PRO STATE of the art

METASTATIC HORMONE SENSITIVE PROSTATE CANCER
Clinical case and evidences from literature

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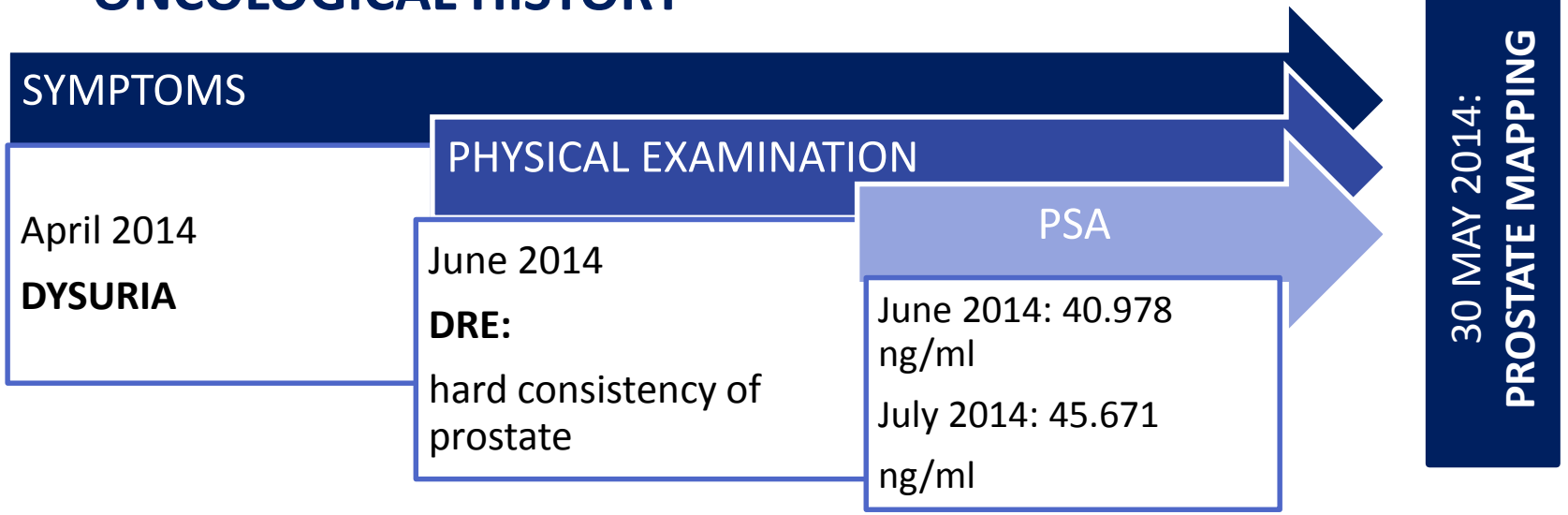
Mr. E.C., 60 years

Past Medical History

- Polymyalgia rheumatica in clinical and serological remission after steroid treatment
- Hepatic steatosis
- GERD
- No allergies
- Family history: smoking father died of lung cancer

ONCOLOGICAL HISTORY



HISTOLOGICAL EXAMINATION

- Acinar prostate adenocarcinoma with cribriform pattern. Gleason Score 8 (4+4), evidence of perineural invasion.

STAGING

Chest and abdominal CT scans (05 Aug 2014):

Some subpleural and pulmonary nodules (metastases?). Pathological mediastinal lymph nodes (39 mm diameter). Enlarged prostate (56 mm diameter) with heterogeneous structure; multiple iliac and lombo-aortic lymph nodes smaller than 1 cm. Osteoblastic lesions in L5 (12 mm), L1, D4, D5 and left scapula.

Bone scan (05 Aug 2014):

Hot spots in bilateral ileum, L5, L3, L1, D5, D4 and left scapula.

De novo metastatic prostate cancer: which terapeutic options?

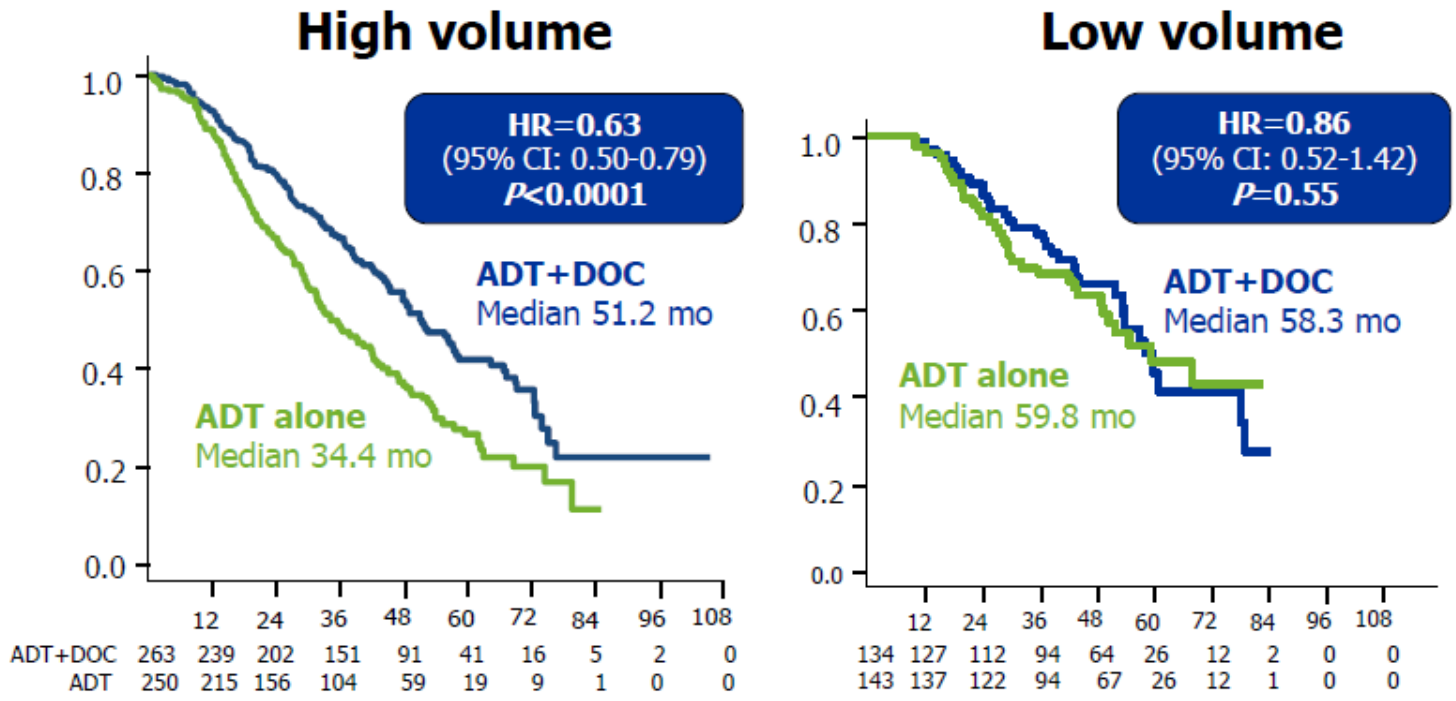
Hormonal therapy

- LHRH-analogue
- LHRH-analogue + Bicalutamide

Hormonal therapy + Chemotherapy

- LHRH-analogue + Docetaxel every three weeks

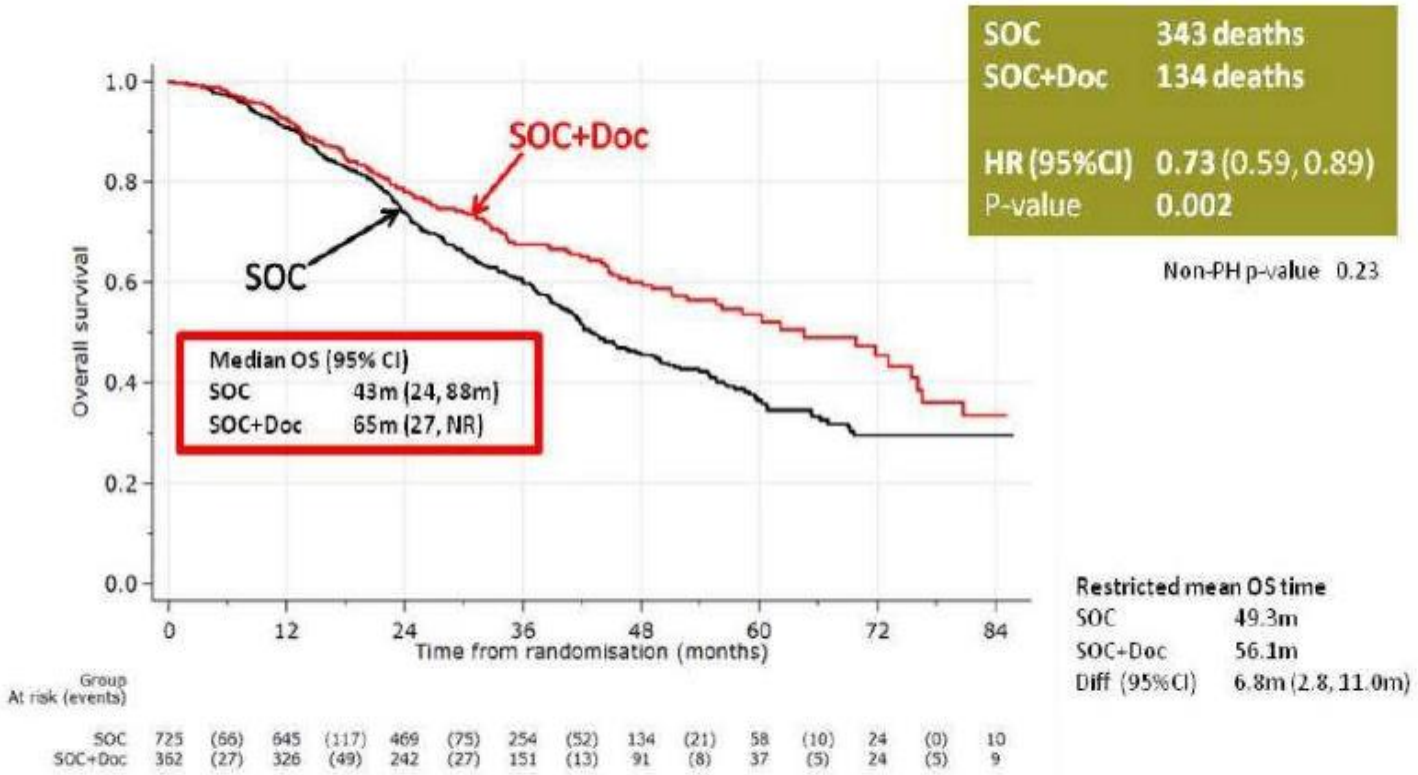
ECOG-ACRIN CHAARTED - OS by Tumor Volume (Update)



Phase III randomized trial in 790 men with metastastic hormone-naïve PCa
Primary endpoint: overall survival

Sweeney CJ et al. Ann Oncol 2016;27(suppl 6):abstract 720 and Sweeney CJ et al. N Engl J Med. 2015;373:737-46.

STAMPEDE – OS in M1 Patients Docetaxel



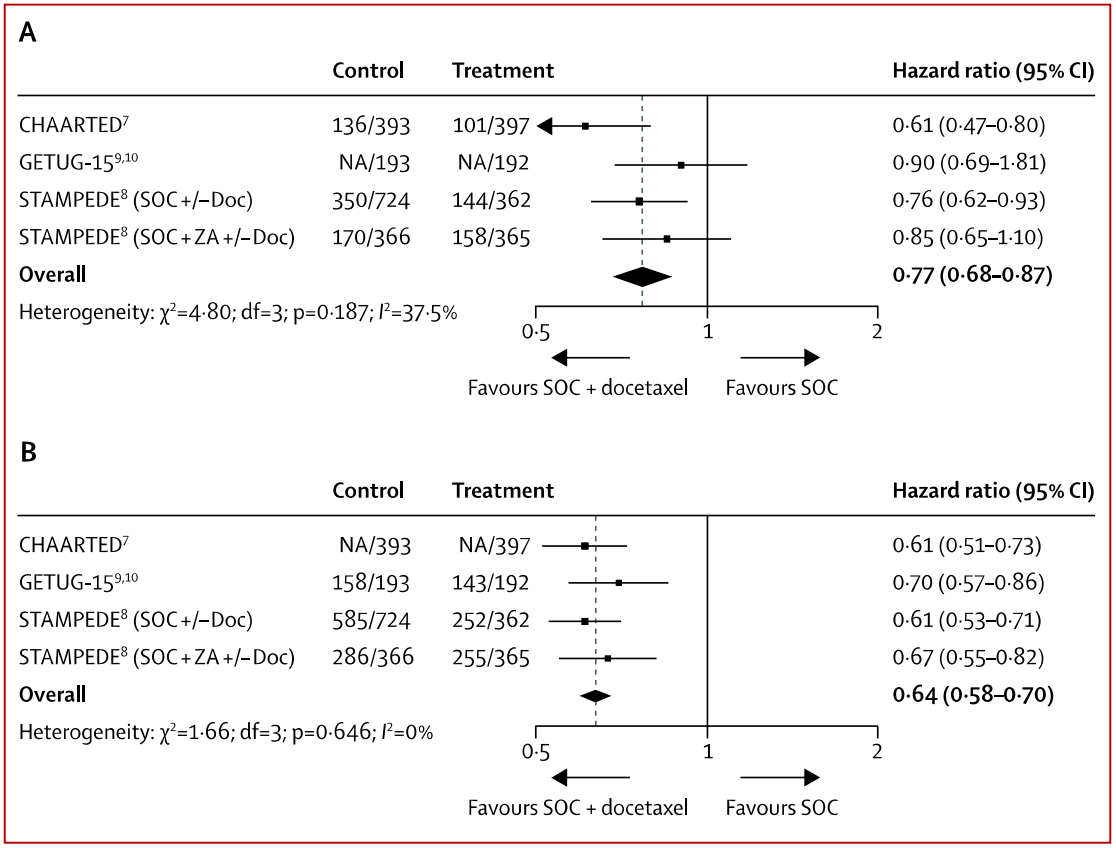
Phase III randomized trial in 2962 men with M0/M1 in 4 groups with zometa with hormone-naïve Pca; Primary endpoint: overall survival

OS: overall survival

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

Addition of docetaxel or bisphosphonates to standard of care in men with localised or metastatic, hormone-sensitive prostate cancer: a systematic review and meta-analyses of aggregate data

Claire L Vale, Sarah Burdett*, Larysa H M Rydzewska, Laurence Albiges, Noel W Clarke, David Fisher, Karim Fizazi, Gwenaelle Gravis, Nicholas D James, Malcolm D Mason, Mahesh K B Parmar, Christopher J Sweeney, Matthew R Sydes, Bertrand Tombal, Jayne F Tierney, for the STOpCaP Steering Group*



OS

PFS

August 2014

- **Hormonal therapy starts with LHRH-ANALOGUE** (Leuprorelin 11,25 1 fl IM every 3 months)

DOCETAXEL

Before starting chemotherapy…

- ECOG PS 0, Asymptomatic
- ECG: Sinus rhythm, absence of ventricular repolarization abnormalities
- Echocardiography: EF 60%

Blood chemistry		
CBC: normal	AST 50 U/L	ALT 101 U/L
Creatinine: 0,9 mg/dL	Bil: 1 mg/dl	GGT: 229 U/L
HBV, HCV: negative	ALP: 686 U/L	
Total cholesterol 215 mg/dl	Triglycerides 229 mg/dl	
	PSA 45.292 ng/ml	

Before starting treatment:

- Hepatological consult (11 Sep 2014): non-alcoholic fatty liver disease (NAFLD) with some stigmata of NASH.
- The low increase in cytolysis and cholestasis markers does not contraindicate the oncological program.

From 29/9/2014 to 12/1/2015: 6 cycles of Docetaxel 75 mg/mq day 1, every 21 days

Toxicity:

- Asthenia G2
- Diarrhea G1
- Neutropenia G3
- Stable hepatic function

PSA (ng/ml):

1.469 (09/2014)

↓

0.225 (12/2014)

↓

0.132 (02/2015)

RESTAGING AFTER CHEMOTHERAPY

PR

PSA 0.103 ng/ml

Chest and abdominal CT scans: volumetric reduction of bilateral lung nodularities; reduction in subcarinal lymphadenopathy. Some small iliac and lombo-aortic lymph nodes; prostate volume reduction (40 mm diameter). Bone forming lesions stable.

Bone scan: significant reduction in number and extent of hot spots in any previously described sites.

Patient continues LHRH analogue

De novo metastatic prostate cancer: which terapeutic options today?

Hormonal therapy

- LHRH-analogue
- LHRH-analogue + Bicalutamide

New generation Hormonal therapy

- LHRH-analogue + **Abiraterone** Acetate and Prednisone

Hormonal therapy + Chemotherapy

- LHRH-analogue + **Docetaxel** every three weeks

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

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] Peter De Porre,[11] Thian Kheoh,[12] Youn C. Park,[13] Mary B. Todd,[14] Kim N. Chi,[15] on behalf of the LATITUDE Investigators

[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]12 de Octubre University Hospital, Madrid, Spain; [6]P.A. Hertsen Moscow Cancer Research Institute, Moscow, Russian Federation; [7]Cerrahpaşa Medical Faculty, Istanbul University, Istanbul, Turkey; [8]Fudan University Shanghai Cancer Center, China; [9]Studienpraxis Urologie, Nürtingen, Germany; [10]Oxford University Hospitals Foundation NHS Trust, Oxford, UK; [11]Janssen Research & Development, Beerse, Belgium; [12]Janssen Research & Development, San Diego, CA; [13]Janssen Research & Development, Raritan, NJ; [14]Janssen Global Services, Raritan, NJ; [15]BC Cancer Agency, Vancouver, BC, Canada

PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17

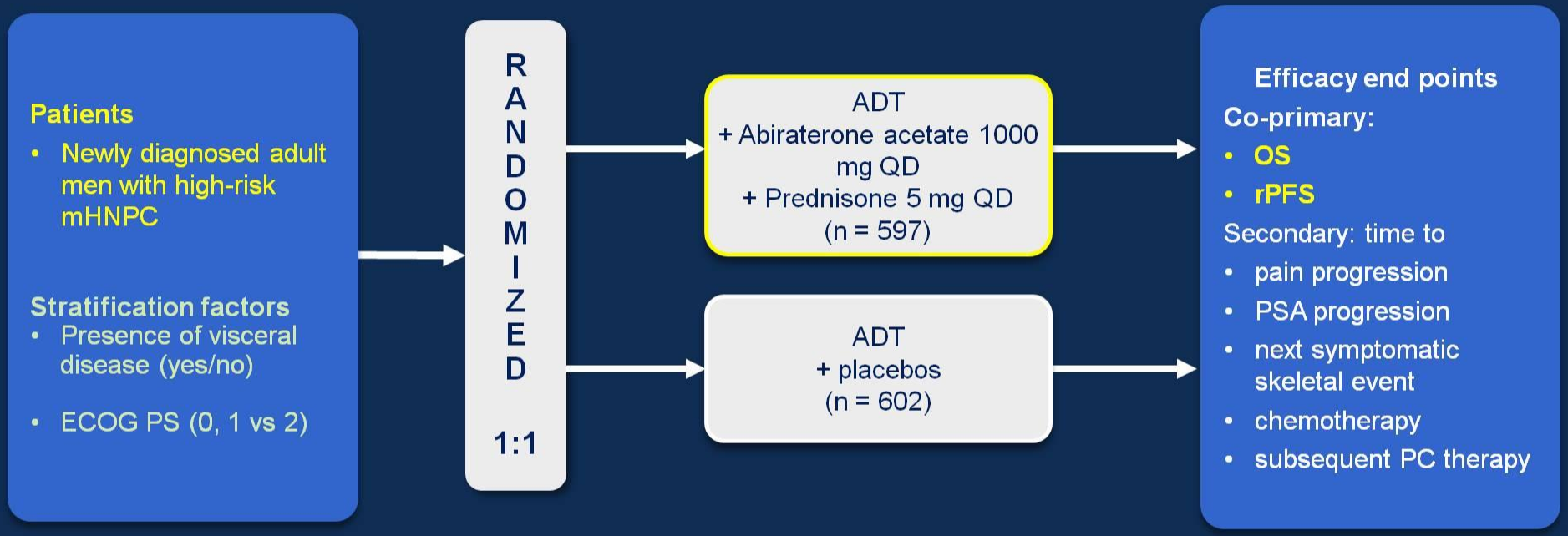
Objective

To evaluate the addition of AA + P to ADT on clinical benefit in men with newly diagnosed, high-risk, mCNPC

High-risk defined as meeting at least 2 of 3 high-risk criteria:

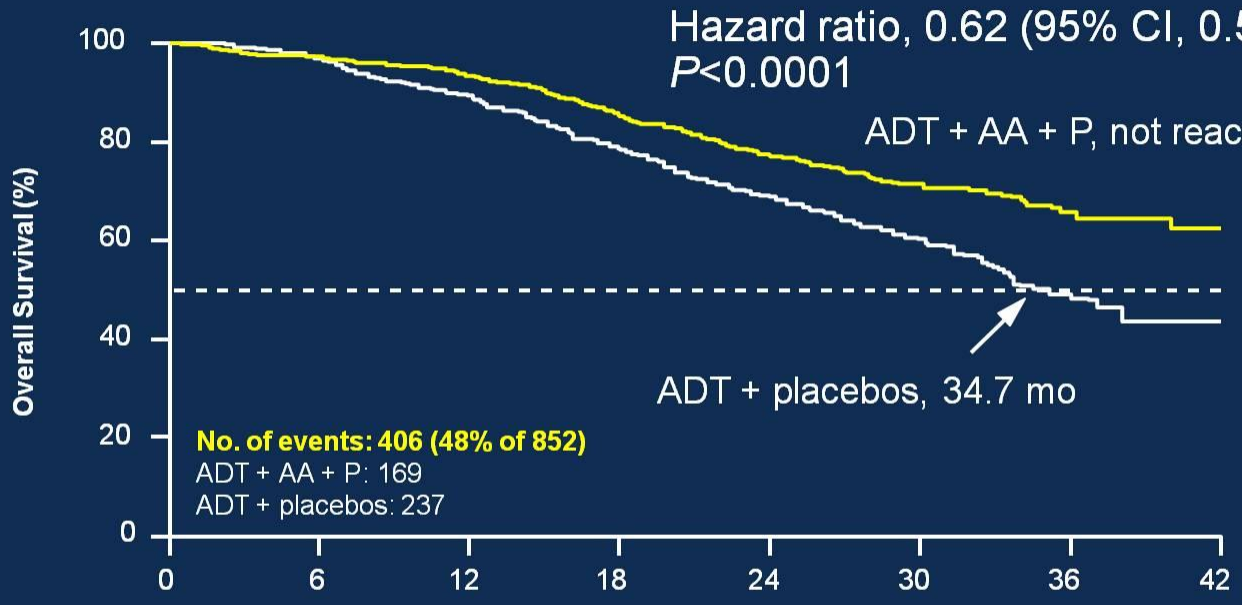
- Gleason score of ≥ 8
- Presence of ≥ 3 lesions on bone scan
- Presence of measurable visceral lesion

Overall study design of LATITUDE



- **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**

Statistically significant 38% risk reduction of death

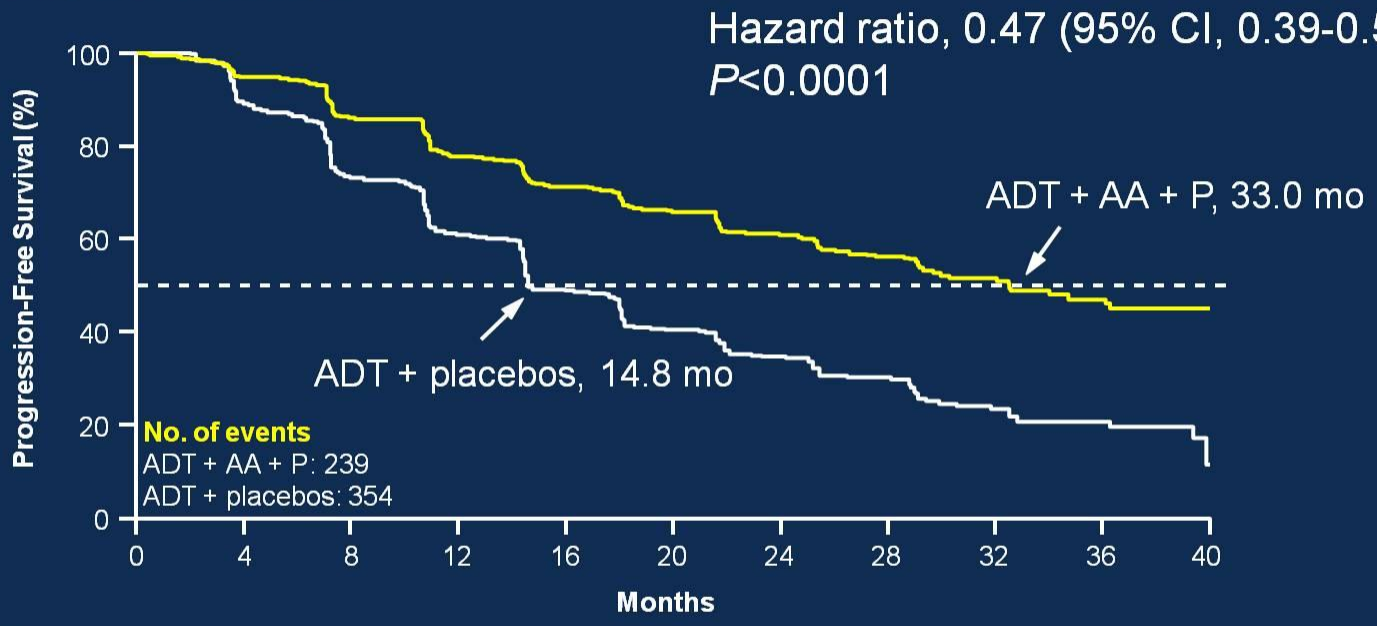


OS rate at 3 years:
ADT + AA + P: 66%
ADT + placebos: 49%

Median follow-up: 30.4 months

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

Statistically significant 53% risk reduction of radiographic progression or death



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

Comparing LATITUDE and CHAARTED Patients

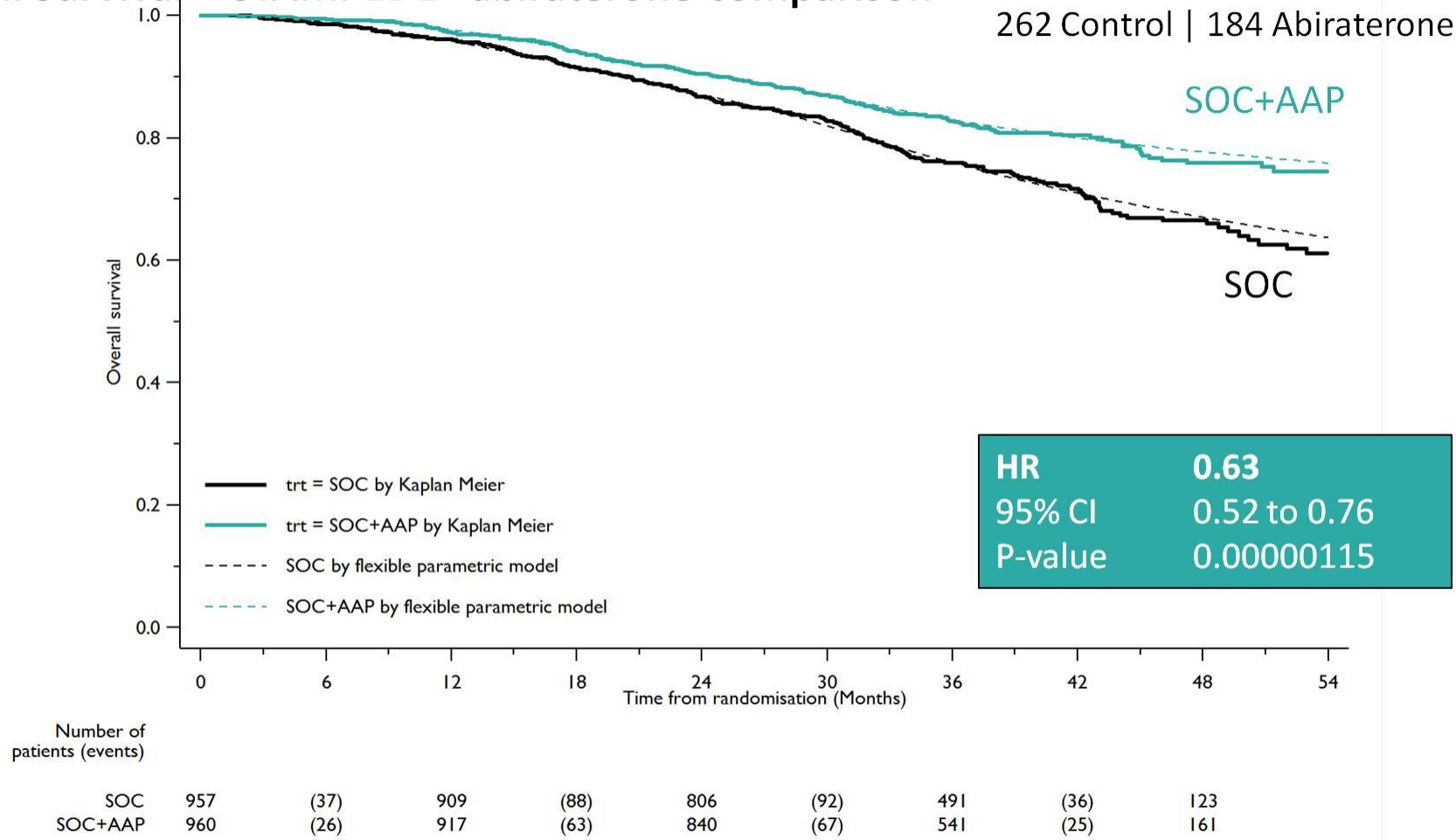
	N	Patient Characteristics	
LATITUDE	1199	GS≥ 8 ≥3 bone mets Visceral mets Median Age	97.5% 97.5% 17% 67.5 yrs
CHAARTED	790	GS ≥ 8 "high vol" ≥4 bone mets Visceral mets Median Age	60% 65% na 24% 63.5 yrs

Comparing Overall Survival Across Studies

	Median OS			3 yr OS rate*	
	HR (95% CI)	Control (months)	Rx (months)	Control	Rx
LATITUDE	0.62 (0.51-0.76)	34.7 mo	NR	49%	66%
CHAARTED High Volume	0.63 (0.50-0.79)	34.4 mo	51.2 mo	~50%	~65%

Overall Survival – STAMPEDE "abiraterone comparison"

Events
262 Control | 184 Abiraterone



Number of patients (events)

SOC	957	(37)	909	(88)	806	(92)	491	(36)	123
SOC+AAP	960	(26)	917	(63)	840	(67)	541	(25)	161

Presented By Nicholas James at 2017 ASCO Annual Meeting

European Commission Extends License for Janssen's ZYTIGA® Plus Prednisone / Prednisolone to Include Earlier Stage Prostate Cancer Patients

Oral, Once-Daily Medication ZYTIGA® (abiraterone acetate) ® Plus Prednisone / Prednisolone Now Approved in Newly Diagnosed High-Risk Metastatic Hormone-Sensitive Prostate Cancer (mHSPC)

November 20, 2017 08:30 AM Eastern Standard Time

- **PSA** (ng/ml): 0,028 (4/2015)→0,014 (09/2015) 0,011 (12/2015)→0,010 (04/2016)

- **Toxicity:** hot flushes, asthenia G1

- **Bone health evaluation:**

  - Blood chemistry: 25OH vitamin D 22.3 ng/ml, PTH 37 pg/ml, calcium in normal range.

  - Dual energy X-ray absorptiometry (**DXA**) (03 June 2015): normal values in column (T score: -1.2), slightly reduction in values in femoral neck (T score: -1.8).

Treatment with calcium 500 mg daily and colecalciferol 400 UI daily

- **PSA** (ng/ml): 0,1 (12/2016)→0,2 (03/2017)
- **Clinical presentation:** asymptomatic; ECOG PS 0
- **Testosterone:** 60 ng/dl
- **Restaging** (March 2017):

  Chest and abdominal CT scans and bone scan: **SD**.

March 2017

- PSA 0,2 ng/ml
- **Testosterone: 60 ng/dl**

Swicth from Leuprorelin 11,25 to **Leuprorelin 22,5** 1 fl sc ogni 3 mesi

June 2017

- PSA 1,47 ng/ml
- **Testosterone: 20 ng/dl**
- Evidence of lumbar and left scapular pain

Disease restaging

Chest + abdominal CT scans and bone scan: node and bone PD

mCRPC first line: which therapeutic options in a patient already treated with upfront docetaxel?

Chemotherapy

- **Docetaxel** every three weeks + Prednisone

Chemotherapy

- **Cabazitaxel** every three weeks + Prednisone

New generation Hormonal therapy

- **Abiraterone Acetate**+ Prednisone
- **Enzalutamide**

Adding abiraterone acetate plus prednisolone (AAP) or docetaxel for patients (pts) with high-risk prostate cancer (PCa) starting long-term androgen deprivation therapy (ADT): directly randomised data from STAMPEDE

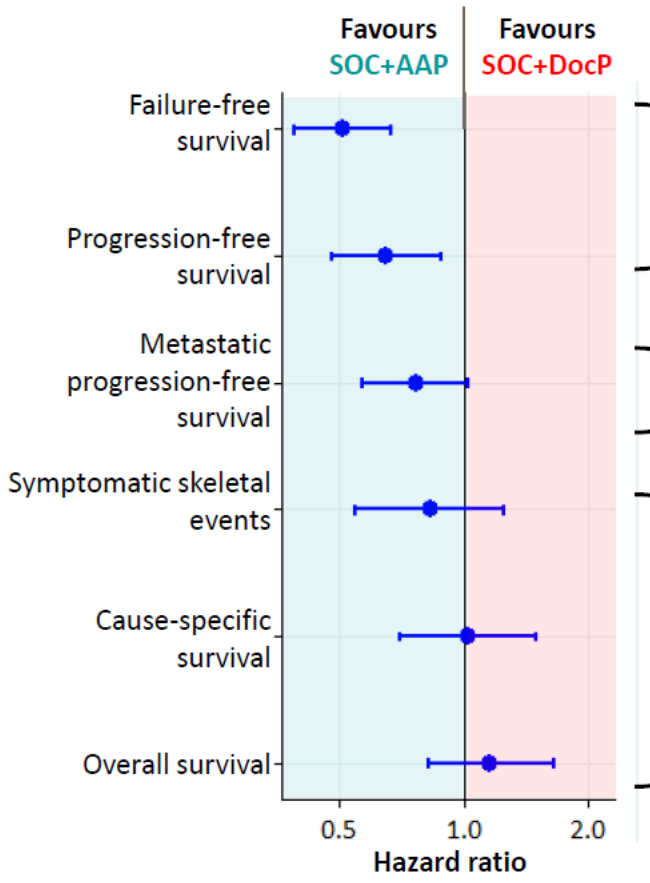
Matthew Sydes
Statistician, Reader in Clinical Trials

MRC Clinical Trials Unit at UCL
Institute of Clinical Trials and Methodology
UCL, London, UK

Co-authors
Malcolm D Mason, Melissa R Spears, Noel W Clarke, David P Dearnaley, Alastair WS Ritchie, J Martin Russell, Clare Gilson, Rob Jones, Johann S de Bono, Silke Gillessen, Robin Millman, Shaun Tolan, John Wagstaff, Simon Chowdhury, Jason Lester, Denise Sheehan, Joanna Gale, Mahesh KB Parmar and Nicholas D James
and the STAMPEDE Investigators

Trial registration: NCT00268476

Sydes M et al, ESMO 2017, abstract LBA31_PR



Summary

Head-to-head data in 566 pts (Nov-2011 to Mar-2013)

Strong evidence favouring AAP

Weak evidence favouring AAP

No good evidence of a difference

→ Proportionately different time spent in each disease state

Toxicity profiles quite different and well known

Sydes M et al, ESMO 2017, abstract LBA31_PR

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European Association of Urology

Platinum Priority – Prostate Cancer

Editorial by XXX on pp. x-y of this issue

Anticancer Activity and Tolerance of Treatments Received Beyond Progression in Men Treated Upfront with Androgen Deprivation Therapy With or Without Docetaxel for Metastatic Castration-naïve Prostate Cancer in the GETUG-AFU 15 Phase 3 Trial

Pernelle Lavaud[a], Gwenaëlle Gravis[b], Stéphanie Foulon[c], Florence Joly[d], Stéphane Oudard[e], Frank Priou[f], Igor Latorzeff[g], Loïc Mourey[h], Michel Soulié[i], Remy Delva[j], Ivan Krakowski[k], Brigitte Laguerre[l], Christine Théodore[m], Jean Marc Ferrero[n], Philippe Beuzeboc[o], Muriel Habibian[p], Frédéric Rolland[q], Gael Deplanque[r], Damien Pouessel[s], Sylvie Zanetta[t], Jean François Berdah[u], Jerome Dauba[v], Marjorie Baciuchka[w], Christian Platini[x], Claude Linassier[y], Nicole Tubiana-Mathieu[z], Jean Pascal Machiels[aa], Claude El Kouri[bb], Alain Ravaud[cc], Etienne Suc[dd], Jean Christophe Eymard[ee], Ali Hasbini[ff], Guilhem Bousquet[gg], Stéphane Culine[hh], Jean-Marie Boher[ii], Gabrielle Tergemina-Clain[c], Clémence Legoupil[c], Karim Fizazi[a,]*

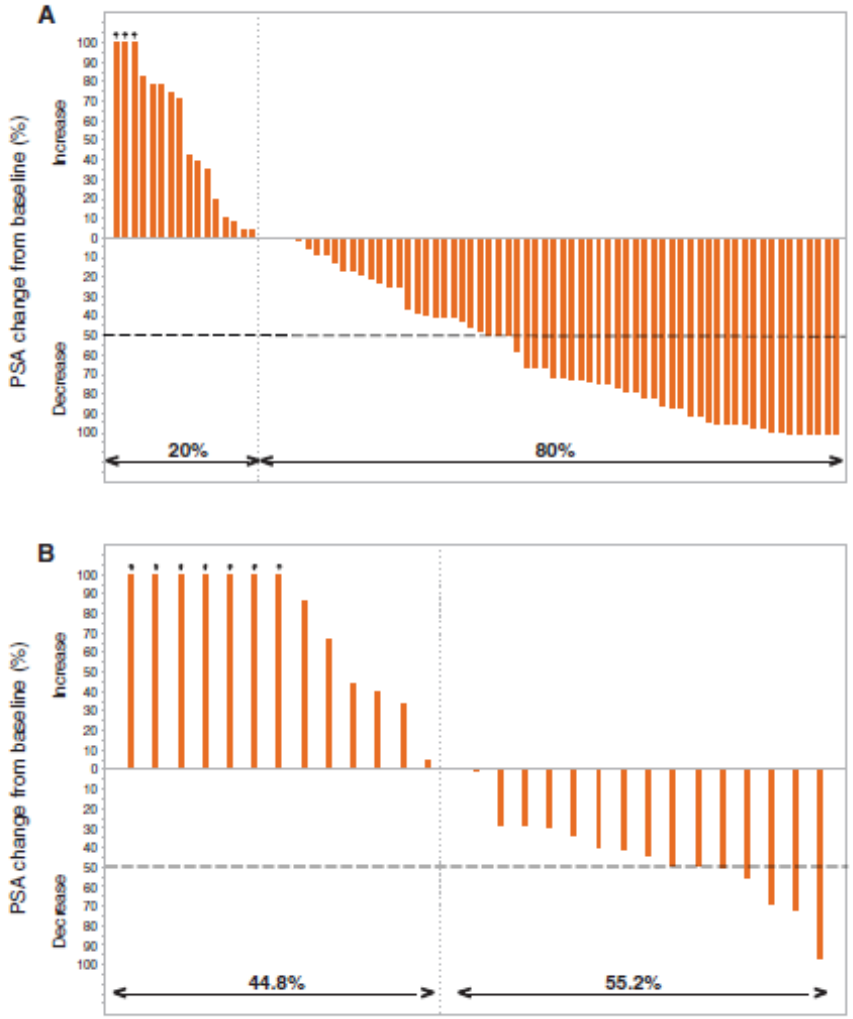

Fig. 1 – Prostate-specific antigen (PSA) declines after docetaxel used in first- or second-line therapy for patients with metastatic castration-resistant prostate cancer. (A) Patients who have progressed after androgen deprivation therapy alone given for castration-naïve prostate cancer. (B) Patients who have progressed after androgen deprivation therapy plus docetaxel given for castration-naïve prostate cancer.