Review of the Stampede Results

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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*

ABSTRACT

BACKGROUND

Abiraterone acetate plus prednisolone improves survival in men with relapsed prostate cancer. We assessed the effect of this combination in men starting long-term androgen-deprivation therapy (ADT), using a multigroup, multistage trial design.

METHODS

We randomly assigned patients in a 1:1 ratio to receive ADT alone or ADT plus abiraterone acetate (1000 mg daily) and prednisolone (5 mg daily) (combination therapy). Local radiotherapy was mandated for patients with node-negative, nonmetastatic disease and encouraged for those with positive nodes. For patients with nonmetastatic disease with no radiotherapy planned and for patients with metastatic disease, treatment continued until radiologic, clinical, or prostate-specific antigen (PSA) progression; otherwise, treatment was to continue for 2 years or until any type of progression, whichever came first. The primary outcome measure was overall survival. The

Setting and hypothesis

- Setting
  - Hormone therapy the mainstay of treatment since 1940s
  - Addition of radiotherapy to N0M0 disease improves outcomes
  - Recruitment prior to inclusion of docetaxel as part of standard care

- Hypothesis
  - Early use of therapies may give a larger absolute benefit in overall survival

Treatment Duration

- Treatment planned was Abi 1000 with Pred 5 daily
  - Two years for those getting RT
  - Until progression for those with metastatic diease/not getting RT

Attard G, et al J Clin Oncol. 2008;26(28):4563-71. de Bono JS, et al NEJM 2011;364(21):1995-2005. Ryan CJ, et al, NEJM. 2013;368(2): 138-48.

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

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

Multi-arm multi-stage (MAMS) design

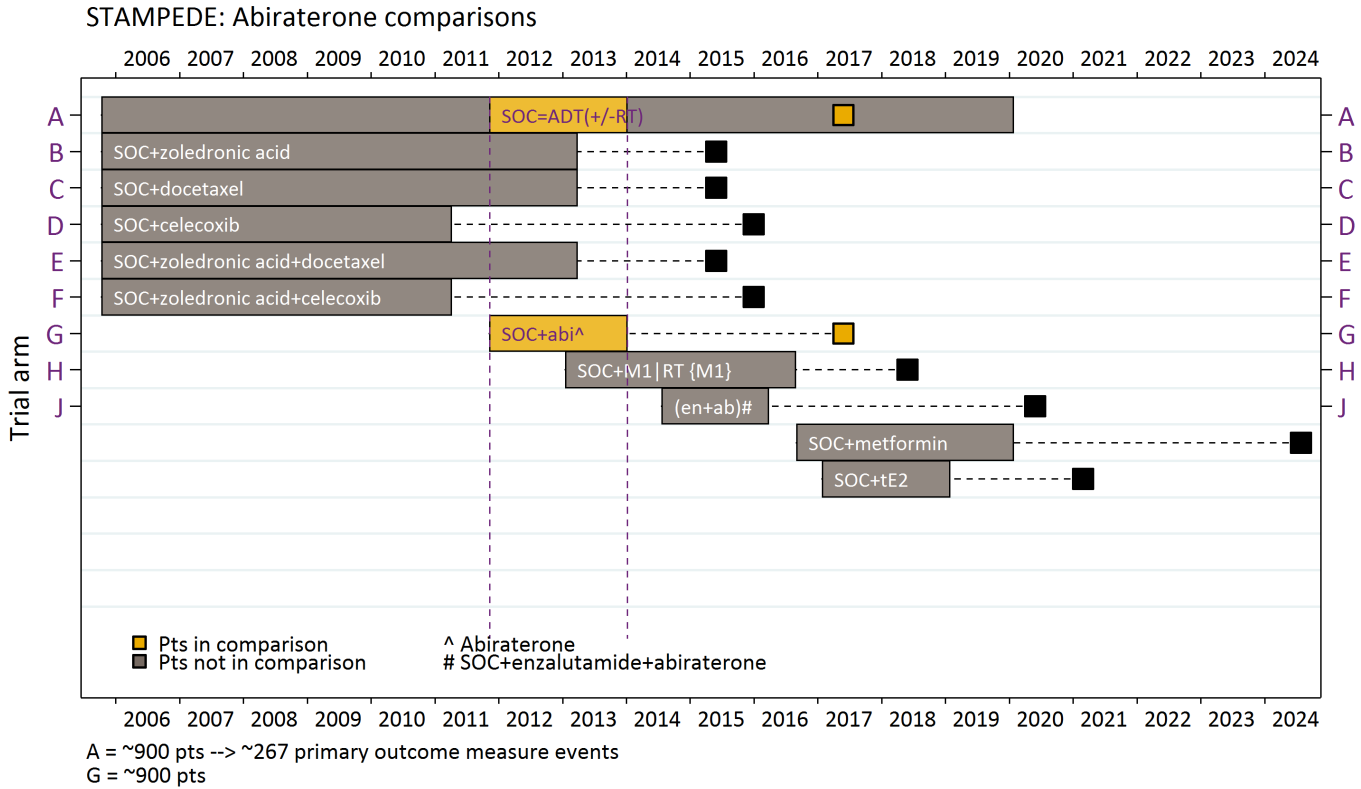
For the “abiraterone comparison”

- Allocation ratio of 1 control to 1 research
- Target 25% relative improvement in overall survival
  - HR=0.75
- Interim analysis
  - 3 lack-of-benefit analyses on failure-free survival
- Main analysis on primary outcome measure

→ Requires **~267** control arm deaths

- Power and alpha 90% and 0.025, 1-sided

Abiraterone comparison: patients



A = ~900 pts --> ~267 primary outcome measure events
G = ~900 pts

Accrual

Comparison

Open: Nov-2011

Closed: Jan-2014

Accrual: 1917

Number of patients

957 **A** Standard-of-care* (SOC)

960 **G** SOC + abiraterone acetate + prednisolone (SOC+AAP)

*SOC = ADT ± RT

Patient characteristics

1%	WHO PS 2	[s]
21%	WHO PS 1	[s]
67yr	Median age (min 39, max 85)	[s]
52%	Metastatic (88% Bony mets)	[s]
20%	N+M0	
28%	N0M0	
99%	LHRH analogues	[s]
41%	Planned for RT (96% of N0M0 pts; 62% of N+M0 pts)	[s]
5%	Previous local therapy	

Balanced by arm

Table 1. Characteristics of the Patients.*

Characteristic	ADT Alone (N=957)	Combination Therapy (N=960)
Age at randomization — yr		
Median (IQR)	67 (62 to 72)	67 (63 to 72)
Range	39 to 84	42 to 85
PSA level before ADT — ng/ml		
Median (IQR)	56 (19 to 165)	51 (19 to 158)
Range	0 to 10,530	0 to 21,460
WHO performance status — no. (%)†		
0	744 (78)	745 (78)
1 or 2	213 (22)	215 (22)
Disease group — no. (%)		
Newly diagnosed node-negative, nonmetastatic disease	256 (27)	253 (26)
Newly diagnosed node-positive, nonmetastatic disease	187 (20)	182 (19)
Newly diagnosed metastatic disease	476 (50)	465 (48)
Previously treated nonmetastatic disease	12 (1)	25 (3)
Previously treated metastatic disease	26 (3)	35 (4)
Gleason score — no. (%)‡		
≤7	223 (23)	221 (23)
8 to 10	721 (75)	715 (74)
Unknown	13 (1)	24 (2)
Planned or current long-term ADT — no. (%)		
Orchiectomy	5 (1)	3 (<1)
Bicalutamide	5 (1)	5 (1)
Dual androgen blockade	4 (<1)	1 (<1)
LHRH-based§	943 (99)	951 (99)
Time to initiation of ADT from randomization — days¶		
Median (IQR)	−45 (−67 to −23)	−44 (−63 to −24)
Range	−85 to 39	−85 to 28
Planned antiandrogen use — no. (%)		
No	50 (5)	61 (6)
Short-term antiandrogen	902 (94)	895 (93)
Long-term antiandrogen	5 (1)	4 (<1)
Radiotherapy planned — no. (%)‖		
No	561 (59)	564 (59)
Yes	396 (41)	396 (41)
Hypertension — no. (%)		
No	571 (60)	557 (58)
Yes, but still fit for trial	385 (40)	401 (42)

Primary Outcomes

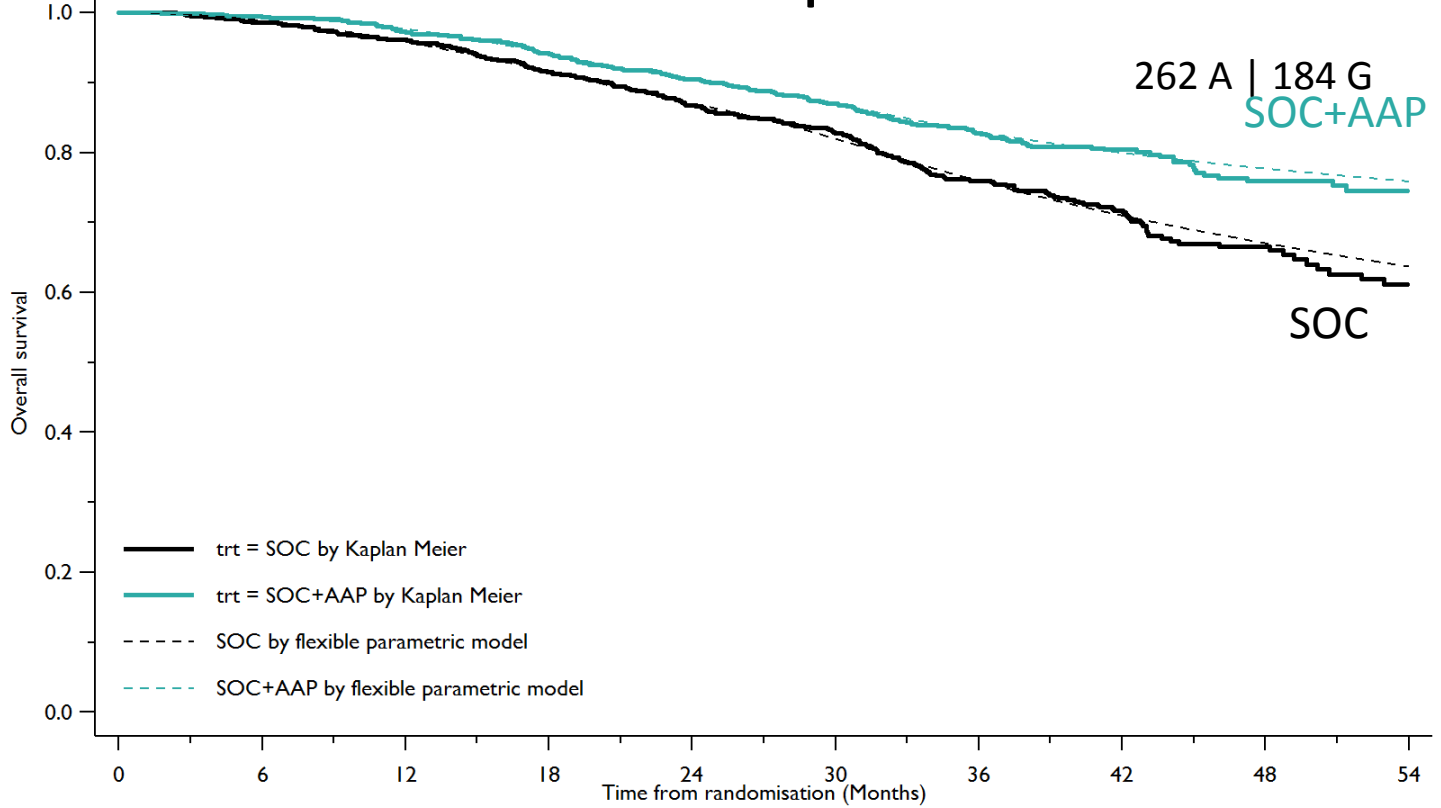
Definitive primary outcome = Overall Survival

Efficacy Stage Analysis:

– triggered by 267 control arm deaths

– observed 262 (98%) control arm deaths 10-Feb-2017

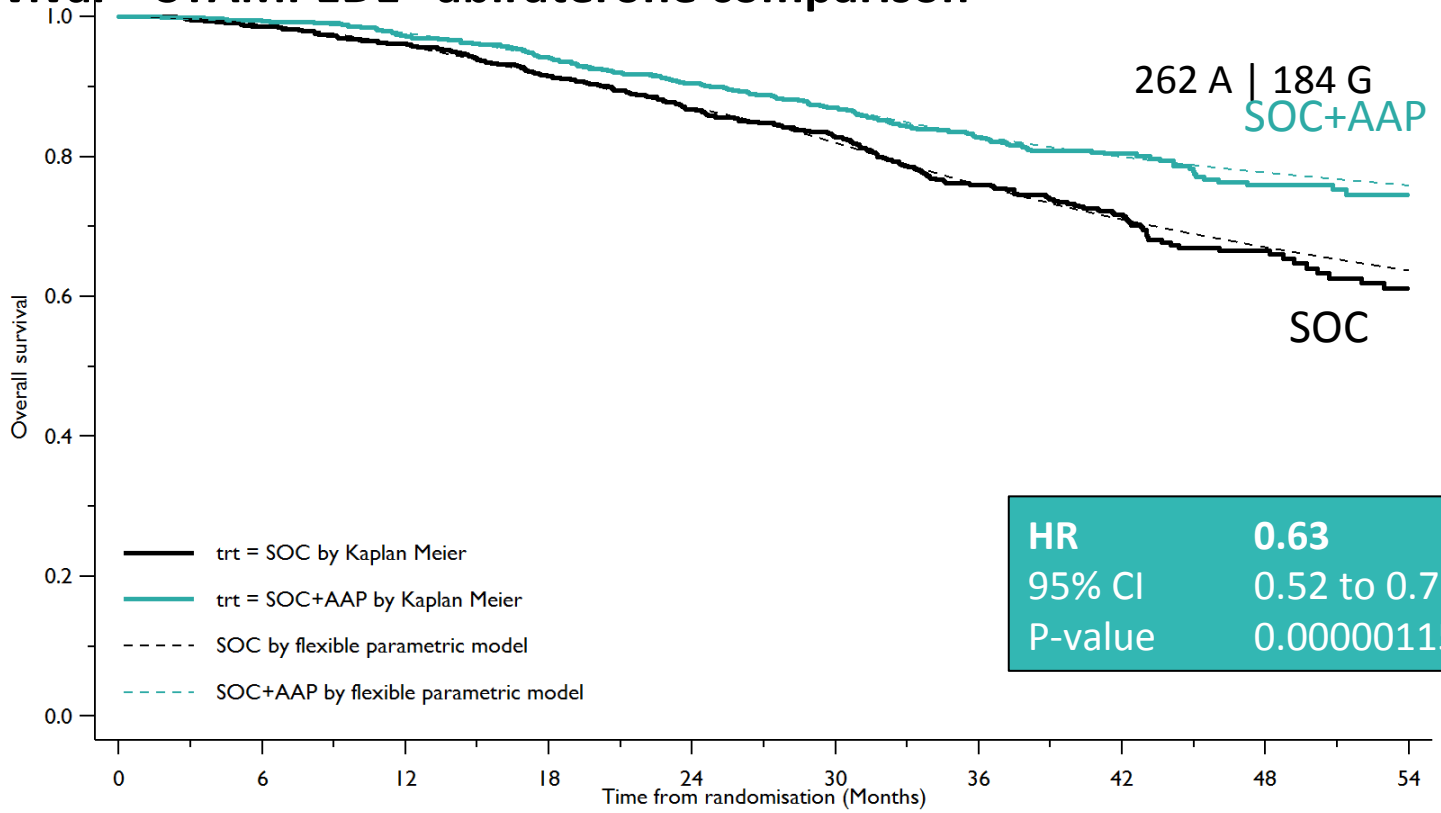
Overall Survival – STAMPEDE "abiraterone comparison"



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

Overall Survival – STAMPEDE "abiraterone comparison"



HR	**0.63**
95% CI	0.52 to 0.76
P-value	0.00000115

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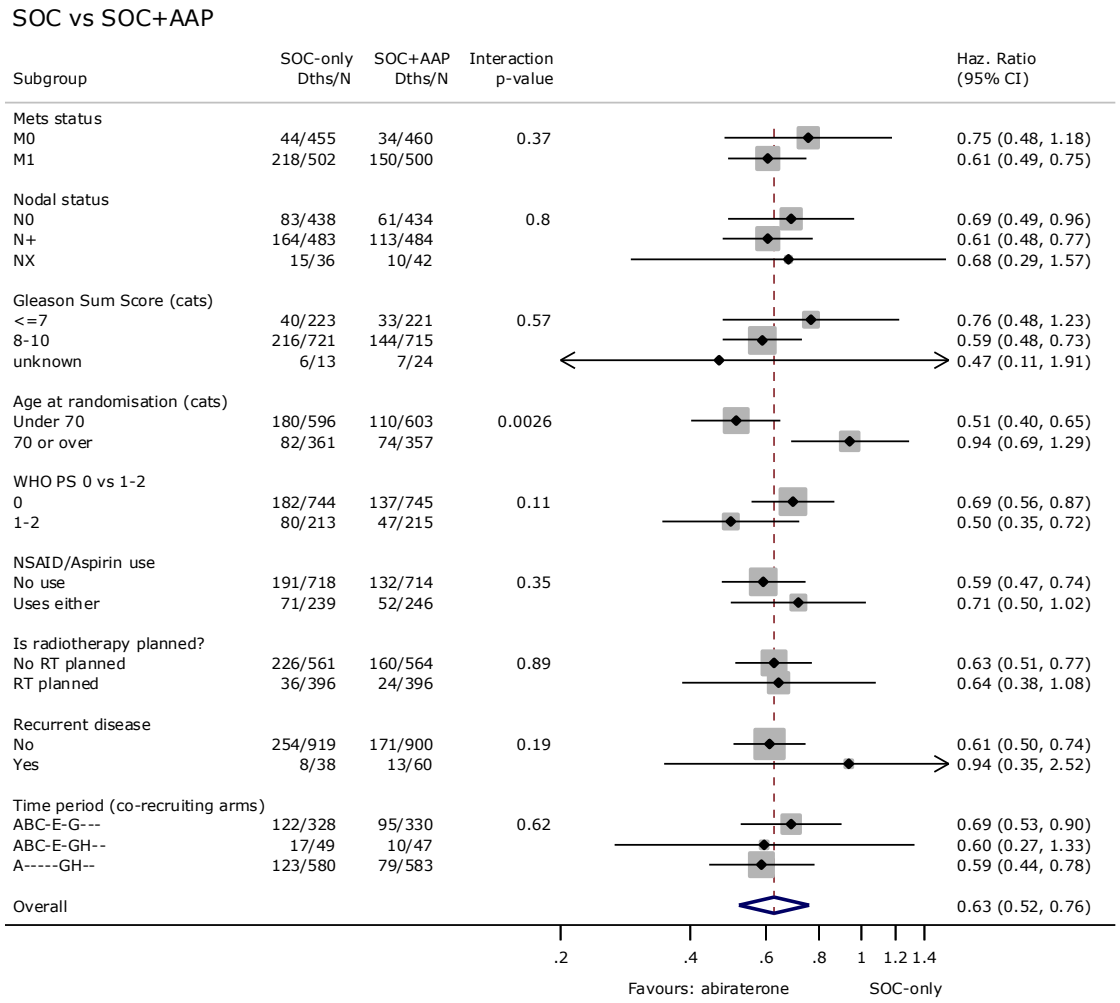
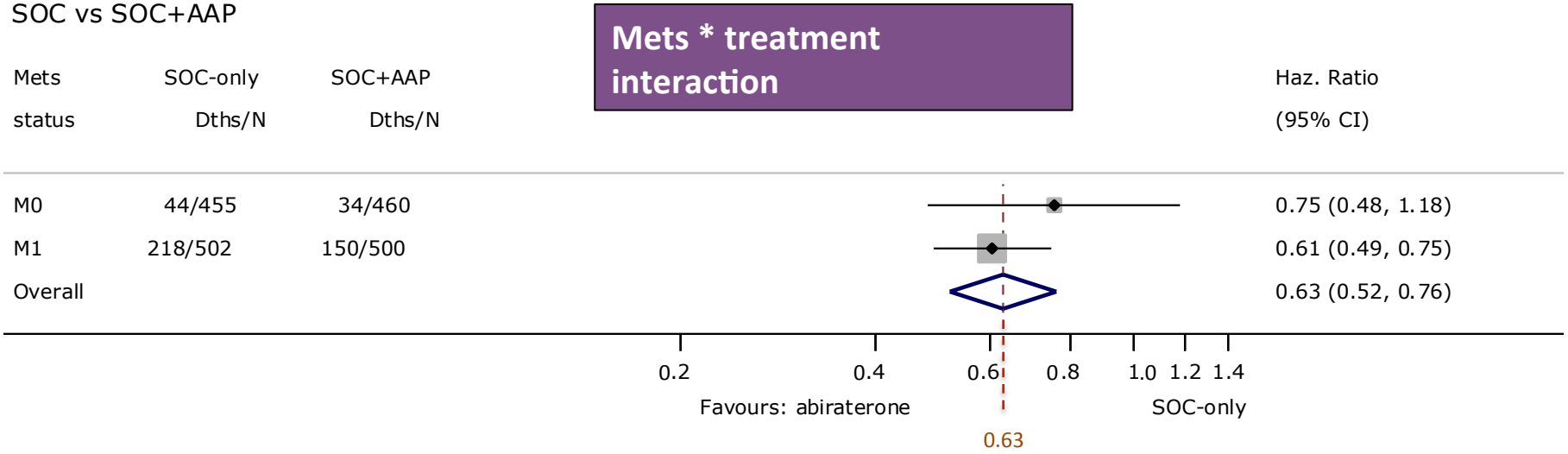


No good evidence of heterogeneity by stratification factors

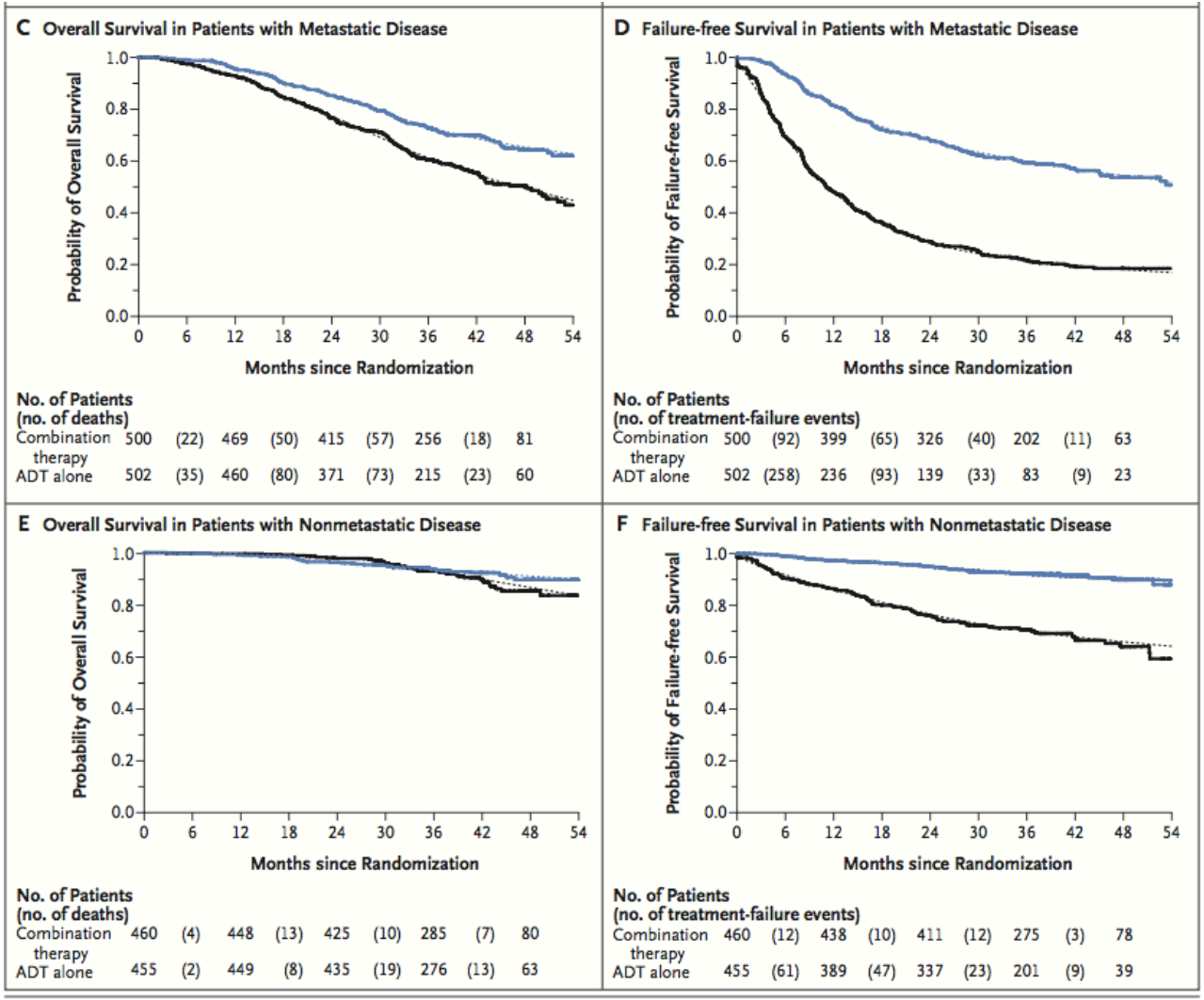
STAMPEDE “abiraterone comparison”
Overall Survival by metastatic status – pre-planned analysis



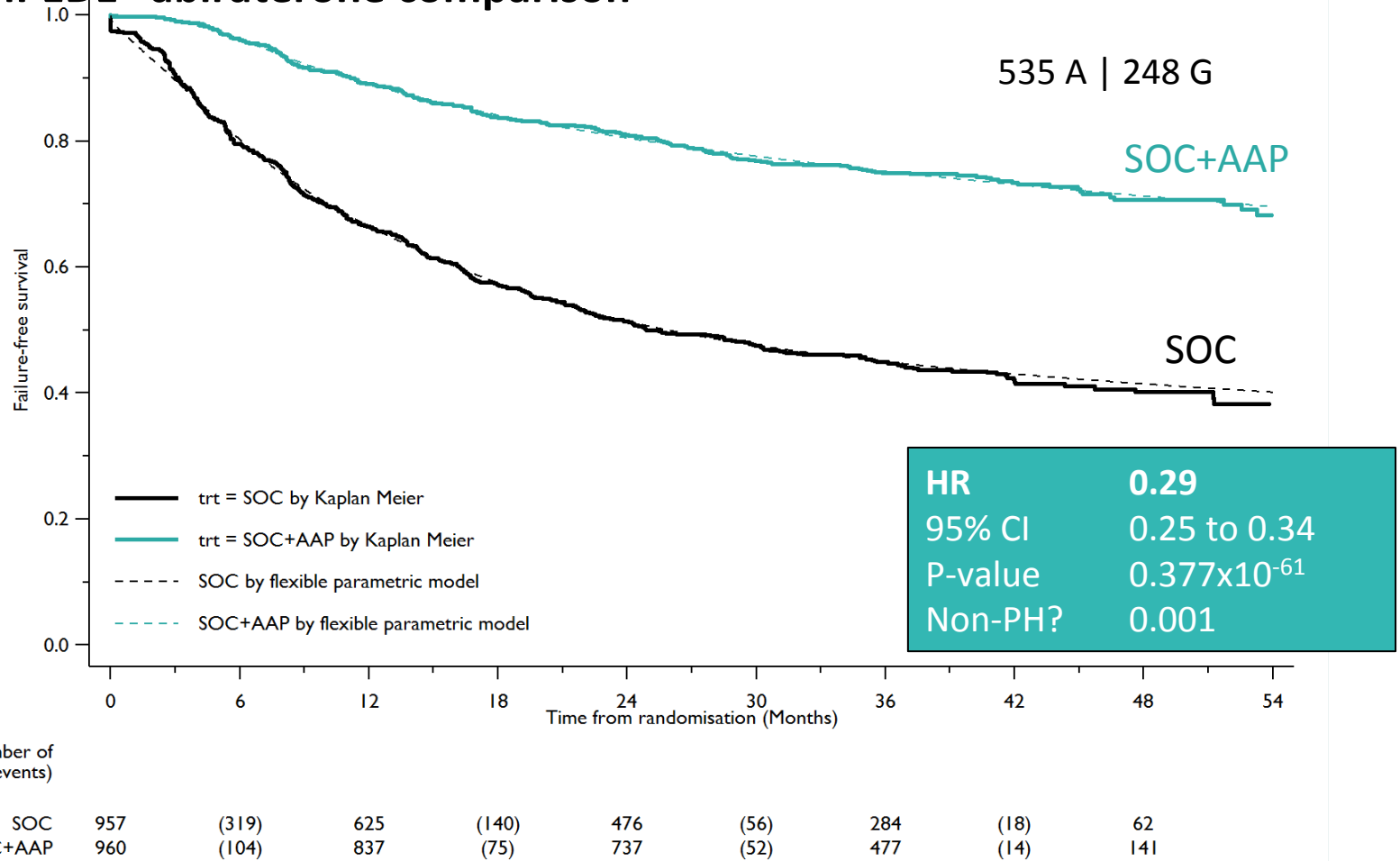
Metastatic

Vs

Non-metastatic disease



FFS – STAMPEDE “abiraterone comparison”



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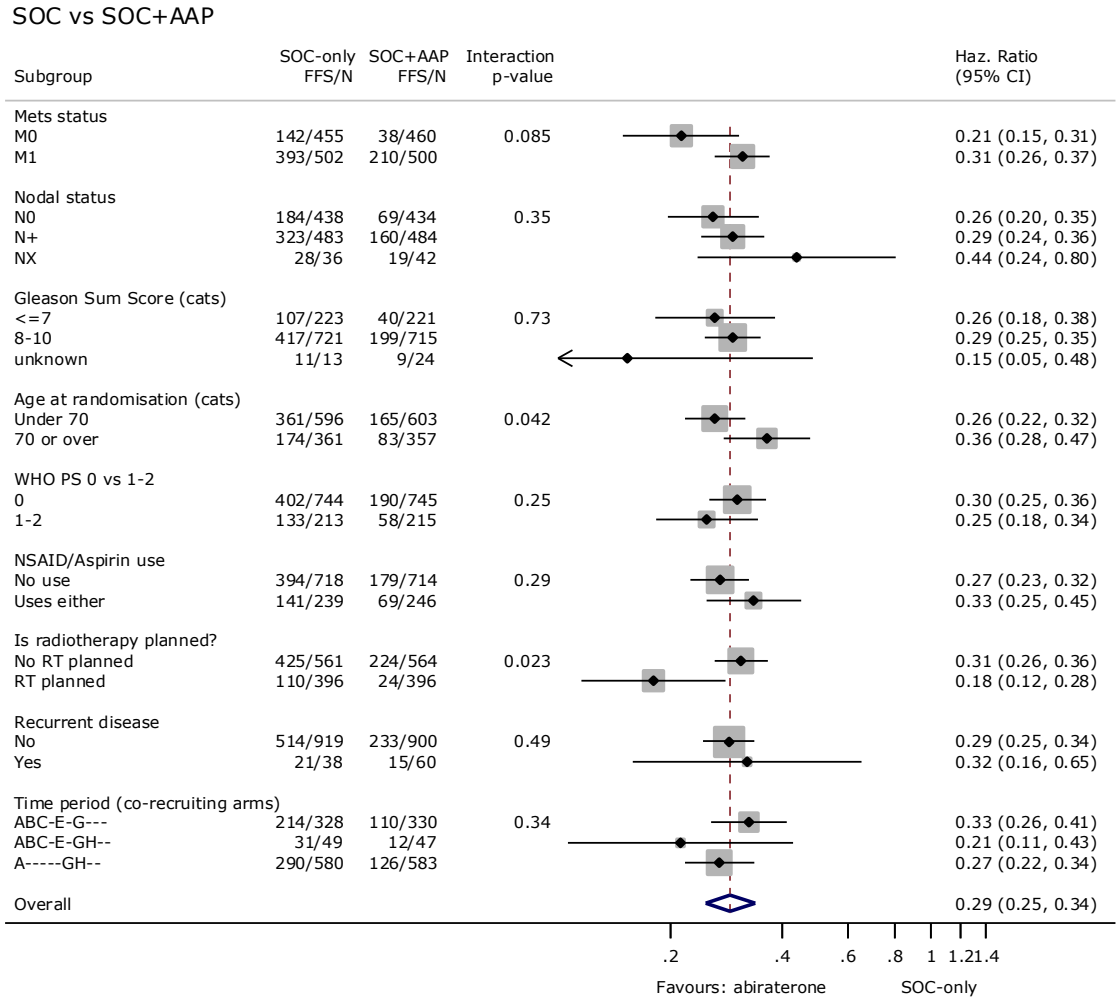

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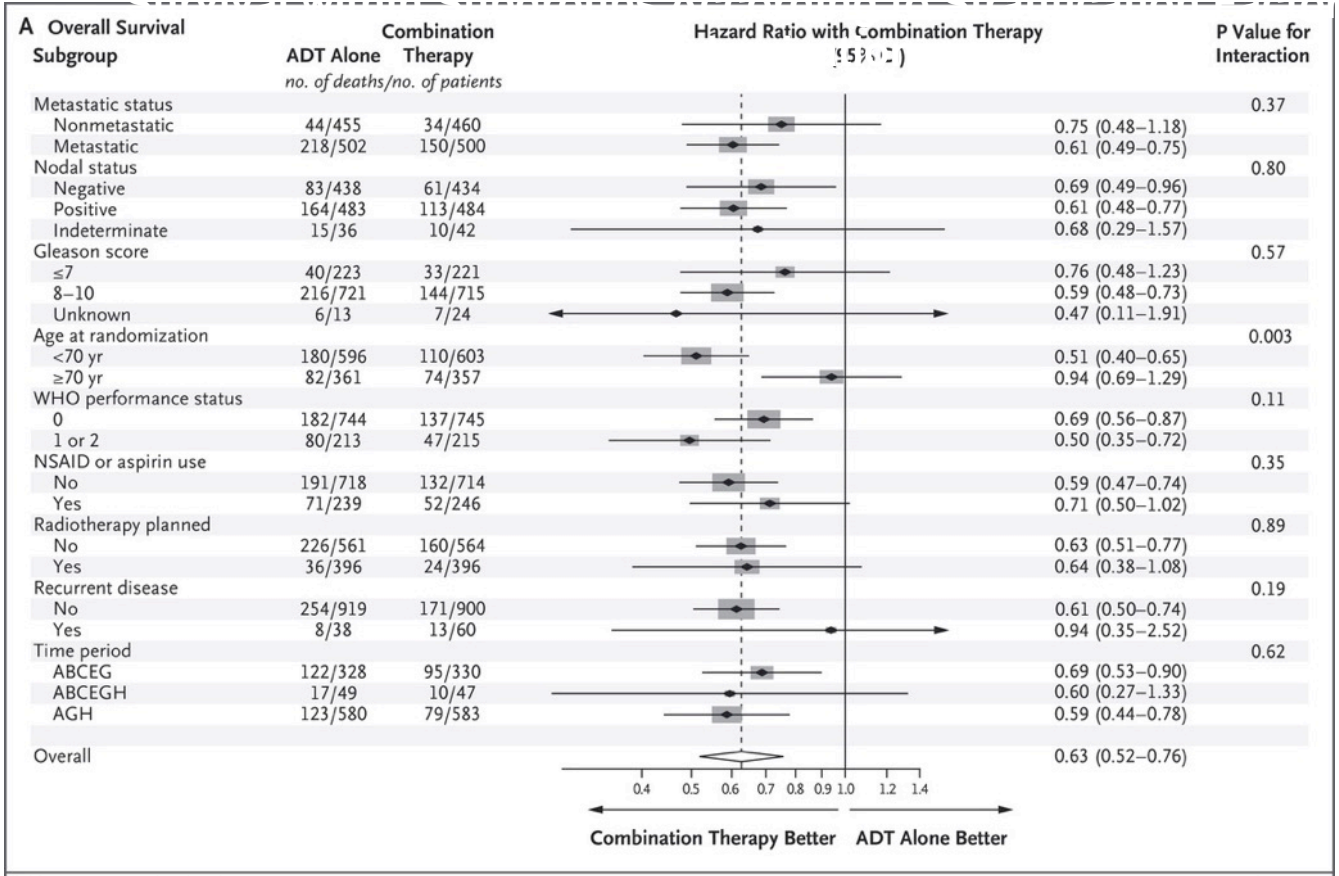
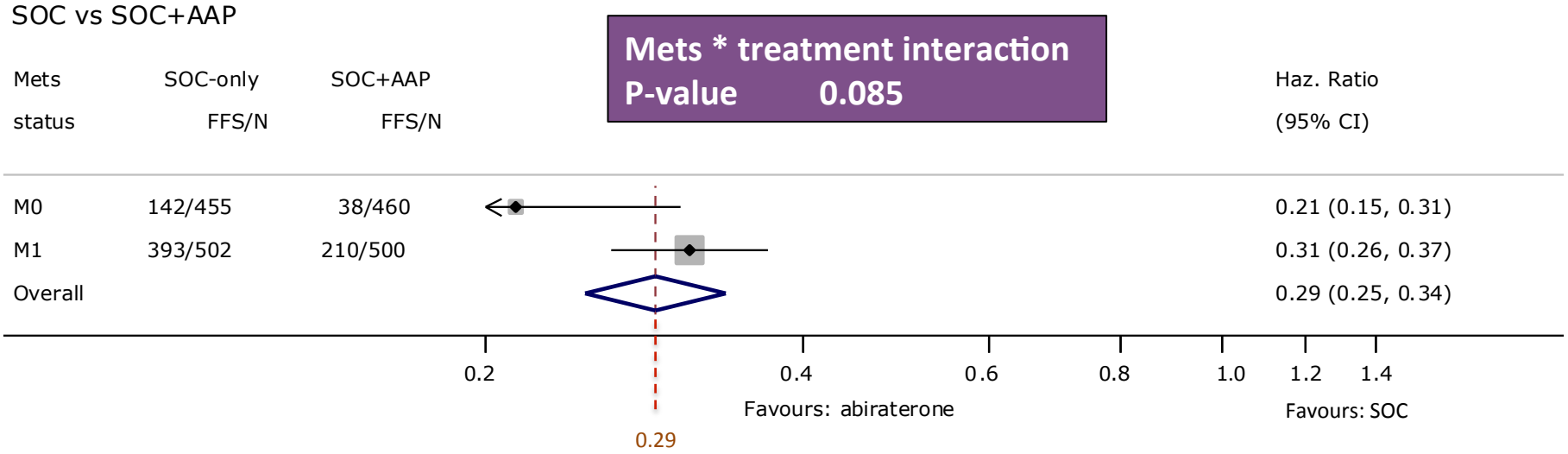

A Overall Survival
Subgroup
ADT Alone
Combination Therapy
no. of deaths/no. of patients
Hazard Ratio with Combination Therapy
P Value for Interaction
Metastatic status 0.37
Nonmetastatic 44/455 34/460 0.75 (0.48–1.18)
Metastatic 218/502 150/500 0.61 (0.49–0.75)
Nodal status 0.80
Negative 83/438 61/434 0.69 (0.49–0.96)
Positive 164/483 113/484 0.61 (0.48–0.77)
Indeterminate 15/36 10/42 0.68 (0.29–1.57)
Gleason score 0.57
≤7 40/223 33/221 0.76 (0.48–1.23)
8–10 216/721 144/715 0.59 (0.48–0.73)
Unknown 6/13 7/24 0.47 (0.11–1.91)
Age at randomization 0.003
<70 yr 180/596 110/603 0.51 (0.40–0.65)
≥70 yr 82/361 74/357 0.94 (0.69–1.29)
WHO performance status 0.11
0 182/744 137/745 0.69 (0.56–0.87)
1 or 2 80/213 47/215 0.50 (0.35–0.72)
NSAID or aspirin use 0.35
No 191/718 132/714 0.59 (0.47–0.74)
Yes 71/239 52/246 0.71 (0.50–1.02)
Radiotherapy planned 0.89
No 226/561 160/564 0.63 (0.51–0.77)
Yes 36/396 24/396 0.64 (0.38–1.08)
Recurrent disease 0.19
No 254/919 171/900 0.61 (0.50–0.74)
Yes 8/38 13/60 0.94 (0.35–2.52)
Time period 0.62
ABCEG 122/328 95/330 0.69 (0.53–0.90)
ABCEGH 17/49 10/47 0.60 (0.27–1.33)
AGH 123/580 79/583 0.59 (0.44–0.78)
Overall 0.63 (0.52–0.76)
0.4 0.5 0.6 0.7 0.8 0.9 1.0 1.2 1.4
Combination Therapy Better
ADT Alone Better
B Failure-free Survival
Subgroup
ADT Alone
Combination Therapy
no. of treatment-failure events/no. of patients
Hazard Ratio with Combination Therapy (95% CI)
P Value for Interaction
Metastatic status 0.08
Nonmetastatic 142/455 38/460 0.21 (0.15–0.31)

STAMPEDE “abiraterone comparison”
FFS by metastatic status – pre-planned analysis



	SOC-only	SOC+AAP
Safety population		
Patients included in adverse event analysis	960	948
Grade 1-5 AE	950 (99%)	943 (99%)
Grade 3-5 AE	315 (33%)	443 (47%)
Grade 5 AE	3	9
Grade 3-5 AEs by category (*incl. expected AEs*)		
Endocrine disorder (*incl. hot flashes, impotence*)	133 (14%)	129 (14%)
Cardiovascular disorder (*incl. hypertension, MI, cardiac dysrhythmia*):	41 (4%)	92 (10%)
Musculoskeletal disorder:	46 (5%)	68 (7%)
Gastrointestinal disorder:	40 (4%)	49 (5%)
Hepatic disorder (*incl. increased AST, increased ALT*):	12 (1%)	70 (7%)
General disorder (*incl. fatigue, oedema*):	29 (3%)	45 (5%)
Respiratory disorder (*incl. breathlessness*):	23 (2%)	44 (5%)
Lab abnormalities (*incl. hypokalaemia*):	21 (2%)	34 (4%)

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Treatment compliance

Abiraterone

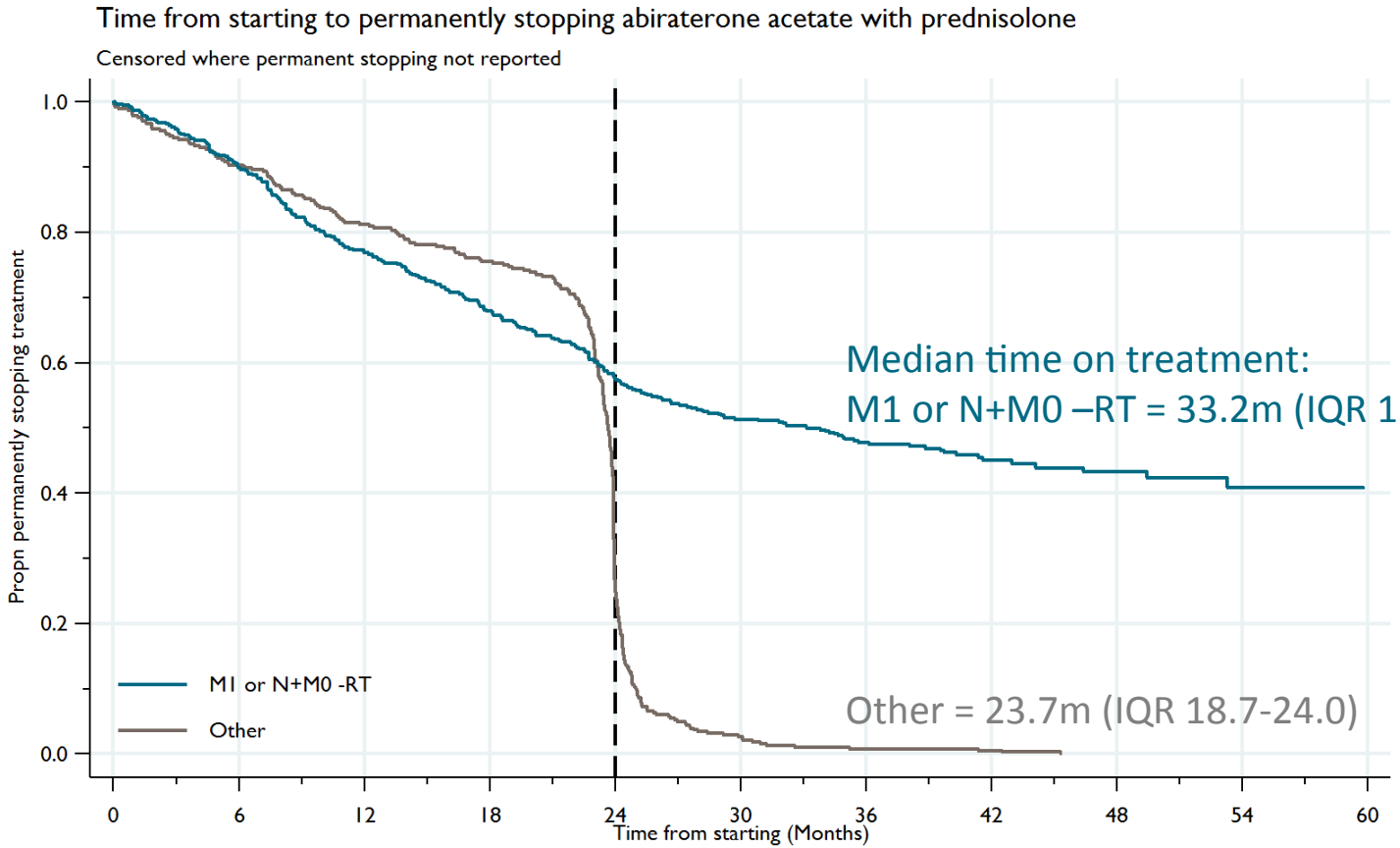
The administration of abiraterone is expected to be as follows:

- **1000mg *od*** abiraterone acetate
- prednisolone or prednisone 5mg od to prevent secondary ACTH excess.

Duration of treatment:

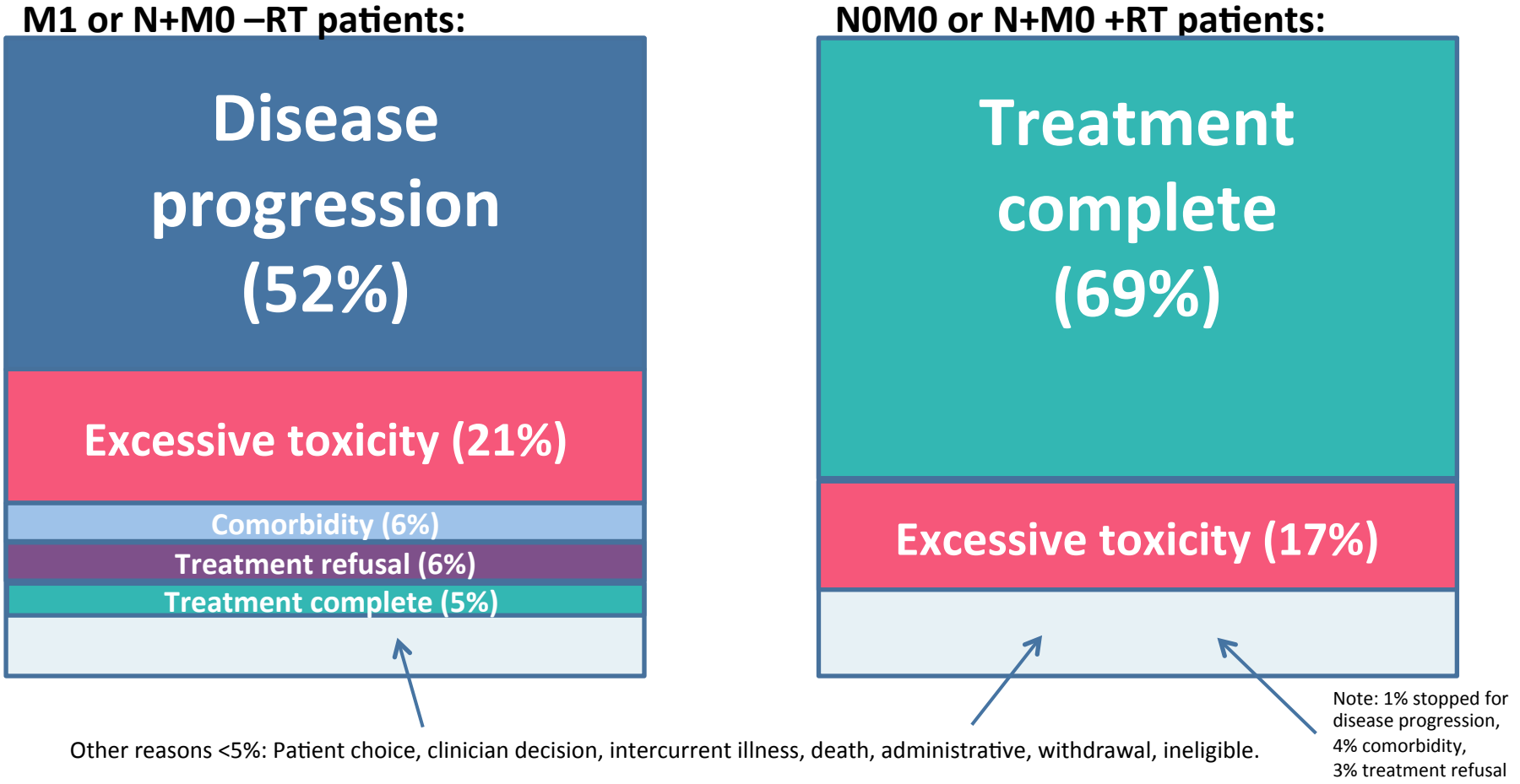
- Capped at 2 years for N0M0 pts and N+M0 pts receiving RT
- Permitted through 3 types of progression for M1 pts and N+M0 pts not receiving RT

Abiraterone duration by planned use



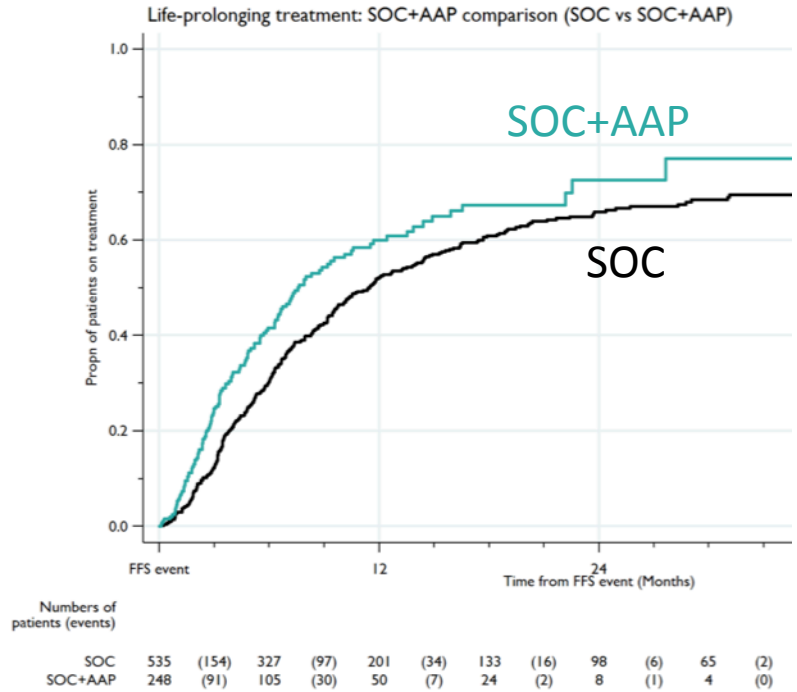
Number of patients (events)																				
M1 or N+M0 -RT	565	(57)	502	(72)	428	(50)	376	(57)	316	(34)	262	(17)	177	(8)	90	(3)	54	(2)	17	(0)	1
Other	384	(37)	347	(35)	312	(22)	290	(188)	102	(92)	10	(7)	3	(1)	2	(2)	0	(0)	0	(0)	0

Reasons for permanently stopping research abiraterone acetate + prednisolone



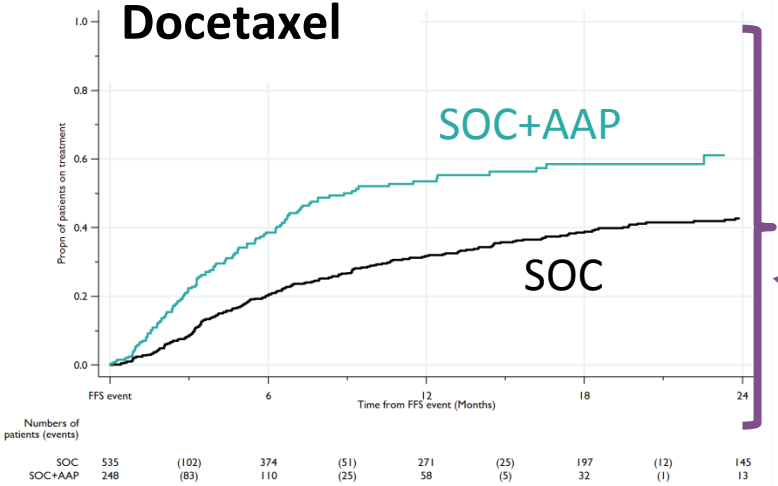
Any “life-prolonging” treatment for progression

Treatment started since first progression	A *SOC*	G *SOC+abi*
Patients randomised	957	960
Patients with progression	535 (56%)	248 (26%)
Reported new treatment	477 (89%)	196 (79%)
Reported “life-prolonging” treatment	310 (58%)	131 (53%)
Docetaxel	200 (37%)	115 (46%)
Enzalutamide	138 (26%)	25 (10%)
Abiraterone	120 (22%)	8 (3%)
Radium-223	24 (5%)	19 (8%)
Cabazitaxel	28 (5%)	15 (6%)

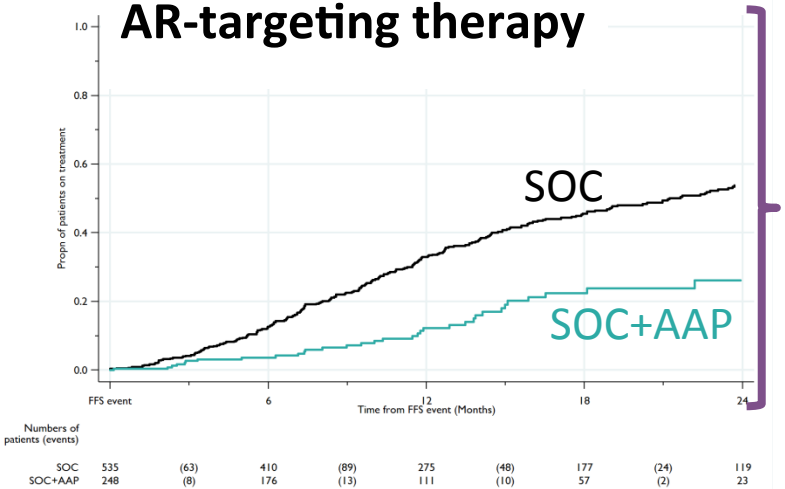


Graph timed from first FFS event

Docetaxel



AR-targeting therapy



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Graph timed from first FFS event

What Stampede Teaches us

- Broader spectrum of disease state than Latitude
  - M+, N+, Locally advanced all benefit over ADT
  - 40% of patients had AA with RT
  - Too early to justify AA/P use in Nonmetastatic disease without OS?

- Finite Duration of Rx (2 yrs) is informative
- Tolerability in early disease population
  - Approx 20% discontinue due to toxicity is not trivial

- Largest population to date with 5 mg prednisone.

What Stampede Doesn't Teach us

- Use in Serologic Relapse
- Duration of Rx in Metastatic disease
  - When is the benefit?
    - Year 1 – better initial disease control?
    - Year 2, 3 – prevent emergence of CRPC?
- What do we tell our patients about duration?
- ADT + Docetaxel → Abiraterone
  - Is resistance overlapping?