Abiraterone acetate plus prednisolone with or without enzalutamide added to androgen deprivation therapy compared to ADT alone for men with high-risk nonmetastatic prostate cancer: primary combined analysis from two comparisons in the STAMPEDE platform protocol

Gerhardt Attard, Louise Brown, Noel Clarke, Laura Murphy, William Cross, Rob Jones, Silke Gillessen, J.Martin Russell, Adrian Cook, Jo Bowen, Anna Lydon, Ian Pedley, Omi Parikh, Simon Chowdhury, Zafar Malik, David Matheson, Chris Parker, Matthew Sydes, Mahesh Parmar, Nicholas James **on behalf of the STAMPEDE investigators***

Conducted by Medical Research Council Trials Unit at University College London, U.K.

ClinicalTrials.gov number, NCT00268476 & Current Controlled Trials number, ISRCTN78818544

*113 U.K. and Swiss sites: list of investigators and collaborators at www.stampedetrial.org

www.stampedetrial.org

2021 ESMO congress

Disclosure slide

Principal investigator for trials sponsored by Janssen, Pfizer/Astellas, Novartis

Received:

- Consulting fees and travel support from Janssen, Astellas, Pfizer, Sanofi-Aventis, Bayer, Beigene, Essa and Novartis
- Speaker's fees from Janssen, Astellas, Astra Zeneca, Pfizer and Sanofi-Aventis
- Grant support from Janssen, AstraZeneca, Astellas

On the Institute of Cancer Research (ICR) rewards to discoverers' list of abiraterone

Trial funding

- U.K. MRC (now part of UKRI) provides core funding to the MRC CTU at UCL
- Cancer Research U.K. approved the trial design & subsequent amendments + provided funding support
- Janssen & Astellas Pharma provided grant funding, abiraterone acetate or enzalutamide respectively, and funds for drug distribution + approved the design for these comparisons & participated in discussions on progress

Background

- Majority of men who die from prostate ca in Europe & North America were M0 at diagnosis[1,2]
- High-risk M0 PCa: ADT (3 years) + local RT[3]
- Post-treatment failure rates remain high
- ICECaP: MFS is a valid surrogate of OS in M0 patients[4]

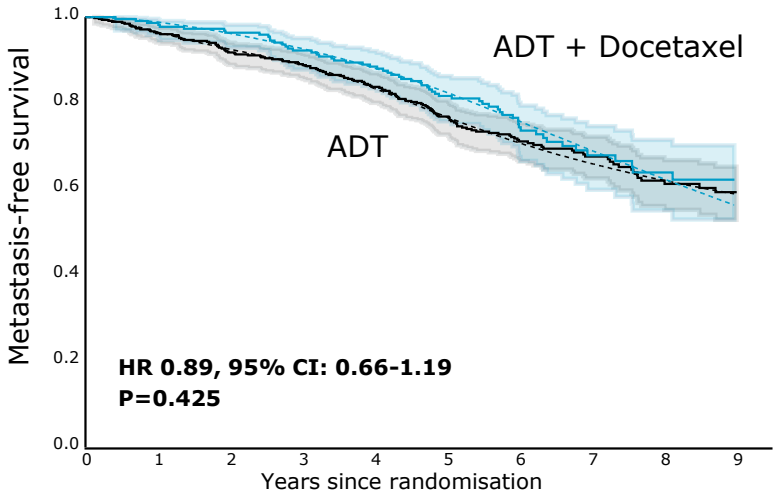
M0, nonmetastatic
ADT, orchiectomy or gonadotropin-releasing hormone [GnRH] agonists or antagonists; RT, radiation therapy
ICECaP, intermediate clinical end points for prostate cancer
MFS, metastasis free survival; OS, overall survival

1. Helgstrand et al. E J Canc 2017;84:18-26
2. Roy & Morgan. Clinical Oncology 2019;31:630-6
3. Bolla et al. N Engl J Med 1997;337:295-300
4. Xie et al. J Clin Oncol 2017;35:3097-104

Background: docetaxel

- Docetaxel improves survival in M1 PCa but **no improvement** in MFS/OS in M0

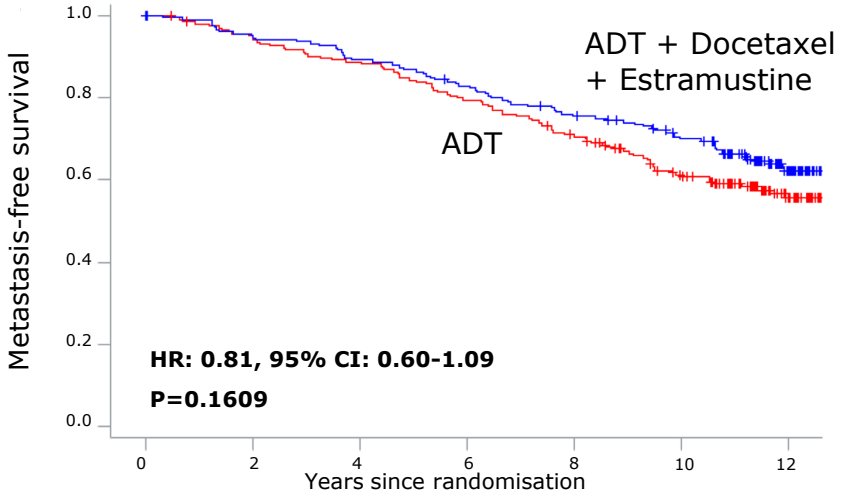
STAMPEDE trial



ADT	460	433	409	391	360	293	195	127	81	48
ADT + D	230	217	210	198	186	147	95	56	41	21

James et al, ESMO 2019, abstract 855PD

GETUG-12 trial

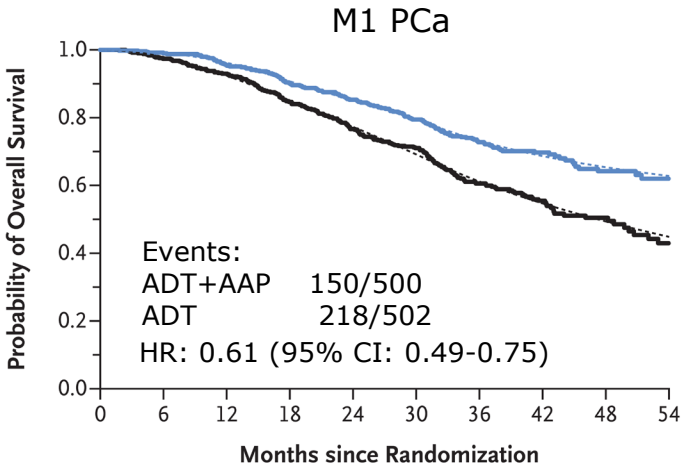


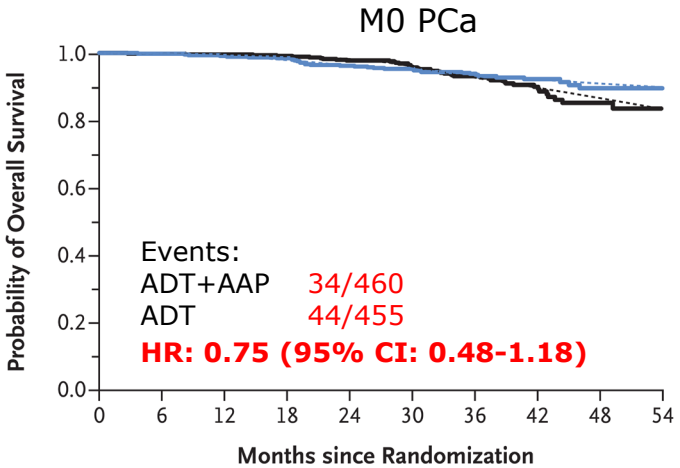
ADT	206	194	181	162	143	111	57
ADT + DE	207	195	183	169	153	136	71

Fizazi et al, ESMO 2018, abstract 791O

Background: 2nd generation hormone therapies

- ADT + AAP/ENZ/apalutamide improve outcomes of M1 PCa[1-5]
- Uncertain benefit in M0 PCa[1] – STAMPEDE trial





No. of Patients (no. of deaths)									
Combination therapy	500	(22)	469	(50)	415	(57)	256	(18)	81
ADT alone	502	(35)	460	(80)	371	(73)	215	(23)	60

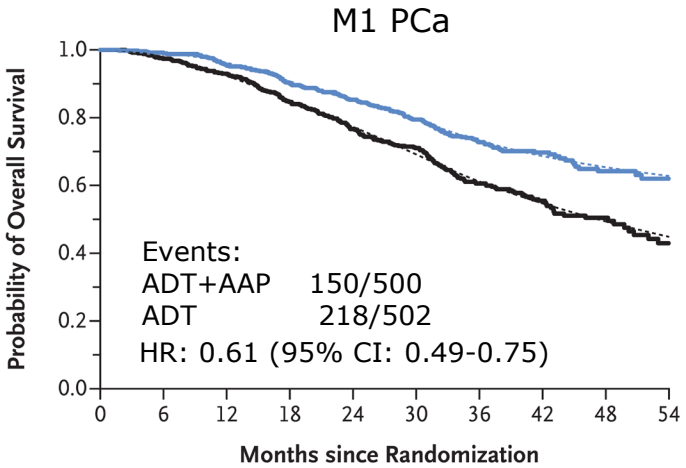
No. of Patients (no. of deaths)									
Combination therapy	460	(4)	448	(13)	425	(10)	285	(7)	80
ADT alone	455	(2)	449	(8)	435	(19)	276	(13)	63

AAP, abiraterone acetate and prednisolone/prednisone
ENZ, enzalutamide; M1, metastatic

1. James ND, et al. N Engl J Med 2017;377:338-51.
2. Armstrong AJ, et al. J Clin Oncol 2019;37:2974-86.
3. Chi KN, et al. N Engl J Med 2019;381:13-24.
4. Davis ID, et al. N Engl J Med 2019;381:121-31.
5. Fizazi K, et al. N Engl J Med 2017;377:352-60.

Background: 2nd generation hormone therapies

- ADT + AAP/ENZ/apalutamide improve outcomes of M1 PCa
- Uncertain benefit in M0 PCa – STAMPEDE trial



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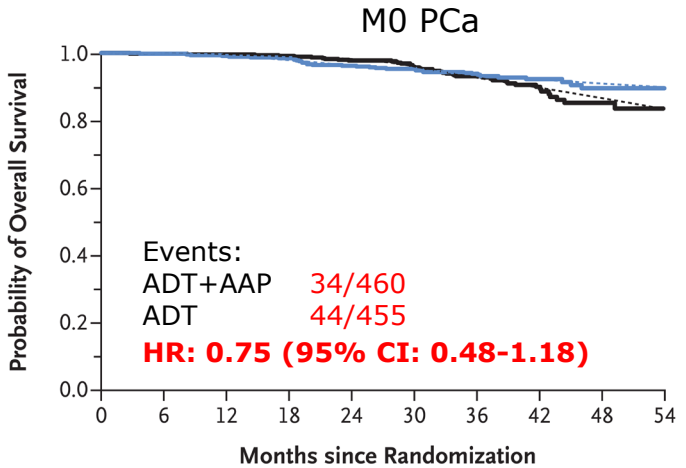

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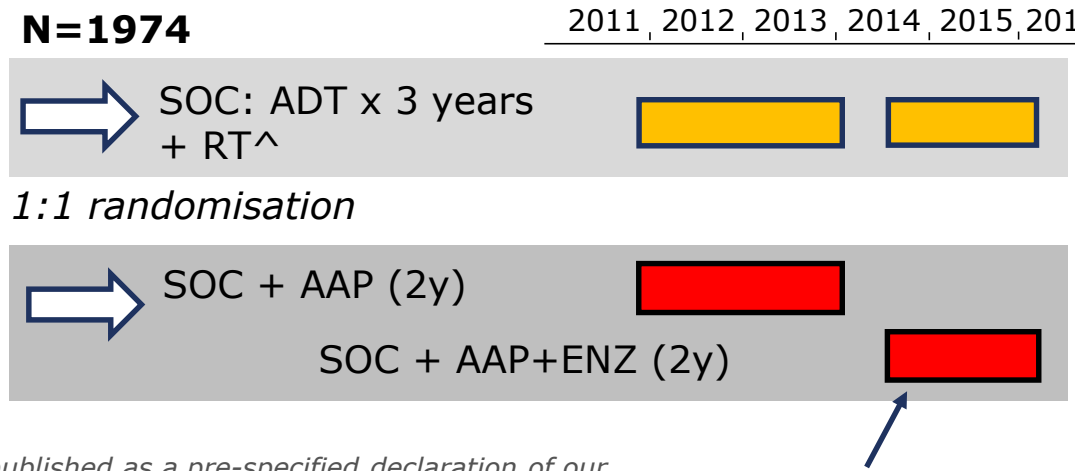
Is there a benefit for AAP in high-risk M0 PCa?

Study design

- M0 pts in AAP comparison: continued FU with **no further** efficacy inspections
- 2019 - amended the reporting plan* to split M1 & M0, power the 1^{ary} end-point on MFS, meta-analyse with new data from AAP+ENZ comparison



- No overlapping controls
- Same protocol & eligibility criteria
- 2 years AAP+/-ENZ
- No evidence of OS benefit with AAP+/-ENZ in mCRPC [1]

*published as a pre-specified declaration of our intentions: Attard G, et al. Eur Urol. Epub 2021 Jul 14

Solid bars: period of accrual

SOC, standard of care
^when indicated

[1]Morris MJ, et al. J Clin Oncol 2019;37:5008

Patient population

M0

No evidence of metastases on bone and CT scan of pelvis, abdo, chest

(pre-defined stratification criterion)

Newly-diagnosed

Any of:

- Node-Positive
- ≥2 of: Stage T3 or T4
  PSA≥40ng/ml
  Gleason 8, 9 or 10

Relapsing after previous RP or RT

Any of:

- Node-positive
- PSA≥4ng/ml, rising & doubling time <6m
- PSA≥20ng/ml

All patients

Written informed consent

Fit for all protocol treatment

Fit for follow-up

Full criteria: www.stampedetrial.org

Statistical analysis plan

- Assuming MFS = 70% @ 5.5 years with ADT alone, we targeted a 25% relative improvement with AAP-based therapy (HR=0.75)
- Power 90% & one-sided type 1 error rate = 1.25%*
- Required >300 events in ADT-alone groups
- Standard fixed-effects individual patient data meta-analyses to pool estimates from both comparisons, stratified as described previously
- Data freeze 3rd Aug 2021

**To account for interim activity analyses and prior partial reporting in combination with M1 patients in 2017*

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Patient characteristics

- Randomised groups were well balanced (**N=1974**)

- Median age = 68 years
- Median PSA = 34 ng/ml
- N1 = 39%
- 3% relapsing after prior treatment

- Planned for local radiotherapy:
  - 99% newly-diagnosed, N0
  - 71% newly-diagnosed, N1
  - 7% previously-treated patients

- Median follow-up = 72 months
  (85 months AAP comparison & 60 months AAP+ENZ comparison)

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Time to permanently stopping treatment

- AAP, months (IQR) 23.7 (17.6-24.1)
- ENZ 23.2 (6.3-24)
- AAP (started with ENZ) 20.7 (4.4-24)

IQR, interquartile range

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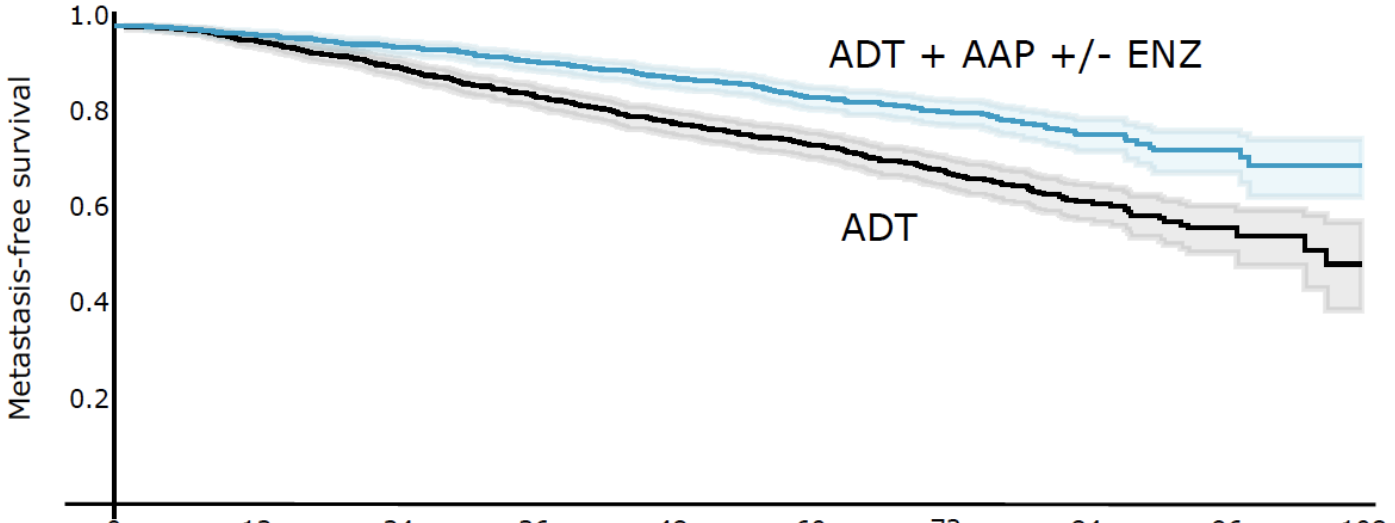
Metastasis-free survival



ADT										
At-risk	988	950	894	836	767	550	329	172	53	9
Censored	0	8	11	14	26	201	387	522	632	673
Event	0	30	83	138	195	237	272	294	303	306
ADT+AAP+/-ENZ										
At-risk	986	948	917	884	839	622	369	198	71	14
Censored	0	21	28	31	45	225	460	615	737	792
Event	0	17	41	71	102	139	157	173	178	180

Events
180 ADT+ AAP +/- ENZ
306 ADT

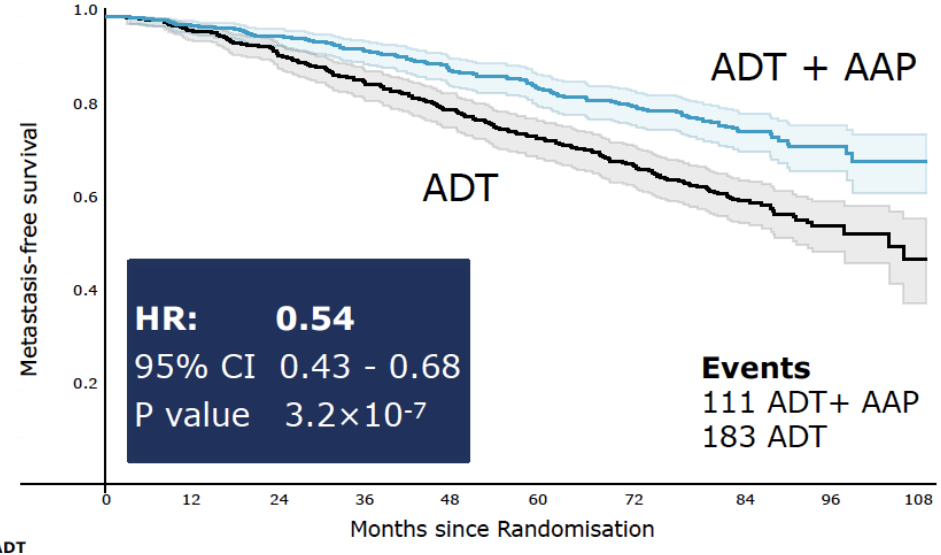
HR:	**0.53**
95% CI:	0.44-0.64
P value	2.9×10^{-11}

6-year MFS improved from 69% to 82%

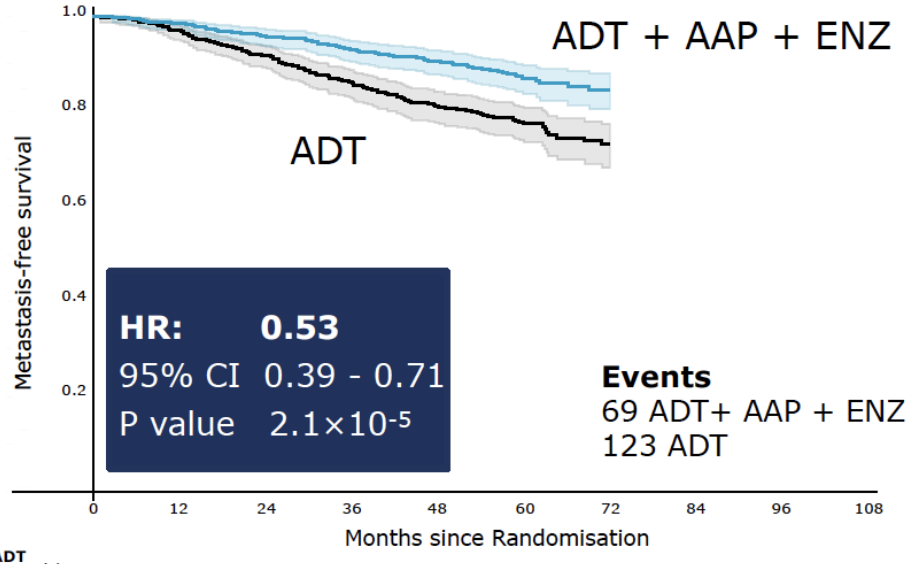
Kaplan-Meier estimates with 95% CI in lighter shade

Non-proportional hazards P=0.46

Metastasis-free survival by randomisation period



ADT										
At-risk	455	438	411	385	351	318	266	172	53	9
Censored	0	3	4	5	8	15	40	112	222	263
Event	0	14	40	65	96	122	149	171	180	183
ADT+AAP										
At-risk	459	441	426	411	391	362	312	198	71	14
Censored	0	9	13	13	14	22	58	157	279	334
Event	0	9	20	35	54	75	89	104	109	111



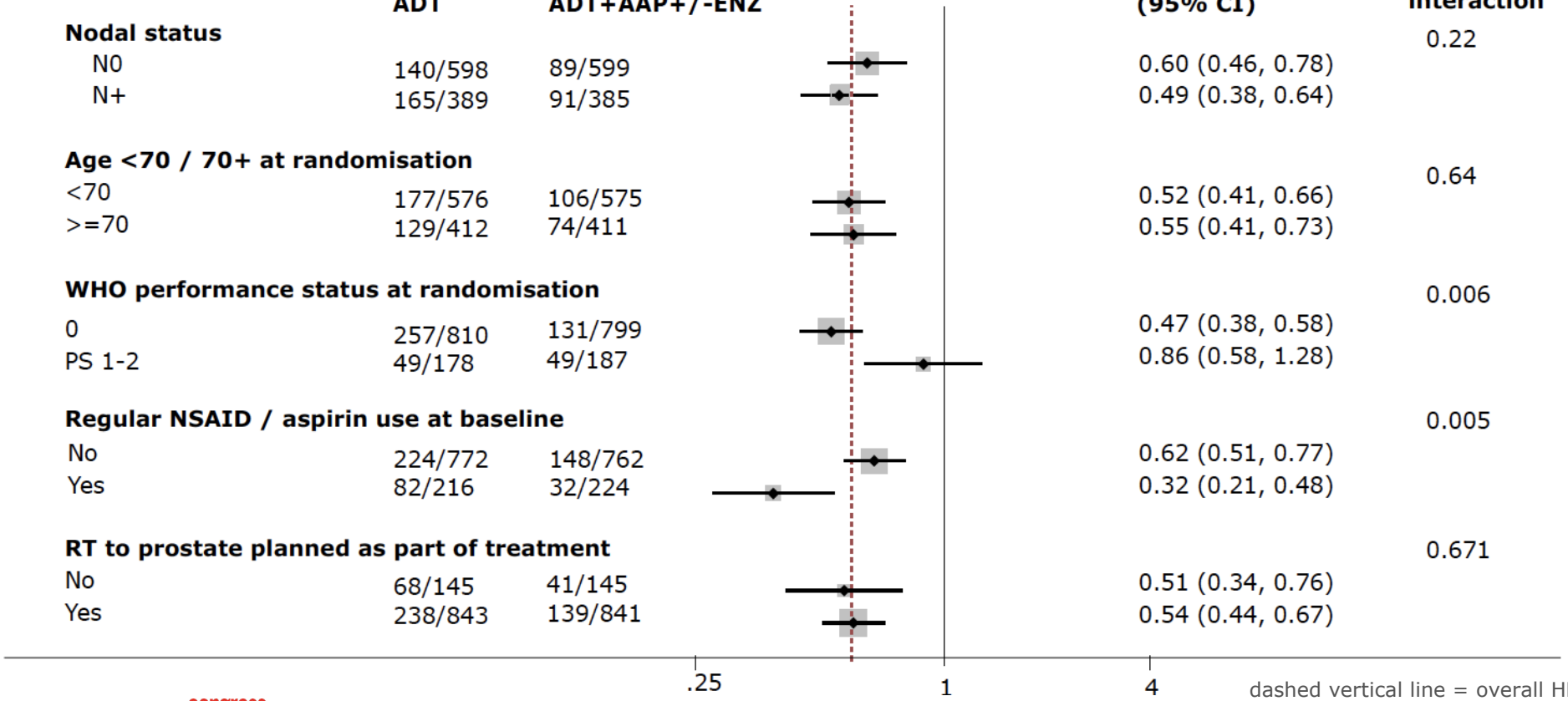
ADT							
At-risk	533	512	483	451	416	232	63
Censored	0	5	7	9	18	186	347
Event	0	16	43	73	99	115	123
ADT+AAP+ENZ							
At-risk	527	507	491	473	448	260	57
Censored	0	12	15	18	31	203	402
Event	0	8	21	36	48	64	68

Kaplan-Meier estimates with 95% CI in lighter shade

Interaction HR: 1.02, 95% CI: 0.70 – 1.50, P=0.908

Metastasis-free survival: Subgroup analysis

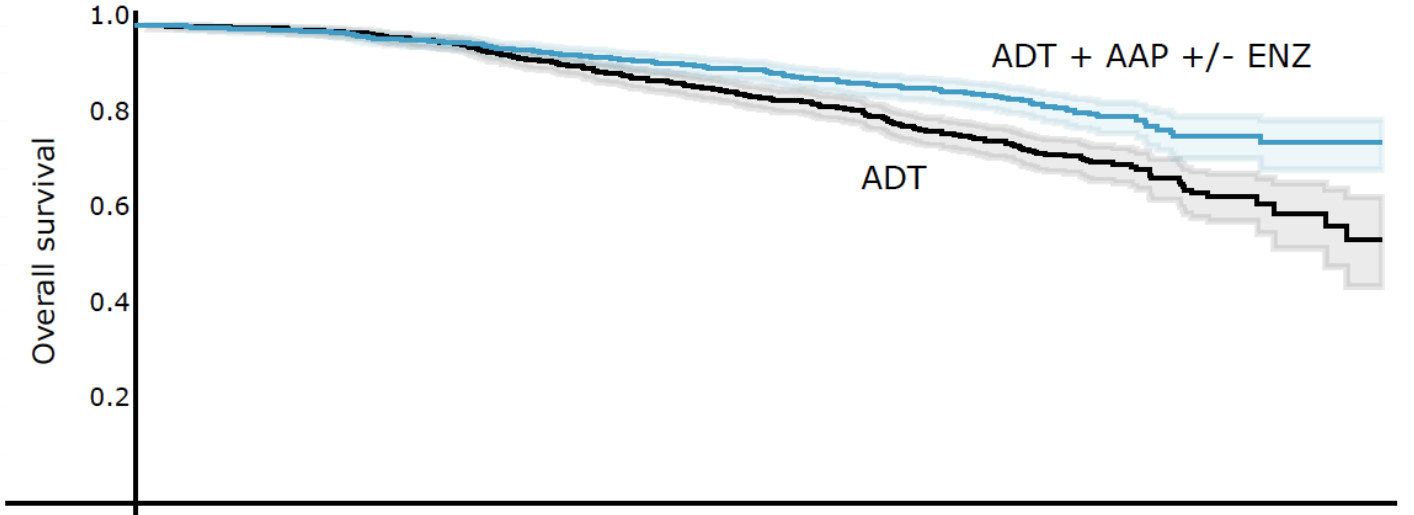
Subgroup	*N events/N patients* ADT	ADT+AAP+/-ENZ	Hazard Ratio (95% CI)	P value for interaction
Nodal status				0.22
N0	140/598	89/599	0.60 (0.46, 0.78)	
N+	165/389	91/385	0.49 (0.38, 0.64)	
Age <70 / 70+ at randomisation				0.64
<70	177/576	106/575	0.52 (0.41, 0.66)	
>=70	129/412	74/411	0.55 (0.41, 0.73)	
WHO performance status at randomisation				0.006
0	257/810	131/799	0.47 (0.38, 0.58)	
PS 1-2	49/178	49/187	0.86 (0.58, 1.28)	
Regular NSAID / aspirin use at baseline				0.005
No	224/772	148/762	0.62 (0.51, 0.77)	
Yes	82/216	32/224	0.32 (0.21, 0.48)	
RT to prostate planned as part of treatment				0.671
No	68/145	41/145	0.51 (0.34, 0.76)	
Yes	238/843	139/841	0.54 (0.44, 0.67)	



dashed vertical line = overall HR
weighting is by sample size

Overall survival

Events
147 ADT+AAP +/- ENZ
236 ADT



SOC										
At-risk	988	974	947	901	837	610	368	200	63	10
Censored	0	8	11	14	28	216	421	568	693	742
Event	0	6	30	73	123	162	199	220	232	236
SOC+AAP+/-ENZ										
At-risk	986	956	928	899	861	645	386	205	74	16
Censored	0	21	29	32	46	234	477	641	766	823
Event	0	9	29	55	79	107	123	140	146	147

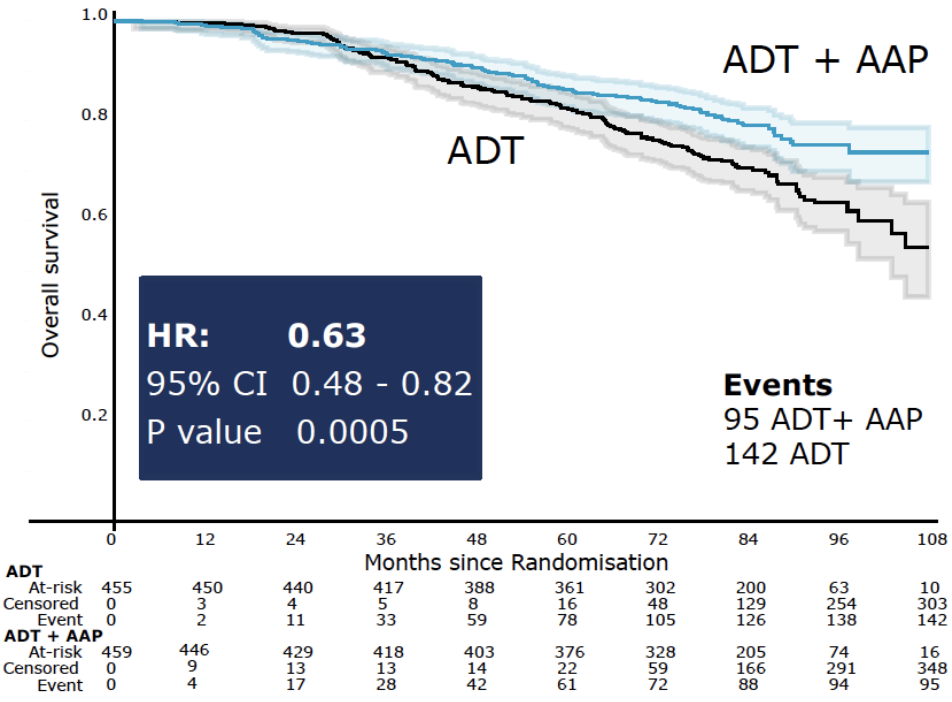
HR: 0.60
95% CI 0.48 to 0.73
P value 9.3×10^{-7}

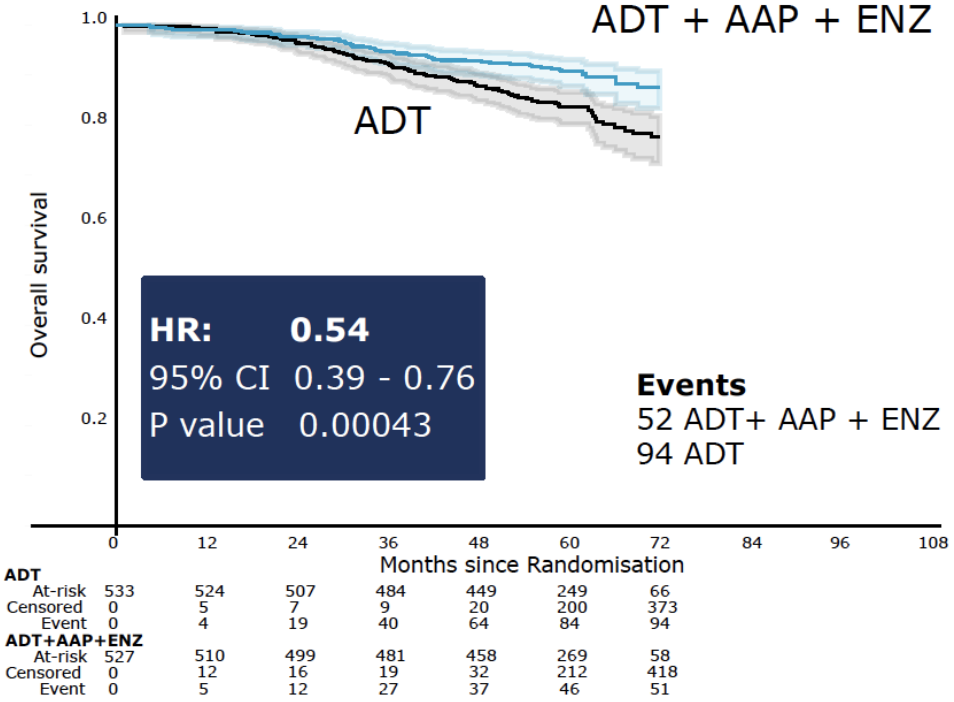
6-year survival improved from 77% to 86%

Kaplan-Meier estimates with 95% CI in lighter shade

Non-proportional hazards P=0.1

Overall survival by randomisation period

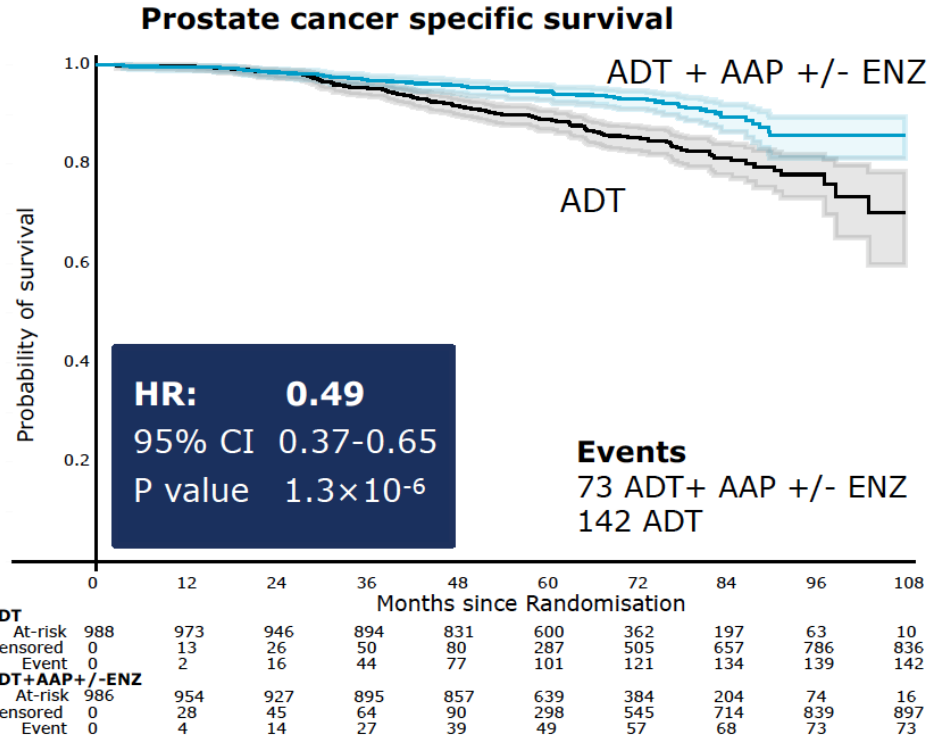


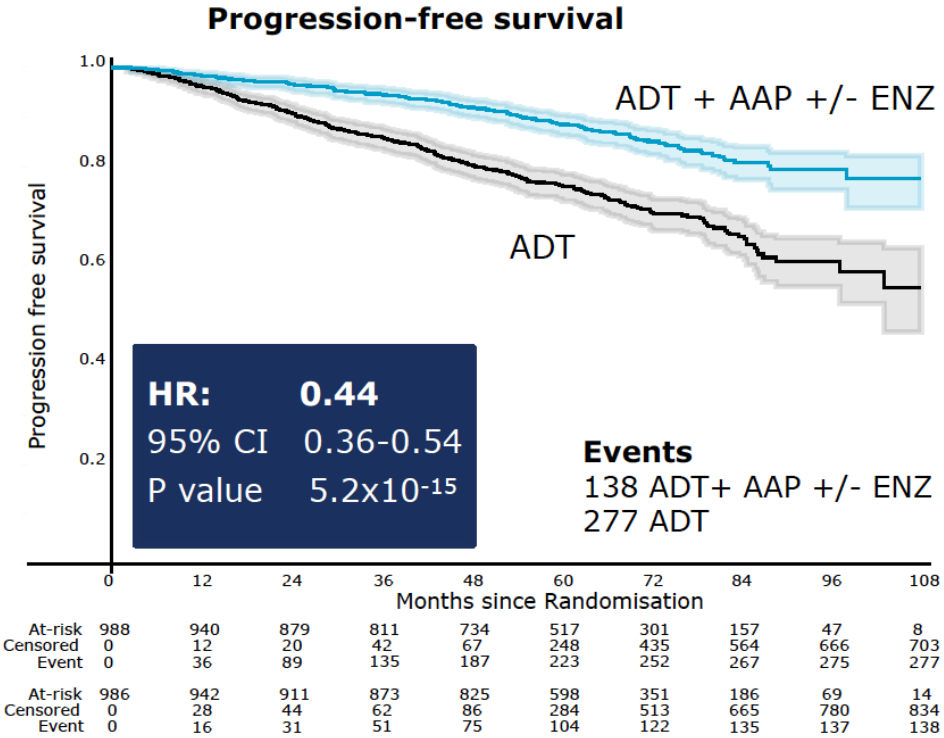


Kaplan-Meier estimates with 95% CI in lighter shade

Interaction between comparisons, P=0.5

Other secondary outcome measures





6-year prostate cancer specific survival improved from 85% to 93%

Kaplan-Meier estimates with 95% CI in lighter shade

Adverse events

Worst toxicity grade in 1st 2 years	ADT only (AAP comparison)		ADT only (AAP + ENZ comparison)		AAP		AAP + ENZ	
	N (454)	%	N (530)	%	N (456)	%	N (522)	%
3	118	26	160	30	151	33	**277**	**53**
4	12	3	12	2	17	4	**23**[¶]	**4**
5	0	0	0	0	**3***	**1**	**4^**	**1**

[¶]Toxicities with the largest difference between AAP vs AAP+ENZ = (Gr 3) erectile dysfunction, hypertension, fatigue, (Gr 3/4) transaminitis

*1 event each of rectal adenocarcinoma, pulmonary haemorrhage and a respiratory disorder

^2 events each of septic shock and sudden death

Limitations

- Have not reported long-term complications beyond 2 years
- Have no data on treatment durations other than 2 years
- Relapsed patients are under-represented
- No evidence for single-agent AR antagonist efficacy

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Conclusions

- **2 years** of AAP-based therapy significantly improves MFS & overall survival of high-risk M0 PCa starting ADT and should be considered **a new standard of care**

- Adding ENZ to AAP increases toxicity but has no discernible effect on efficacy

Gerhardt Attard MD FRCP PhD

Acknowledgements

>**11,000 patients** who have joined the trial & their families + friends who have supported them

>3,000 site staff at >100 hospitals

www.stampedetrial.org

Janssen and Astellas pharma

Medical Research Council & Cancer Research UK