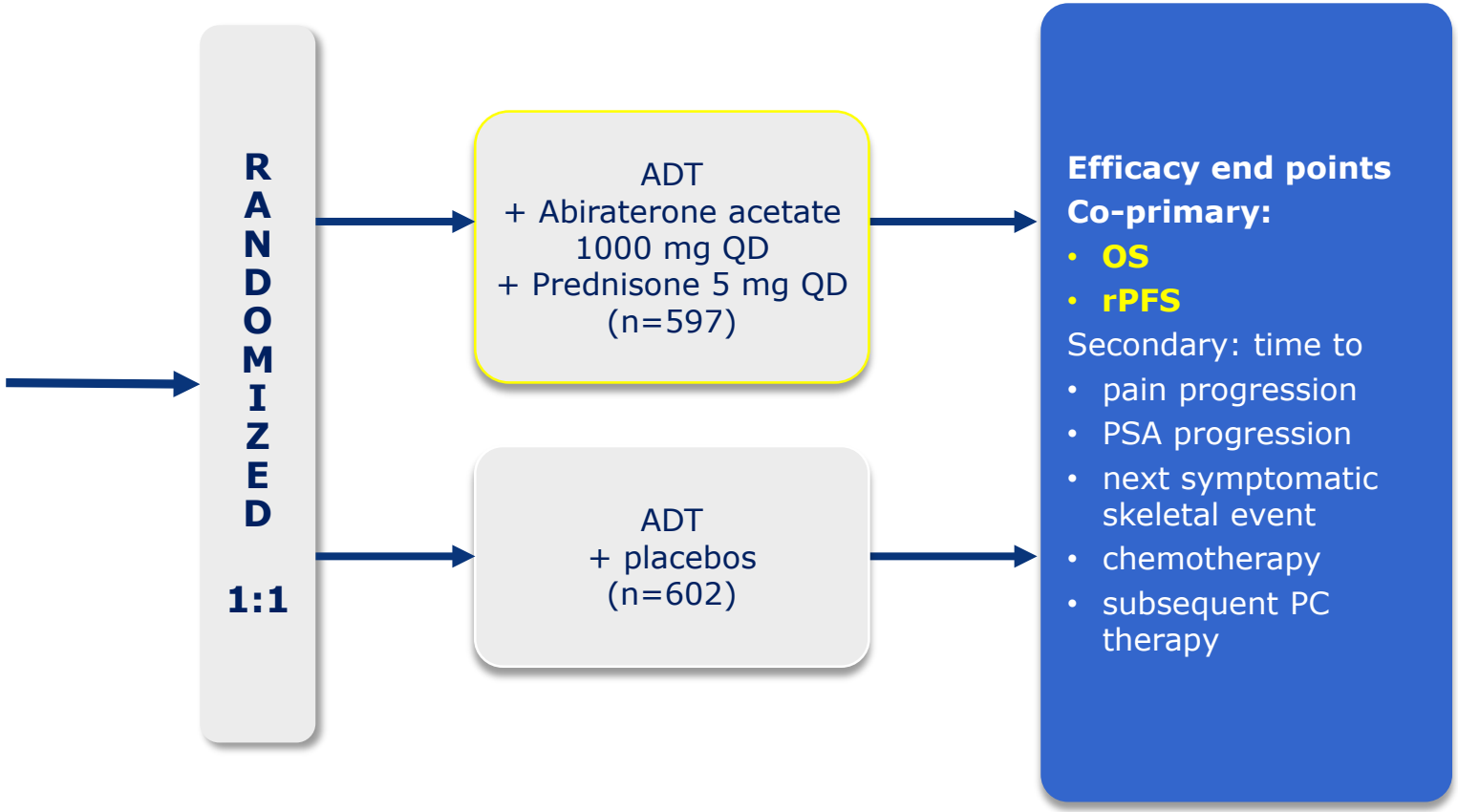
- Newly diagnosed adult men with high-risk mHNPC

Meets at least 2 of 3 high-risk criteria

- **Gleason score of ≥8**
- **Presence of ≥ 3 lesions on bone scan**
- **Presence of measurable visceral lesion**

Stratification factors

- Presence of visceral disease (yes/no)
- ECOG PS (0, 1 vs 2)



- **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**

PRESENTED AT: 2019 Genitourinary Cancers Symposium | #GU19

Final analysis of phase 3 LATITUDE study in patients (pts) with newly diagnosed high-risk metastatic castration naïve prostate cancer (NDx-HR mCNPC) treated with abiraterone acetate + prednisone (AA+P) added to androgen deprivation therapy (ADT)

Karim Fizazi,[1] NamPhuong Tran,[2] Luis Fein,[3] Nobuaki Matsubara,[4] Alfredo Rodriguez-Antolin,[5] Boris Y. Alekseev,[6] Mustafa Özgüroğlu,[7] Dingwei Ye,[8] Susan Feyerabend,[9] Andrew Protheroe,[10] Giri Sulur,[2] Yesenia Luna,[2] Susan Li,[11] Suneel Mundle,[12] Kim N. Chi[13]

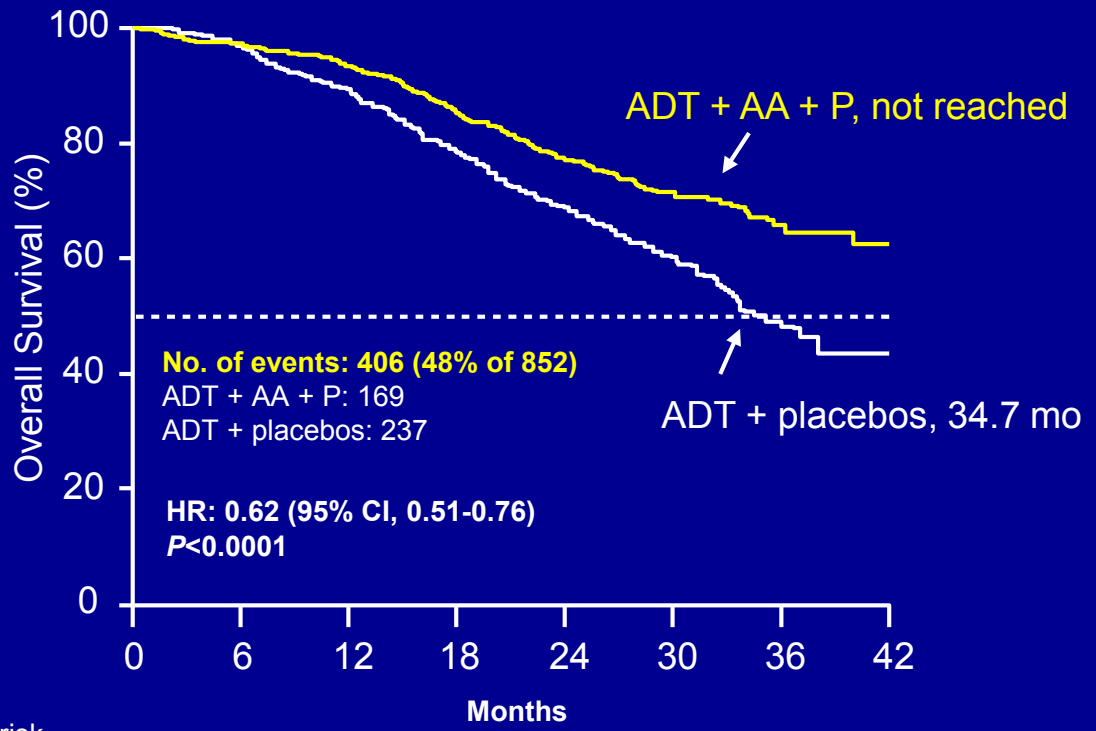
[1]Gustave Roussy, University of Paris Sud, Villejuif, France; [2]Janssen Research & Development, Los Angeles, CA; [3]Instituto de Oncologia de Rosário, Rosário, Argentina; [4]National Cancer Center Hospital East, Chiba, Japan; [5]612 de Octubre University Hospital, Madrid, Spain; [6]PA Hertsen Moscow Cancer Research Institute, Moscow, Russian Federation; [7]Cerrahpaşa Medical Faculty, Istanbul University, Istanbul, Turkey; [8]Fudan University Shanghai Cancer Center, Shanghai, China; [9]Studienpraxis Urologie, Nürtingen, Germany; [10]Oxford University Hospitals Foundation NHS Trust, Oxford, UK; [11]Janssen Research & Development, Spring House, PA; [12]Janssen Research & Development, Raritan, NJ; [13]BC Cancer Agency – Vancouver Centre, Vancouver, BC, Canada

Presented by: Kim Chi

First interim analysis: Coprimary endpoints

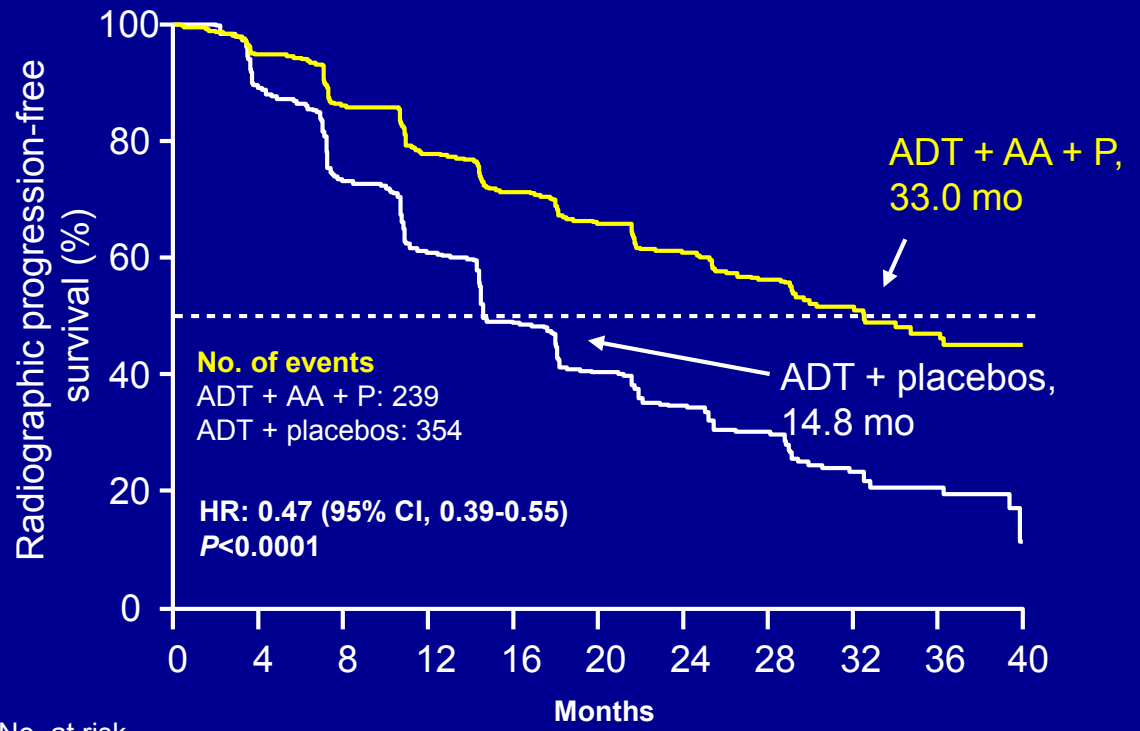
(Cut off: October 31, 2016)

Overall Survival



No. at risk								
ADT + AA + P	597	565	529	479	388	233	93	9
ADT + placebos	602	564	504	432	332	172	57	2

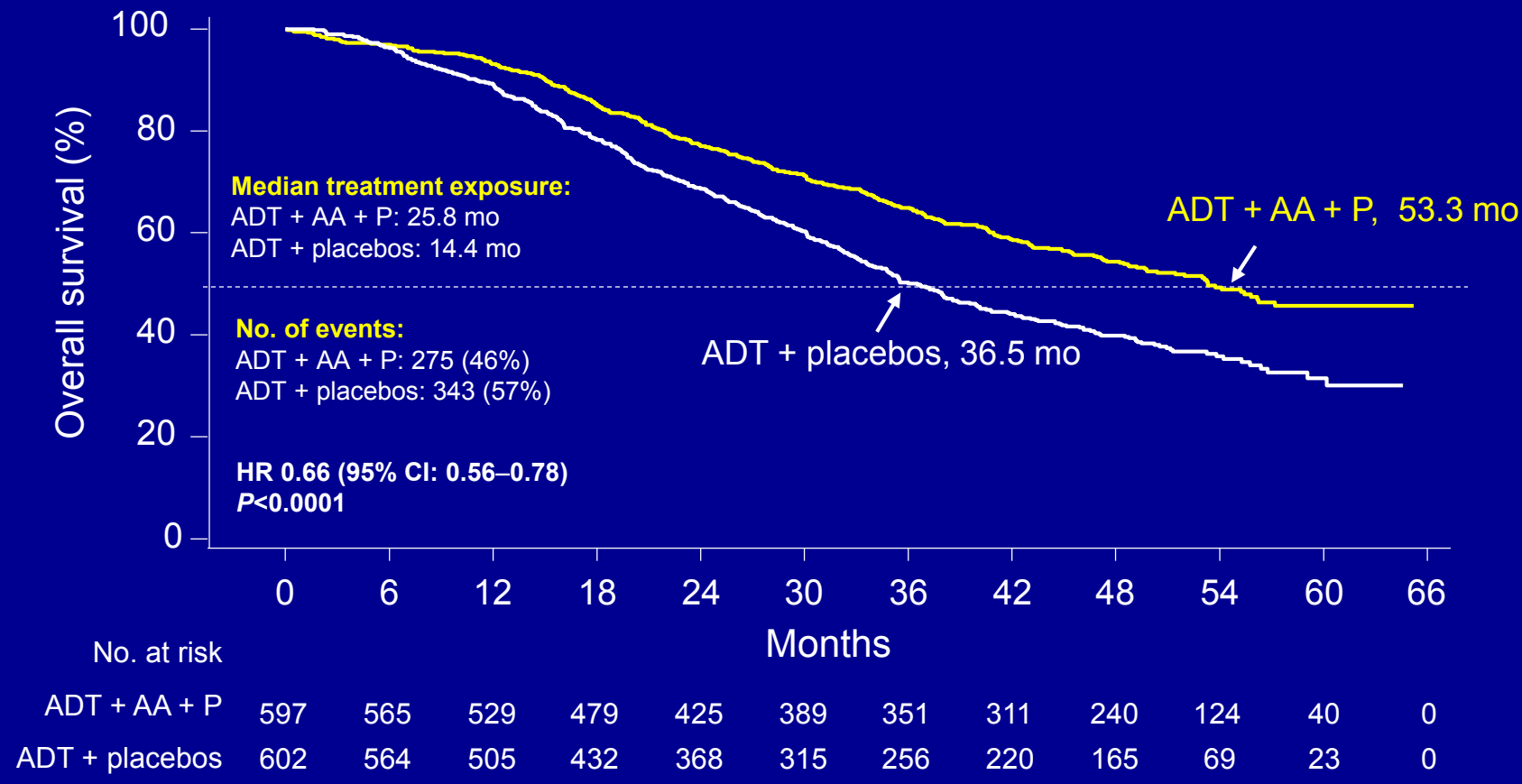
rPFS



No. at risk											
ADT + AA + P	597	533	464	400	353	316	251	177	102	51	21
ADT + placebos	602	488	367	289	214	168	127	81	41	17	7

1. Fizazi K, et al, N Engl J Med. 2017;377:352-360

Final Analysis: Overall Survival



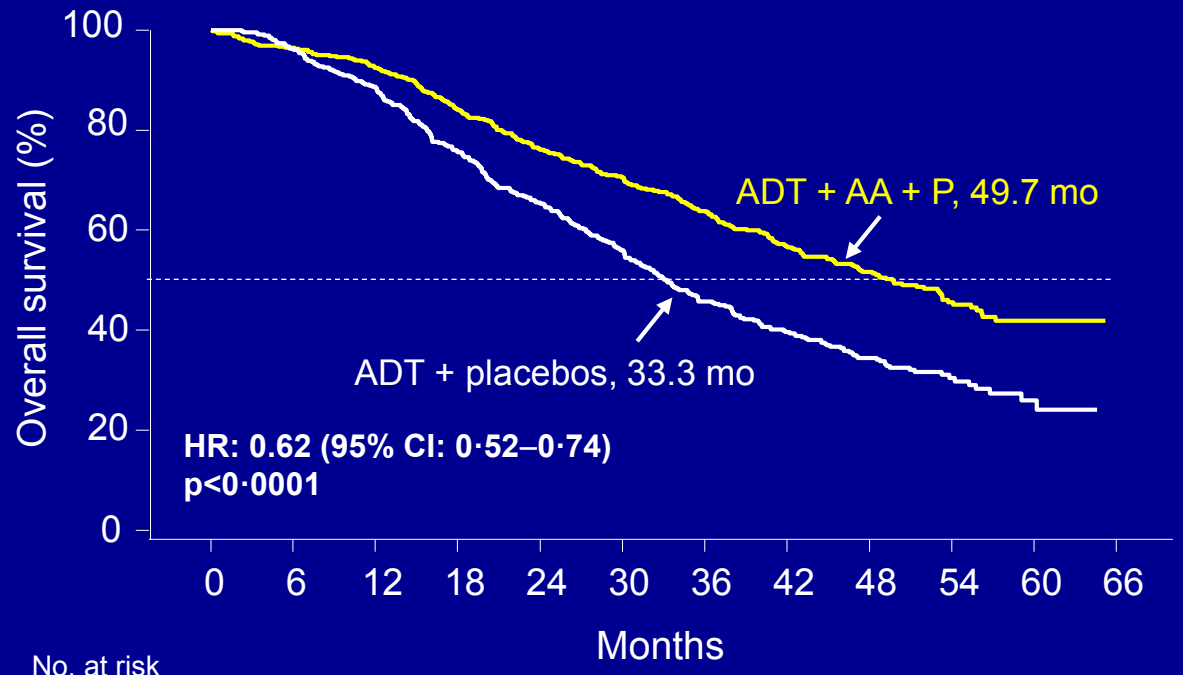
- **Median OS for patients receiving ADT + AA+P reached 4.5 years, 16.8 months longer than ADT+ placebos**

Final Analysis: Secondary endpoints

Secondary End Points	ADT + AA + P (n = 597)	ADT + placebos (n = 602)	HR (95% CI)	*P* Value
	Median (months)	Median (months)		
Time to pain progression	47.4	16.6	0.72 (0.61–0.86)	0.0002
Time to skeletal related event	NR	NR	0.75 (0.60–0.95)	0.0181
Time to chemotherapy initiation	NR	57.6	0.51 (0.41–0.63)	<0.0001
Time to subsequent PC therapy	54.9	21.2	0.45 (0.38–0.53)	<0.0001
Time to PFS2 (randomization to progression on subsequent therapy/death)	53.3	30.1	0.58 (0.49–0.68)	<0.0001

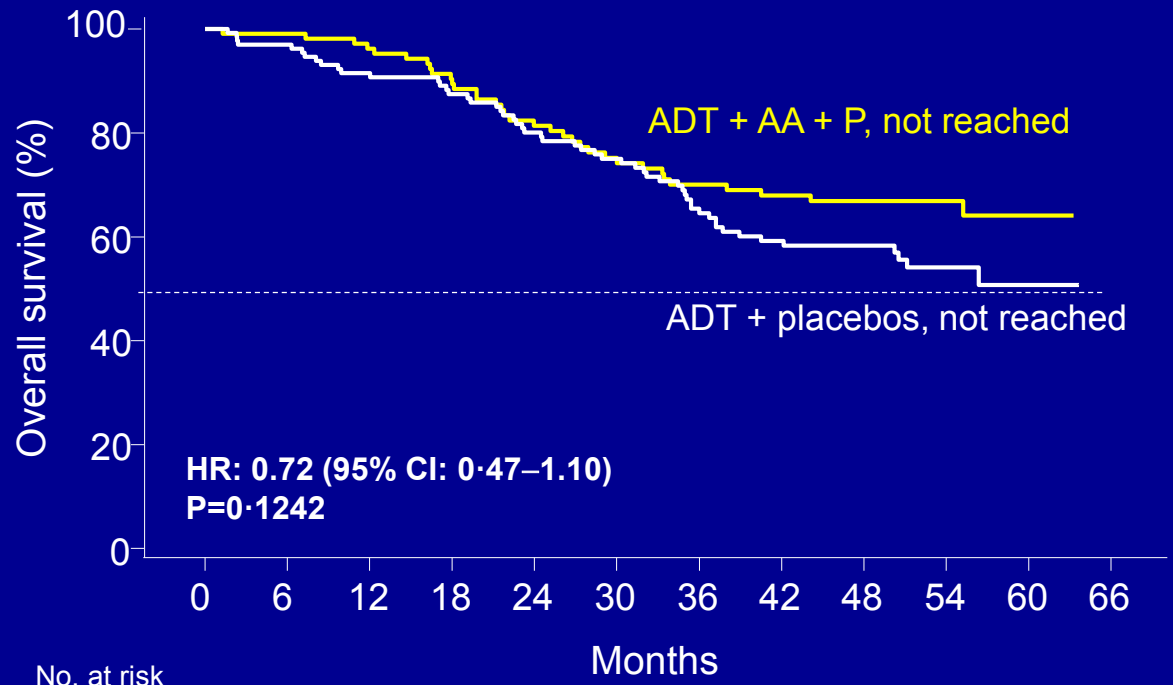
LATITUDE: Overall Survival in High and Low Volume
(CHAARTED definition*)

High volume



No. at risk												
ADT + AA + P	487	460	429	386	345	317	283	246	188	97	31	0
ADT + placebos	468	438	389	323	270	266	181	154	113	46	14	0

Low volume



No. at risk												
ADT + AA + P	110	105	100	93	80	72	68	65	52	27	9	0
ADT + placebos	133	125	115	108	97	88	74	66	52	23	9	0

CHAARTER Definition of High and Low Volume: *Presence of visceral metastases and/or ≥4 bone metastases, with at least one outside the vertebral column or pelvis

Adverse events of special interest

Graded adverse events	ADT + AA+P n=597		ADT+ Placebos n=602		Placebo cross over to AA+P n=72	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Hypertension	22%	<1%	10%	<1%	4%	0
Hepatotoxicity	8%	1%	4%	0	4%	0
ALT increased	5%	<1%	1%	0	3%	0
AST increased	4%	<1%	2%	0	1%	0
Hypokalemia	11%	1%	2%	<1%	3%	0
Cardiac Disorders	3%	1%	1%	0	0	0
Fluid retention/edema	1%	0	1%	0	0	0
Osteoporosis including osteoporosis-related fractures	2%	0	2%	<1%	0	0
Cataract	1%	0	<1%	0	0	0

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

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.

Post hoc analyses

- General population
- High volume sec CHAARTED

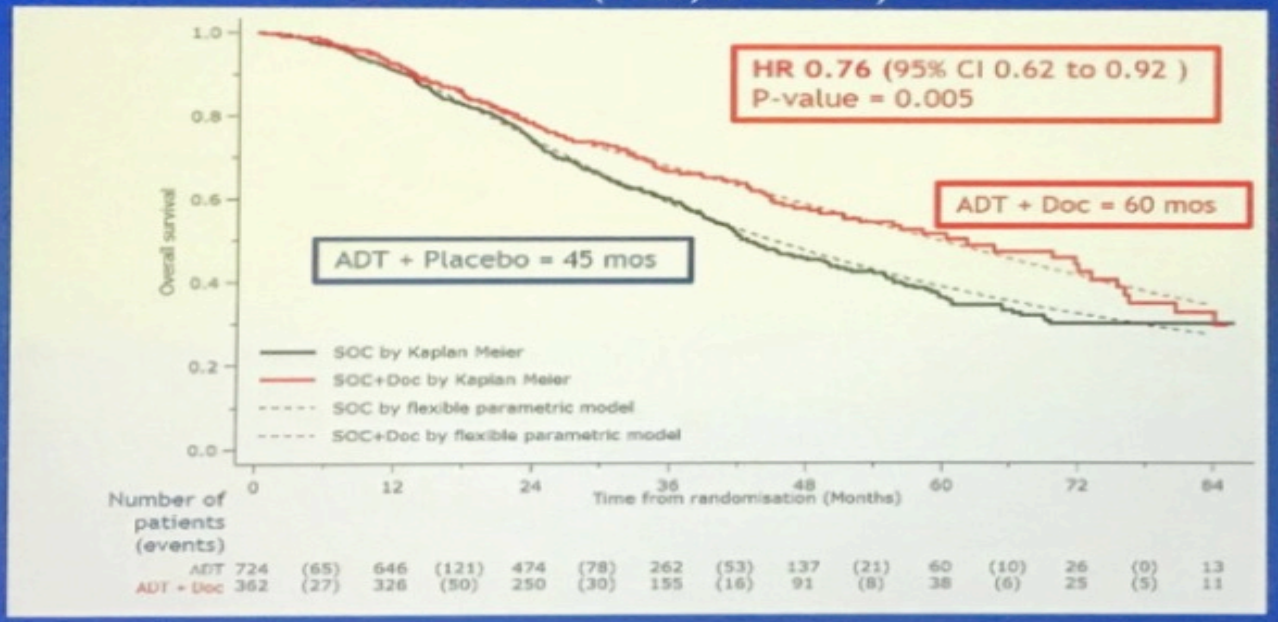
CHAARTED HV long term data

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.

STAMPEDE Trial with Docetaxel: OS in M1 and M0 Subsets

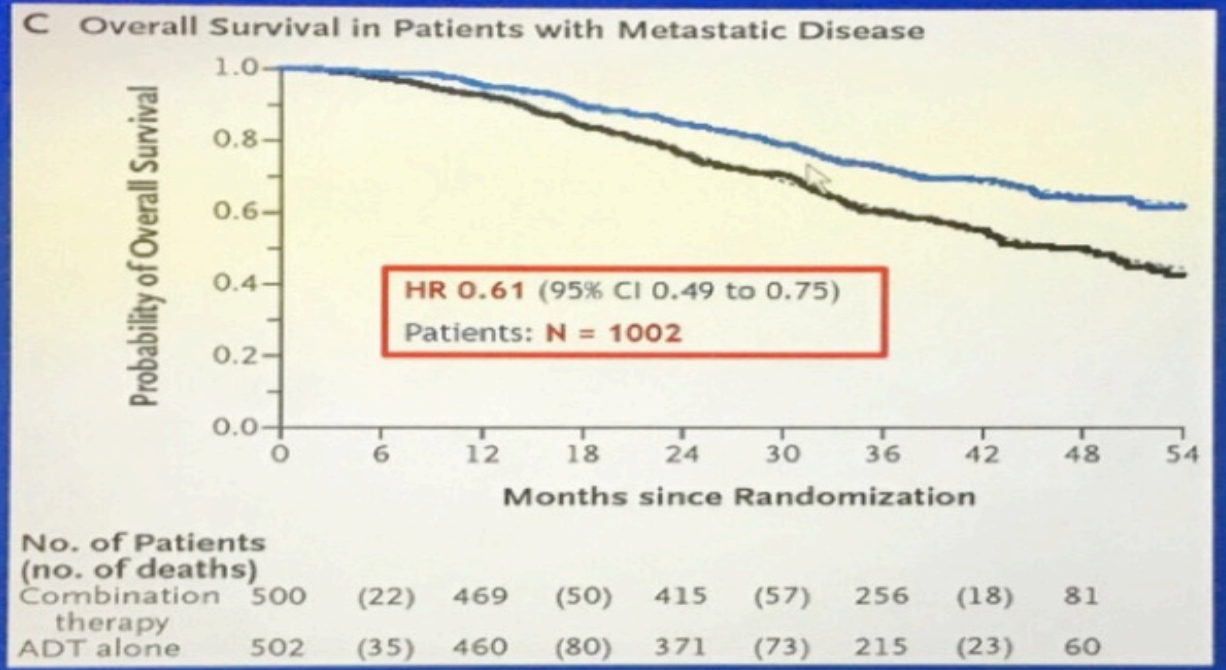
M1 disease (61%, n=1817)

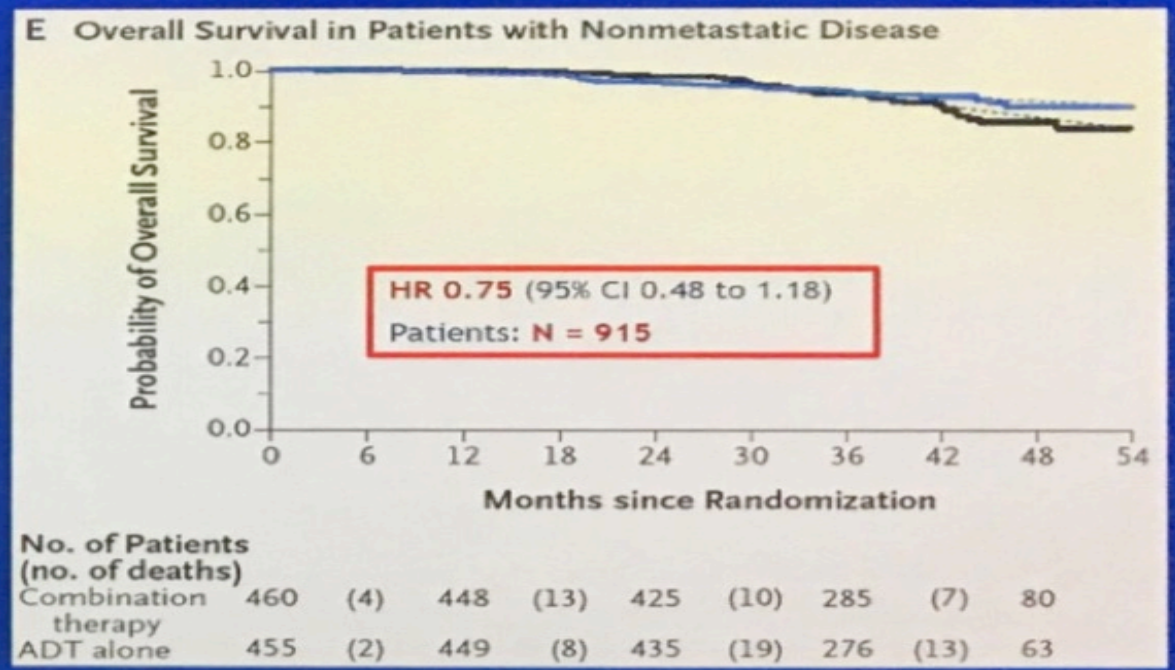


SOC *vs* SOC+ Doc	SOC-only	SOC+ Doc	Hazard ratio	HR (95% CI)
Metastasis status				
M0	65/460	31/230		0·95 (0·62-1·47)
M1	350/724	144/362		0·76 (0·62-0·92)
Nodal status				
N0	139/522	45/260		0·58 (0·41-0·81)
N+	241/594	111/298		0·85 (0·68-1·07)
NX	35/68	19/34		1·02 (0·57-1·83)

James ND et al. *Lancet* 2016; 387:1163-77.

STAMPEDE Trial with Abiraterone: OS in M1 and M0 Subsets



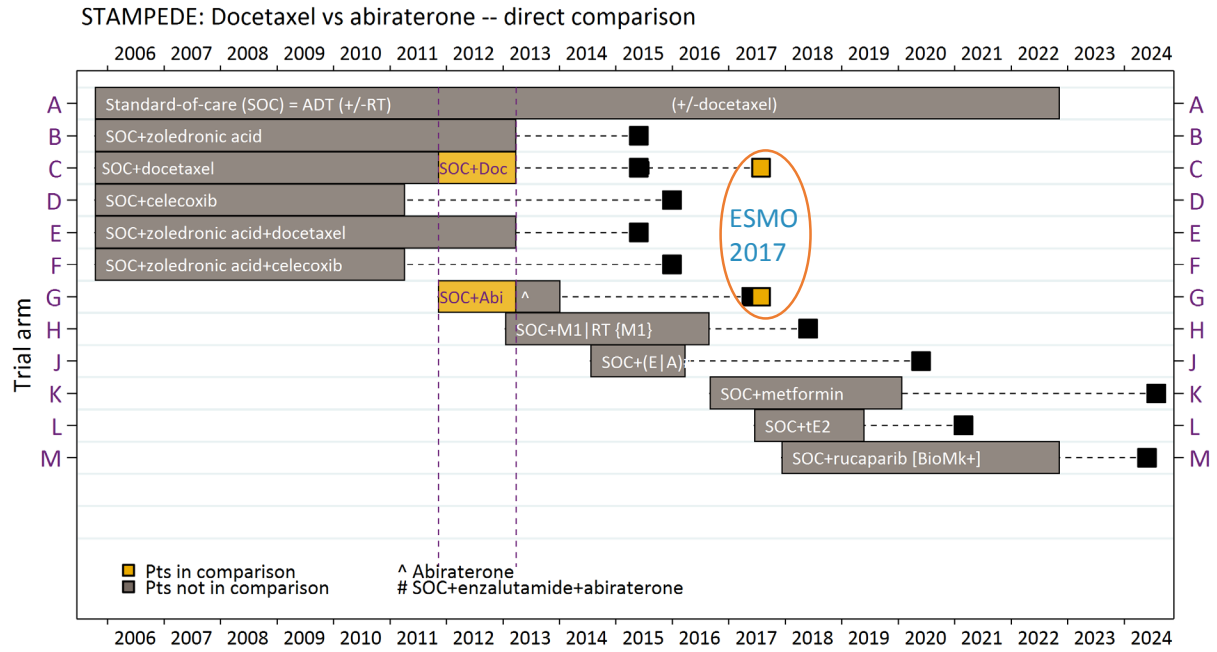


James ND et al. *N Engl J Med* 2017; 377:338-351

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)

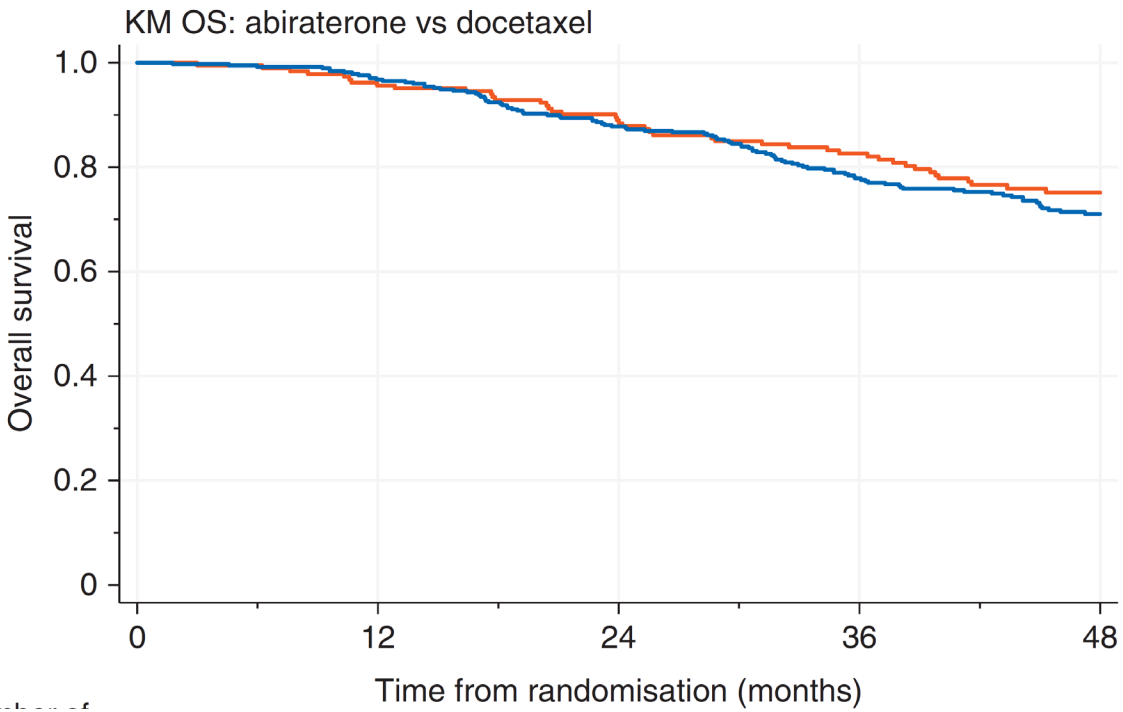
Patients: 189 ADT+DOC
377 ADT+AA+P

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)

Sydes et al Annals Oncology 2018

STAMPEDE: ADT+AA+P vs ADT+DOC



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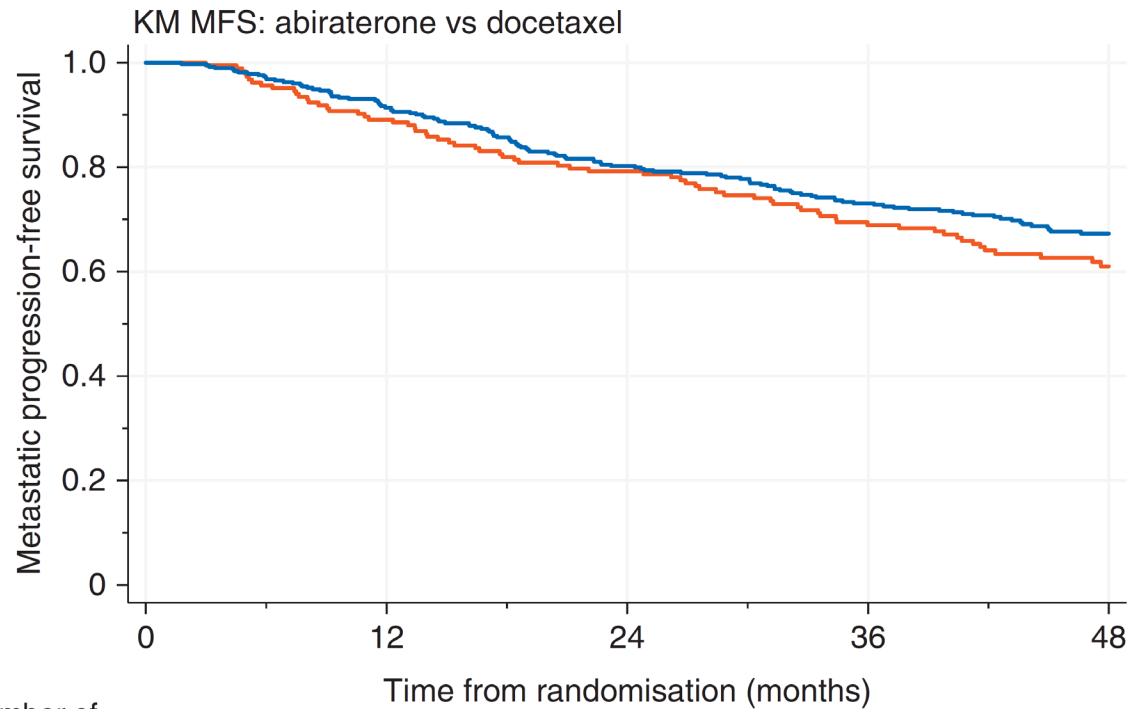

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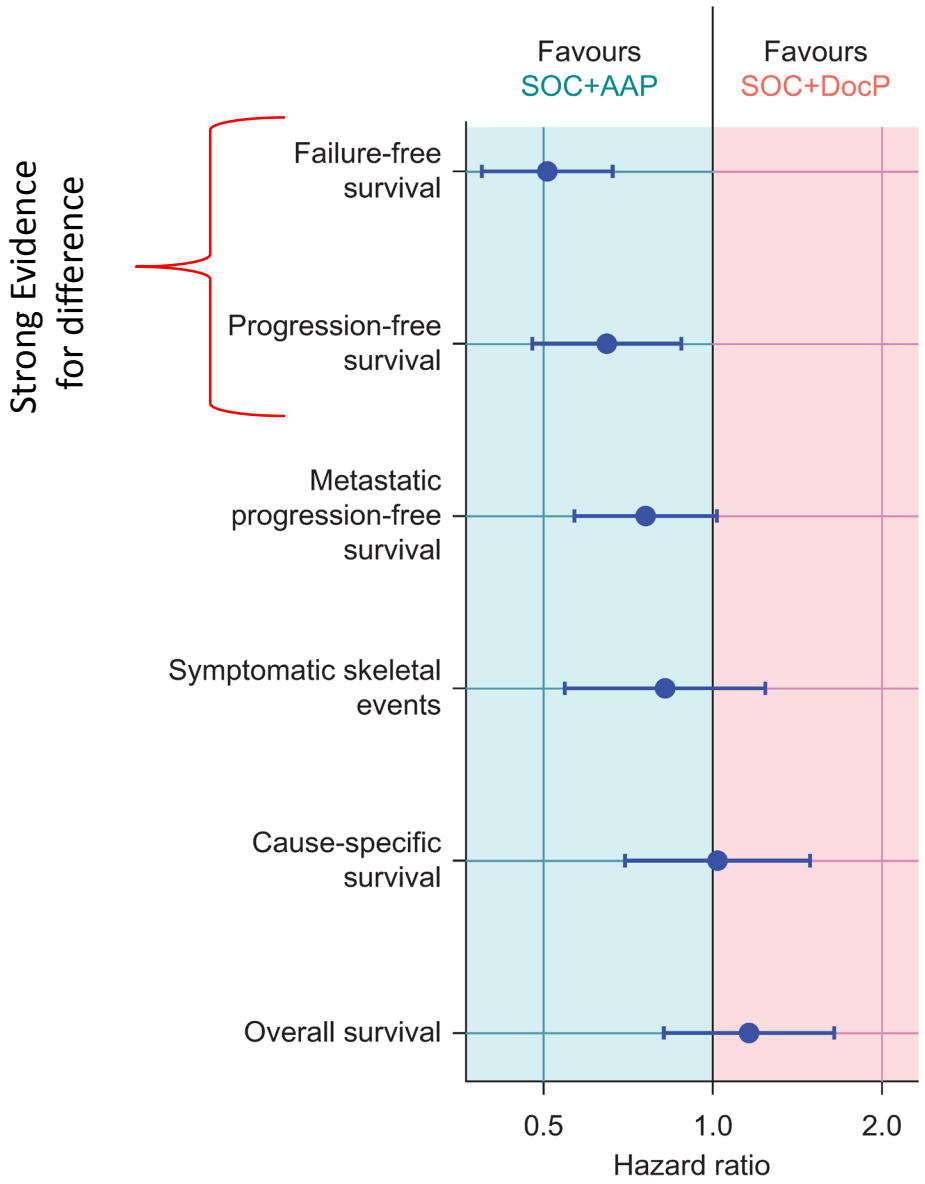

Figure 4. Depiction of disease state over time.

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)

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Current mCSPC Datasets in One Slide

High level summary of treatment effect on OS as measured by Hazard Ratio (HR)

Trial	All M1	High Volume /High risk	Low Volume	Median Follow-up (mos)
ADT + / Docetaxel				
GETUG15[1]	HR(OS): 0.88	HR(OS)-HV: 0.78	HR (OS): 1.02	83.9
CHAARTED[2]	HR(OS): 0.72	HR(OS)-HV: 0.63	HR (OS): 1.04	57.6
STAMPEDE-Doc[3]	HR(OS): 0.76	N/A	N/A	43
ADT +/- Abiraterone				
LATITUDE[4]	N/A	HR (OS): 0.62	[6]*20% (OS: N/R yet) (post hoc to align with other studies)*	30.4
STAMPEDE-Abi[5]	HR(OS): 0.61	HR (OS): 0.66	HR (OS): 0.54	41.5

HV-High: volume ≥ 4 bone mets with one beyond axial skel and/or visceral mets
PR-Poor risk: de novo metastatic + ≥ 2 of [GI ≥ 8+ ≥3 bone mets + visceral mets]
(NB: 20% of LATITUDE poor risk are de novo low volume) [6]
HR(OS): Hazard Ratio for overall survival
N/R: not reported (yet)

[1]Gravis et al Lancet Oncology 2015; [2]Kyriakopolous et al JCO 2018; [3]James et al Lancet 2015; [4]Fizazi et al NEJM 2017; [5]James et al NEJM 2017; [6] Fizazi et al GU ASCO 2018

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Summary of mHSPC treatment choices

Patient	Disease setting	Treatment option
Chemofit	High volume	Docetaxel or abiraterone (consider docetaxel first to ensure can give it)
Not chemofit	High volume	Abiraterone
Chemofit	Low volume	Consider radiate primary Abiraterone (?intermittent)
Not chemofit	Low volume	Consider radiate primary Abiraterone (?intermittent)

Ongoing Trials in mHSPC

Trial Name	Arms	# Pts.	1° Endpoint	NCT#	Ant. Read-Out
ENZAMET	ADT +/- DOCE + Enza *vs.* NSAA	1100	OS	NCT02446405	2020
ARCHES	ADT +/- DOCE + Enza *vs.* Placebo	1100	rPFS	NCT02677896	2023
TITAN	ADT +/- DOCE + Apa *vs.* Placebo	1000	OS	NCT02489318	2021
ARASENS	ADT + DOCE + ODM-201 *vs.* Placebo	1300	OS	NCT02799602	2022
S1216	ADT + TAK-700 *vs.* Bicalutamide	1304	OS	NCT01809691	2022
PEACE-1	ADT +/- DOCE, +/- RT, +/- Abi	916	OS, rPFS	NCT01957436	2020

Hahn AW.... Agarwal N. *Curr Opin Urol* 2017; 27(6):559-565

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New Scenary in CRPC

Prostate Cancer

M1 hormonosensitive

ADT

Docetaxel

Abiraterone

Enzalutamide

ODM 201

Apalutamidee

CPRC M1

1st Line

2nd Line

Docetaxel?

Abiraterone

Enzalutamide

Docetaxel

Cabacitaxel

Radium-223

Loaclized Disease/ N0

M0

ADT

Enzalutamide

ODM 201

Apalutamide

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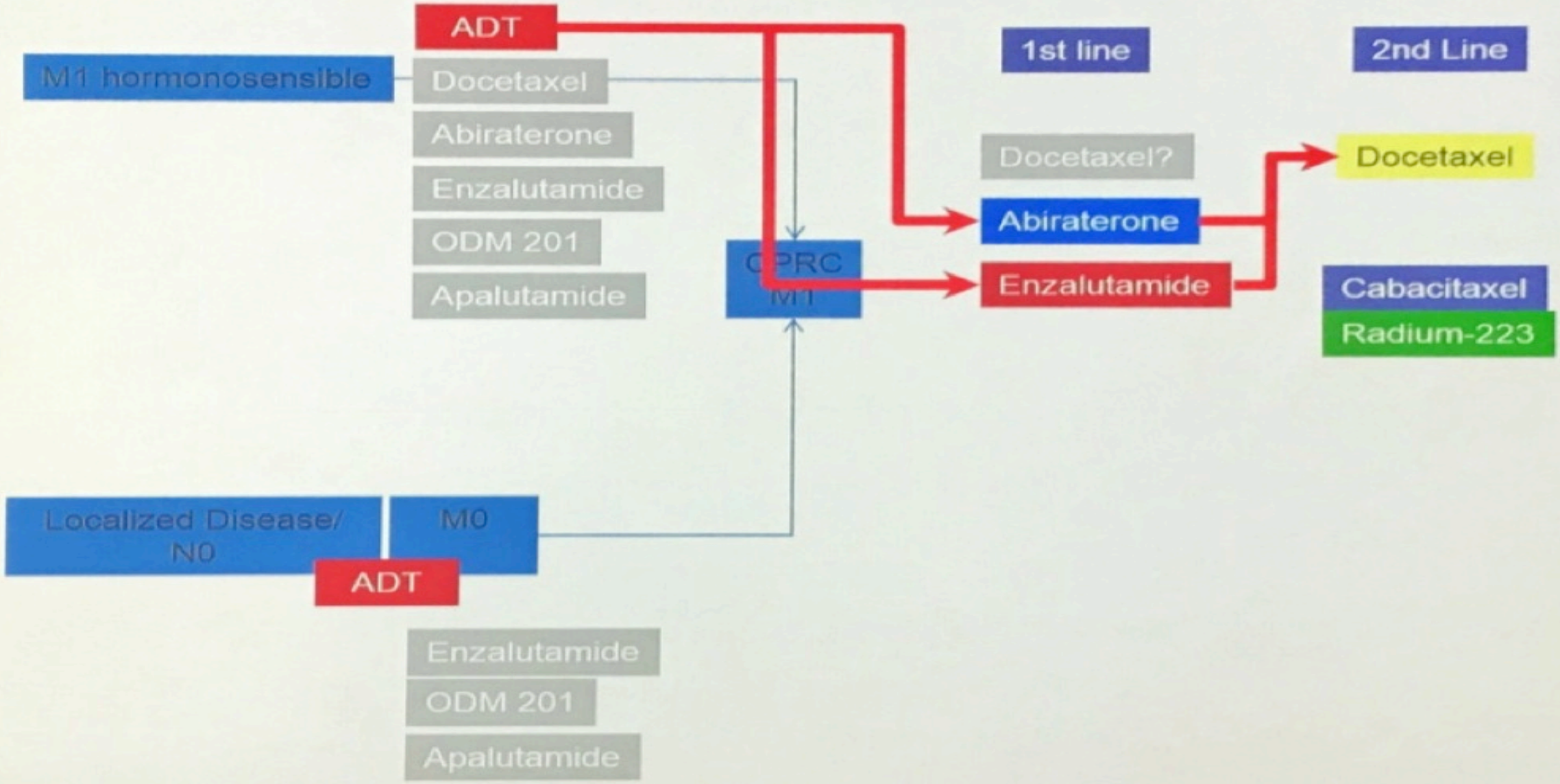
New Scenary inCRPC

Prsotate Cancer



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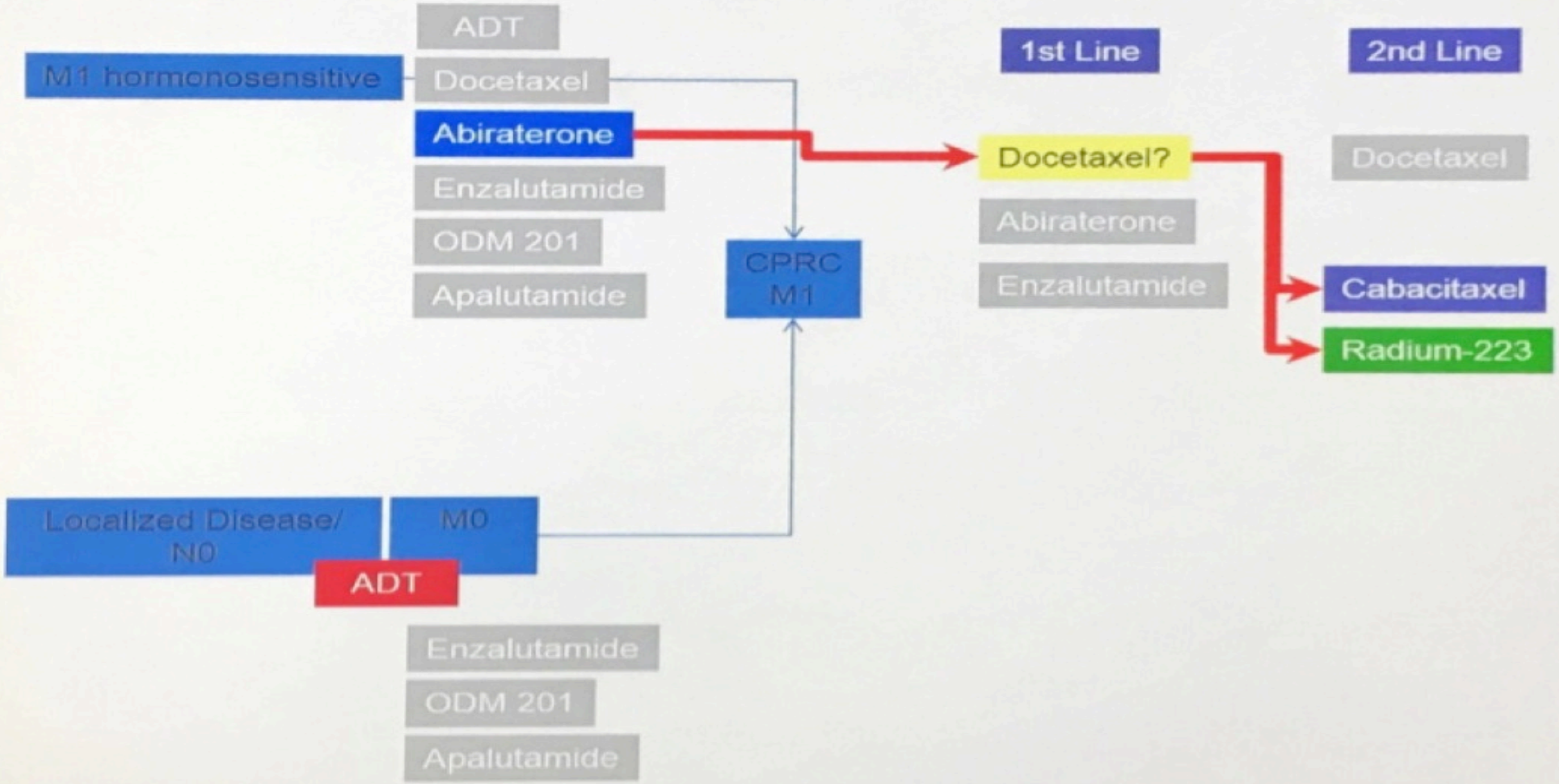
New Scenary in CRPC

Prostate Cancer



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

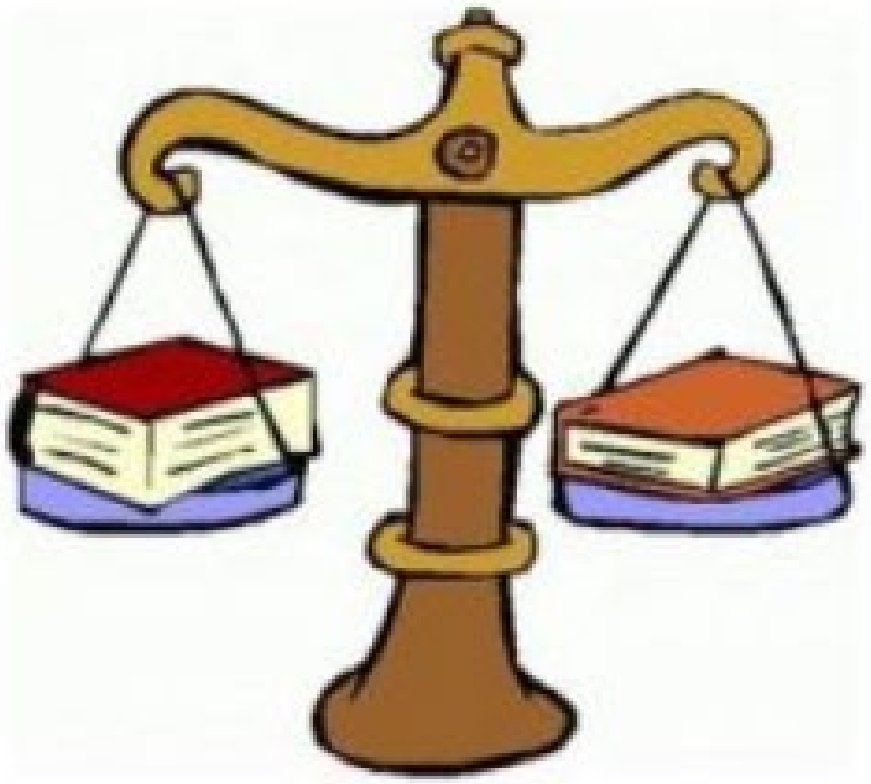
Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer

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

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.,

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,

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:

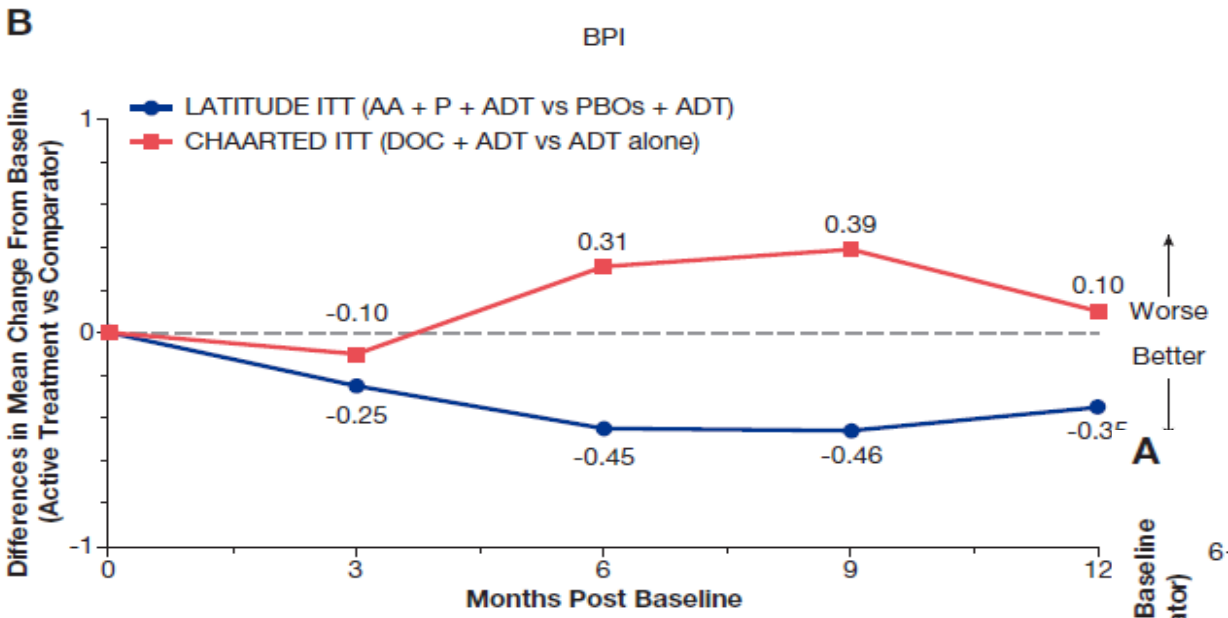
- **≥4 bone lesions with ≥1 beyond the vertebral bodies/pelvis**
- **Visceral metastasis**

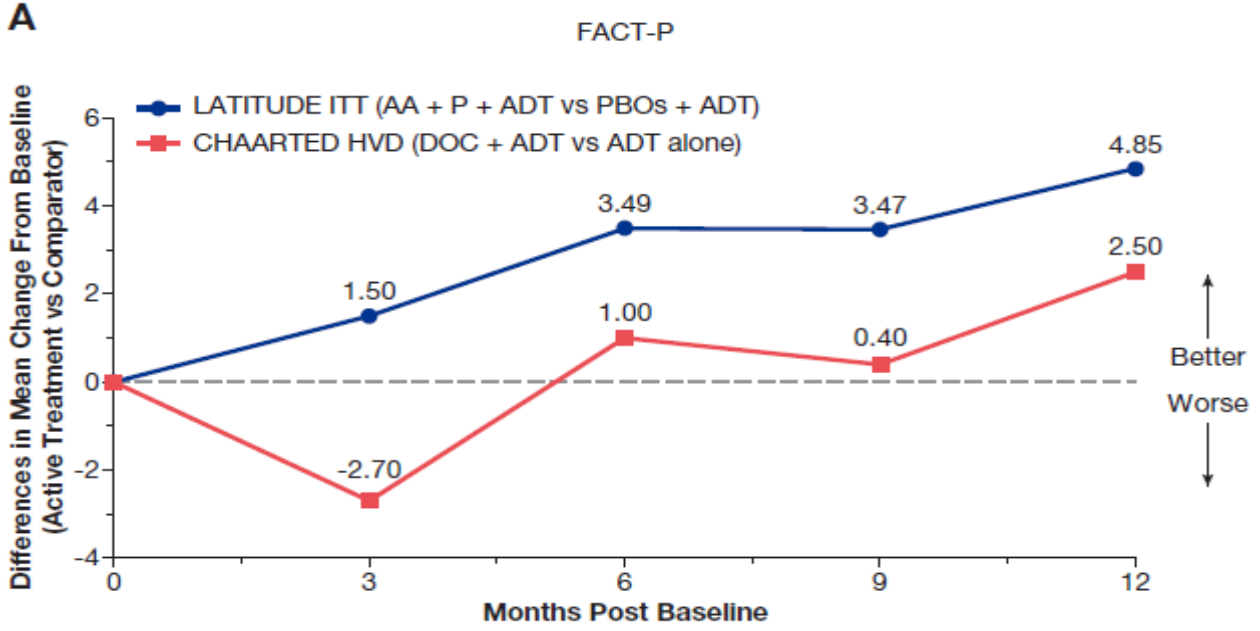
Not head-to-head comparison studies

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

LATITUDE vs CHARTEED: QL analysis

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





- Il trattamento continuativo è vantaggioso rispetto al trattamento di breve durata in termini di QoL e controllo del dolore

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

Adverse Events – Worst Toxicity Ever

Direct Comparison

	SOC + DOC	SOC + AAP
Grade 3-5 adverse events		
Febrile neutropenia	29 (17%)	3 (1%)
Neutropenia	22 (13%)	4 (1%)
Cardiovascular disorder	6 (3%)	32 (9%)
Hypertension	0	12 (3%)
Myocardial infarction	2 (1%)	4 (1%)
Cardiac dysrhythmia	1 (1%)	5 (1%)
Hepatic disorder	1 (1%)	32 (9%)
Increase AST	0	6 (2%)
Increase ALT	1 (1%)	23 (6%)
Respiratory disorder	12 (7%)	11 (3%)
Dyspnea	4 (2%)	1 (1%)

Sydes MR et al. Annals of Oncology. 2018, Feb 266[Epub ahead of print].

Clinical Guidance for Therapy Selection in Metastatic Hormone-Naïve Prostate Cancer

Favor docetaxel-ADT

- Patients:
  - Prefer finite therapy (18 weeks) rather than longer term therapy
  - Difficulty swallowing oral medications
  - Poor diabetic control (who wish to avoid chronic prednisone)
  - Hypervolemia or heart failure

Favor abiraterone-ADT

- Patients:
  - Unfit for chemotherapy
  - Prefer oral therapy
  - Neuropathy
  - Prefer fewer clinic visits

Favor ADT alone

- Patients:
  - High degree of comorbidities
  - Excellent PSA decline with ADT alone especially if low burden of metastatic disease

McNamara M et al. Prostate Cancer Prostatic Dis. 2017, Dec 20[Epub ahead of print].

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age
- comorbilities
- social-familiar situation
Cognitive status

- symptoms?

pain?
Performance Status

- Clinical and biological parameters

Patient preferences

Risk to die from PCa
Risk of toxicities
Lost of windows of opportunity

RISK/BENEFIT

Thank you!!!