Pulci Statistiche

Valter Torri

IRCCS – Istituto di ricerche farmacologiche

Mario Negri - Milano

Gestione ottimale del paziente con carcinoma della prostata - Milano, 25-26.09.18

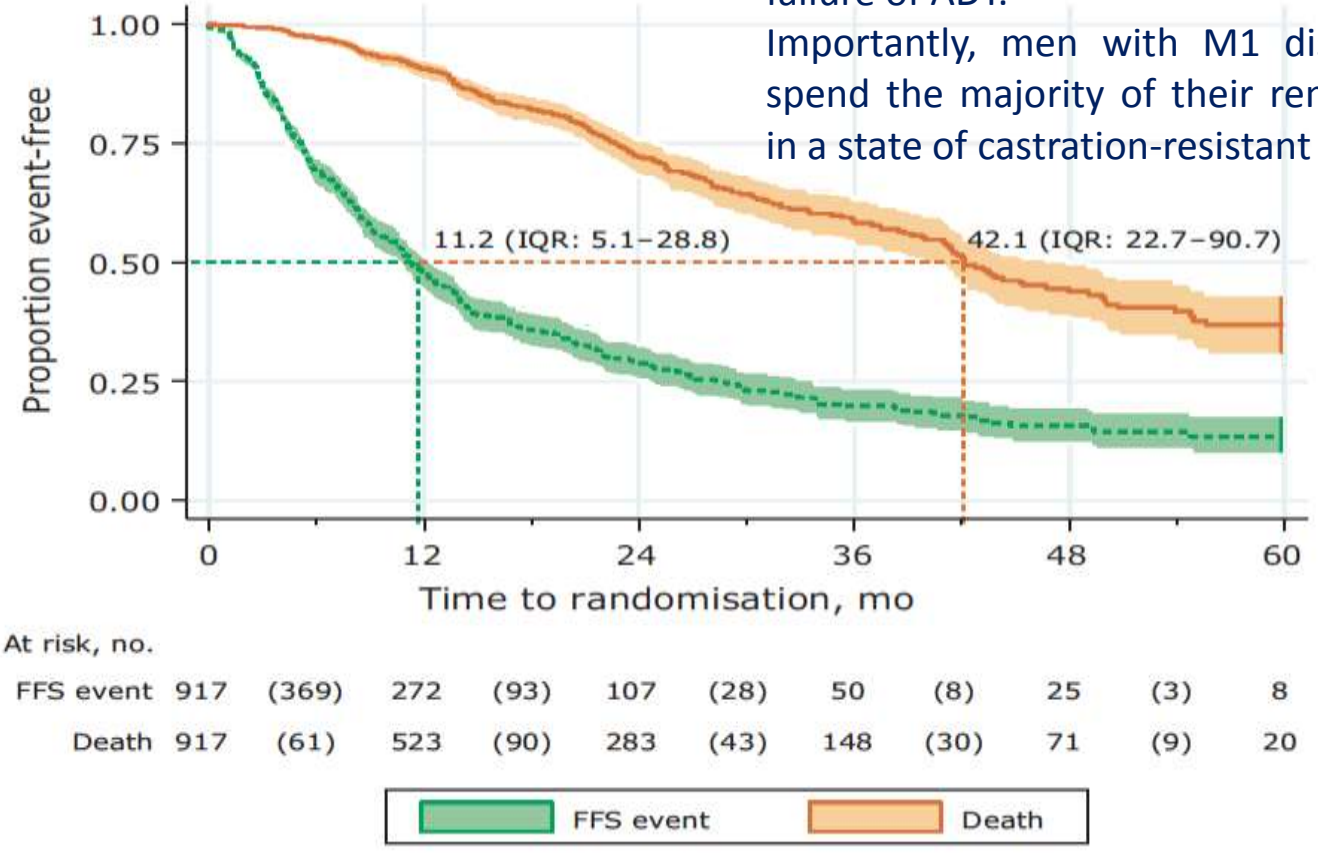
Survival with Newly Diagnosed Metastatic Prostate Cancer in the "Docetaxel Era": Data from 917 Patients in the Control Arm of the STAMPEDE Trial (MRC PR08, CRUK/06/019)

Nicholas David James[a,], Melissa R. Spears[b], Noel W. Clarke[c], David P. Dearnaley[d,e], Johann S. De Bono[d,e], Joanna Gale[f], John Hetherington[g], Peter J. Hoskin[h], Robert J. Jones[i], Robert Laing[j], Jason F. Lester[k], Duncan McLaren[l], Christopher C. Parker[d,e], Mahesh K.B. Parmar[b], Alastair W.S. Ritchie[b], J. Martin Russell[m], Răto T. Strebel[n], George N. Thalmann[o], Malcolm D. Mason[k], Matthew R. Sydes[b]*

EUROPEAN UROLOGY 67 (2015) 1028–1038

Survival remains disappointing in men presenting with M1 disease who are started on only long-term ADT, despite active treatments being available at first failure of ADT.

Importantly, men with M1 disease now spend the majority of their remaining life in a state of castration-resistant relapse

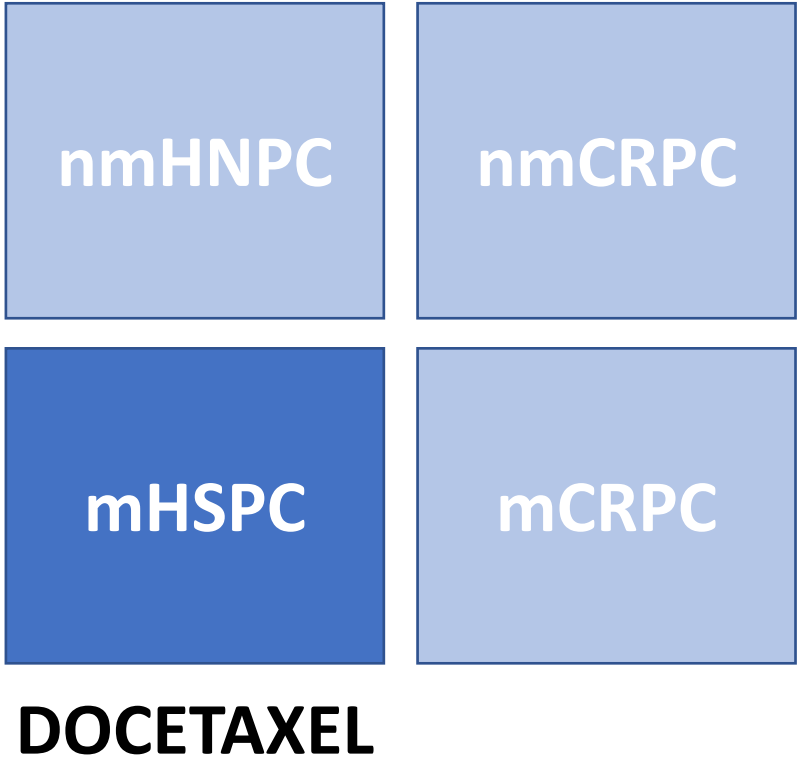


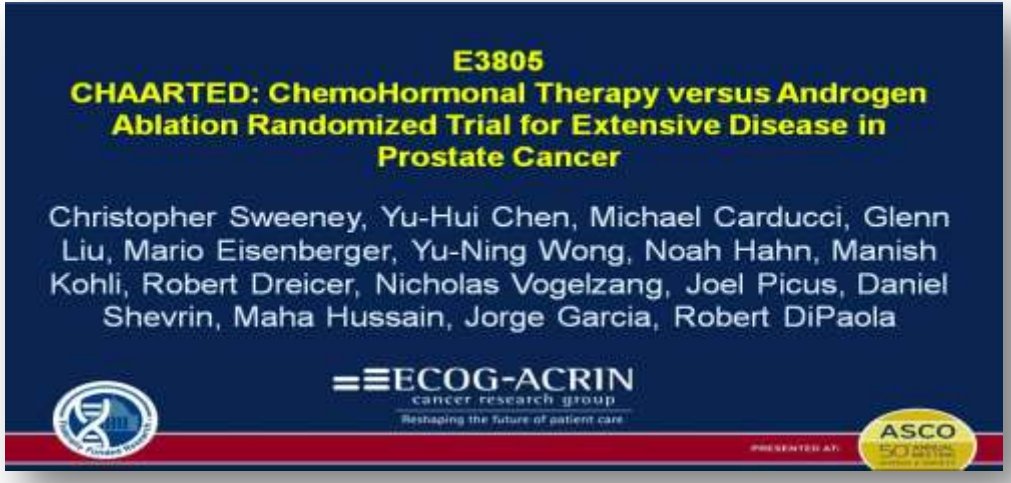
Il quesito

1. Ci sono dati a favore di un cambiamento dello stato dell'arte nel trattamento del mHSPC?
   - DOC+SOC?
   - ABT+SOC?

Le questioni metodologiche

1. Valutare la qualità dei risultati ottenuti
2. Descrivere il rapporto beneficio/danno
    - Nei confronti diretti e indiretti a disposizione


nmHNPC
nmCRPC
mHSPC
mCRPC
DOCETAXEL


E3805
CHAARTED: ChemoHormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer
Christopher Sweeney, Yu-Hui Chen, Michael Carducci, Glenn Liu, Mario Eisenberger, Yu-Ning Wong, Noah Hahn, Manish Kohli, Robert Dreicer, Nicholas Vogelzang, Joel Picus, Daniel Shevrin, Maha Hussain, Jorge Garcia, Robert DiPaola
ECOG-ACRIN
cancer research group
Reshaping the future of patient care
ASCO

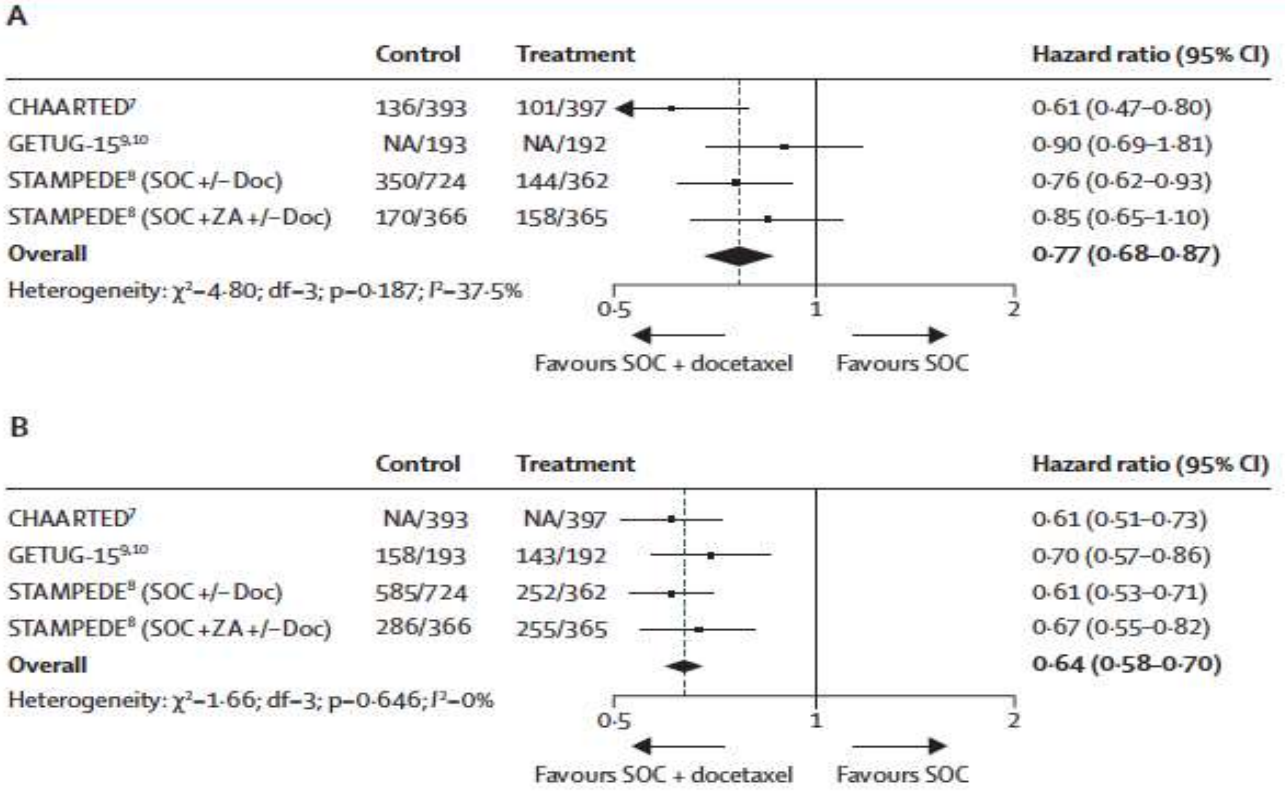

Androgen deprivation therapy (ADT) plus docetaxel (D) versus ADT alone for hormone-naïve metastatic prostate cancer (PCa): long-term analysis of the GETUG-AFU 15 phase III trial
G Gravis, J-M Boher, F Joly, S Oudard, L Albiges, F Priou, I Latorzeff, R Delva, I Krakowski, B Laguerre, F Rolland, C Théodore, G Deplanque, J-M Ferrero, D Pouessel, L Mourey, P Beuzeboc, M Habibian, M Soulie and K Fizazi, on behalf of the GETUG.
Presented at the Genitourinary Cancers Symposium


CANCER RESEARCH UK
MRC Clinical Trials Unit
UCL
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
ASCO

Comparison of study PICOs

	Accrual period	Number of patients	Control	Treatment	Metastatic status	Median age (range)	Gleason score of 8–10 (%)	Performance status of 0–1 (%)	Median follow-up (survival)	Treatment on progression (control group only)
Docetaxel trials										
GETUG-12[21,28]	November 2002–December, 2006	413	ADT (goserelin 10·8 mg every 3 months for 3 years)	ADT plus docetaxel (70 mg/m² for four cycles) plus estramustine	M0	63 (46–77)	42%	Unknown	7 years, 6 months	Not reported
TAX 3501[29]	December, 2005–September, 2007	228	ADT (leuprolide 22·5 mg every 3 months for 18 months)	ADT plus docetaxel (75 mg/m² every 3 weeks for six cycles)	M0	61·9*	52%	Unknown	3 years, 3 months	Not reported
RTOG 0521[30]	December, 2005–August, 2009	612	ADT (LHRH agonist plus oral anti-androgen plus RT)	ADT plus docetaxel (75 mg/m² every 3 weeks for six cycles) plus prednisone	M0	66 (unknown)	84%	Unknown	6 years	Not reported
STAMPEDE (standard of care with or without docetaxel)[31]	September, 2005–March, 2013	1776	ADT (plus radiotherapy for M0 patients)	ADT plus docetaxel (75 mg/m² every 3 weeks for six cycles) plus predisone	M0 and M1	65 (40–82)	70%	99%	3 years, 6 months	40% received docetaxel (49% received life-extending treatments)
STAMPEDE (standard of care plus zoledronic acid with or without docetaxel)[31]	September, 2005–March, 2013	1186	ADT (plus radiotherapy for M0 patients) plus zoledronic acid (4 mg every 3–4 weeks for 2 years)	ADT (plus radiotherapy for M0 patients) + zoledronic acid (4 mg for 3–4 weeks for 2 years) plus docetaxel (75 mg/m² every 3 weeks for six cycles)	M0 and M1	66 (42–84)	71%	99%	3 years, 6 months	36% received docetaxel (45% received life-extending treatments)
GETUG-15[32,33]	October, 2004–December, 2008	385	ADT (LHRH agonist or surgical castration or combined androgen blockade)	ADT plus docetaxel (75 mg/m² every 3 weeks for up to nine cycles)	M1	63·5 (57–70)	56%	100%	6 years, 11 months	62% received docetaxel
CHAARTED[7]	July, 2006–November, 2012	790	ADT (LHRH agonist or LHRH antagonist) or surgical castration	ADT plus docetaxel (75 mg/m² every 3 weeks for six cycles)	M1	64 (36–91)	61%	98%	2 years, 5 months	147 (51%) of 287 men received docetaxel (104 of 287 men received abiraterone or enzalutamide)

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



Overall survival

Failure-free survival

Vale, Lancet Oncol 2016

Statistical Design: History of CHAARTED

Intent to treat analysis, 80% power 1-sided alpha=2.5% to detect 33% improvement in median OS (with all versions)

	Original Design high volume only	First Revision allow low volume	Final Design Adjustment of projected OS based on new data (S9346)
Sample size	568	600	780
Median OS High volume, ADT	24 months	24 months	33 months (44 months in C-HT)
Median OS Low volume, ADT	Not enrolled	48 months	67 months (89 months in C-HT)
% with high volume	100% (projected)	50% (projected)	70% (projected)

High volume: visceral metastases and/or 4 or more bone metastases (at least 1 beyond pelvis and vertebral column)

Presented by: Christopher J. Sweeney, MBBS

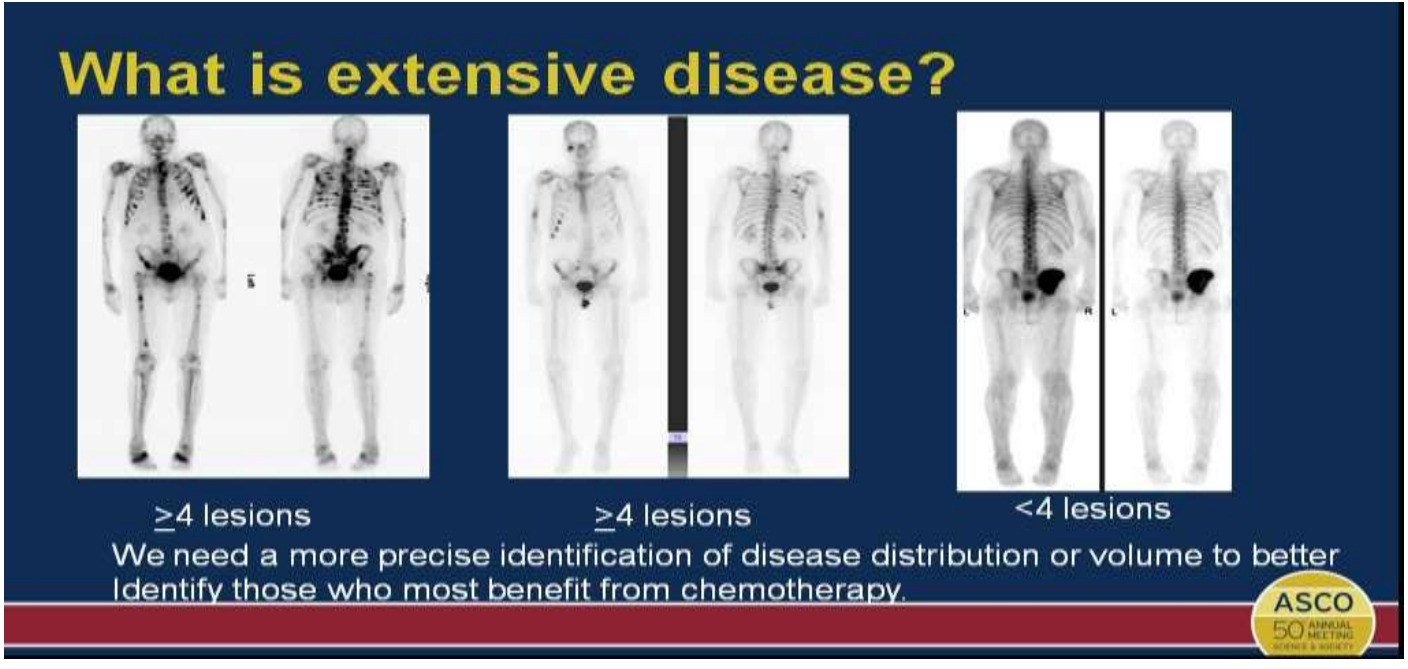
PRESENTED AT: ASCO 50 ANNUAL MEETING SCIENCE & SOCIETY

Presented By Christopher Sweeney at 2014 ASCO Annual Meeting

CHAARTED
definition of risk

High volume

- ✓ visceral mets and/or
- ✓ ≥4 bone mets (at last 1 beyond pelvis and spine)



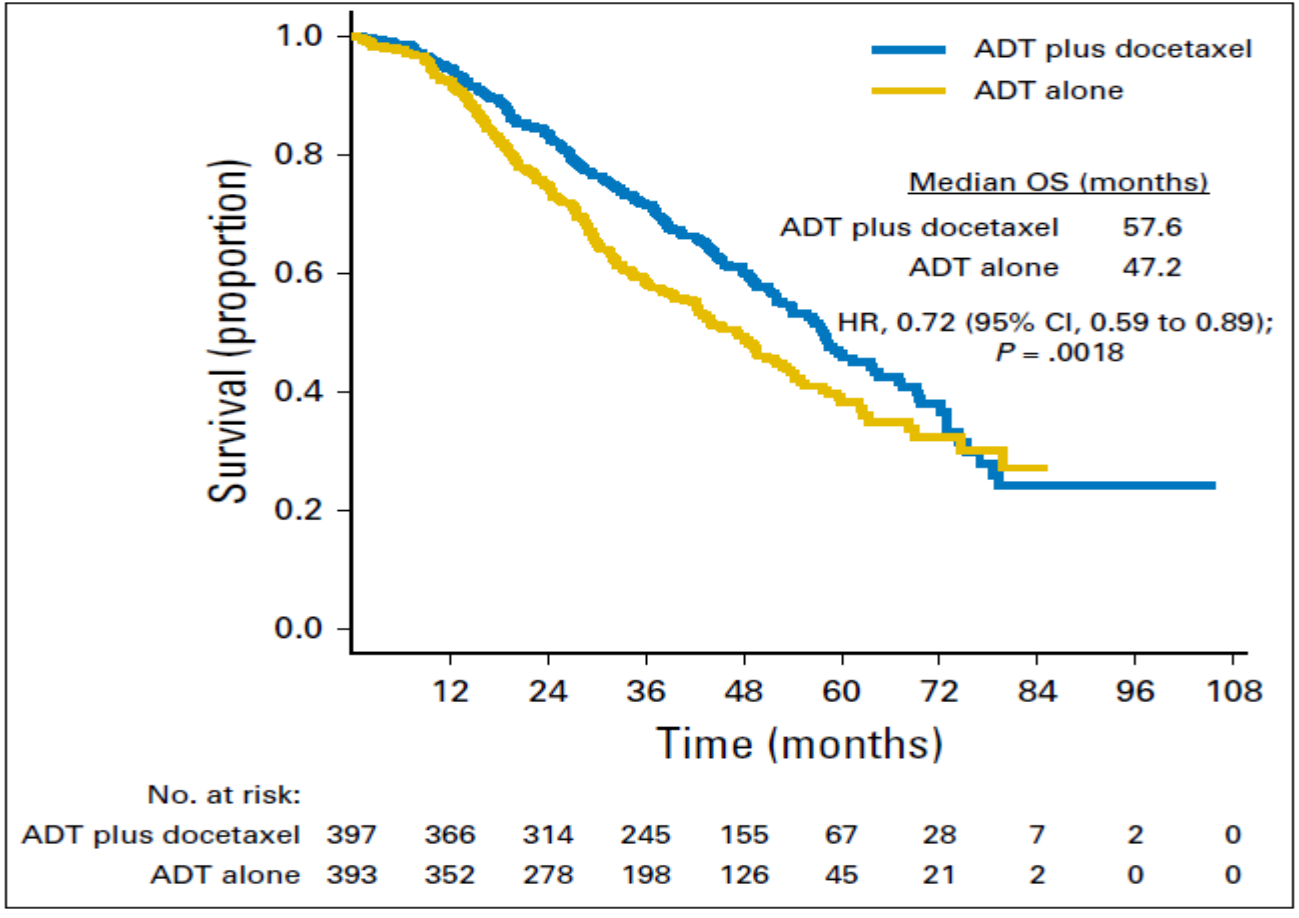
Presented By Michael Morris at 2014 ASCO Annual Meeting

CHAARTED Overall

Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer: Long-Term Survival Analysis of the Randomized Phase III E3805 CHAARTED Trial

Christos E. Kyriakopoulos, Yu-Hui Chen, Michael A. Carducci, Glenn Liu, David F. Jarrard, Noah M. Hahn, Daniel H. Shevrin, Robert Dreicer, Maha Hussain, Mario Eisenberger, Manish Kohli, Elizabeth R. Plimack, Nicholas J. Vogelzang, Joel Picus, Matthew M. Cooney, Jorge A. Garcia, Robert S. DiPaola, and Christopher J. Sweeney

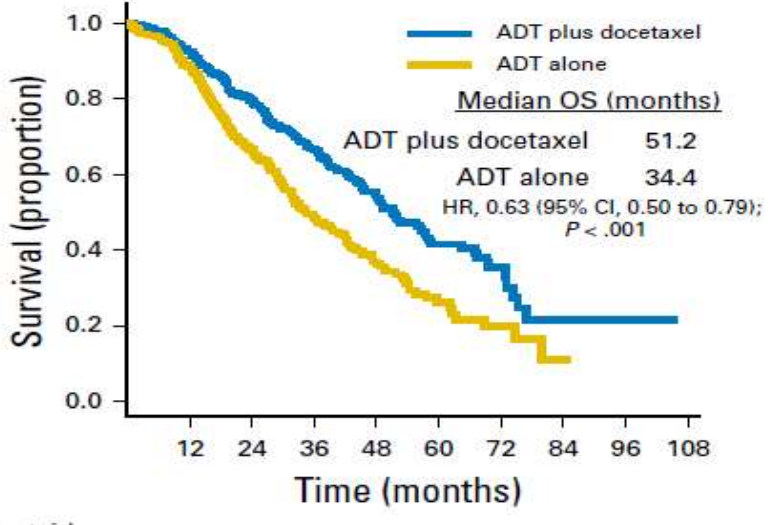
Primary endpoint:



CHAARTED by tumor burden

Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer: Long-Term Survival Analysis of the Randomized Phase III E3805 CHAARTED Trial

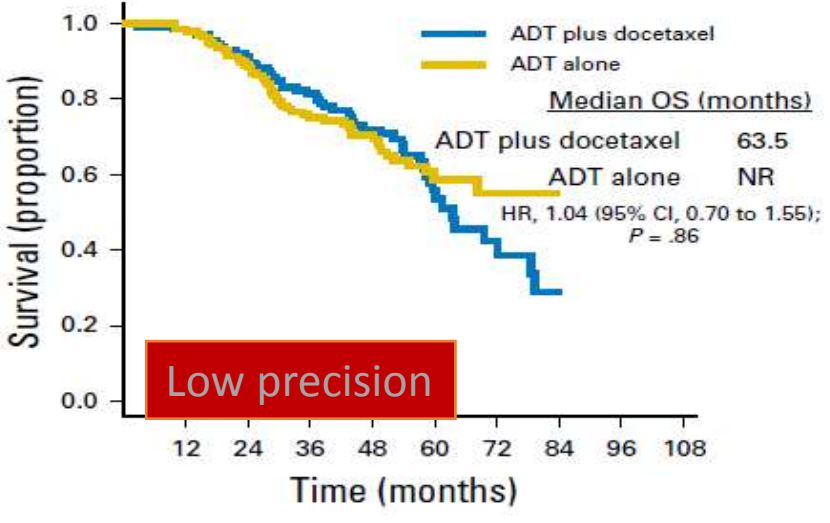
Christos E. Kyriakopoulos, Yu-Hui Chen, Michael A. Carducci, Glenn Liu, David F. Jarrard, Noah M. Hahn, Daniel H. Shevrin, Robert Dreicer, Maha Hussain, Mario Eisenberger, Manish Kohli, Elizabeth R. Plimack, Nicholas J. Vogelzang, Joel Picus, Matthew M. Cooney, Jorge A. Garcia, Robert S. DiPaola, and Christopher J. Sweeney



No. at risk:

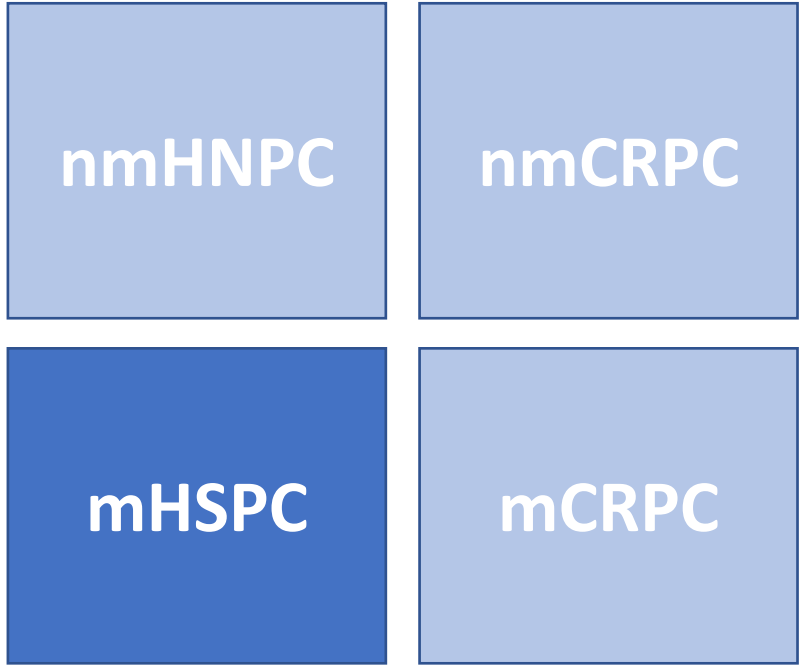
ADT plus docetaxel	263	239	202	151	91	41	16	5	2	0
ADT alone	250	215	156	104	59	19	9	1	0	0

High burden



	134	127	112	94	64	26	12	2	0	0
	143	137	122	94	67	26	12	1	0	0

Low burden



ABIRATERONE

Comparison of study PICOs

Trial	Accrual dates	Number of M1 patients	*De novo* or relapsed M1?	Control	Treatment	Median age (range)	Gleason score of 8–10 (%)	Performance status 0–1 (%)	Median follow-up (survival)
STAMPEDE [12] (Arm A versus arm G) M1 patients only	11/2011–01/2014	1002	*De novo* (95%) or relapsed after local therapy (5%)	ADT (LHRH agonist or antagonist or orchiectomy)	ADT + abiraterone (1000 mg/d) + prednisone (5 mg/d)	67 (62–72)	737 (74%)	988 (97%)	41 months
LATITUDE [11]	02/2013–12/2014	1199	*De novo*	ADT (LHRH agonists or orchiectomy)	ADT + abiraterone (1000 mg/d) + prednisone (5 mg/d)	67 (33–92)	1170 (98%)	1157 (96%)	30.4 months
PEACE-1[a] (NCT01957436) (patients not receiving docetaxel in addition to ADT)	11/2013–to date	≈476 expected	*De novo*	ADT (LHRH agonist or antagonist or orchiectomy)	ADT + abiraterone (1000 mg/d) + prednisone (10 mg/d)	Not yet available	Not yet available	Not yet available	Not yet available
				ADT (LHRH agonist or antagonist or orchiectomy) + radiotherapy (74 Gy, 37 fractions)	ADT + abiraterone (1000 mg/d) + prednisone (10 mg/d) + radiotherapy (74 Gy, 37 fractions)				
PEACE-1[b] (NCT01957436) (patients receiving docetaxel in addition to ADT)	11/2015–ongoing	Target ≈650 (≈300+ accrued to date)		ADT (LHRH agonist or antagonist or orchiectomy) + docetaxel[c] (75 mg/m^2 q 21 days; 6 cycles)	ADT + docetaxel[c] + abiraterone (1000 mg/d) + prednisone (10 mg/d)	Not yet available	Not yet available	Not yet available	Not yet available
				ADT (LHRH agonist or antagonist or orchiectomy) + docetaxel[c] (75 mg/m^2 q 21 days; 6 cycles) + radiotherapy (74 Gy, 37 fractions)	ADT + docetaxel[c] + abiraterone (1000 mg/d) + prednisone (10 mg/d) + radiotherapy (74 Gy, 37 fractions)				

ADT, androgen deprivation therapy; LHRH, luteinising hormone–releasing hormone.

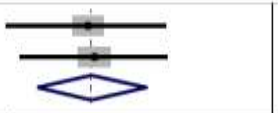
[a] Patients randomised to PEACE-1, who have not received docetaxel in addition to ADT are eligible for this comparison.

[b] Patients randomised to PEACE-1, who have received docetaxel in addition to ADT will be eligible for a subsequent comparison of the systematic review (PROSPERO CRD42017058300).

[c] Docetaxel use is left to the investigator's discretion (stratification factor).

A

Trial name	AAP+ADT events/patients	ADT events/patients	Hazard Ratio (95% CI)	% Weight
STAMPEDE	150/500	218/502	0.61 (0.49, 0.75)	46.34
LATITUDE	169/597	237/602	0.62 (0.51, 0.76)	53.66
Overall	319/1097	455/1104	0.62 (0.53, 0.71)	



B

Trial name	AAP+ADT events/patients	ADT events/patients	Hazard Ratio (95% CI)	% Weight
STAMPEDE	173/500	301/502	0.43 (0.36, 0.52)	45.14
LATITUDE	239/597	354/602	0.47 (0.39, 0.55)	54.86
Overall	412/1097	655/1104	0.45 (0.40, 0.51)	

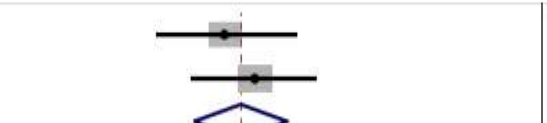


Fig. 2. Effect of adding AAP to ADT on (A) overall survival and (clinical/radiological) progression-free survival (B) in men with mHSPC.

Discussant: **Stéphane Oudard, MD, PhD**
Georges Pompidou Hospital,
Oncology Department, Paris, France

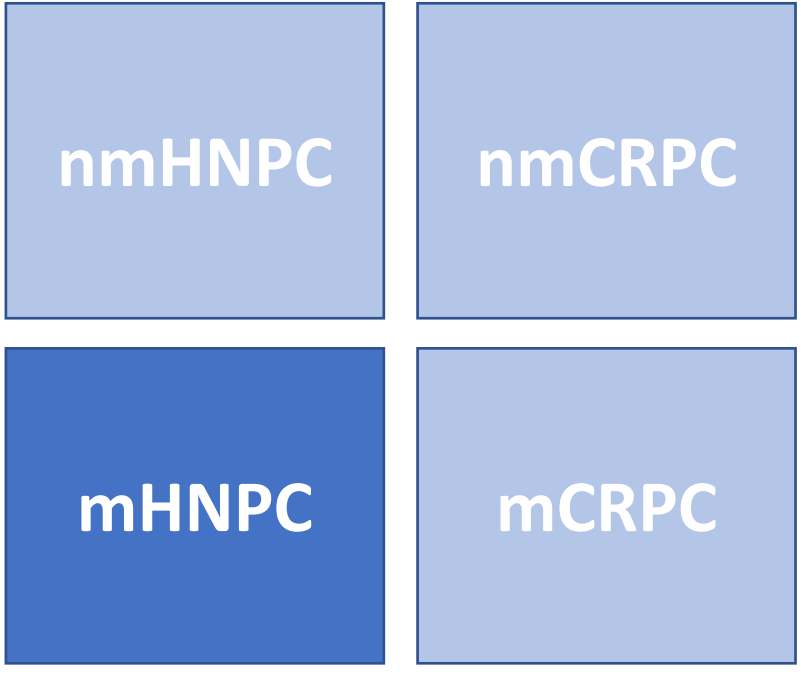
SOME CRITICISMS OF THESE META-ANALYSES

- **Not performed on individual patient characteristics**

- **Tumor burden is not considered**
  - Higher in CHAARTED and LATITUDE than in GETUG-15 and ZAPCA[1-3]
  - Not specified in CALBG 90202 and STAMPEDE[4-5]

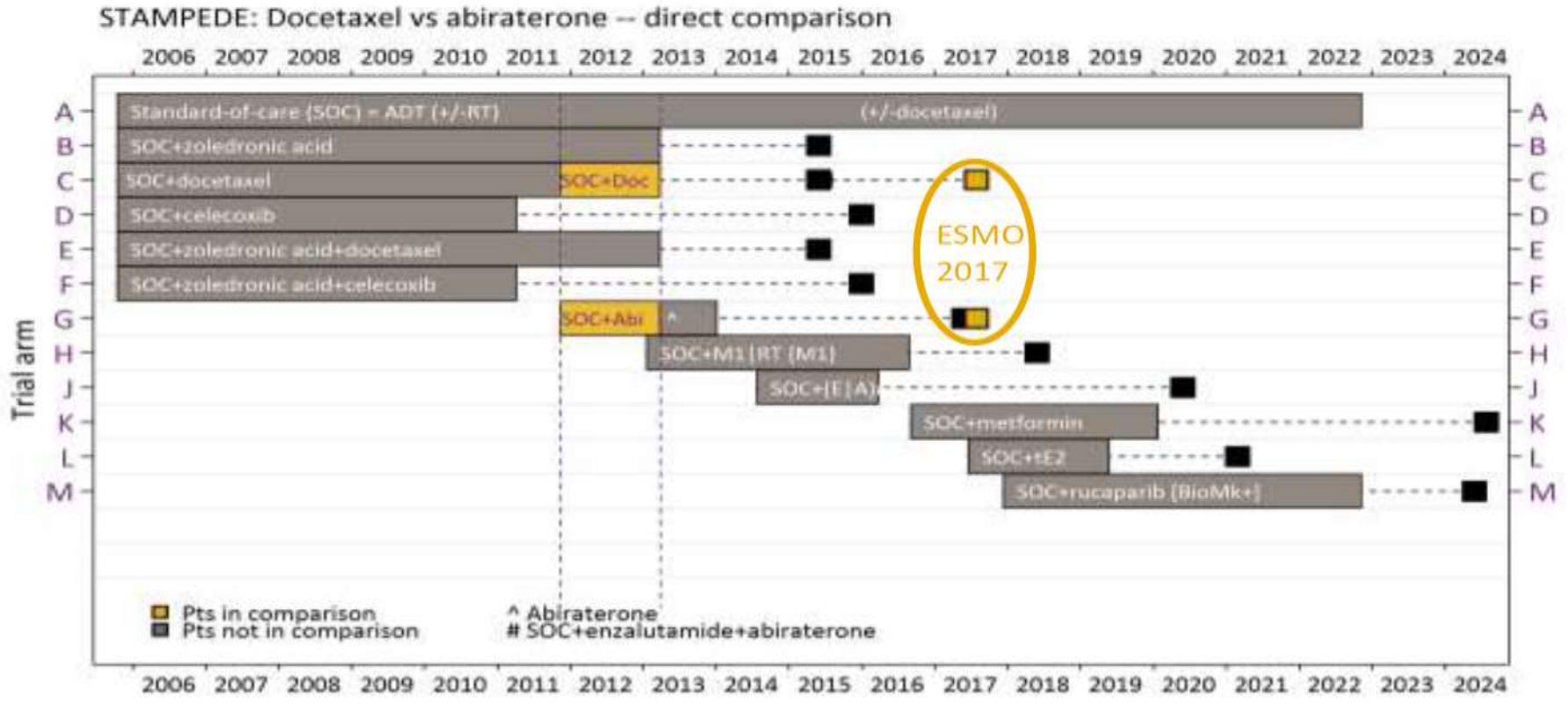
- **Impact of subsequent therapies not considered**
  - GETUG-15 (ADT+DOC vs ADT): 85% received DOC at progression in ADT arm (early vs deferred study)[1]
  - LATITUDE (ADT+ ABI vs ADT): only 27.5% received ABI or ENZA at progression in ADT arm[2]

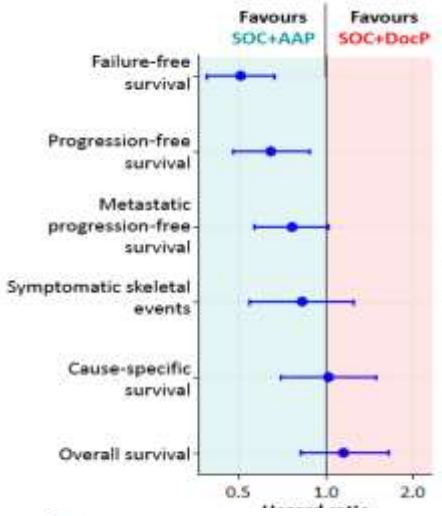
1. Gravis G et al. Cancer Treat Rev. 2017;55:211-217; 2. Fizazi K et al. NEJM 2017;377: 352-60; 3. Kamba T et al. Int J Clin Oncol. 2017 Feb;22(1):166-173; 4. Smith MR et al. JCO 2014 32:1143-1150; James N et al. NEJM. 2017;377:338-351



ABI vs DOCE

STAMPEDE: SOC+AAP vs SOC+DocP





Summary

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

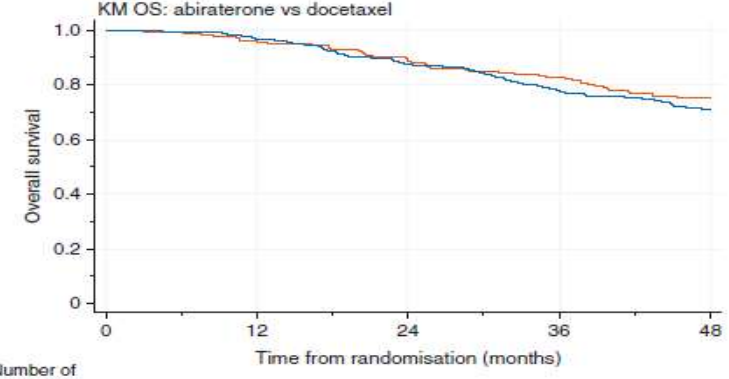
Strong evidence favouring AAP

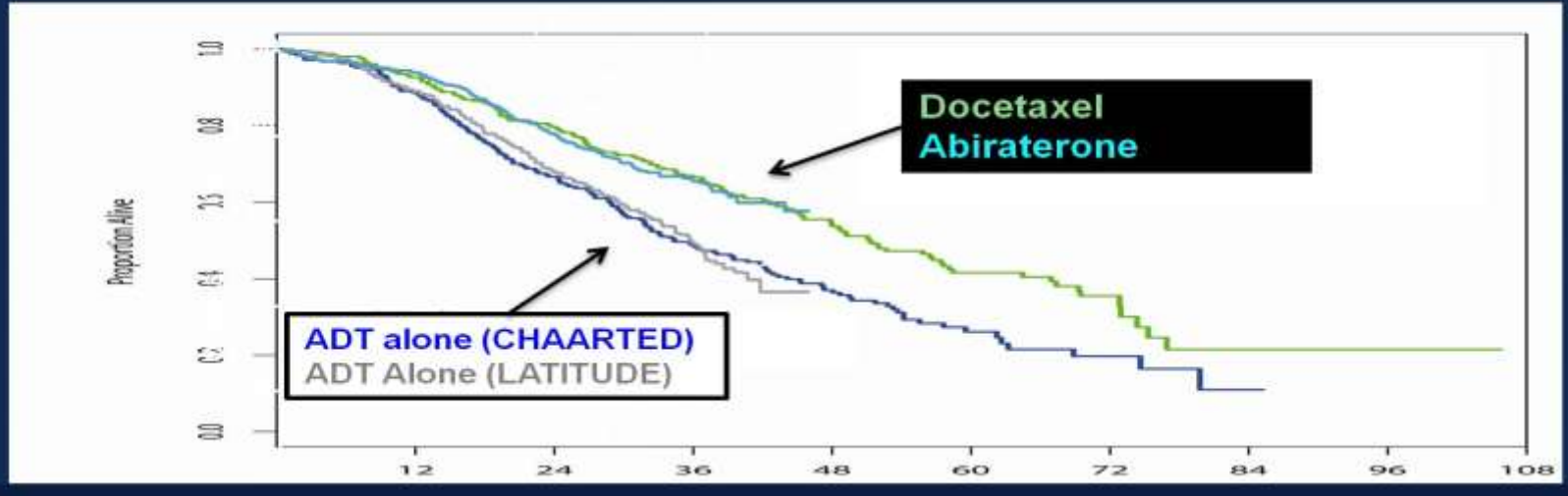
Weak evidence favouring AAP

No good evidence of a difference

→ Proportionately different time spent in each disease state

Toxicity profiles quite different and well known





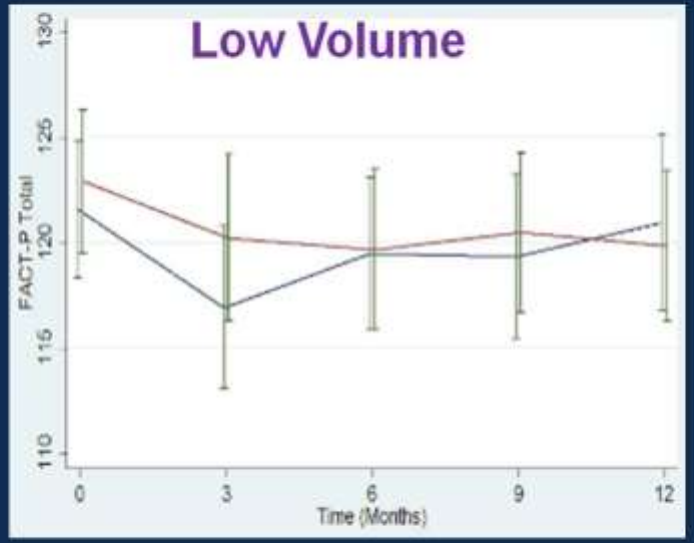
Overlay of LATITUDE KM Plot on CHAARTED (high volume) KM Plot

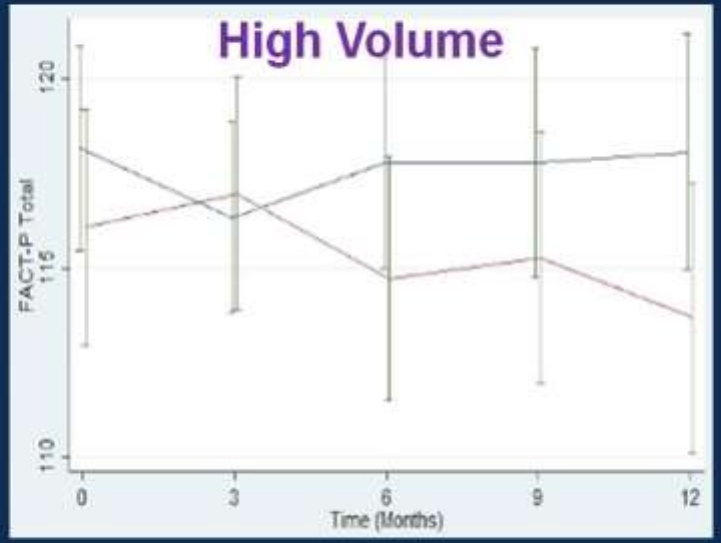
Grade 3–5 AEs in ≥2% of patients

AE, %	CHAARTED[1] ADT + Docetaxel (n=390)			LATITUDE[2] ADT + Abiraterone (n=597)		STAMPEDE ARM G[3] ADT + Abiraterone (n=948)
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 3–5
Allergic reaction	1.8	0.3	0	–	–	–
Fatigue	4.1	0	0	2	0	2
Neutropenia	3.1	9.0	0	–	–	–
Febrile neutropenia	3.8	2.3	0	–	–	–
Pulmonary disorder	–	–	0.3	–	–	–
Hypertension	–	–	–	20	0	1
Hypokalaemia	–	–	–	10	1	<1
ALT increased	–	–	–	5	<1	<1
Hyperglycaemia	–	–	–	4	<1	–
AST increased	–	–	–	4	<1	<1
Bone pain	–	–	–	3	0	–
Cardiac disorder	–	–	–	3	1	10
Endocrine disorder	–	–	–	–	–	14
Gastrointestinal disorder	–	–	–	–	–	5
General disorder	–	–	–	–	–	5

1. Sweeney et al. N Engl J Med 2015; 2. Fizazi et al. NEJM 2017; 3. James et al. NEJM 2017

QOL FACT-P: CHAARTED



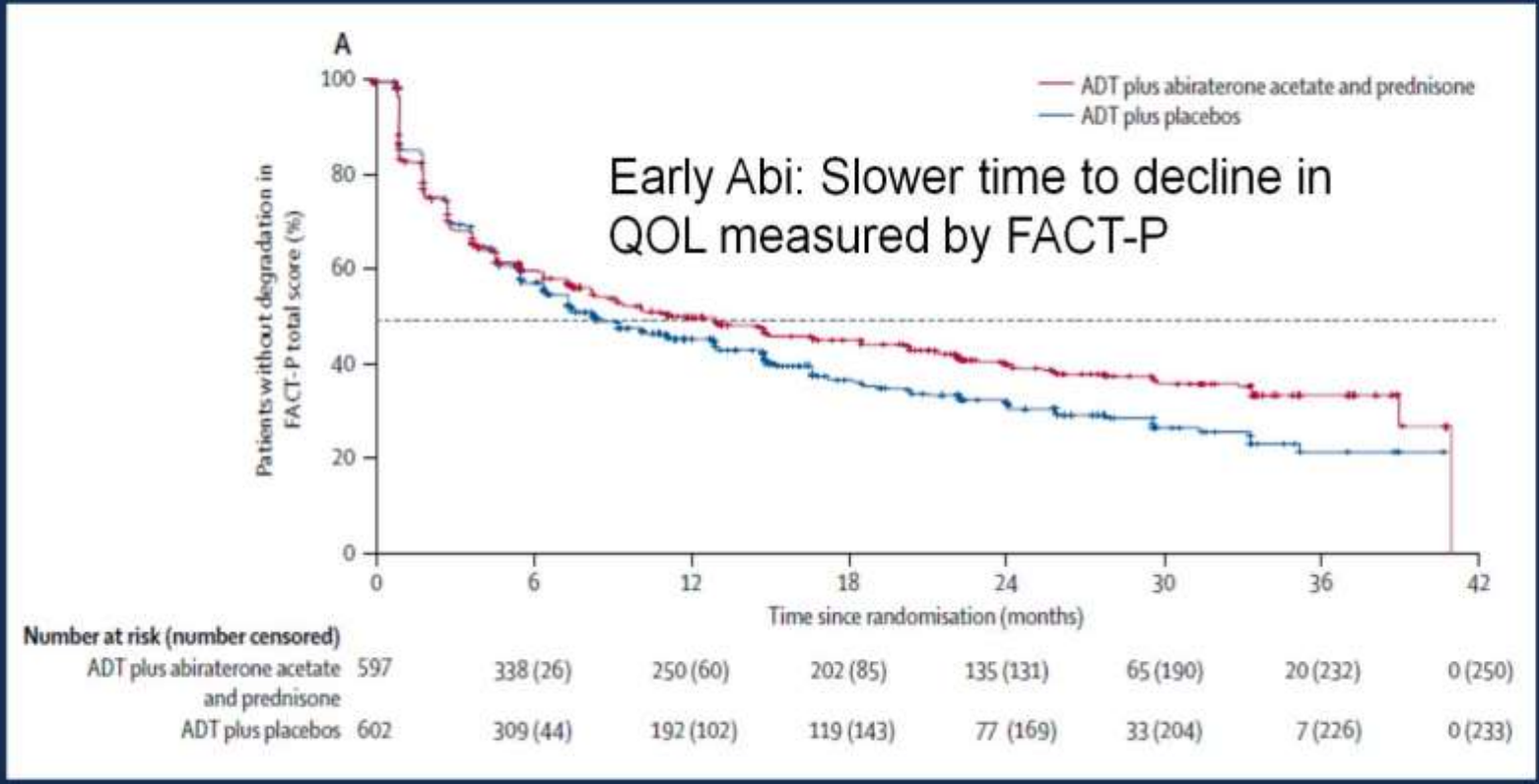


ADT alone (red curves) in low volume had no change in QOL over 12 months in low volume but decline in high volume (progression of disease with symptoms, PSA rise, treatment)

ADT plus docetaxel (blue curves) decline in QOL in low vol on chemo; But no decline and better 12 month QOL in high volume

Morgans et al submitted for publication

LATITUDE: QOL FACT-P results



Number at risk (number censored)								
ADT plus abiraterone acetate and prednisone	597	338 (26)	250 (60)	202 (85)	135 (131)	65 (190)	20 (232)	0 (250)
ADT plus placebos	602	309 (44)	192 (102)	119 (143)	77 (169)	33 (204)	7 (226)	0 (233)

Chi et al Lancet Onc 2018

Presented By Nicholas Van As at 2018 Genitourinary Cancers Symposium: Translating Evidence to Multidisciplinary Care

What is indirect comparison?

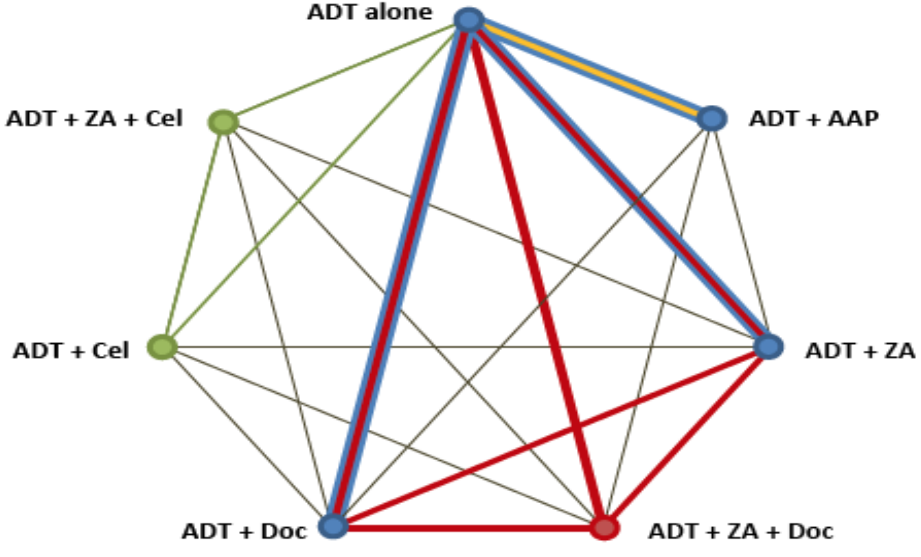
Fujian Song
BMed MMed PhD
Reader in Research Synthesis, Faculty of Health, University of East Anglia

Basic assumptions underlying indirect comparisons include a **homogeneity assumption** for standard meta-analysis, **similarity assumption** for adjusted indirect comparison and **consistency assumption** for the combination of direct and indirect evidence. It is essential to fully understand and appreciate these basic assumptions in order to use adjusted indirect and mixed treatment comparisons appropriately.

What are the optimal systemic treatments for men with metastatic, hormone-sensitive prostate cancer? A STOPCAP systematic review and network meta-analysis

C.L. Vale, D.J. Fisher, J. Carpenter, I. R. White, S. Burdett, N.W. Clarke, K. Fizazi, G Gravis, N.D. James, M.D. Mason, M.K.B Parmar, L.H. Rydzewska, C.J. Sweeney, M.R. Spears, M.R. Sydes and J.F. Tierney

- Three prior systematic reviews from the Systemic Treatment Options for Cancer of the Prostate (STOPCAP) Collaborators, plus one trial, have shown improved survival when the following were added to androgen deprivation therapy (ADT) for men with metastatic hormone-sensitive prostate cancer (mHSPC):
  - Abiraterone acetate plus prednisolone/prednisone (AAP; Rydzewska, 2017)
  - Docetaxel (Doc), but not zoledronic acid (ZA; Vale 2015)
  - Celecoxib (Cel) in combination with ZA (Mason, 2017)

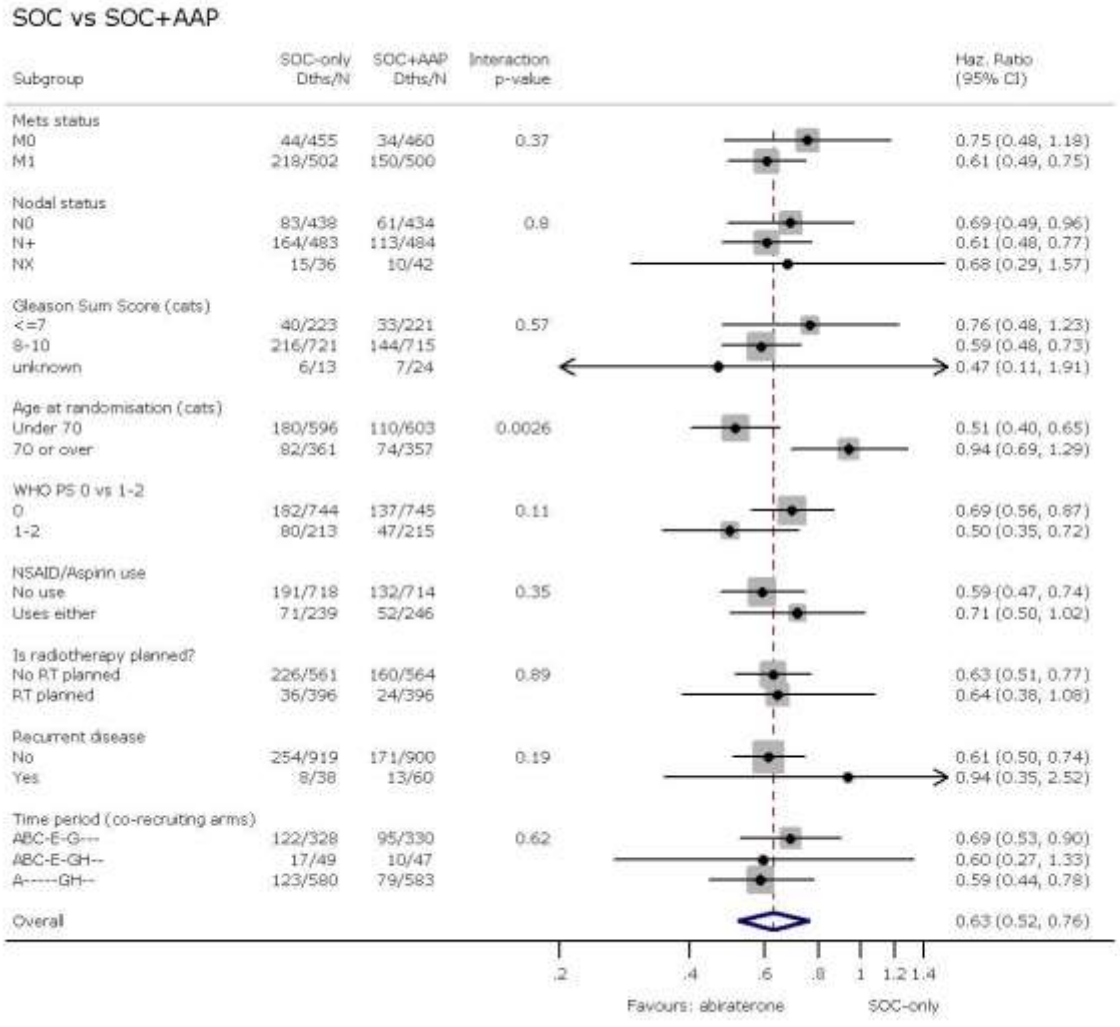


Comparison of study PICOs

Trial	Recruitment period	Median follow-up (months)	Treatment	Treatment (*N*)	Control (*N*)	Definition of FFS
CALGB 90202 [21]	June 2004 to April 2012	Unknown	ADT + ZA	323	322	Time to first bone progression, PSA progression, or death
GETUG 15 [22]	Oct 2004 to Dec 2008	84	ADT + Doc	192	193	Time to PSA progression, clinical progression or death
STAMPEDE (Arms A versus D) [3]	Oct 2005 to April 2011	69	ADT + Cel	188	377	Time to PSA failure, progression of local, lymph-node, or distant metastases; or death from prostate cancer
STAMPEDE (Arms A versus F) [3]	Oct 2005 to April 2011	69	ADT + ZA + Cel	190	377	Time to PSA failure, progression of local, lymph-node, or distant metastases; or death from prostate cancer
STAMPEDE (Arms A versus B) [13]	Oct 2005 to March 2013	43	ADT +ZA	366	724	Time to PSA failure, progression of local, lymph-node, or distant metastases; or death from prostate cancer
STAMPEDE (Arms A versus C) [13]	Oct 2005 to March 2013	43	ADT + Doc	362	724	Time to PSA failure, progression of local, lymph-node, or distant metastases; or death from prostate cancer
STAMPEDE (Arms A versus E) [13]	Oct 2005 to March 2013	43	ADT + ZA + Doc	365	724	Time to PSA failure, progression of local, lymph-node, or distant metastases; or death from prostate cancer
CHAARTED [23]	July 2006 to Dec 2012	54	ADT + Doc	397	393	Time to PSA rise or clinical progression
ZAPCA (KYUH TRIG0705) [24]	May 2008 to Dec 2010	42	ADT +ZA	109	110	Time to earliest date of PSA progression, clinical progression, first SRE, death for any reason, or cessation of protocol treatment for any reason
STAMPEDE (Arms A versus G) [12]	Nov 2011- Jan 2014	40	ADT + AAP	500	502	Time to PSA failure, progression of local, lymph-node, or distant metastases; or death from prostate cancer
LATITUDE [14]	Feb 2013 to Dec 2014	30	ADT + AAP	597	602	Time to radiographic progression or death from any cause

AAP, abiraterone acetate plus prednisolone/prednisone; ADT, androgen-deprivation therapy; Cel, celecoxib; Doc, docetaxel; FFS, failure-free survival; SRE, skeletal related events; ZA, zoledronic acid.

Overall Survival – STAMPEDE "abiraterone comparison"



No good evidence of heterogeneity by stratification factors

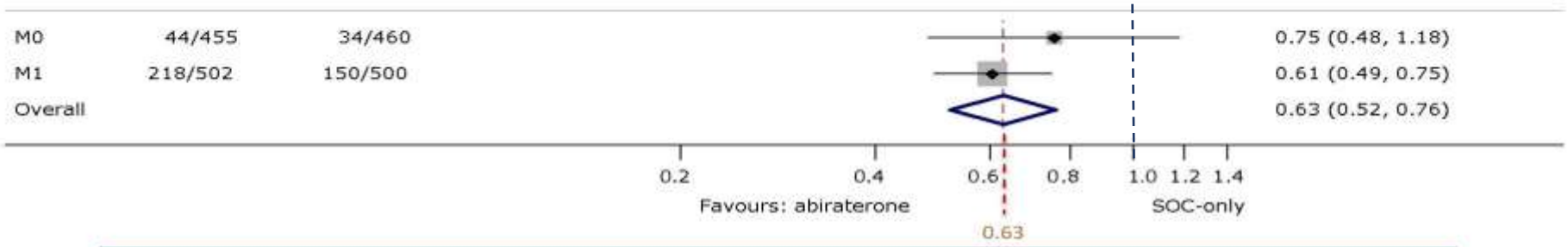
Presented By Nicholas James at 2017 ASCO Annual Meeting

STAMPEDE "abiraterone comparison"
Overall Survival by metastatic status – pre-planned analysis

SOC vs SOC+AAP

Mets * treatment interaction
P-value = 0.37

Mets status	SOC-only Dths/N	SOC+AAP Dths/N	Haz. Ratio (95% CI)
M0	44/455	34/460	0.75 (0.48, 1.18)
M1	218/502	150/500	0.61 (0.49, 0.75)
Overall			0.63 (0.52, 0.76)



No good evidence of heterogeneity by metastatic status

Discussant: **Stéphane Oudard**, **MD, PhD**
Georges Pompidou Hospital,
Oncology Department, Paris, France

SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

- Ranking of the **OS results** from the network suggest that:
  - **ADT + AAP** is likely to be the optimal treatment (**93% probability**)
  - **ADT + DOC** is most likely to be the second-best (**43% probability**)

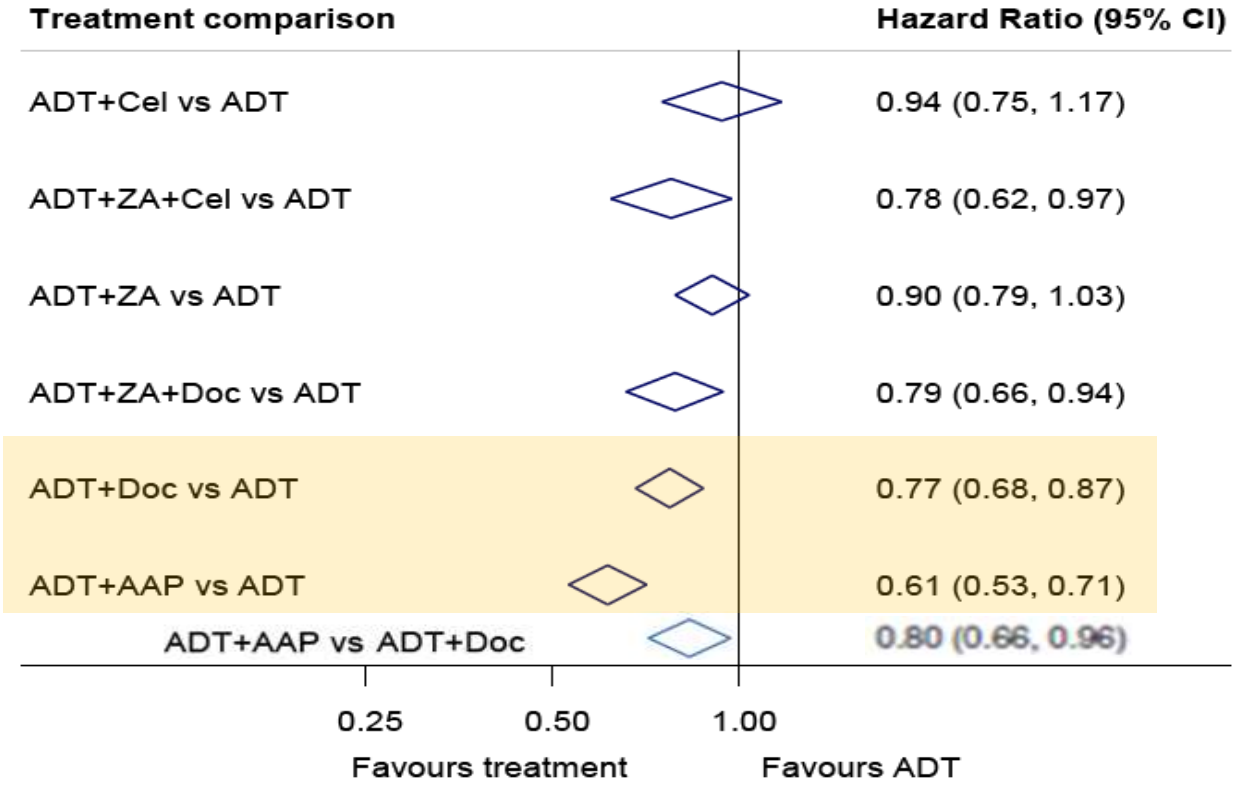
	AAP	DOC	ZA+ DOC	ZA+ Cel	ZA	Cel	ADT
Best	**92.5**	2.1	1.5	3.9	0.0	0.0	0.0
2nd best	6.6	**43.4**	20.8	*28.4*	0.0	0.8	0.0
3rd best	0.7	*34.8*	**31.3**	*28.6*	2.1	2.5	0.0
4th best	0.1	17.9	*34.5*	**26.9**	10.9	9.7	0.0
5th best	0.1	1.7	9.3	9.2	**49.6**	*28.2*	1.9
6th best	0.0	0.1	2.5	2.6	*33.0*	**35.0**	26.8
Worst	0.0	0.0	0.1	0.4	4.4	23.8	**71.3**

Vale C et al, LBA33 ESMO 2017

What are the optimal systemic treatments for men with metastatic, hormone-sensitive prostate cancer? A STOPCAP systematic review and network meta-analysis

C.L. Vale, D.J. Fisher, J. Carpenter, I. R. White, S. Burdett, N.W. Clarke, K. Fizazi, G Gravis, N.D. James, M.D. Mason, M.K.B Parmar, L.H. Rydzewska, C.J. Sweeney, M.R. Spears, M.R. Sydes and J.F. Tierney

Figure 3. Overall Survival



Network meta-analyses of aggregate data suggest "abiraterone" better

- These indirect comparisons are inherently limited by
  - Docetaxel is handicapped by including a study (GETUG15) completed in an era with limited access to life prolonging therapies for CRPC
  - Abiraterone had an inherent positive bias by having greater proportion of patients with "poor risk" disease with a clear treatment effect with short follow-up
    - It could be better prognosis patients may dilute the effect with longer follow-up as we are seeing with docetaxel

- Need individual patient data and longer follow-up

Wallis et al Eur Urol, 2017, Vale et al ESMO 2017

Backup Slides

MAIN INCLUSION CRITERIA

- Metastatic PCa with measurable or evaluable disease
- ECOG performance status ≤ 2
- No chemotherapy for metastatic disease
- Ongoing ADT was allowed if < 60 days
- Systemic treatment for local disease had to be discontinued > 1 year (without metastases or PSA increase)

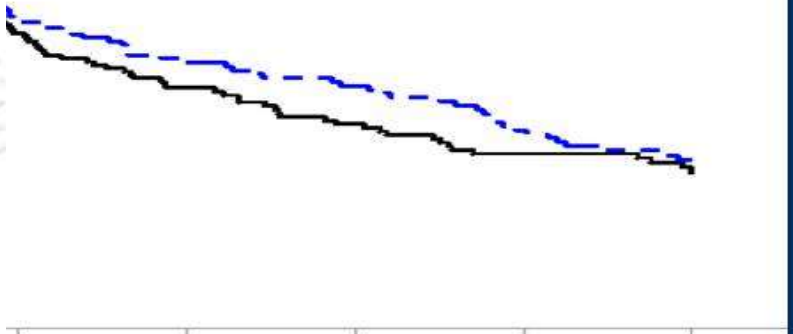
UPDATED ANALYSIS: OVERALL SURVIVAL

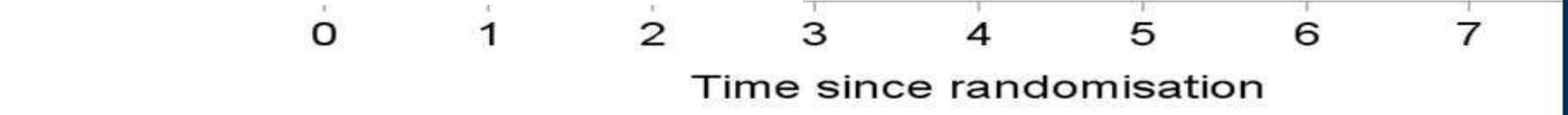
When are results precise enough?

Consider

- Small sample size
  - (Optimal Information Size, OIS)
- Number of events
- Wide confidence intervals
  - uncertainty about magnitude of effect

Median OS
ADT alone: 46.5 [39.1- 60.6]
ADT + D: 60.9 [46.1- 71.4]
HR: 0.9 [0.7-1.2]
p=0.44

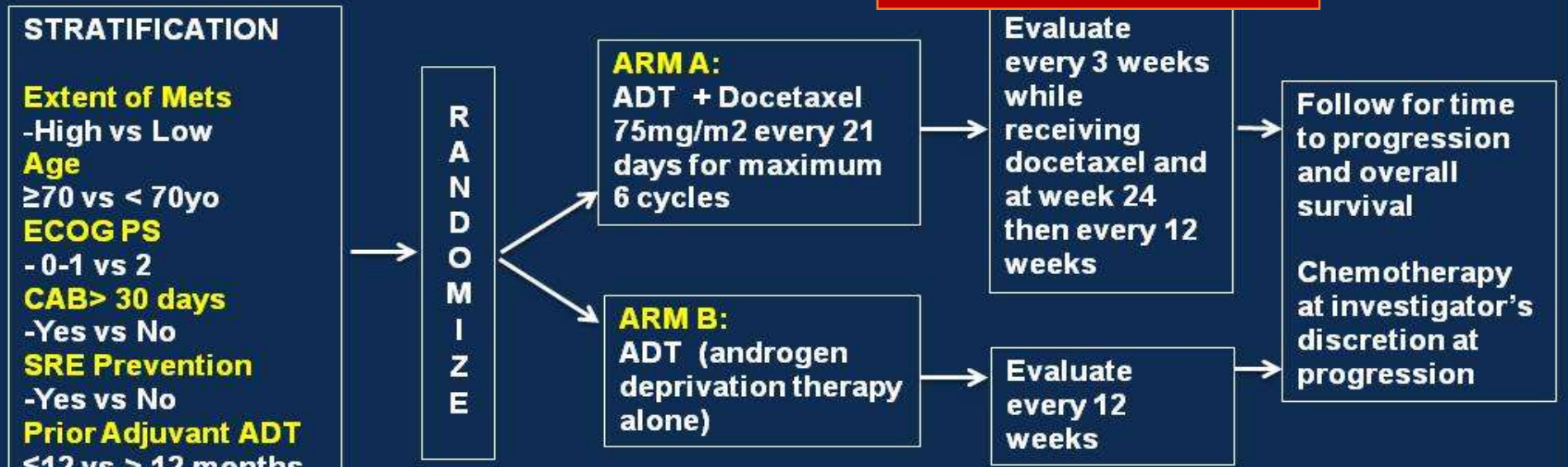




ADT	193	171	148	105	66	53	43	29
ADT +D	192	175	145	100	70	58	47	27

E3805 – CHAARTED Treatment

Risk of performance bias



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

Presented by: Christopher J. Sweeney, MBBS

PRESENTED AT: ASCO 50 ANNUAL MEETING SCIENCE & SOCIETY

Presented By Christopher Sweeney at 2014 ASCO Annual Meeting

STAMPEDE Trial

Inclusion criteria

Newly-diagnosed

Any of:

- Metastatic
- Node-Positive
- ≥2 of: Stage T3/4
  PSA≥40ng/ml
  Gleason 8-10

Relapsing after previous RP or RT with ≥1 of:

- PSA ≥4ng/ml and rising with doubling time <6m
- PSA ≥20ng/ml
- Node-positive
- Metastatic

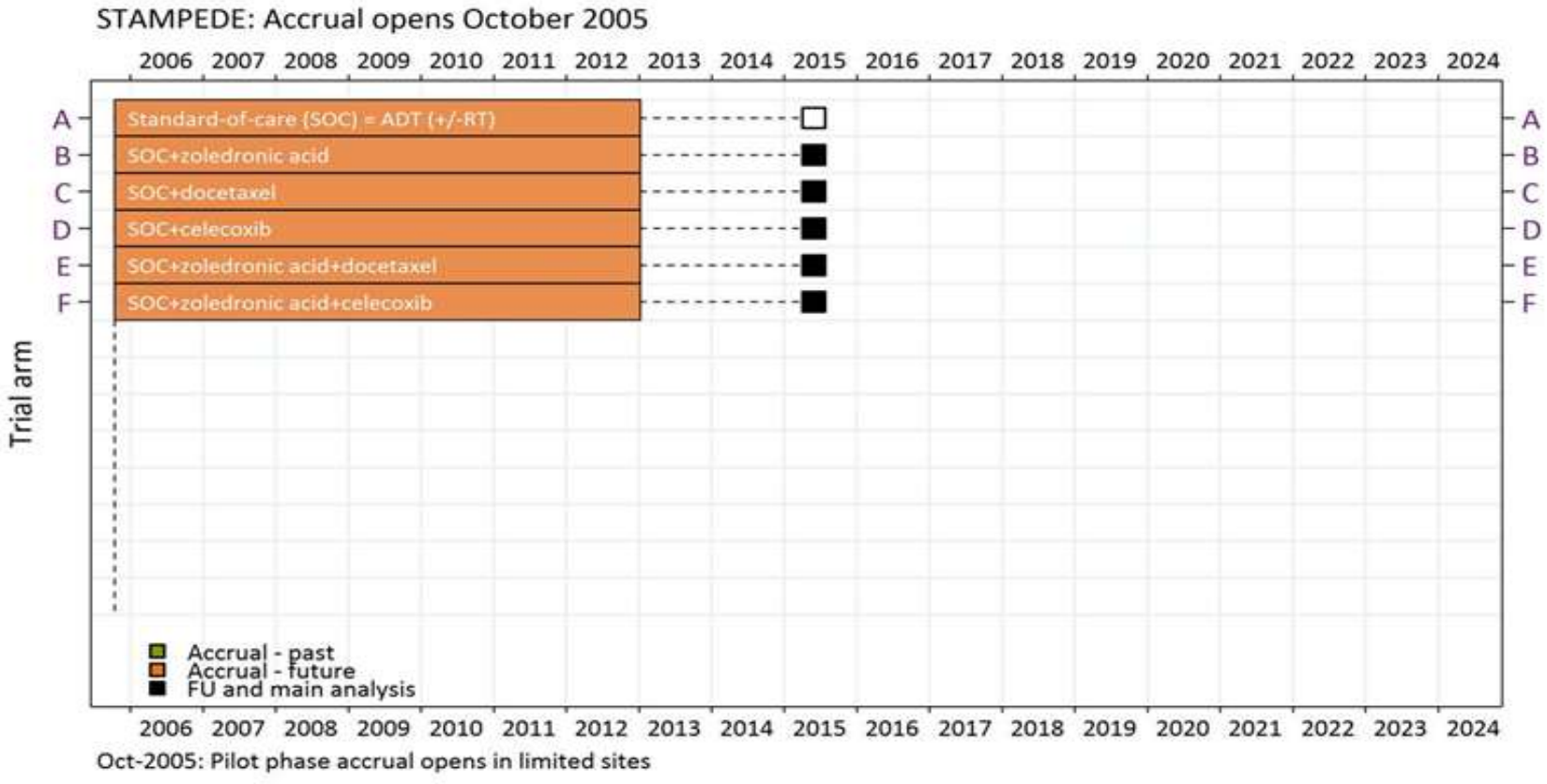
All patients

- Fit for all protocol treatment
- Fit for follow-up
- WHO performance status 0-2
- Written informed consent

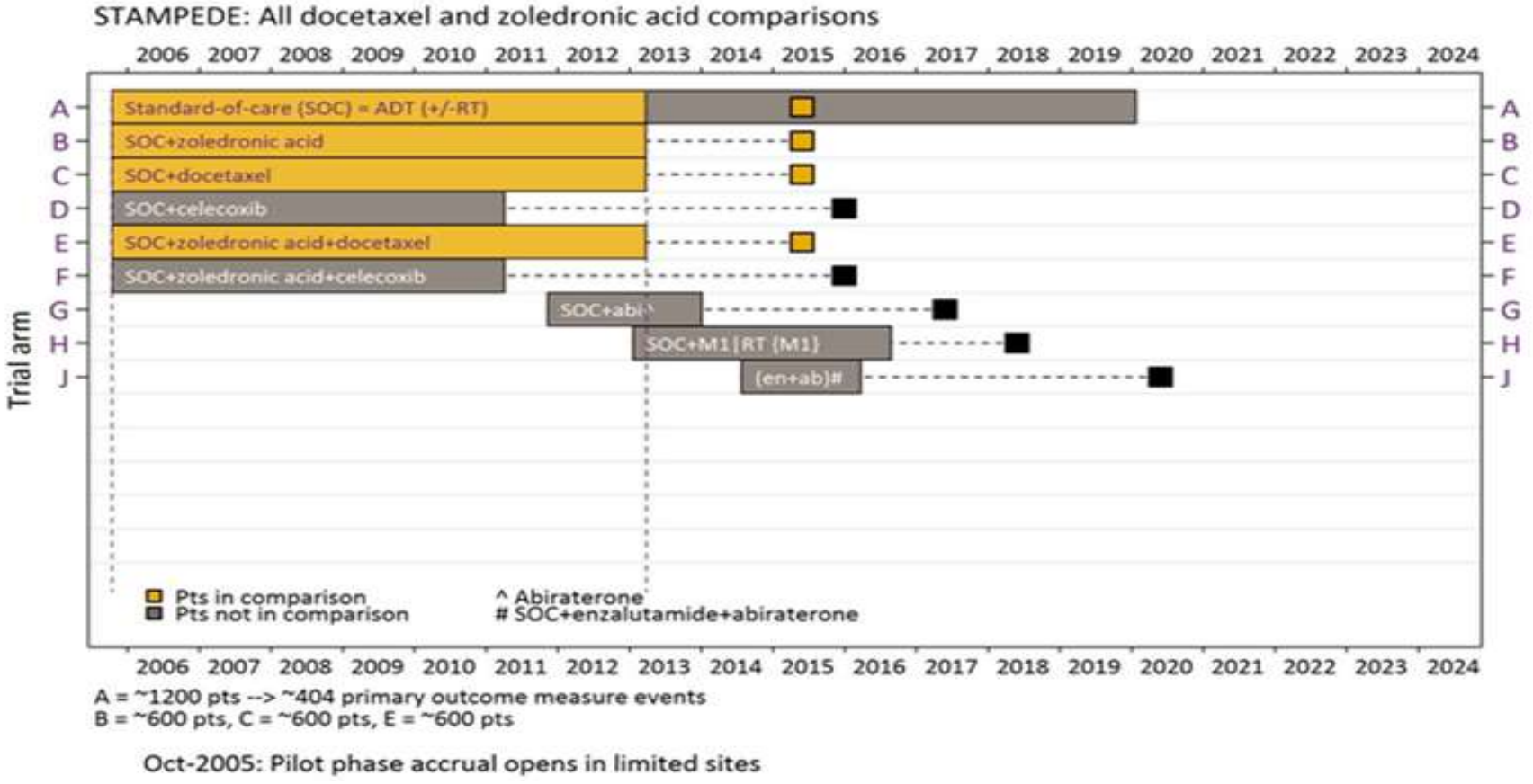
Full criteria

www.stampedetrial.org

Trial activity: original research arms



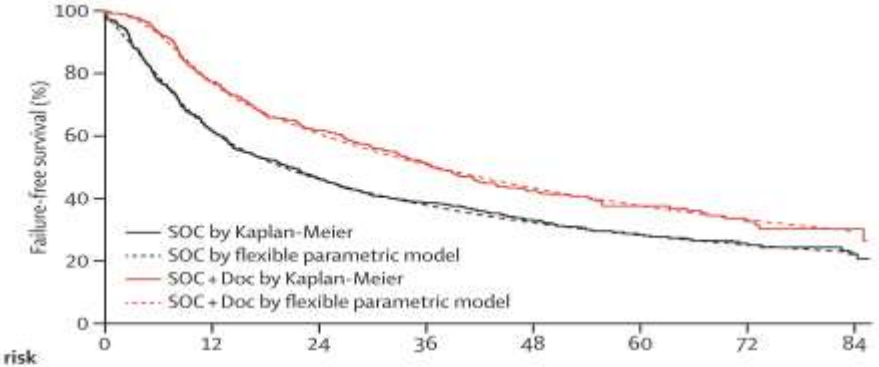
Docetaxel & ZA comparisons: patients



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

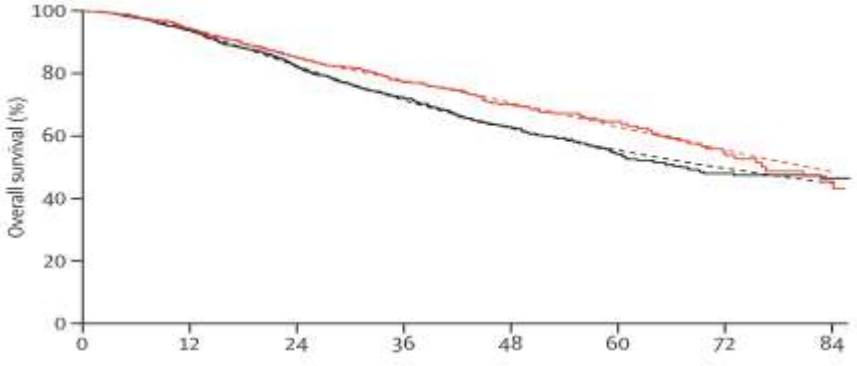
Nicholas D James, Matthew R Sydes, Noel W Clarke, Malcolm D Mason, David P Dearnaley, Melissa R Spears, Alastair W S Ritchie, Christopher C Parker, J Martin Russell, Gerhardt Attard, Johann de Bono, William Cross, Rob J Jones, George Thalmann, Claire Amos, David Matheson, Robin Millman, Mymoona Alzouebi, Sharon Beesley, Alison J Birtle, Susannah Brock, Richard Cathomas, Prabir Chakraborti, Simon Chowdhury, Audrey Cook, Tony Elliott, Joanna Gale, Stephanie Gibbs, John D Graham, John Hetherington, Robert Hughes, Robert Laing, Fiona McKinna, Duncan B McLaren, Joe M O'Sullivan, Omi Parikh, Clive Peedell, Andrew Protheroe, Angus J Robinson, Narayanan Srihari, Rajaguru Srinivasan, John Staffurth, Santhanam Sundar, Shaun Tolan, David Tsang, John Wagstaff, Mahesh K B Parmar, for the STAMPEDE investigators*

Lancet 2016; 387: 1163–77

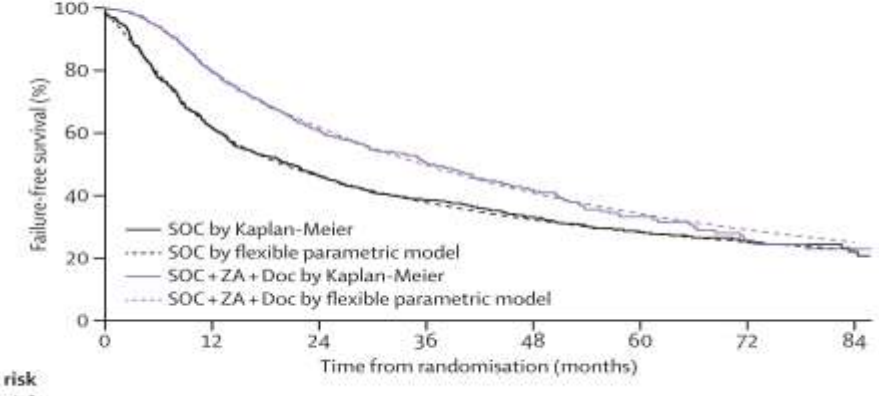


Number at risk (events)

SOC	1184 (449)	712 (174)	493 (73)	291 (33)	162 (20)	88 (7)	46 (4)	19
SOC + Doc	592 (131)	441 (88)	324 (48)	189 (28)	106 (10)	57 (6)	30 (2)	11

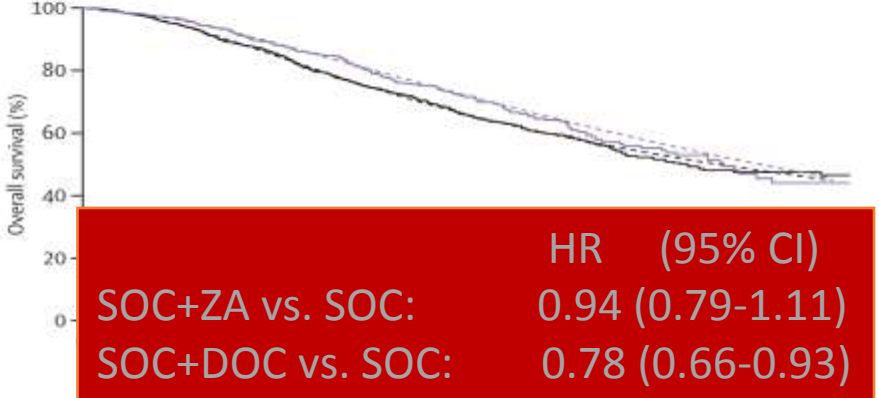


	1184 (73)	1093 (134)	876 (92)	538 (60)	322 (35)	166 (17)	87 (2)	43
	592 (33)	545 (52)	447 (35)	290 (22)	181 (12)	93 (13)	51 (6)	20



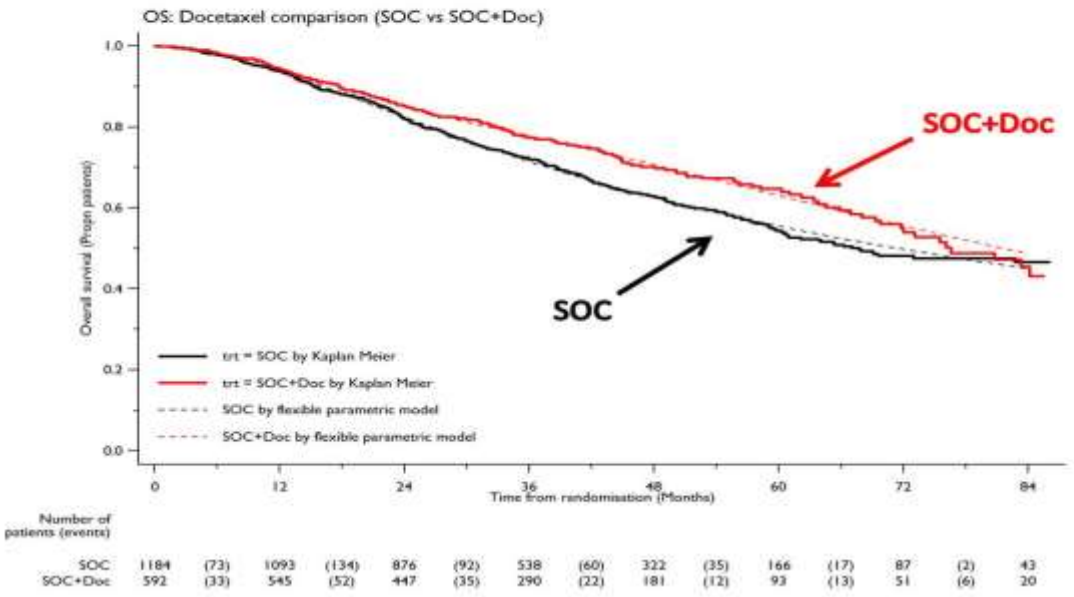
Number at risk (events)

SOC	1184 (449)	712 (174)	493 (73)	291 (33)	162 (20)	88 (7)	46 (4)	19
SOC + ZA + Doc	593 (117)	447 (102)	308 (45)	181 (26)	106 (18)	45 (8)	21 (2)	13



	HR (95% CI)
SOC+ZA vs. SOC:	0.94 (0.79-1.11)
SOC+DOC vs. SOC:	0.78 (0.66-0.93)
SOC+ZA+DOC vs. SOC:	0.82 (0.69-0.97)

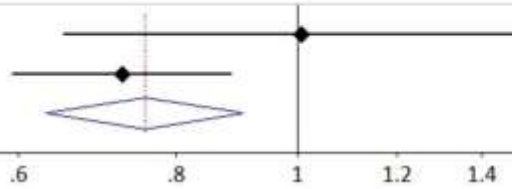
Docetaxel: Survival



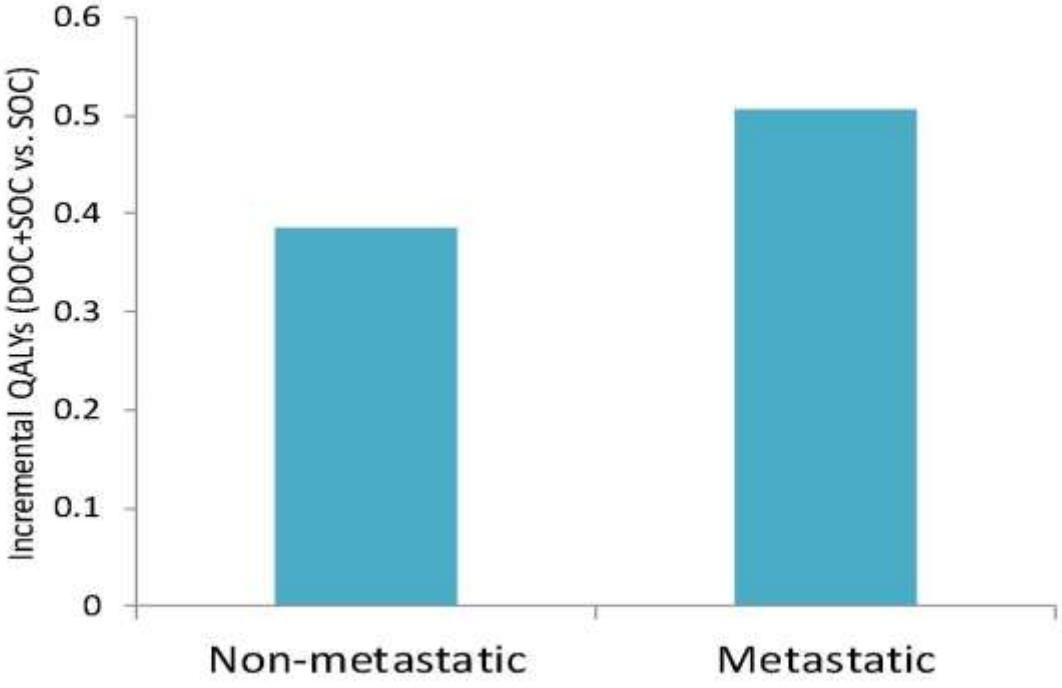
HR (95%CI) 0.78 (0.66, 0.93)
P-value 0.006

Non-PH p-value 0.87

Mets status	OS events	No. pts	Haz. Ratio (95% CI)
M0	93	689	1.01 (0.65, 1.56)
M1	477	1087	0.73 (0.59, 0.89)
Overall	570	1776	0.76 (0.63, 0.91)



Impact of docetaxel on Quality Adjusted Life Years (QALYs)



SOC Standard of care
DOC Docetaxel

>0 favours Docetaxel

UCL THE UNIVERSITY of York CHE MRC

Addition of docetaxel to first-line long-term hormone therapy in prostate cancer (STAMPEDE): long-term survival, quality-adjusted survival and cost-effectiveness analysis

Nicholas James
on behalf of
Beth Woods, Eleftherios Sideris, Matthew Sydes,
Melissa Spears, Mark Sculpher and the STAMPEDE Investigators

University Hospitals Birmingham NHS
UNIVERSITY OF BIRMINGHAM

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

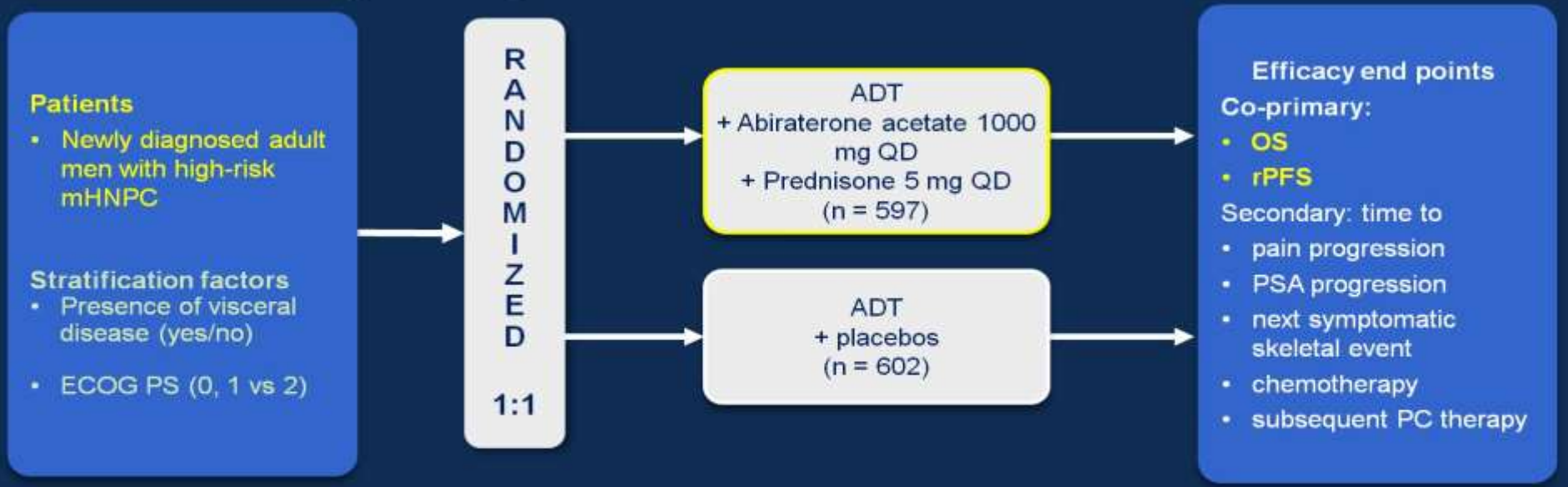
Objective

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

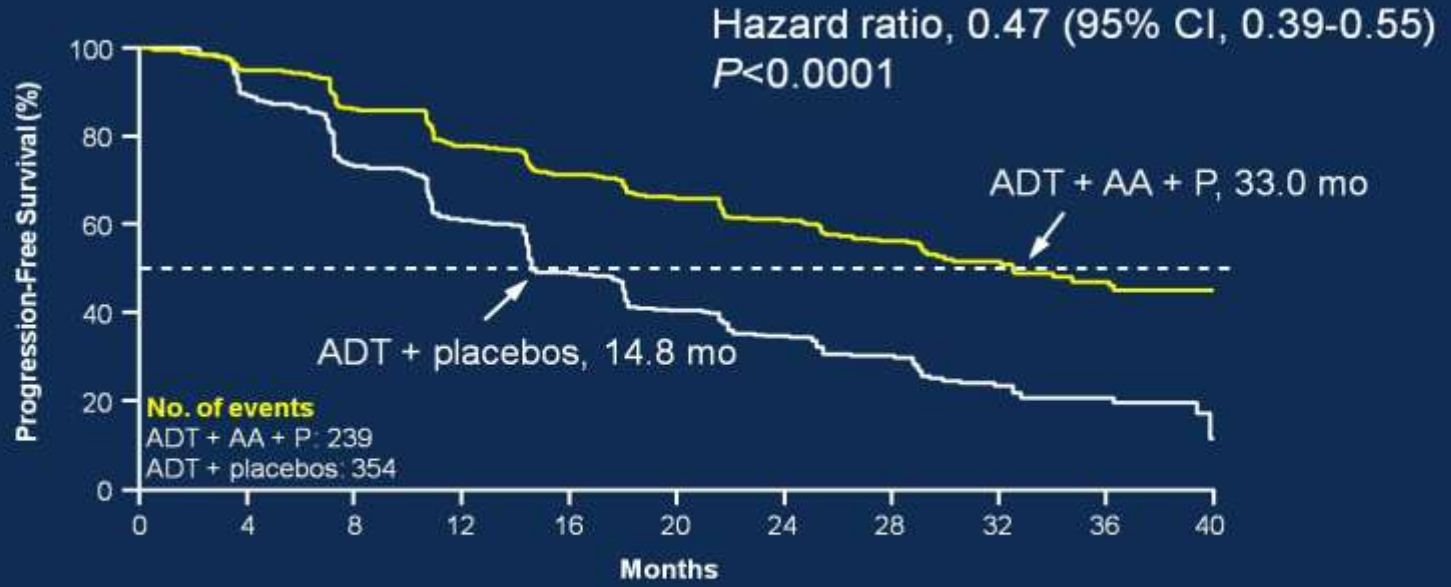
Overall study design of LATITUDE



- 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

Presented By Karim Fizazi at 2017 ASCO Annual Meeting

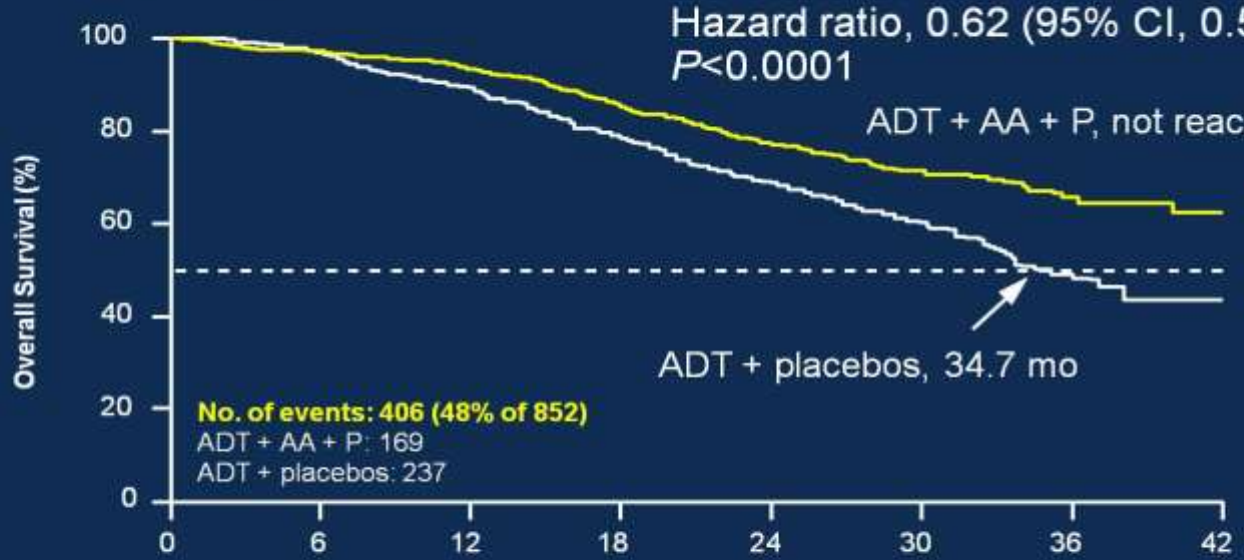
Statistically significant 53% risk reduction of radiographic progression or death



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

Presented By Karim Fizazi at 2017 ASCO Annual Meeting

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

Presented By Karim Fizazi at 2017 ASCO Annual Meeting

Summary of adverse events

	ADT + AA + P (n = 597)	ADT + placebos (n = 602)
Adverse Events (AE)	n (%)	n (%)
Any AE	558 (93)	557 (93)
Grade 3 or 4 AE	374 (63)	287 (48)
Any Serious AE	165 (28)	146 (24)
Any AE leading to treatment discontinuation	73 (12)	61 (10)
AE leading to death	28 (5)	24 (4)

MRC Clinical Trials Unit

Smarter studies
Global impact
Better health

UNIVERSITY OF BIRMINGHAM

CANCER RESEARCH UK

UCL

Adding abiraterone for men with high-risk prostate cancer starting long-term androgen deprivation therapy: Survival results from STAMPEDE

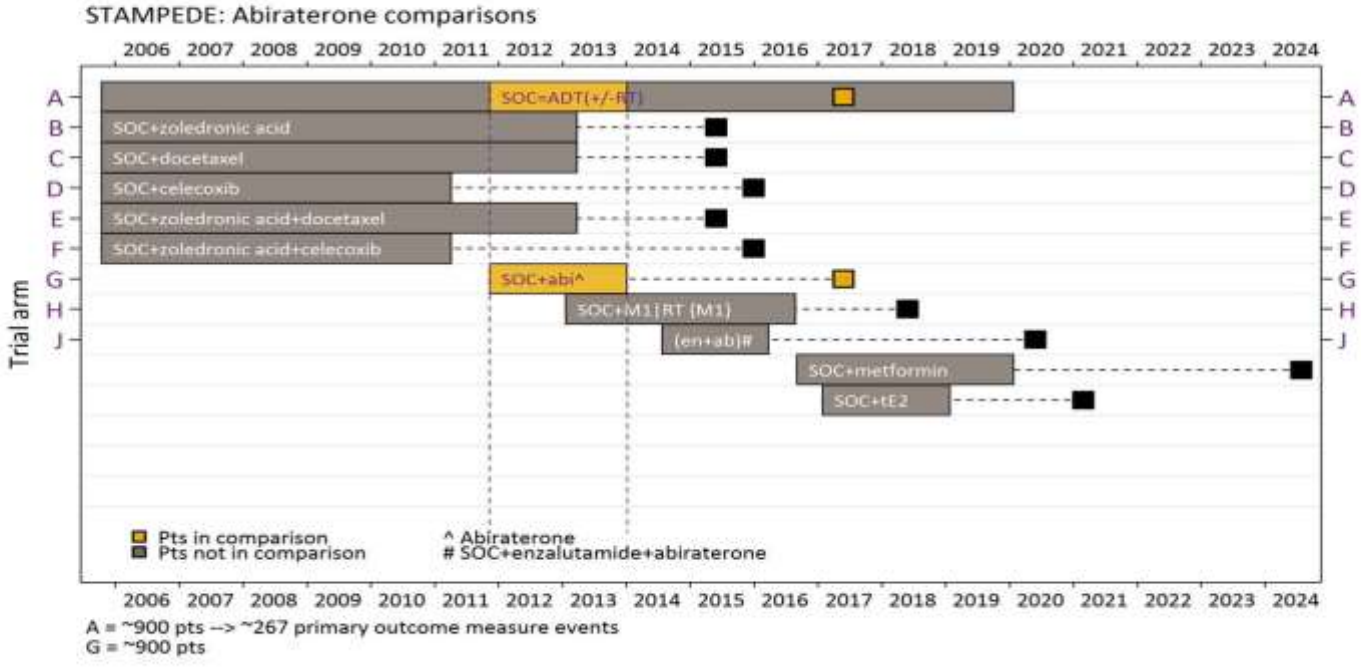
Nicholas James
University of Birmingham and Queen Elizabeth Hospital Birmingham
on behalf of

Johann De Bono, Melissa R Spears, Noel W Clarke, Malcolm D Mason, David P Dearnaley, Alastair WS Ritchie, J Martin Russell, Clare Gilson, Rob Jones, Silke Gillessen, David Matheson, San Aung, Alison Birtle, Simon Chowdhury, Joanna Gale, Zafar Malik, Joe O'Sullivan, Anjali Zarkar, Mahesh KB Parmar, Matthew R Sydes and the STAMPEDE Investigators

PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17

Presented By Nicholas James at 2017 ASCO Annual Meeting

Abiraterone comparison: patients



Inclusion criteria

Newly-diagnosed

Any of:

- Metastatic
- Node-Positive
- ≥2 of: Stage T3/4
  PSA≥40ng/ml
  Gleason 8-10

Relapsing after previous RP or RT with ≥1 of:

- PSA ≥4ng/ml and rising with doubling time <6m
- PSA ≥20ng/ml
- Node-positive
- Metastatic

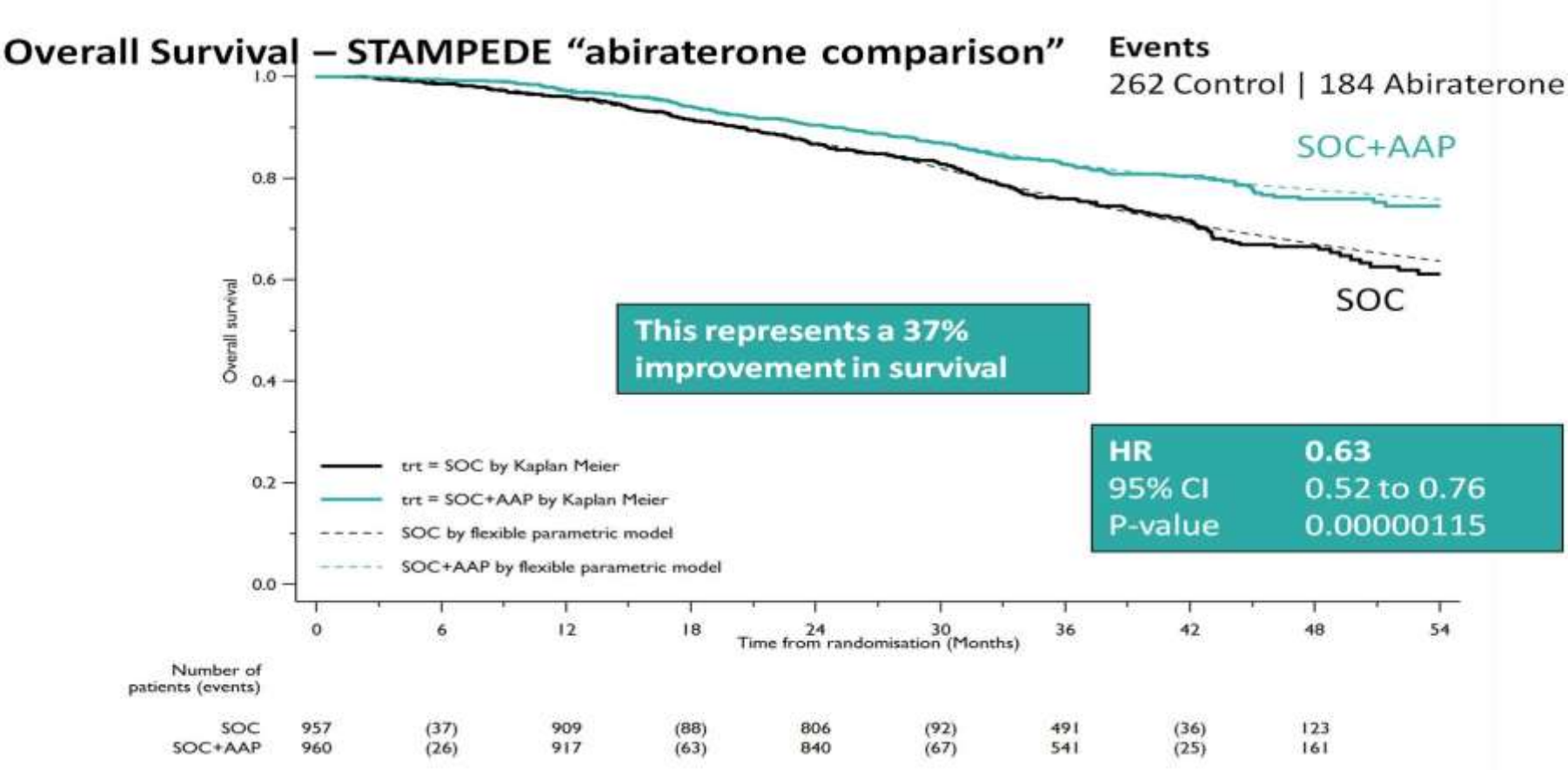
All patients

- Fit for all protocol treatment
- Fit for follow-up
- WHO performance status 0-2
- Written informed consent

Full criteria

www.stampedetrial.org

Overall Survival – STAMPEDE "abiraterone comparison"



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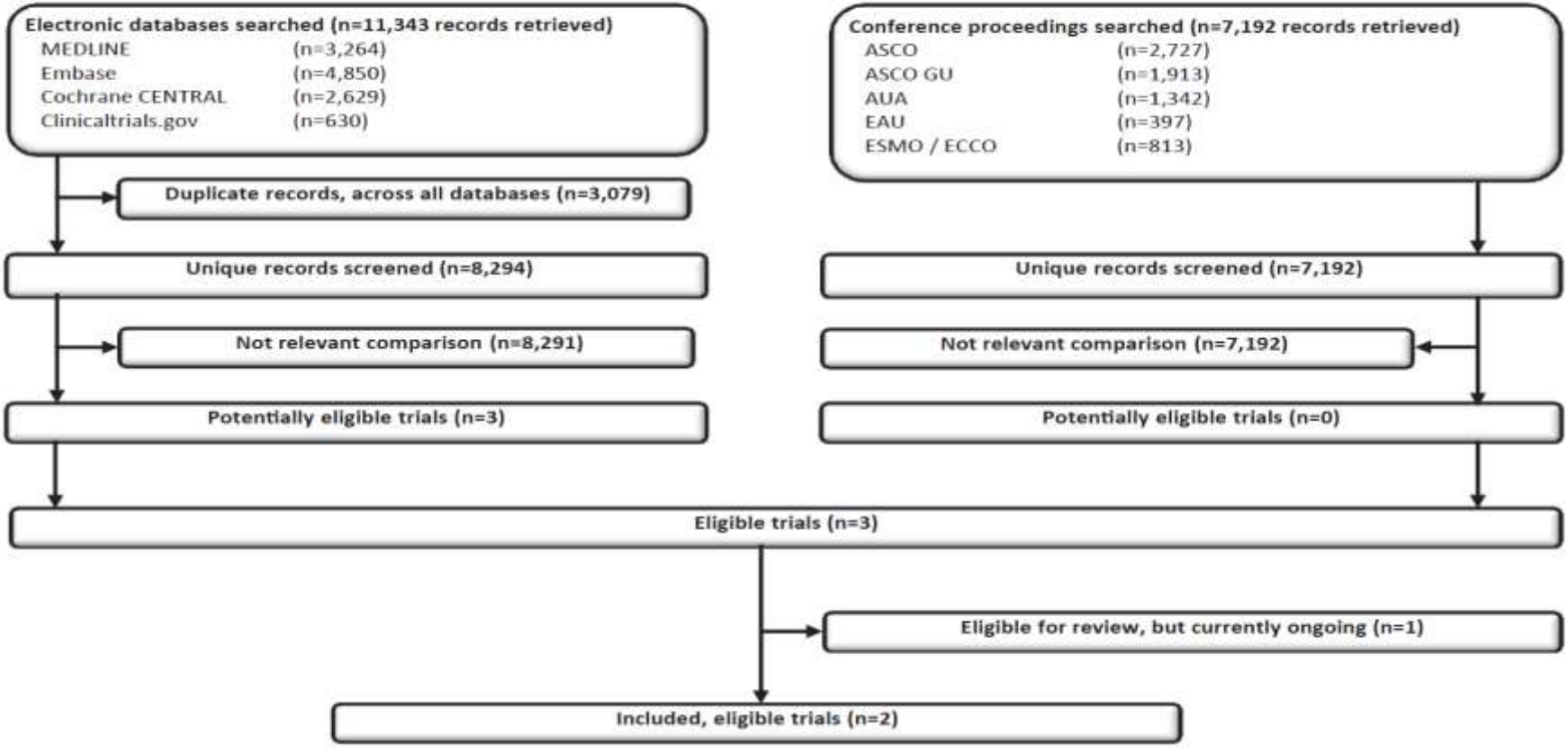
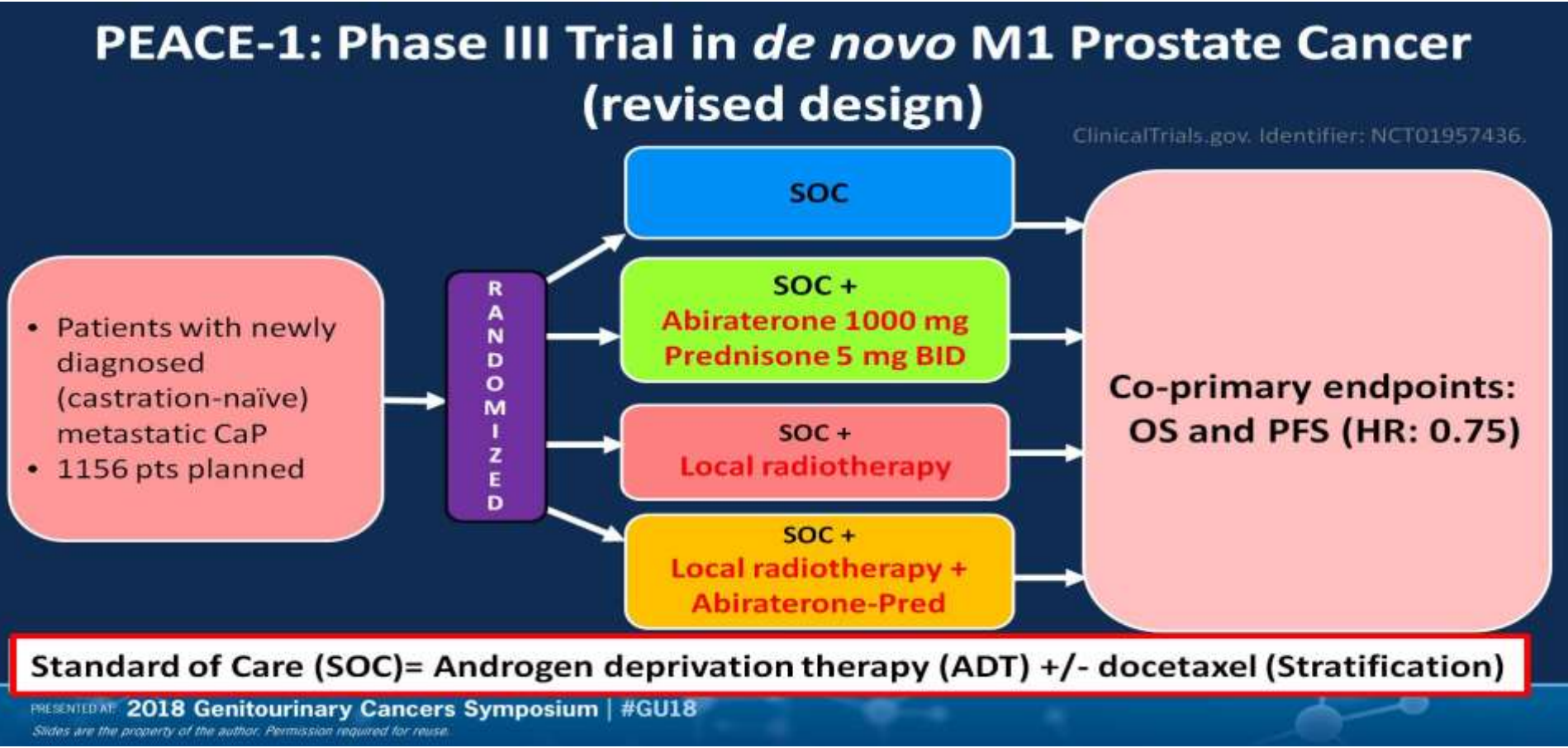
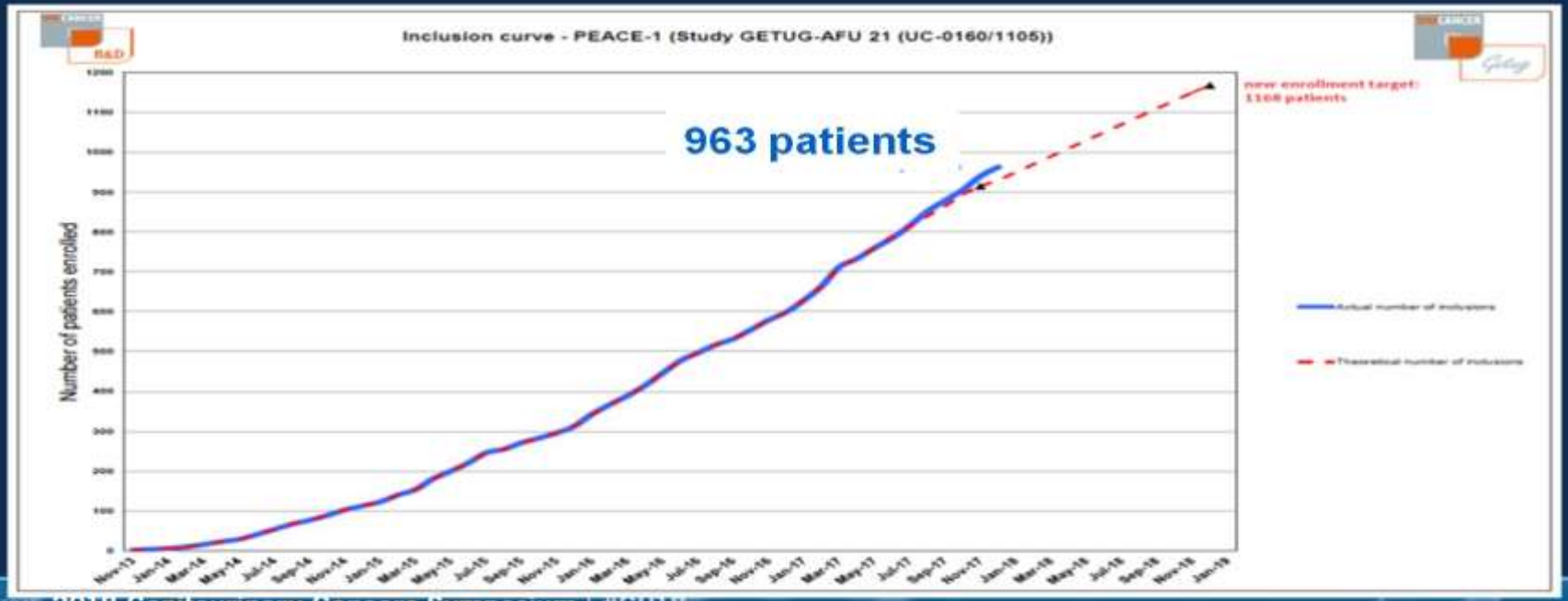


Fig. 1. **PRISMA flow diagram of trial identification, screening, eligibility and inclusion**. ASCO, American Society of Clinical Oncology; AUA, American Urological Association; EAU, European Association of Urology; ECCO, European Cancer Organisation; ESMO, European Society for Medical Oncology; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.



Presented By Nicholas Van As at 2018 Genitourinary Cancers Symposium: Translating Evidence to Multidisciplinary Care

Current accrual in PEACE-1



Presented By Nicholas Van As at 2018 Genitourinary Cancers Symposium: Translating Evidence to Multidisciplinary Care

Cost of early docetaxel vs abiraterone

- If you had to manage your pharmacy budget for GU Oncology for 100 mCSPC pts

- Upfront Docetaxel 6 cycles: visits + infusion + cost of drug: **$10,000 per pt**
  - Plus add-on abiraterone for rising PSA for CRPC at $8,000 per month in USA
  - Median time to progression for CRPC: 18 months = **Abiraterone $144,000 per pt**
  - **~$150,000 per pt and ~$15 million to Rx 100 patients**

- Upfront abiraterone median time to progression: ~ 36 months
  - [$8K x 36 months x 100 pts] + [$10K x 100 docet CRPC] = **~$30 million to Rx 100 pts**