UCL

MRC Clinical Trials Unit

Treating the primary in metastatic prostate cancer: Lessons from the STAMPEDE trial

Nicholas James

@Prof_Nick_James

University Hospitals Birmingham NHS
NHS Foundation Trust

UNIVERSITY OF BIRMINGHAM

Disclosures

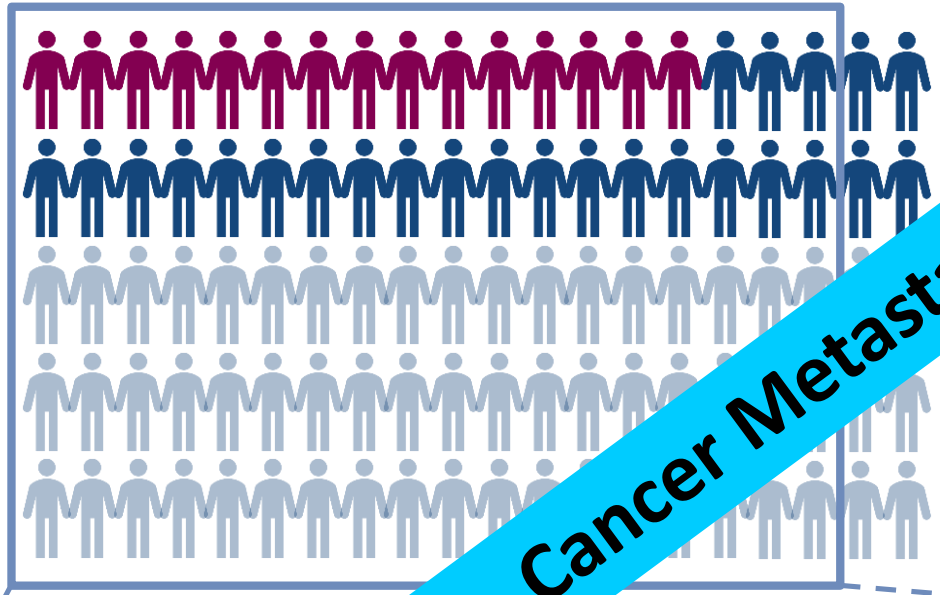
- Trial funding from:
  - Cancer Research UK
  - Medical Research Council
  - Astellas
  - Janssen
  - Novartis
  - Pfizer
  - Sanofi-Aventis
- Speaking fees and Advisory Boards
  - Astellas, Janssen, Novartis, Pfizer, Sanofi-Aventis, Bayer, Clovis, Merck, Ferring, Astra Zeneca

Focus of talk

- I will focus on newly diagnosed metastatic hormone sensitive prostate cancer (mHSPC) with no prior therapy
- Treatment of the primary
- The issue of volume of disease
- Which treatments can we combine?

What Do We Know ?

Prostate Cancer Mortality



patients with prostate
er have metastases at the
time of diagnosis[1]

@ 40% of prostate cancer deaths arise in patients with primary metastatic disease

Patient to androgen deprivation therapy in around 90% of cases;
ver, most cases will progress to CRPC after 2–3 years[2]

Prostate Cancer Metastases are Important

NPCA Annual Re 17

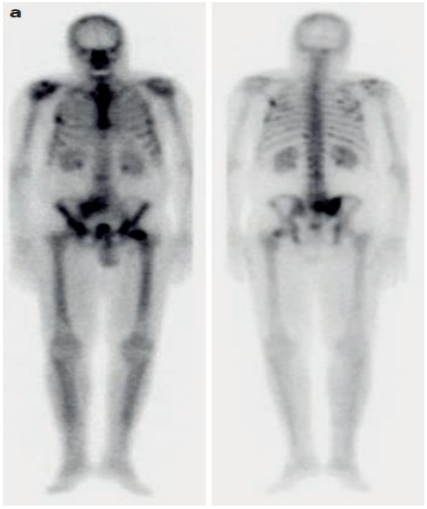
Karantanos T *et al.* *Oncogene* 2013;32:5501–11

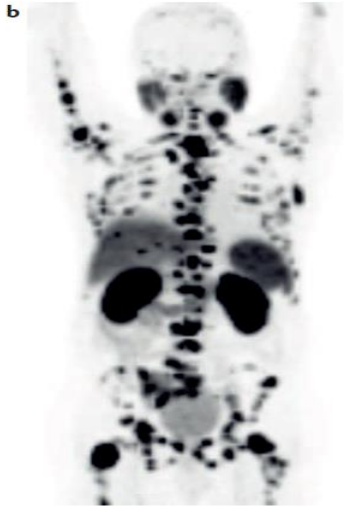
mHSPC: what do we know?

- Androgen deprivation therapy remains a fixed part of therapy
- At least 7 drugs work in relapsed disease
  - Abiraterone
  - Enzalutamide, apalutamide, darolutamide
  - Docetaxel, cabazitaxel
  - Radium-223
- Using at least 4 of these upfront improve survival
  - Docetaxel
  - Abiraterone
  - Enzalutamide, apalutamide
- Radiotherapy improves survival in low volume disease

What we don’t know

- The best order of therapy in CRPC
- Whether ADT + 1 therapy is better than ADT + 2 therapies in mHSPC
- Whether any biomarker can help us with drug selection
- Whether PSMA PET detected metastasis invisible on CT and bone scan matters





MRC Clinical Trials Unit

Smarter Studies
Global Impact
Better Health

STAMPEDE

UCL

Radiotherapy to the primary tumour for men with newly-diagnosed metastatic prostate cancer: Survival results from STAMPEDE

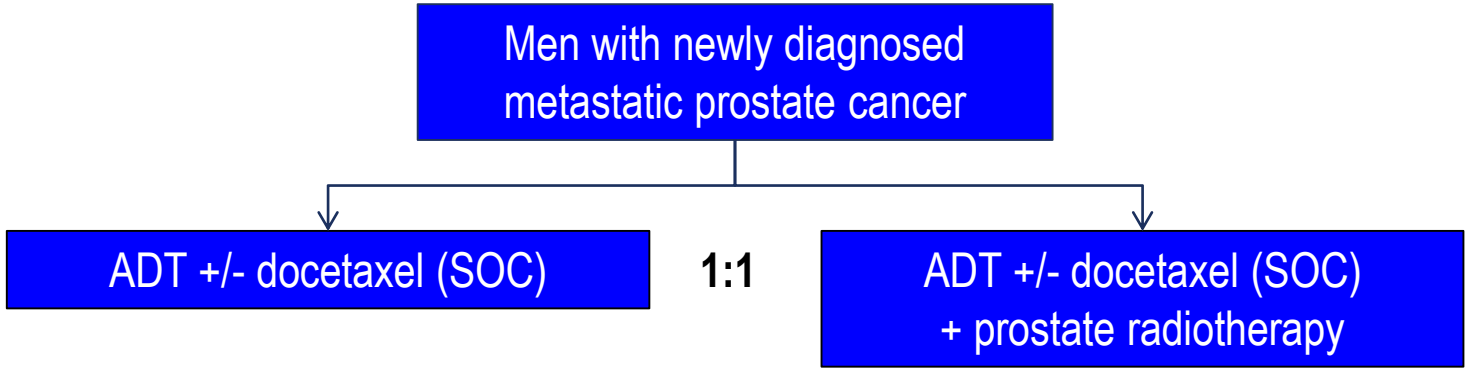
CC Parker, ND James, CD Brawley, NW Clarke, G Attard, S Chowdhury, W Cross, DP Dearnaley, S Gillessen, C Gilson, RJ Jones, MD Mason, R Millman, C Eswar, J Gale, JF Lester, DJ Sheehan, AT Tran, MKB Parmar, MR Sydes.

MUNICH 2018 ESMO congress

The ROYAL MARSDEN NHS Foundation Trust

CANCER RESEARCH UK

Study design



Stratification variables

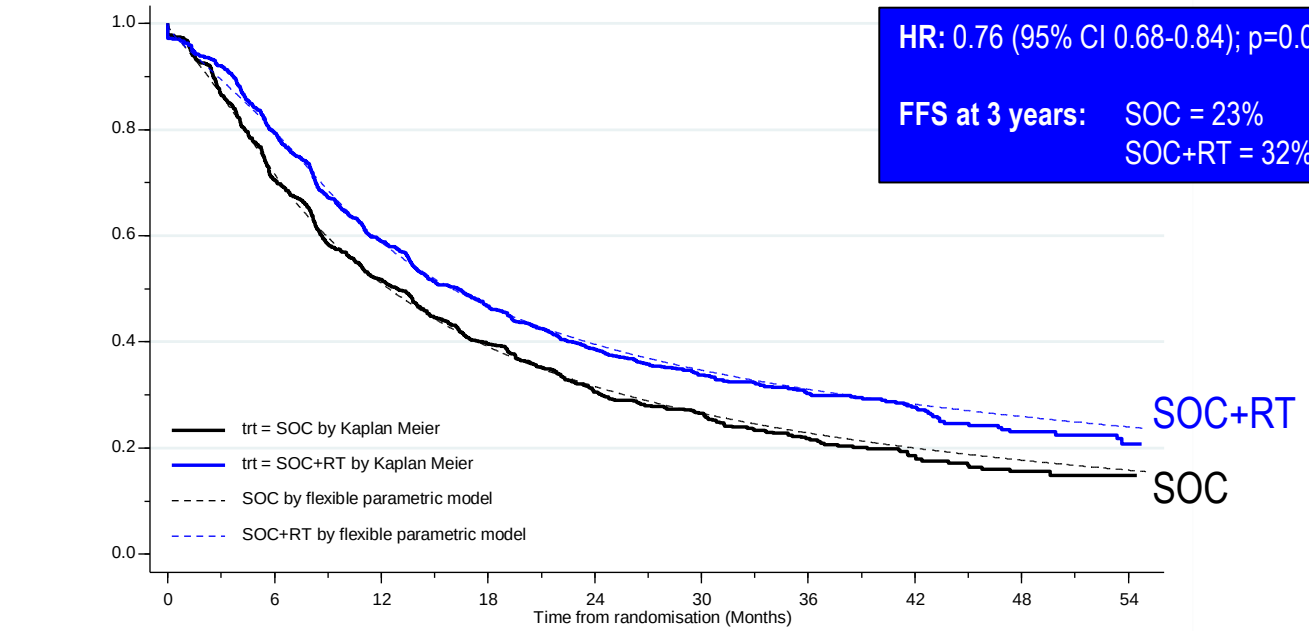
Age (<70 vs ≥70 years), nodal involvement (N0 vs N1 vs Nx), randomising site, WHO performance status (0 vs 1 or 2), type of ADT, aspirin or NSAID use, docetaxel use

RESULTS: Baseline characteristics

Characteristic		SOC (n=1029)	SOC+RT (n=1032)
Age at randomisation (years)	Median (IQR) Range	68 (63-73) 37-86	68 (63-73) 45-87
Pre-ADT PSA (ng/ml)	Median (IQR) Range	98 (30-316) 1-20590	97 (33-313) 1-11156
Metastatic burden	Low High Not classified	409 (42%) 567 (58%) 53	410 (43%) 553 (57%) 69
Site of metastases	Bone Liver Lung Distant lymph nodes Other	919 (89%) 23 (2%) 42 (4%) 294 (29%) 35 (3%)	917 (89%) 19 (2%) 48 (5%) 304 (29%) 33 (3%)
Docetaxel use	No Yes	845 (82%) 184 (18%)	849 (82%) 183 (18%)

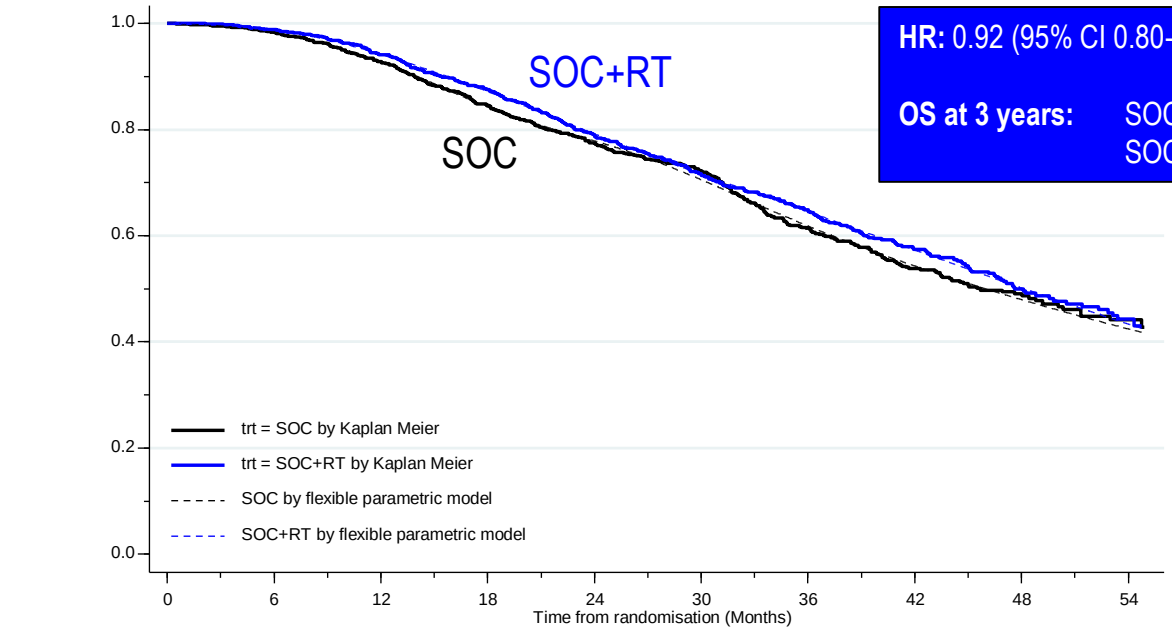
Failure-free survival: all patients

Events 758 SOC | 685 SOC+RT

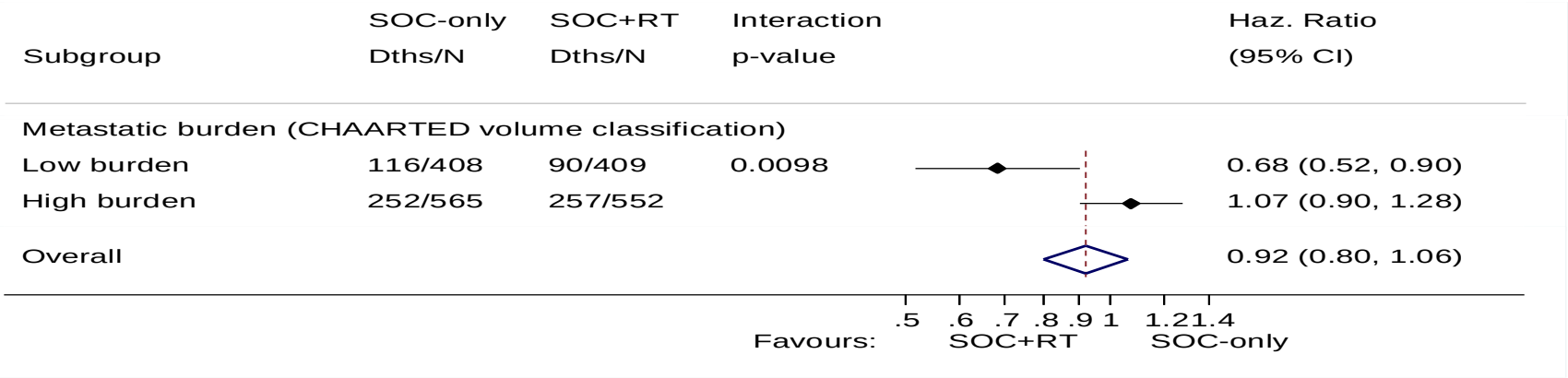


Overall survival: all patients

Events 391 SOC | 370 SOC+RT



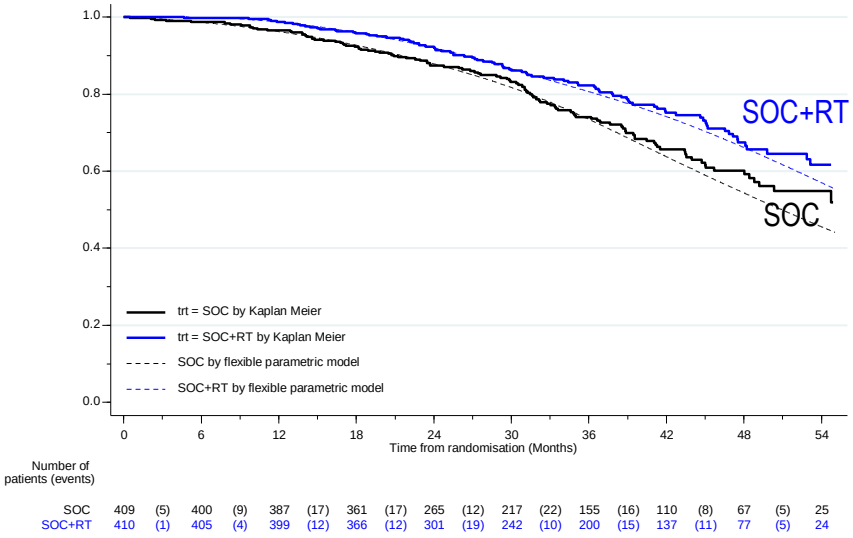
Overall survival: subgroup analysis by metastatic disease burden



Clear evidence that effect size does differ by disease burden (p=0.0098)

Overall survival: metastatic burden subgroup analysis

Low burden

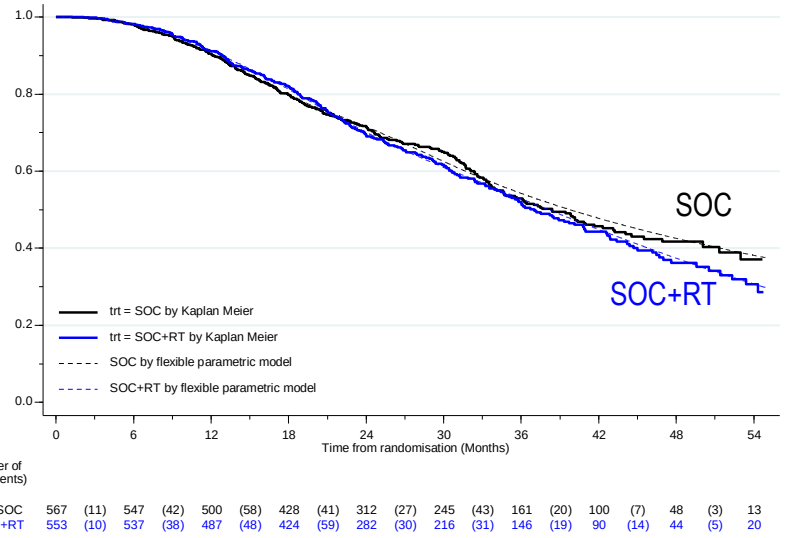


Number of patients (events)

SOC	409	(5)	400	(9)	387	(17)	361	(17)	265	(12)	217	(22)	155	(16)	110	(8)	67	(5)	25
SOC+RT	410	(1)	405	(4)	399	(12)	366	(12)	301	(19)	242	(10)	200	(15)	137	(11)	77	(5)	24

HR: 0.68 (95% CI 0.52-0.90); p=0.007
3 year OS (%): SOC = 73%
SOC+RT = 81%

High burden



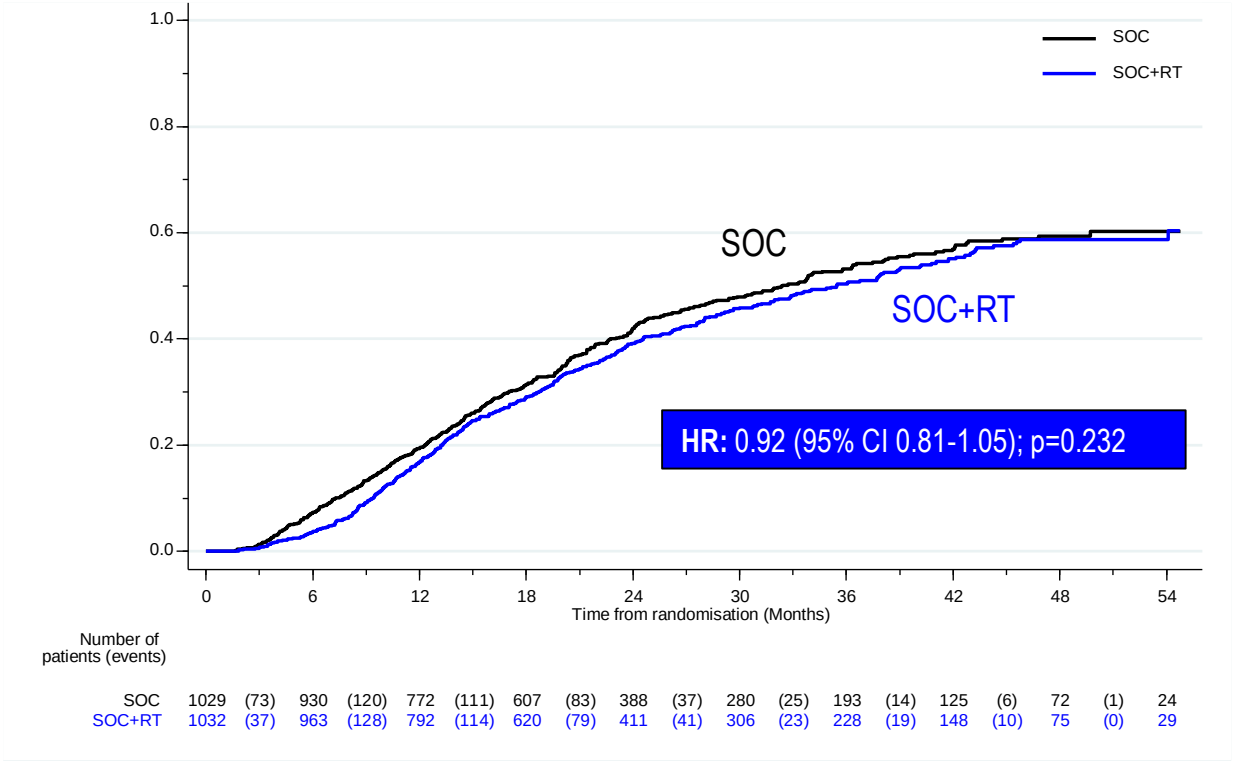
Number of patients (events)

SOC	567	(11)	547	(42)	500	(58)	428	(41)	312	(27)	245	(43)	161	(20)	100	(7)	48	(3)	13
SOC+RT	553	(10)	537	(38)	487	(48)	424	(59)	282	(30)	216	(31)	146	(19)	90	(14)	44	(5)	20

HR: 1.07 (95% CI 0.90-1.28); p=0.420
3 year OS (%): SOC = 54%
SOC+RT = 53%

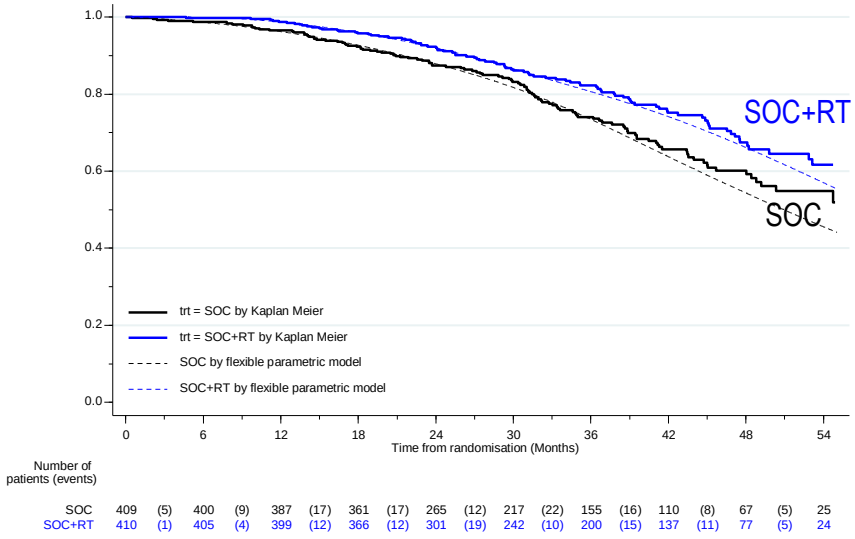
MUNICH 2018 ESMO

Time from randomisation to life-prolonging treatment



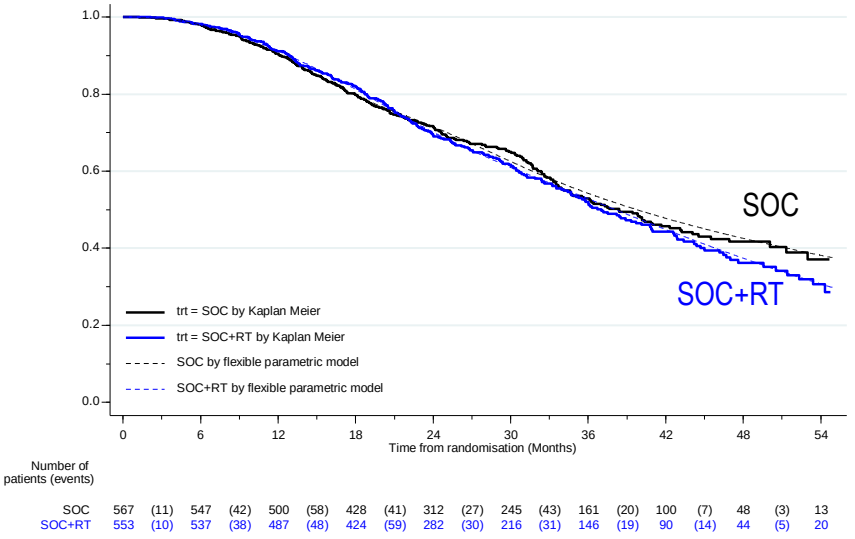
DISCUSSION: Overall survival: metastatic burden subgroup analysis

Low burden



HR: 0.68 (95% CI 0.52-0.90); p=0.007
3 year OS (%): SOC = 73%
SOC+RT = 81%

High burden



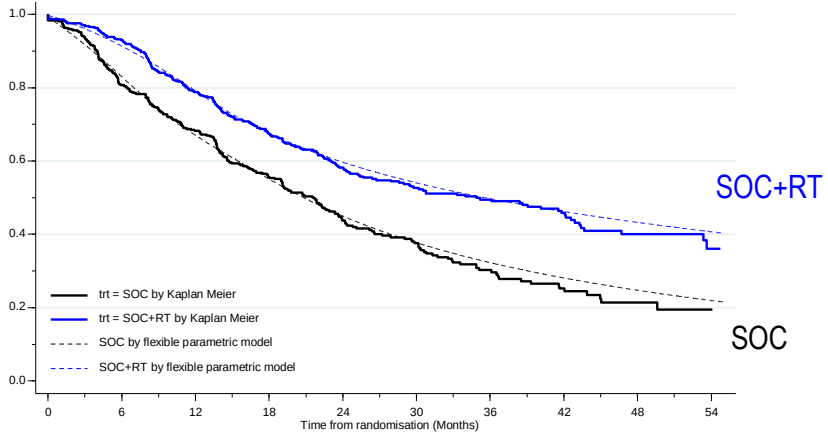
HR: 1.07 (95% CI 0.90-1.28); p=0.420
3 year OS (%): SOC = 54%
SOC+RT = 53%

MUNICH 2018 ESMO

MRC CTU at UCL

STAMPEDE Failure-free survival: metastatic burden subgroup analysis

Low burden

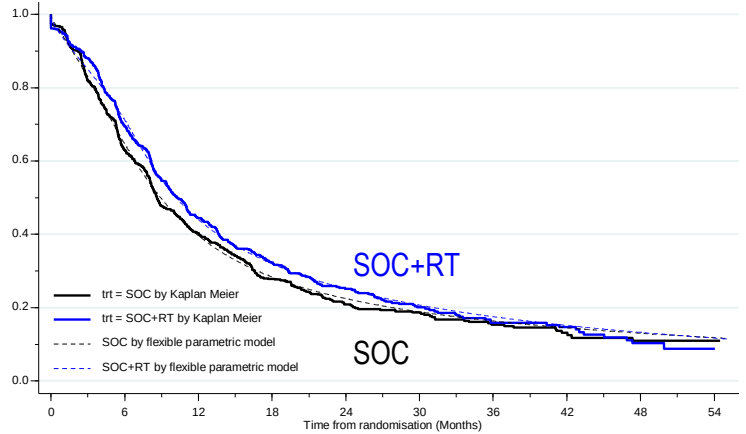


Number of patients (events)

SOC	409	(78)	324	(50)	269	(49)	211	(39)	121	(16)	83	(15)	53	(8)	32	(4)	16	(1)	6
SOC+RT	410	(29)	377	(57)	319	(45)	255	(32)	178	(16)	142	(8)	113	(7)	75	(8)	35	(2)	12

HR: 0.59 (95% CI 0.49-0.72); $p=4.83 \times 10^{-8}$
3 year FFS: SOC = 33%
SOC+RT = 50%

High burden



Number of patients (events)

SOC	567	(207)	350	(126)	223	(68)	147	(32)	83	(8)	59	(10)	41	(5)	21	(3)	11	(0)	3
SOC+RT	553	(168)	379	(135)	237	(64)	166	(34)	96	(17)	60	(11)	35	(2)	22	(6)	10	(1)	5

HR: 0.88 (95% CI 0.77-1.01); p=0.059
3 year FFS: SOC = 17%
SOC+RT = 18%

Test for interaction: p = 0.0024

Credibility of claims of subgroup effects in RCTs: systematic review

Sun et al. BMJ 2012; 344:e1553

Was the subgroup variable a baseline characteristic?	✓
Was the subgroup variable a stratification factor?	X explicitly; ✓ in effect
Was the subgroup hypothesis specified a priori?	✓
Was the analysis one of a small number of subgroups tested?	✓
Was the test of interaction significant?	✓
Was the significant interaction effect independent?	✓
Was the direction of the subgroup effect correctly pre-specified?	✓
Was the effect consistent with previous studies?	✓
Was the effect consistent across related outcomes?	✓
Indirect supportive evidence eg. biological rationale?	✓

Credibility of claims of subgroup effects in RCTs: systematic review

Sun et al. BMJ 2012; 344:e1553

Was the subgroup variable a baseline characteristic?	✓
Was the subgroup variable a stratification factor?	X explicitly; ✓ in effect
Was the subgroup hypothesis specified a priori?	✓
Was the analysis one of a small number of subgroups tested?	✓
Was the test of interaction significant?	✓
Was the significant interaction effect independent?	✓
Was the direction of the subgroup effect correctly pre-specified?	✓
Was the effect consistent with previous studies?	✓
Was the effect consistent across related outcomes?	✓
Indirect supportive evidence eg. biological rationale?	✓

RESULTS: Baseline characteristics

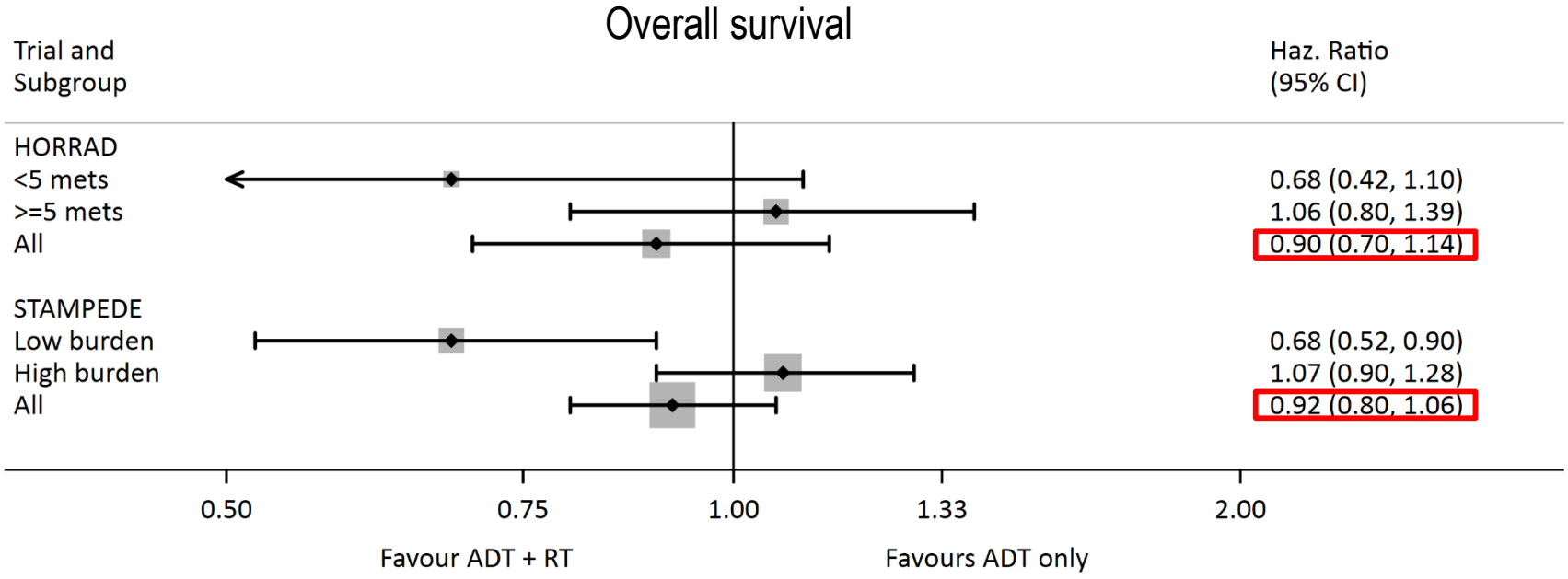
Characteristic		SOC (n=1029)	SOC+RT (n=1032)
Age at randomisation (years)	Median (IQR) Range	68 (63-73) 37-86	68 (63-73) 45-87
Pre-ADT PSA (ng/ml)	Median (IQR) Range	98 (30-316) 1-20590	97 (33-313) 1-11156
Metastatic burden	Low High Not classified	409 (42%) 567 (58%) 53	410 (43%) 553 (57%) 69
Site of metastases	Bone Liver Lung Distant lymph nodes Other	919 (89%) 23 (2%) 42 (4%) 294 (29%) 35 (3%)	917 (89%) 19 (2%) 48 (5%) 304 (29%) 33 (3%)
Docetaxel use	No Yes	845 (82%) 184 (18%)	849 (82%) 183 (18%)

Credibility of claims of subgroup effects in RCTs: systematic review

Sun et al. BMJ 2012; 344:e1553

Was the subgroup variable a baseline characteristic?	✓
Was the subgroup variable a stratification factor?	X explicitly; ✓ in effect
Was the subgroup hypothesis specified a priori?	✓
Was the analysis one of a small number of subgroups tested?	✓
Was the test of interaction significant?	✓
Was the significant interaction effect independent?	✓
Was the direction of the subgroup effect correctly pre-specified?	✓
Was the effect consistent with previous studies?	✓
Was the effect consistent across related outcomes?	✓
Indirect supportive evidence eg. biological rationale?	✓

The effect is consistent with HORRAD

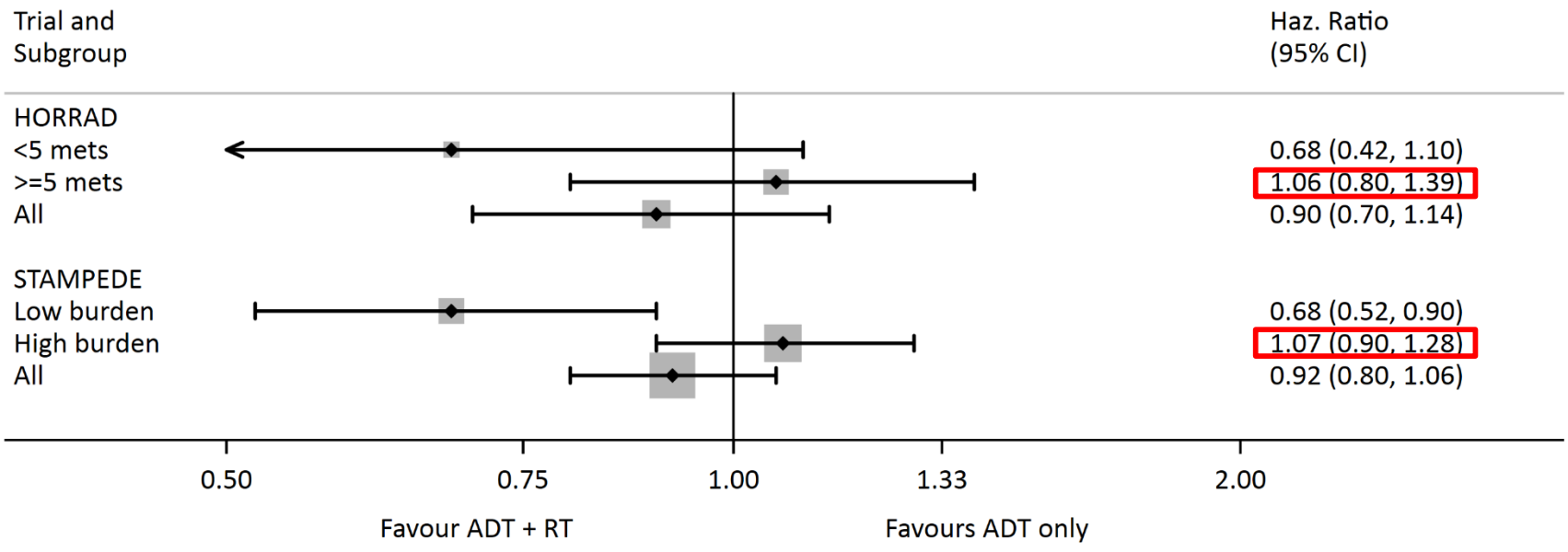


MUNICH 2018 ESMO congress

Boeve et al. Eur Urol (2018)

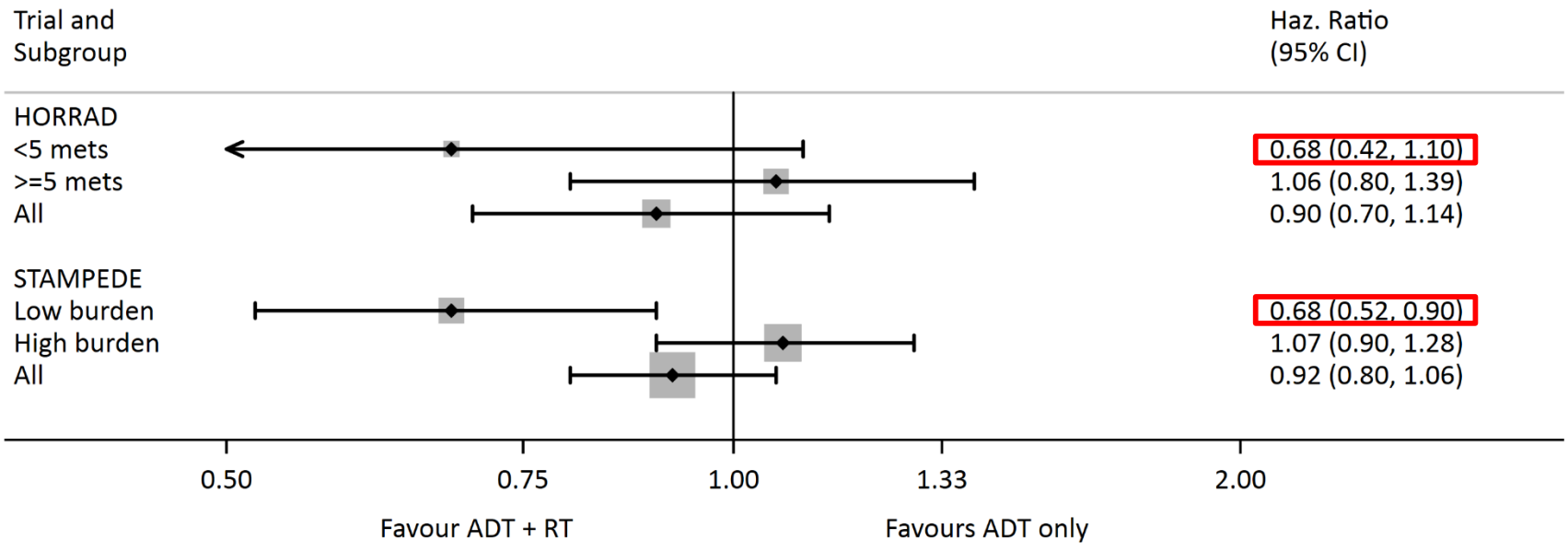
MRC CTU at UCL

The effect is consistent with HORRAD



Boeve et al. Eur Urol (2018)

The effect is consistent with HORRAD



Boeve et al. Eur Urol (2018)

Credibility of claims of subgroup effects in RCTs: systematic review

Sun et al. BMJ 2012; 344:e1553

Was the subgroup variable a baseline characteristic?	✓
Was the subgroup variable a stratification factor?	X explicitly; ✓ in effect
Was the subgroup hypothesis specified a priori?	✓
Was the analysis one of a small number of subgroups tested?	✓
Was the test of interaction significant?	✓
Was the significant interaction effect independent?	✓
Was the direction of the subgroup effect correctly pre-specified?	✓
Was the effect consistent with previous studies?	✓
Was the effect consistent across related outcomes?	✓
Indirect supportive evidence eg. biological rationale?	✓

Radiotherapy as a Standard of Care

Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial

Christopher C Parker, Nicholas D James, Christopher D Brawley, Noel W Clarke, Alex P Hoyle, Adnan Ali, Alastair W S Ritchie, Gerhardt Attard, Simon Chowdhury, William Cross, David P Dearnaley, Silke Gillessen, Clare Gilson, Robert J Jones, Ruth E Langley, Zafar I Malik, Malcolm D Mason, David Matheson, Robin Millman, J Martin Russell, George N Thalmann, Claire L Amos, Roberto Alonzi, Amit Bahl, Alison Birtle, Omar Din, Hassan Douis, Chinnamani Eswar, Joanna Gale, Melissa R Gannon, Sai Jonnada, Sara Khaksar, Jason F Lester, Joe M O'Sullivan, Omi A Parikh, Ian D Pedley, Delia M Pudney, Denise J Sheehan, Narayanan Nair Srihari, Anna T H Tran, Mahesh K B Parmar, Matthew R Sydes*, on behalf of the Systemic Therapy for Advanced or Metastatic Prostate cancer: Evaluation of Drug Efficacy (STAMPEDE) investigators†*

Published Online
October 21, 2018
http://dx.doi.org/10.1016/
S0140-6736(18)32486-3

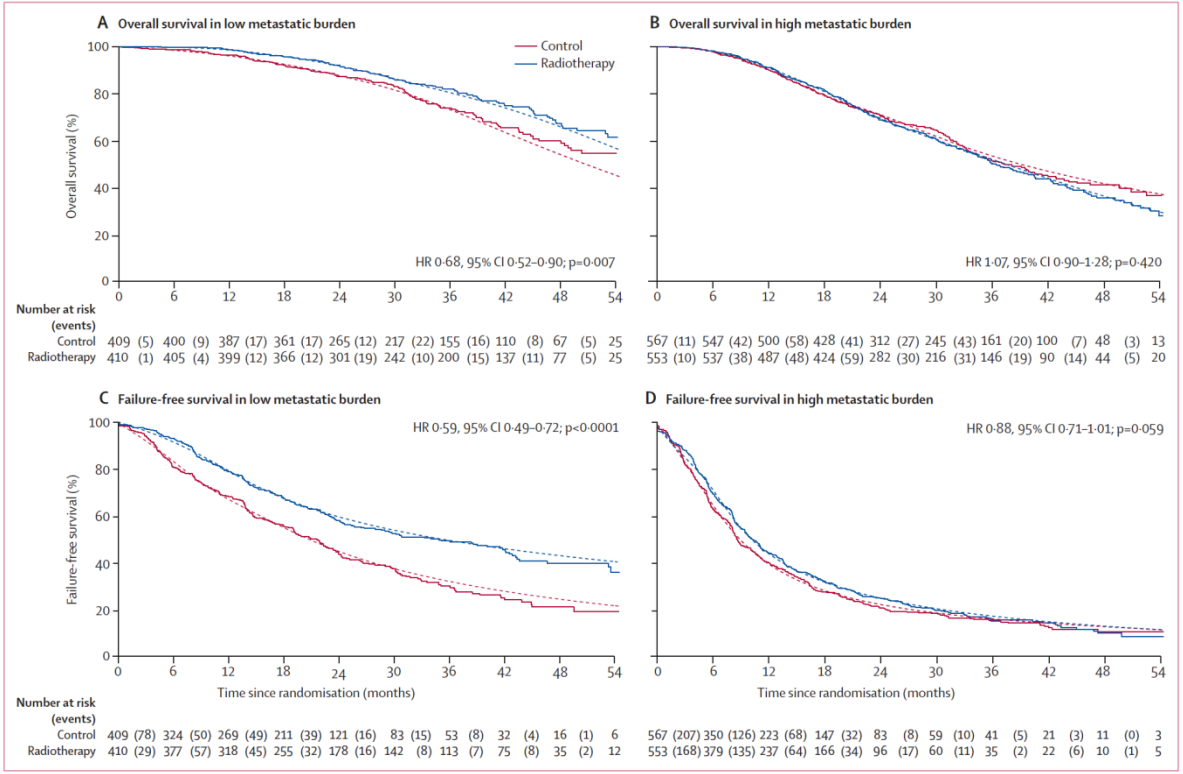


Figure 4: **Overall survival and failure-free survival by treatment and metastatic burden**

Summary

- Prostate radiotherapy did not improve survival for unselected patients (HR=0·92, 95%CI 0·80-1·06; p=0.266)

- Prostate radiotherapy did improve survival (from 73% to 81% at 3 years) in those with a low metastatic burden (HR=0·68, 95%CI 0·52-0·90; p=0·007). Test for interaction: p=0.0098

- Prostate radiotherapy was well tolerated

Conclusions and implications

- Prostate radiotherapy should be a standard treatment option for men with newly diagnosed metastatic prostate cancer with a low metastatic burden

- Prostate radiotherapy should also be standard for men with pelvic nodal disease (N1, M0)

- Local treatment to the primary tumour should be tested for patients with small volume metastatic disease from other malignancies

WHAT WE KNOW ABOUT mHSPC - DOCETAXEL

Selected trials showing survival advantage in mCRPC

Trial	Disease state	Trial design	HR	Median survival, mo
Tax 327[1] (n=1006)	mCRPC with or without symptoms	docetaxel/prednisone vs mitoxantrone/prednisone	0.76	18.9 vs 16.5 Δ 2.4
TROPIC[3] (n=755)	Post-docetaxel	cabazitaxel/prednisolone vs mitoxantrone/prednisone	0.70	15.1 vs 12.7 Δ 2.4
COU-AA-301[4] (n=1195)	Post-docetaxel	abiraterone/low-dose prednisolone vs placebo/low-dose prednisolone	0.74	15.8 vs 11.2 Δ 4.6
AFFIRM[5] (n=1199)	Post-docetaxel	enzalutamide vs placebo	0.63	18.4 vs 13.6 Δ 4.8
PREVAIL[7] (n=1717)	Post-ADT in asymptomatic or mildly symptomatic	enzalutamide vs placebo	0.71	32.4 vs 30.2 Δ 2.2
COU-AA-302[8] (n=1088)	Post-ADT in asymptomatic or mildly symptomatic	abiraterone/low-dose prednisolone vs placebo/low-dose prednisolone	0.81	34.7 vs 30.3 Δ 4.4

**BSC: best supportive care; HR: hazard ratio; mCRPC: metastatic CRPC*

[1]Tannock IF et al. N Engl J Med 2004;351:1502-12; [3]de Bono JS et al. Lancet 2010;376:1147-54; [4] Fizazi K et al. Lancet Oncol 2012;13:983-92[5]Scher HI et al. N Engl J Med 2012;367:1187-97; [7]Beer et al. N Engl J Med 2014;371:424-33; [8]Ryan C et al. Lancet Oncol 2015;16:152–60

Trials showing survival advantage in metastatic patients

Trial	Disease state	Trial design	HR	Median survival, mo
STAMPEDE[1] M1 newly diagnosed	HNPC	Docetaxel/SOC vs SOC	0.76	60.0 vs 45.0 Δ 15.0
CHAARTED	HNPC	Docetaxel/SOC vs SOC	0.61	57.6 vs 44.0 Δ 13.6
Tax 327[2] (n=1006)	mCRPC with or without symptoms	docetaxel/prednisone vs mitoxantrone/prednisone	0.76	Δ 2.4
TROPIC[4] (n=755)	Post-docetaxel	cabazitaxel/prednisolone vs mitoxantrone/prednisone	0.70	Δ 2.4
COU-AA-301[5] (n=1195)	Post-docetaxel	abiraterone/low-dose prednisolone vs placebo/low-dose prednisolone	0.74	Δ 4.6
AFFIRM[6] (n=1199)	Post-docetaxel	enzalutamide vs placebo	0.63	Δ 4.8
PREVAIL[8] (n=1717)	Post-ADT in asymptomatic or mildly symptomatic	enzalutamide vs placebo	0.71	Δ 2.2
COU-AA-302[9] (n=1088)	Post-ADT in asymptomatic or mildly symptomatic	abiraterone/low-dose prednisolone vs placebo/low-dose prednisolone	0.81	Δ 4.4

**BSC: best supportive care; HR: hazard ratio; mCRPC: metastatic CRPC*

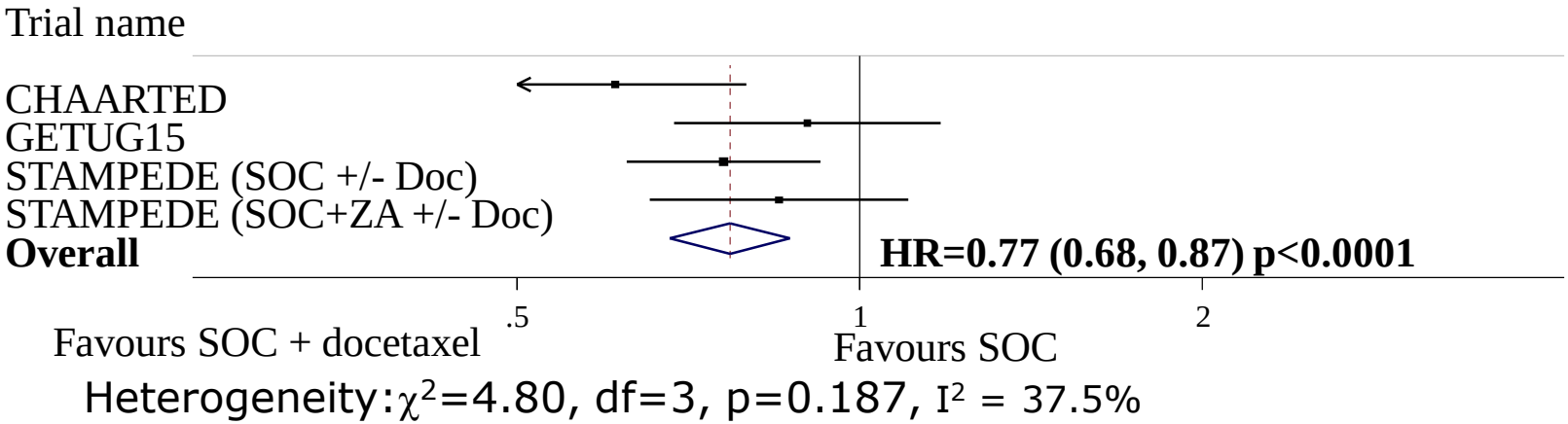
[1]James, N et al. Eur J Cancer 2015;51(S3): abstract 19LBA (presented at ECC 2015;[2]Tannock IF et al. NEJM 2004;351:1502-12;[3]Kantoff PW et al. NEJM 2010;363:411–22;[4]de Bono JS et al. Lancet 2010;376:1147-54;[5] Fizazi K et al. Lancet Oncol 2012;13:983-92;[6]Scher HI et al. NEJM 2012;367:1187-97;[7]Parker C et al. NEJM 2013;369:213-23;[8]Beer et al. NEJM 2014;371:424-33;[9]Ryan C et al. Lancet Oncol 2015;16:152–60

Forest Plot interpretation

- Is designed to test whether effects consistent or inconsistent among subgroups
- Must be interpreted with insight into the plausibility of biological differences
- If the whole trial is powered to just meet its endpoints, it is highly likely some subgroups will have hazard ratios that cross 1

M1 docetaxel: Survival

Results based on 2993 men / 1254 deaths



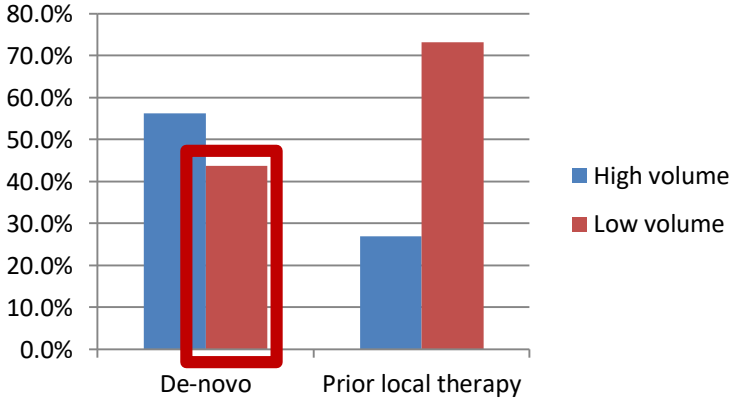
10% absolute improvement in survival (from 40% to 50%) at 4 years

Vale, C et al. Lancet Oncology 2016

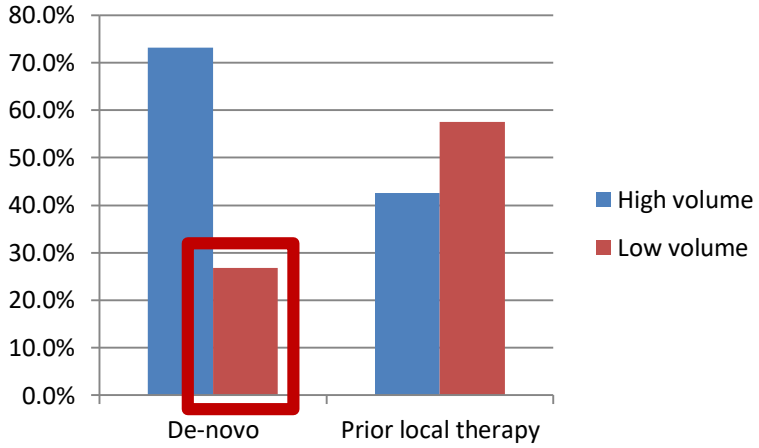
OS effects with docetaxel

- Similar in all 3 trials
- No suggestion of heterogeneity of effect despite different case mixes

Prior therapy – docetaxel trials



GETUG15

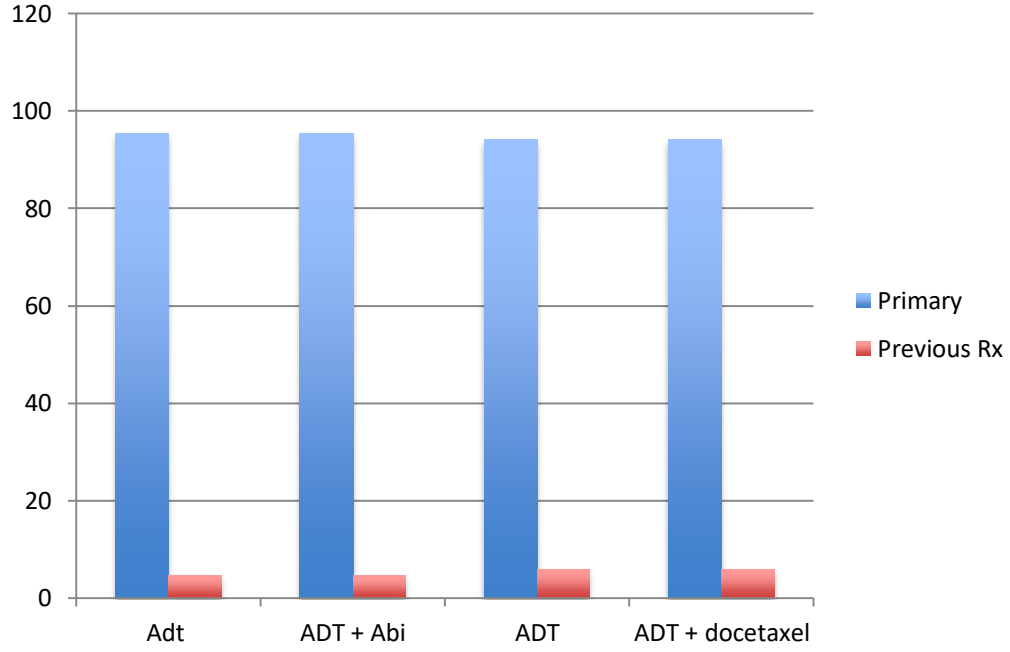


CHAARTED

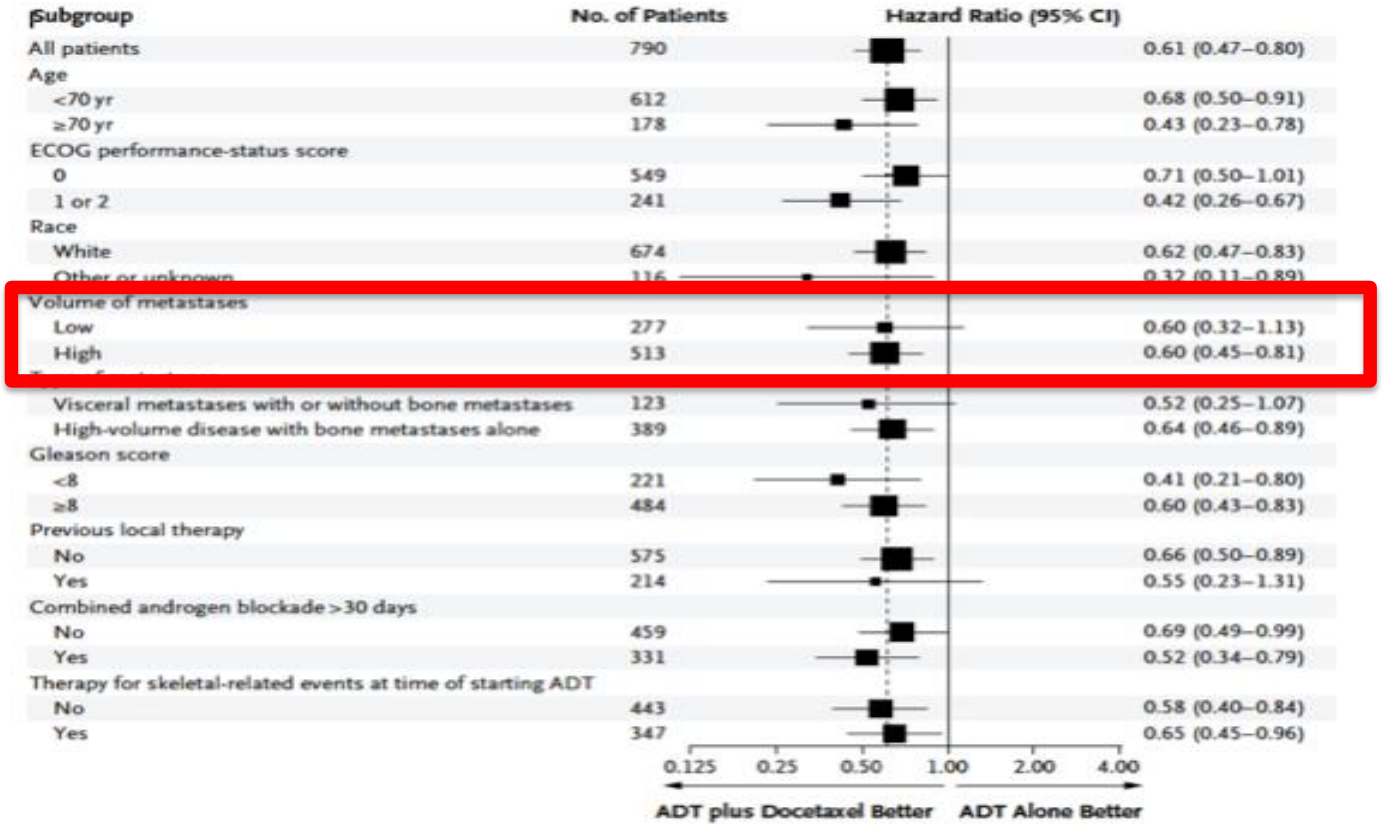
De novo mHSPC CHAARTED and GETURG 15

- Low and varying proportions de novo mHSPC
- Plausible that de novo and relapsed disease may behave differently
- Only de novo disease relevant to question of treating primary in mHSPC

Prior therapy - STAMPEDE

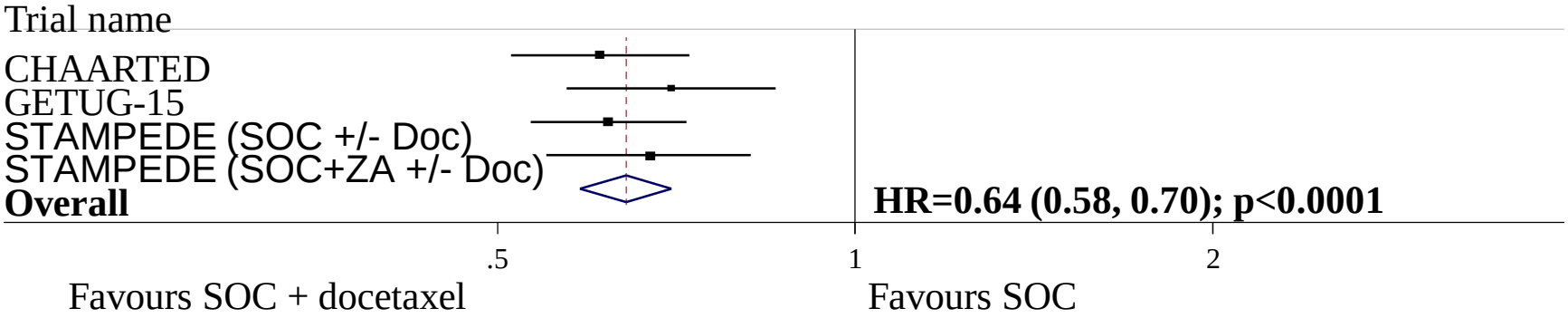


CHAARTED Forest Plot



M1 docetaxel: Failure-free survival

Results based on 2993 men / 2198 events



Heterogeneity: $\chi^2=1.66$, df=3, p=0.646, $I^2=0\%$

15% absolute reduction in failure (from 80% to 65%) at 4 years

Vale, C et al. Lancet Oncology 2016

FFS effects with docetaxel

- Similar in all 3 trials
- No suggestion of heterogeneity of effect despite different case mixes

UPFRONT ANDROGEN RECEPTOR TARGETING

What we know about mHSPC – AR targeting

- 3 drugs now known to improve overall survival
  - Abiraterone (STAMPEDE, LATITUDE)
  - Enzalutamide (Enzamet)
  - Apalutamide (TITAN)
- Hazard ratios for improvement in survival very similar

Trial	Drug	Docetaxel	Hazard ratio
STAMPEDE	Abiraterone	No	0.63
LATITUDE	Abiraterone	No	0.62
ENZAMET	Enzalutamide	Yes (44%)	0.67
TITAN	Apalutamide	Yes (11%)	0.68

Can we combine docetaxel and AR therapy?

- Yes, but is there a benefit?
- TITAN

Prior docetaxel	Hazard ratio	Confidence intervals	Apalutamide + ADT	ADT
Yes	1.27	0.52-3.09	11/58	9/55
No	0.63	0.47-0.85	72/467	108/472

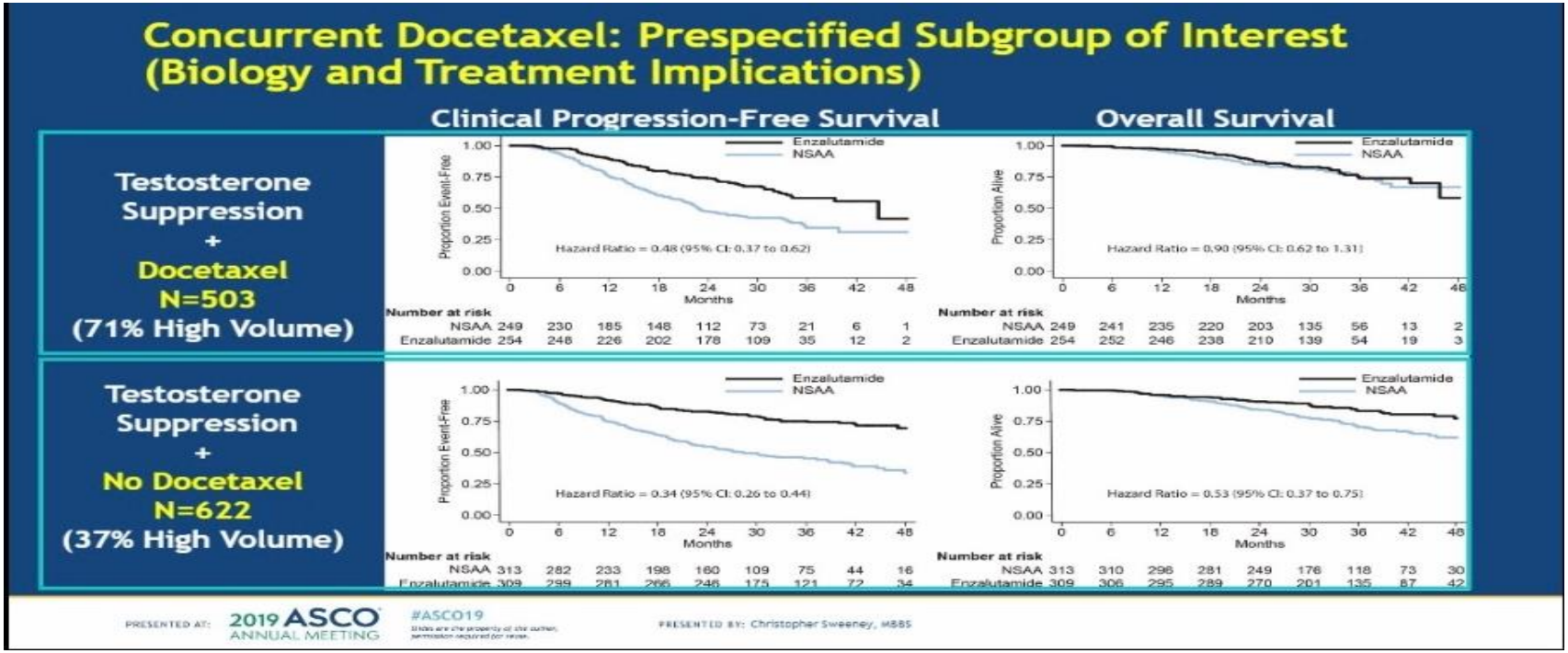
Can we combine docetaxel and AR therapy?

- ENZAMET

Prior docetaxel	Hazard ratio	Confidence intervals
Yes (44%)	0.90	0.62-1.31
No	0.53	0.37-0.75

Can we combine docetaxel and AR therapy?

- ENZAMET

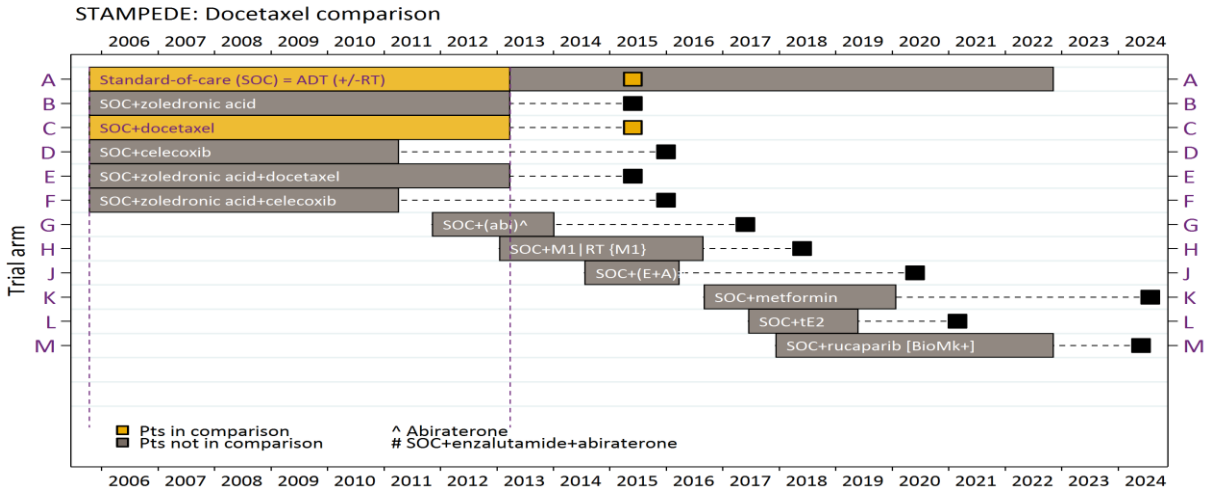


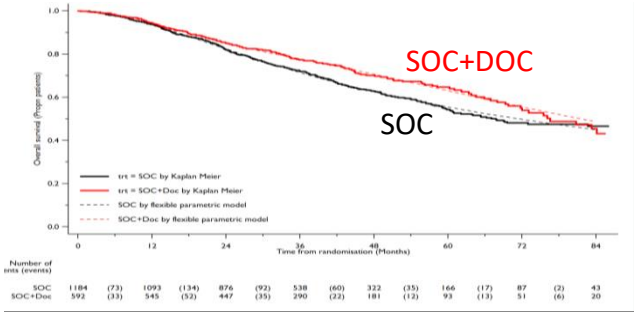
Can we combine docetaxel and AR therapy?

- Weak (at best) evidence of dual benefit
- Best current choice is AR targeted therapy or docetaxel

CAN WE CHOOSE BETWEEN DOCETAXEL AND ART?

STAMPEDE: SOC+DocP vs SOC





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

Recruitment: Oct-2005 to Mar-2013

Reported: ASCO 2015

Published: Lancet 2016

Patients: 1184 SOC
592 SOC+DocP

Allocation ratio: 2:1

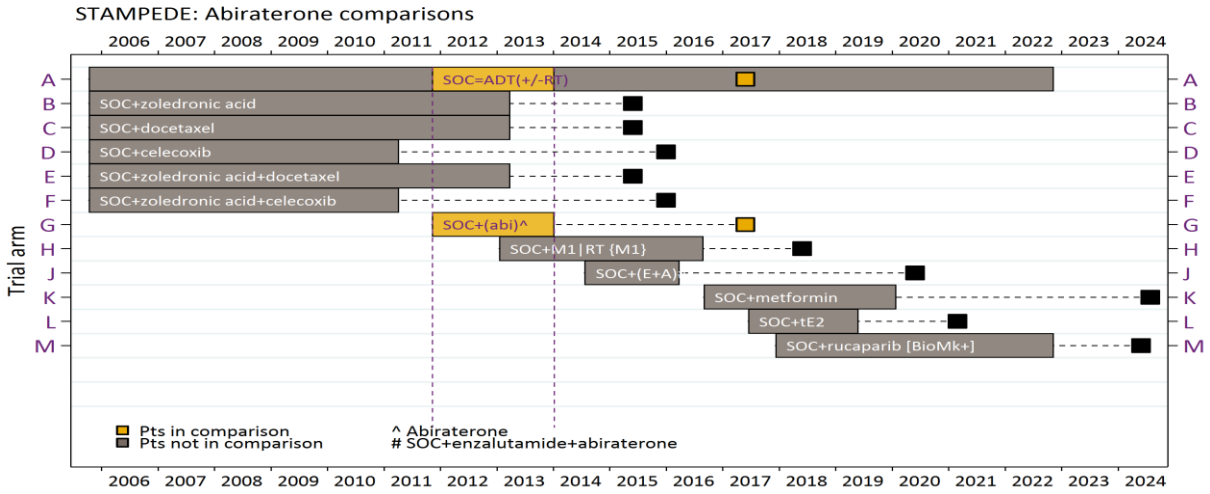

Articles

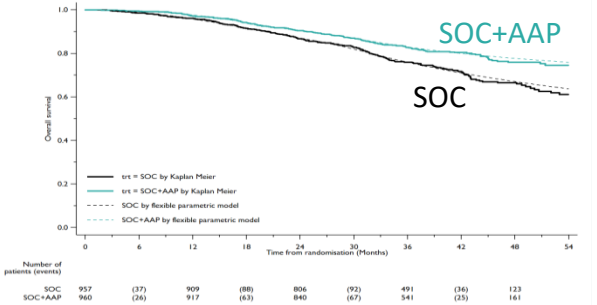
Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial

Articles

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

STAMPEDE: SOC+AAP vs SOC





HR (95%CI) 0.63 (0.52, 0.76)
P-value 0.00000115

Recruitment: Nov-2011 to Jan-2014

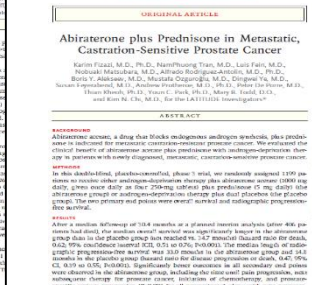
Reported: ASCO 2017

Published: NEJM 2017

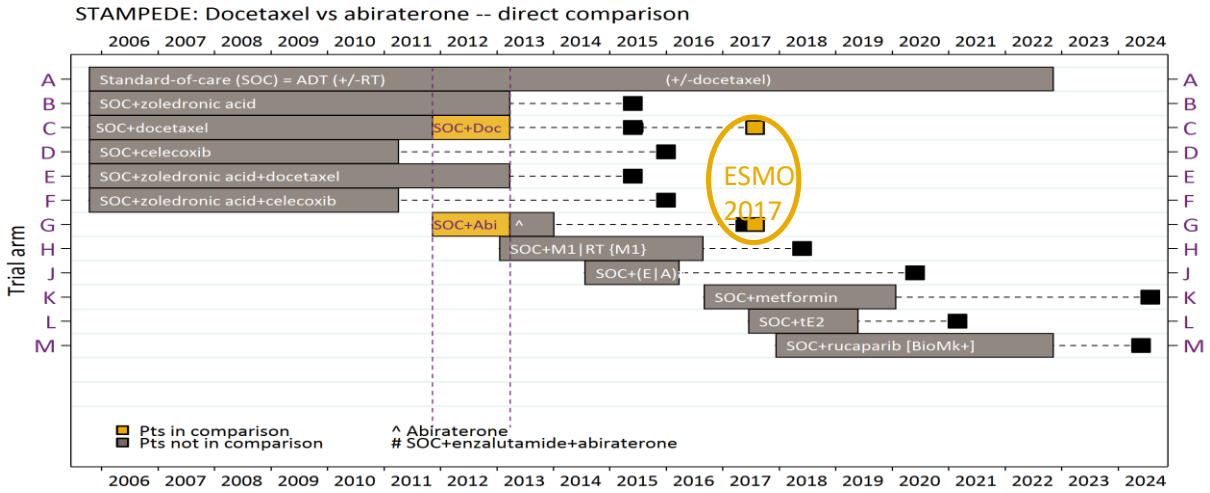
Patients: 957 SOC
960 SOC+AAP

Allocation ratio: 1:1


Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy


Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer

STAMPEDE: SOC+AAP vs SOC+DocP



AAP and DocP may work in quite different ways

Evidence about whether to give both is pending

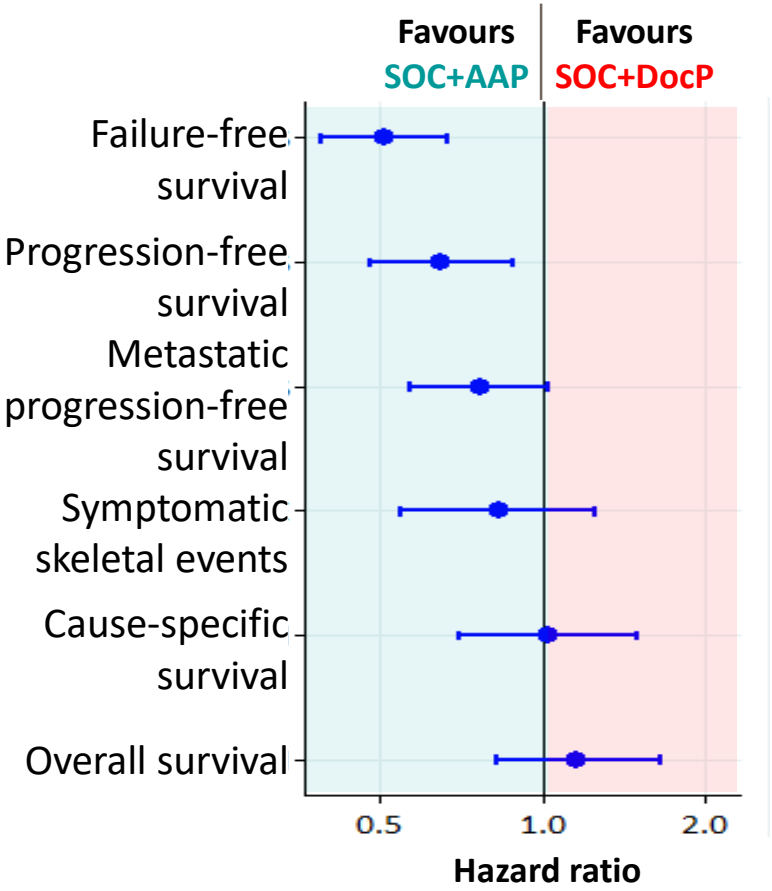
Recruitment: Nov-2011 to Mar-2013

Reported: ESMO 2017

Published: **Sydes et al, Annals of Oncology, 2018 in press**

Patients: 189 SOC+DocP
377 SOC+AAP

566 patients randomised contemporaneously to either research arm



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

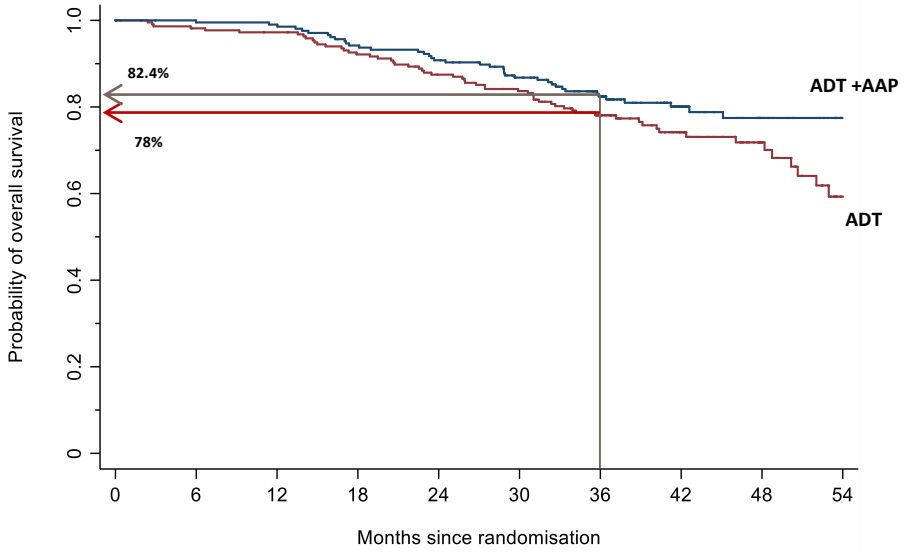
Docetaxel vs. AR therapy in mHSPC

- No evidence of survival difference in STAMPEDE
- Upfront abiraterone gives longer HSPC but shorter CRPC
- Upfront docetaxel gives shorter HSPC but longer CRPC
- Impact on bone events similar
- Docetaxel much cheaper

ABIRATERONE SPLIT BY RISK AND VOLUME

RESULTS: OVERALL SURVIVAL

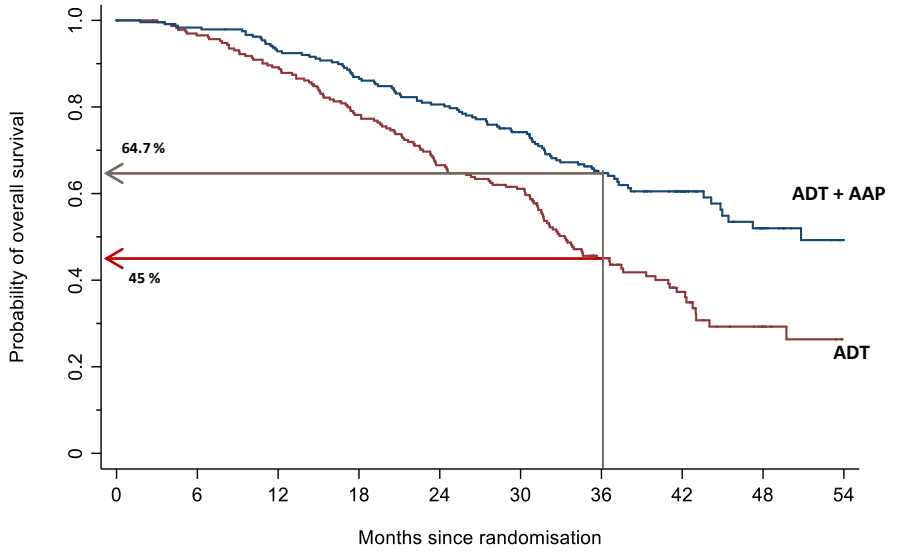
Low Risk



No. of patients (Events)

AAP	208	(2)	205	(17)	186	(16)	131	(5)	45
ADT alone	220	(6)	210	(21)	186	(19)	125	(7)	43

High Risk



No. of patients (Events)

AAP	241	(17)	220	(29)	190	(35)	106	(12)	28
ADT alone	232	(25)	204	(51)	148	(44)	71	(15)	13

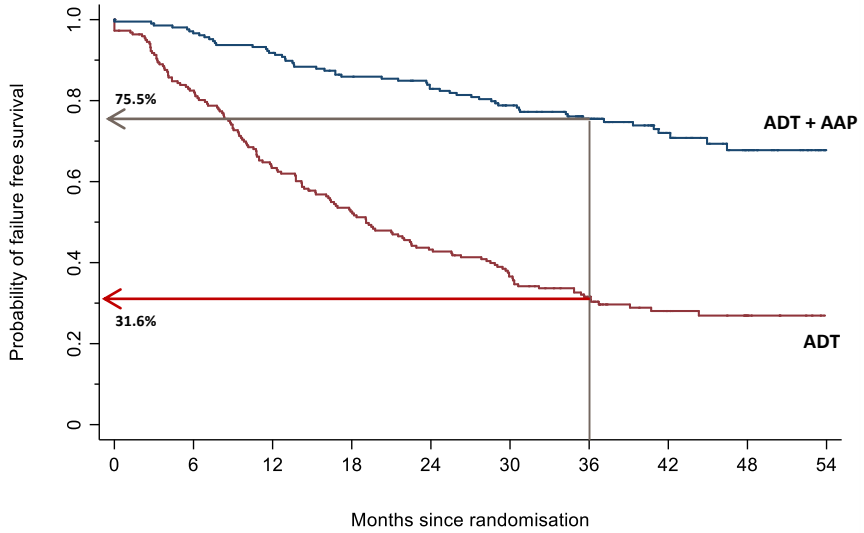
Hoyle, A et al; Proc ESMO 2018

OS - 4.4%
HR 0.66 (0.44-0.98)
p=0.041

OS – 19.7%
HR 0.54 (0.41-0.70)
p<0.001

RESULTS: FAILURE FREE SURVIVAL

Low Risk

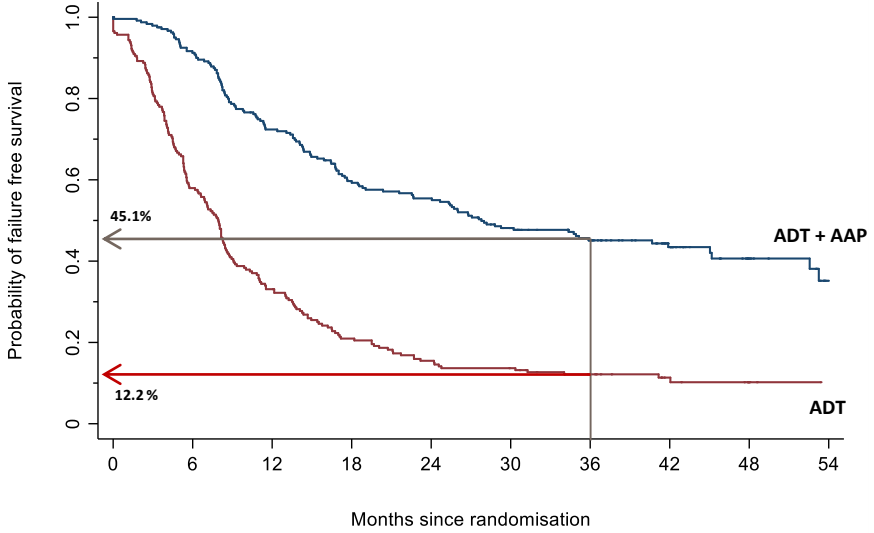


No. of patients (Events)

AAP	208	(17)	189	(18)	165	(14)	115	(7)	37
ADT alone	220	(79)	136	(43)	92	(24)	54	(6)	18

FFS – 43.9%
HR 0.24 (0.17-0.33)
p<0.001

High Risk



No. of patients (Events)

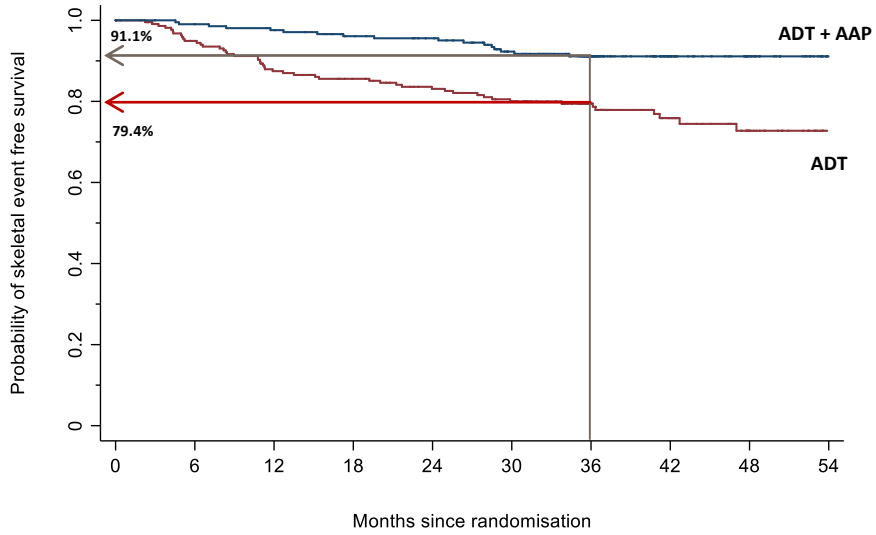
AAP	241	(66)	172	(40)	130	(23)	73	(4)	20
ADT alone	232	(154)	75	(39)	34	(7)	20	(2)	4

FFS – 27.8%
HR 0.31 (0.25-0.39)
p<0.001

Hoyle, A et al; Proc ESMO 2018

RESULTS: SKELETAL RELATED EVENT FREE SURVIVAL

Low Risk

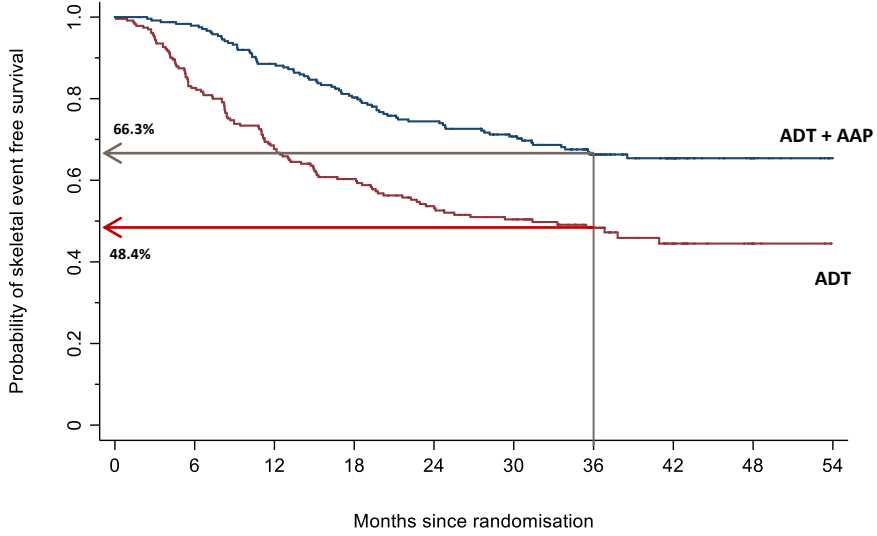


No. of patients (Events)

AAP	208	(5)	200	(4)	181	(8)	124	(0)	44
ADT alone	220	(27)	187	(9)	164	(7)	109	(6)	35

SRE – 11.7%
HR 0.31 (0.18-0.54), p<0.001

High Risk

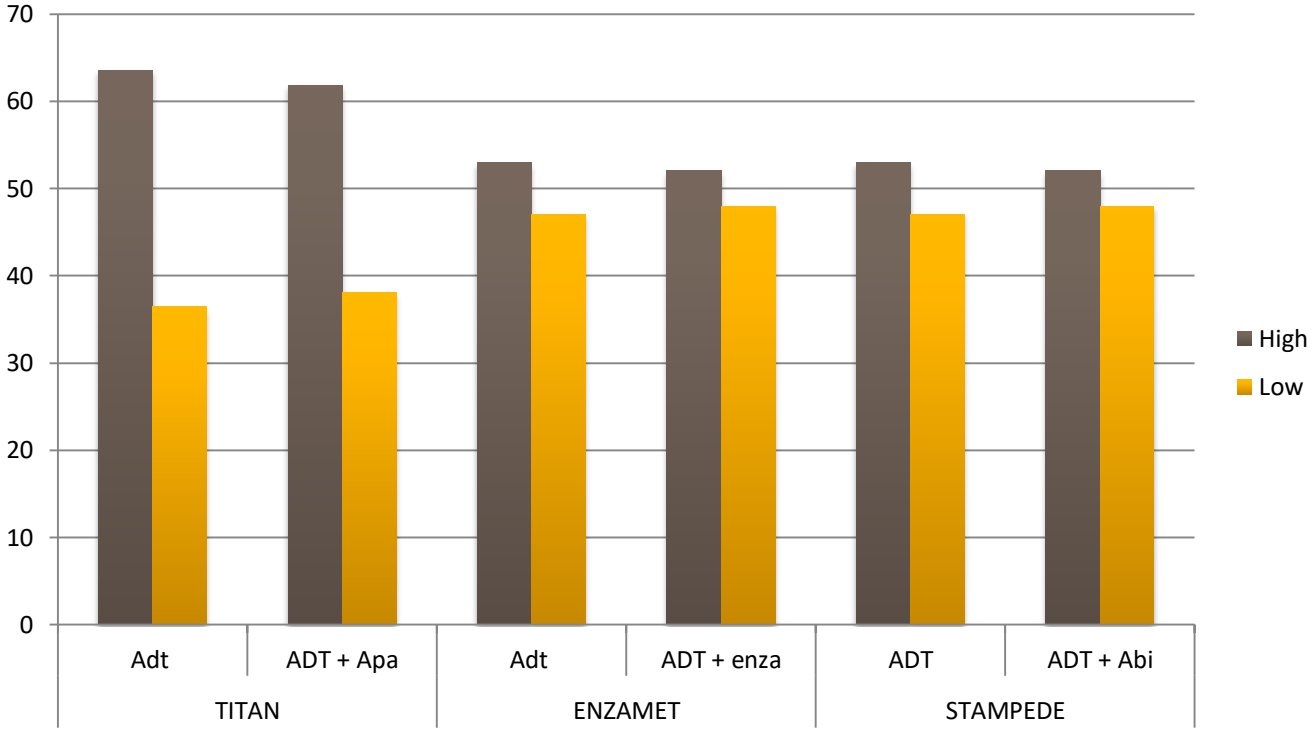


No. of patients (Events)

AAP	241	(27)	205	(32)	163	(16)	92	(1)	25
ADT alone	232	(74)	152	(29)	101	(9)	55	(3)	9

SRE – 17.9%
HR 0.48 (0.36-0.64), p<0.001

Risk groups – AR therapy trials



mHSPC – volume effects

- 3 drugs show no volume effects on overall survival
  - Abiraterone (STAMPEDE)
  - Enzalutamide (Enzamet)
  - Apalutamide (TITAN)
- Hazard ratios for improvement in survival very similar in patients not receiving docetaxel

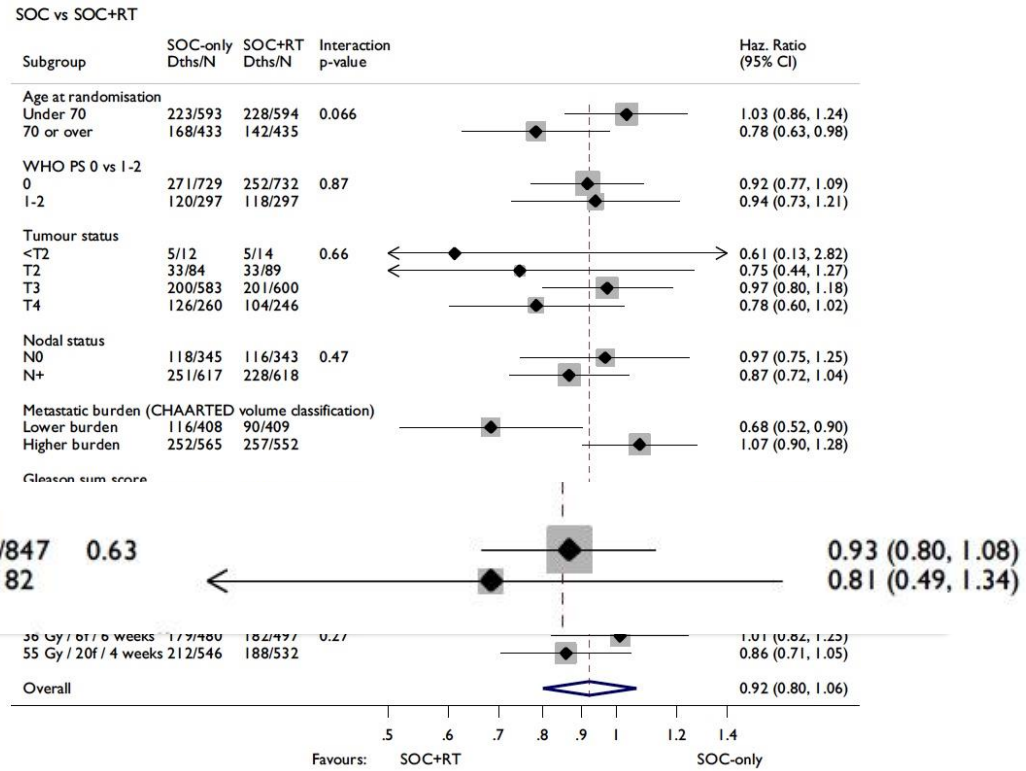
Which combinations in low volume disease?

- Combinations with good evidence
  - ADT + RT
  - ADT + docetaxel
  - ADT + androgen receptor targeting (ART)
- Combinations with weak evidence
  - ADT + docetaxel + androgen receptor targeting (ART)
  - ADT + docetaxel + RT
  - ADT + RT+ androgen receptor targeting (ART)

ADT + RT + docetaxel

Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial

Christopher C Parker, Nicholas D James, Christopher D Brawley, Noel W Clarke, Alex P Hoyle, Adnan Ali, Alastair W S Ritchie, Gerhardt Attard, Simon Chowdhury, William Cross, David P Dearnaley, Silke Gillessen, Clare Gilson, Robert J Jones, Ruth E Langley, Zafar I Malik, Malcolm D Mason, David Matheson, Robin Millman, J Martin Russell, George N Thalmann, Claire L Amos, Roberto Alonzi, Amit Bahl, Alison Birtle, Omar Din, Hassan Douis, Chinnamani Eswar, Joanna Gale, Melissa R Gannon, Sai Jonnada, Sara Khaksar, Jason F Lester, Joe M O'Sullivan, Omi A Parikh, Ian D Pedley, Delia M Pudney, Denise J Sheehan, Narayanan Nair Srihari, Anna T H Tran, Mahesh K B Parmar*, Matthew R Sydes*, on behalf of the Systemic Therapy for Advanced or Metastatic Prostate cancer: Evaluation of Drug Efficacy (STAMPEDE) investigators†

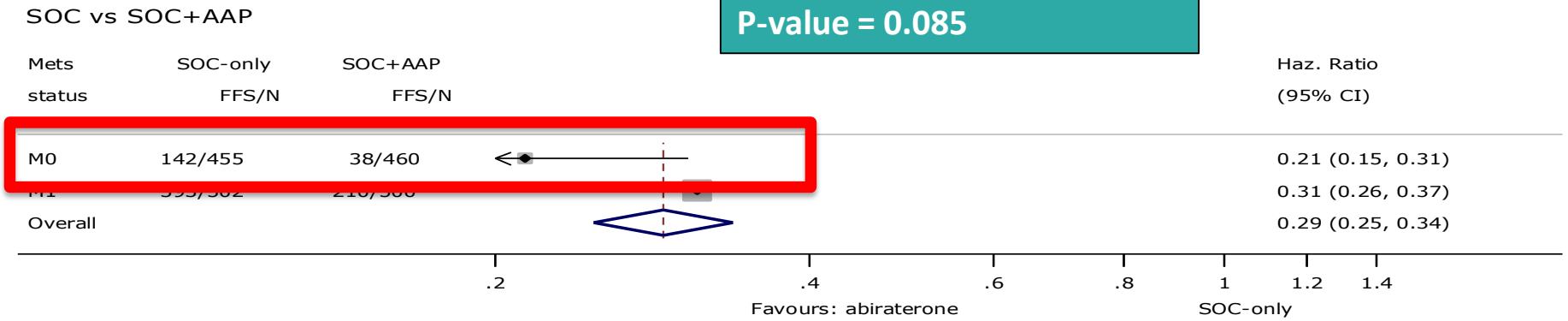


ADT + RT + abiraterone

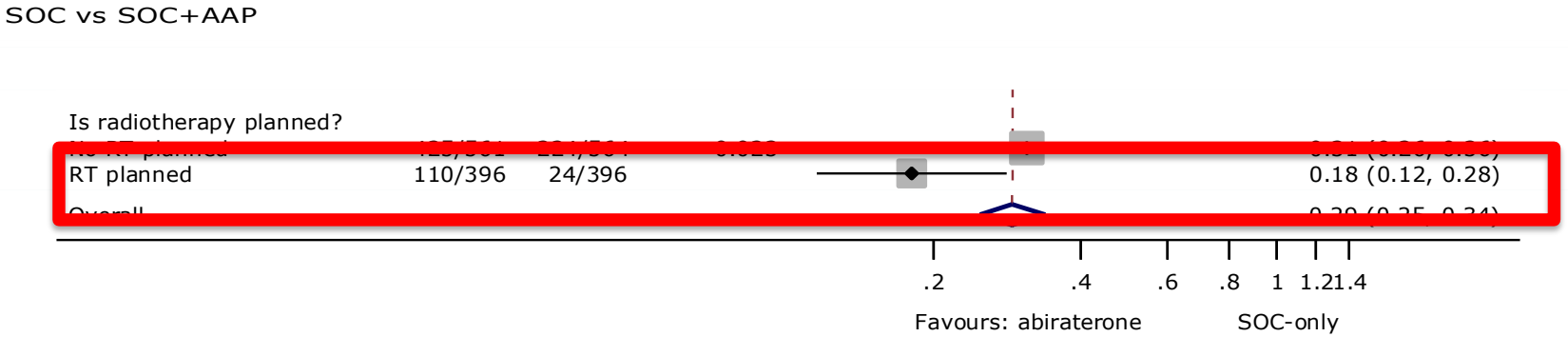
Failure-free survival

Events
535 Control | 248 Abiraterone

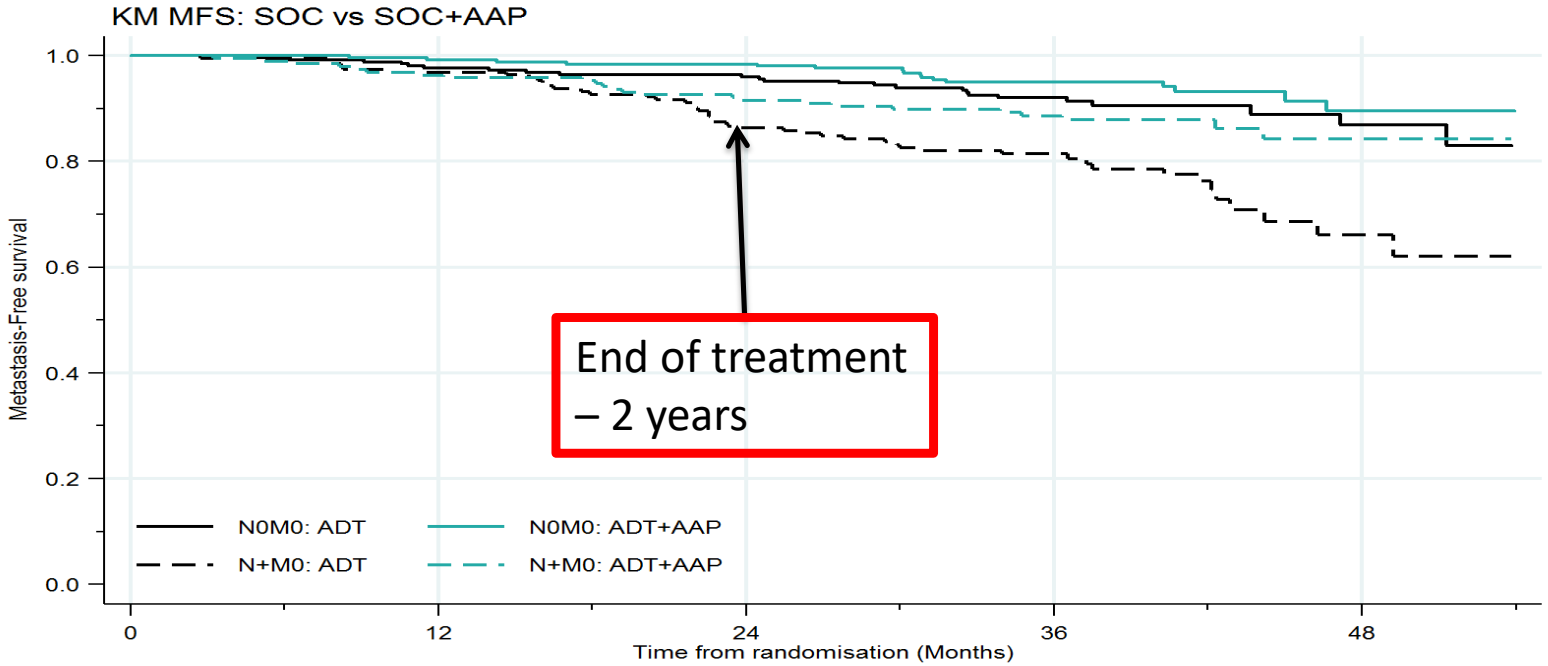
Mets * treatment interaction
P-value = 0.085



Failure-free survival



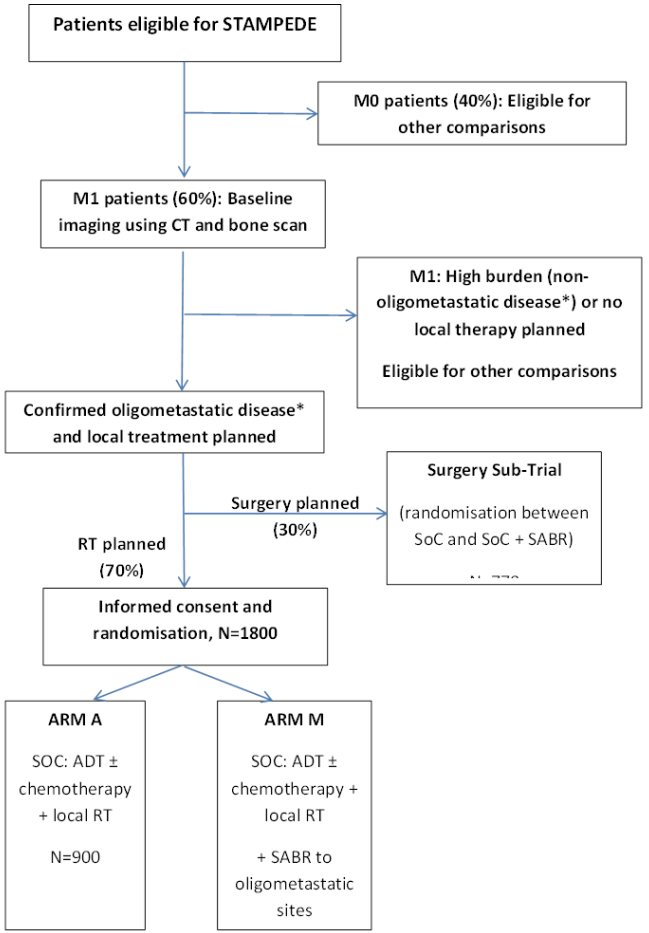
Metastasis-free survival in M0 subgroup



Number of patients (events)									
N0M0: ADT	252	(6)	244	(4)	237	(9)	150	(4)	31
N0M0: ADT+AAP	255	(2)	249	(2)	240	(8)	156	(4)	41
N+M0: ADT	192	(6)	185	(20)	163	(9)	101	(10)	22
N+M0: ADT+AAP	192	(7)	181	(9)	169	(5)	117	(3)	36

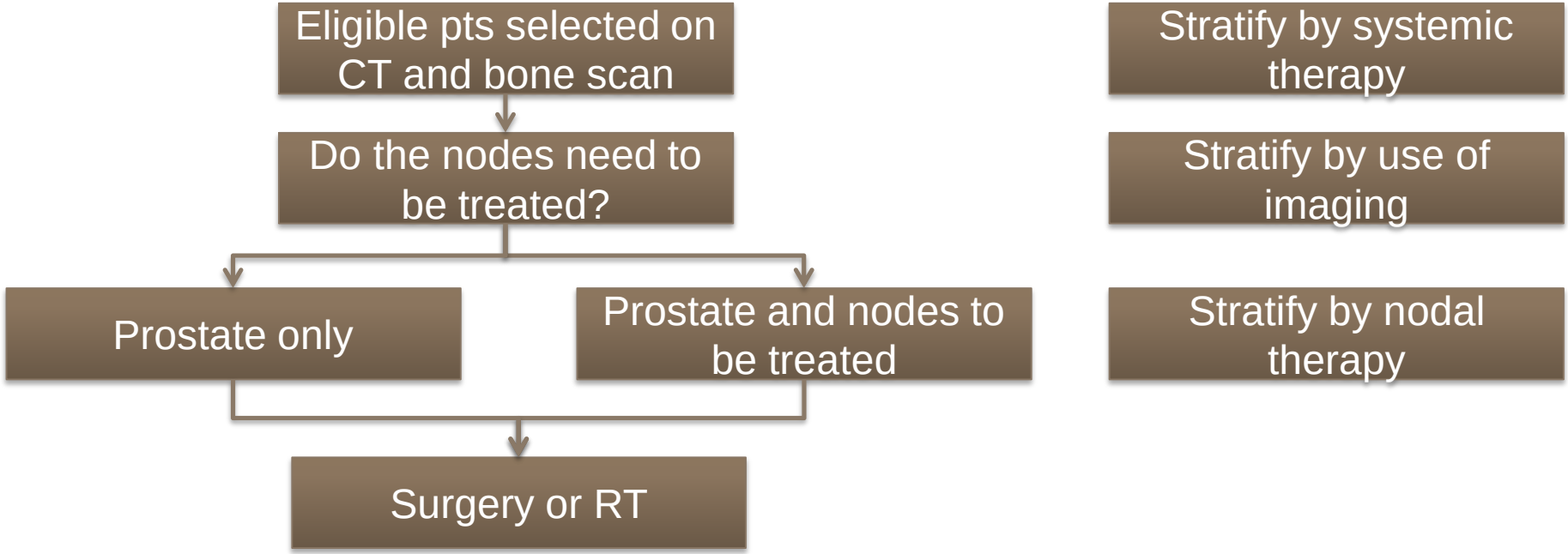
Trial schema for the oligometastatic comparison

STAMPEDE Arm M



** Oligometastatic disease defined as patients with 5 or fewer extra-pelvic metastases in bone and/or lymph node, as detected on baseline CT and bone scan*

Selection of therapy



Conclusion

- ADT plus 1 drug therapy improves survival in mHSPC
- ADT + radiotherapy improves survival in low volume mHSPC
- No good evidence to support 2 drug combinations with ADT
- The next STAMPEDE arm will address treatment to primary +/- SBRT to up to 5 metastases

STAMPEDE investigators

UNITED KINGDOM

- **Aberystwyth, Bronglais General Hospital** (*4;* S Durrani)
- **Ashford, William Harvey Hospital** (*0;* C Thomas, N Mithal)
- **Aylesbury, High Wycombe & Stoke Mandeville Hospital** (*1;* A Sabharwal, P Camilleri, C Alcock, J Brady, A Protheroe)
- **Ayr, Ayr Hospital** (*14;* H Glen, J Ansari, R Mahmood)
- **Barnet, Barnet General Hospital** (*14;* U McGovern, A Eichholz)
- **Barnstaple, North Devon District Hospital** (*25;* D Sheehan)
- **Basingstoke, Basingstoke and North Hampshire Hospital** (*12;* R Shaffer, T Guerrero-Urbano)
- **Bath, Royal United Hospital** (*22;* O Frim, M Beresford, H Newman, P Kehagioglou)
- **Bebington, Clatterbridge Centre for Oncology** (*64;* S Tolan, J Littler, I Syndikus, A Ibrahim, A Montazeri)
- **Belfast, Belfast City Hospital** (*118;* J O'Sullivan, D Mitchell, P Lin, D Stewart, S Jain)
- **Birmingham, Birmingham Heartlands Hospital** (*32;* A Zarkar)
- **Birmingham, City Hospital** (*24;* D Ford)
- **Birmingham, Queen Elizabeth Hospital** (**Birmingham)** (*141;* N James, E Porfiri, D Ford)
- **Blackburn, Royal Blackburn Hospital** (*62;* O Parikh)
- **Bolton, Royal Bolton Hospital** (*23;* T Elliott, M Pantelides)
- **Boston, Pilgrim Hospital** (*;* T Sreenivasan, M Panades)
- **Bournemouth, Royal Bournemouth Hospital** (*83;* S Brock, J Davies)
- **Bradford, Bradford Royal Infirmary** (*24;* S Brown)
- **Brighton, Royal Sussex County Hospital** (*63;* A Robinson, G Plataniotis, D Bloomfield, M Wilkins)
- **Bristol, Bristol Haematology & Oncology Centre** (*60;* A Bahl, M Beresford, S Hilman, P Wilson, C Herbert)
- **Burnley, Burnley General Hospital** (*8;* N Charnley, O Parikh)
- **Burton-on-Trent, Queens Hospital Burton** (*37;* S Chetiyawardana, D Muthukumar, P P
- **Bury St Edmunds, West Suffolk Hospital** (*16;* C Woodward, Y Rimmer)
- ar)
- C Thomas, N Mithal, R Raman, A Edwa
- J Lester, J Staffurth, J Tanguay, N Pala
- Sidek)
- U Panwar, P Leone)

Recognising more than **3,000 site staff** at more than 100 hospitals

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

STAMPEDE investigators

UNITED KINGDOM

- **Cheltenham, Cheltenham General Hospital** (*10;* J Bowen, P Jenkins)
- **Chester, Countess of Chester Hospital** (*66;* A Ibrahim)
- **Colchester, Essex County Hospital** (*7;* B Sizer, M Kumar)
- **Coventry, University Hospital Coventry and Warwickshire** (*24;* A Stockdale, J Worlding)
- **Crewe, Leighton Hospital** (*41;* J Wylie)
- **Darlington, Darlington Memorial Hospital** (*27;* J Hardman, C Peedell, M Kagzi, T Mukhopadhyay)
- **Derby, London Road Community Hospital** (*16;* P Chakraborti, D Muthukumar)
- **Derby, Royal Derby Hospital** (*71;* P Chakraborti, D Muthukumar, P Pattu)
- **Doncaster, Doncaster Royal Infirmary** (*0;* M Alzouebi, C Ferguson, M Alzouebi)
- **Dorchester, Dorset County Hospital** (*21;* P Crellin, S Andrews)
- **Dudley, Russells Hall Hospital** (*46;* P Ramachandra, P Keng-Koh)
- **Durham, University Hospital of North Durham** (*17;* R McMenemin)
- **Eastbourne, Eastbourne District General Hospital** (*52;* F McKinna)
- **Edinburgh, Western General Hospital** (*105;* D McLaren)
- **Edmonton, North Middlesex Hospital** (*15;* J Newby, A Thompson, S Karp, F Neave)
- **Exeter, Royal Devon and Exeter Hospital** (*102;* D Sheehan, R Srinivasan, V Ford)
- **Gillingham, Medway Maritime Hospital** (*18;* H Taylor)
- **Glasgow, Beatson W.Scotland Cancer Centre** (*41;* R Jones, M Russell, J Wallace, J Graham, R Mahmood, C Lamb, A Al-hasso, B Venugopal)
- **Guildford, Royal Surrey County Hospital** (*30;* R Laing, J Money-Kyrle, S Khaksar, K Wood, T Guerrero-Urbano)
- **Harlow, Princess Alexandra Hospital (Harlow)** (*10;* N Gupta, L Melcher)
- **Hereford, Hereford County Hospital** (*9;* W Grant, A Cook)
- **High Wycombe, Wycombe Hospital** (*15;* A Sabharwal, A Protheroe, P Camilleri, T Pwint
- **Huddersfield, Huddersfield Royal Infirmary** (*76;* U Hofmann)
- nms, J Hetherington)
- Kelly, A Sadozye, C Macgregor)
- araman, C Scrase, G Banerjee)
- n, M Crawford, C Sentamans)
- **l** (*19;* M Churn, L Capaldi)

Recognising more than **3,000 site staff** at more than 100 hospitals

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

STAMPEDE investigators

UNITED KINGDOM

- **Larbert, Forth Valley Royal Hospital** (*22;* N Sidek)
- **Leeds, St James University Hospital** (**Leeds)** (*26;* W Cross, S Prescott, D Bottomley, S Jain, C Loughrey, A Paul, A Henry, P Whelan)
- **Lincoln, Lincoln County Hospital** (*15;* T Sreenivasan, D Ballesteros-Quintail, M Panades, K Baria)
- **Liverpool, Royal Liverpool University Hospital** (*37;* Z Malik, C Eswar, P Robson)
- **Liverpool, Triemlispital** (*1;* D Siciliano)
- **Liverpool, University Hospital Aintree** (*16;* P Robson)
- **London, Charing Cross Hospital** (*26;* A Falconer)
- **London, Guy's Hospital** (*104;* S Chowdhury, P Harper, S Morris, R Popert, R Beaney)
- **London, Hammersmith Hospital** (*0;* A Falconer, S Mangar)
- **London, Queen Elizabeth Hospital** (**Woolwich)** (*18;* S Hughes)
- **London, Royal Free Hospital** (*15;* M Vilarino-Varela, K Pigott)
- **London, Royal Marsden Hospital** (*9;* V Khoo)
- **London, St Bartholomews Hospital** (*3;* K Tipples, P Wells)
- **London, St George's Hospital** (*29;* L Pickering)
- **London, St Mary's Hospital** (*0;* A Falconer, S Stewart)
- **London, University College Hospital** (*21;* U McGovern, S Harland, H Payne)
- **Maidstone, Maidstone Hospital** (*84;* S Beesley, A Clarke, H Taylor)
- **Manchester, Christie Hospital** (*1;* N Clarke, T Elliott, J Wylie, J Livsey, J Logue, R Cowan)
- **Manchester, Withington Hospital** (*7;* V Sangar)
- **Margate, Queen Elizabeth The Queen Mother Hospital** (*1;* C Thomas, R Raman, N Mithal)
- **Middlesbrough, James Cook University Hospital** (*31;* C Peedell, J Hardman, H Van, D Shakespeare, D Chadwick)
- **Newcastle-upon-Tyne, Freeman Hospital** (*21;* A Azzabi, R McMenemin, J Frew)
- **Northwood, Mount Vernon Hospital** (*19;* P Hoskin, R Alonzi, P Ostler, N Anyamene, R H
- **City Campus** (*59;* S Sundar, J Mills, E
- Choudhury)
- ble)

Recognising more than **3,000 site staff** at more than 100 hospitals

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

STAMPEDE investigators

UNITED KINGDOM

- **Portsmouth, Queen Alexandra Hospital** (*141;* J Gale)
- **Preston, Royal Preston Hospital** (*92;* A Birtle, O Parikh, M Wise)
- **Reading, Royal Berkshire Hospital** (*24;* P Rogers, H O'Donnell, R Brown)
- **Redditch, Alexandra Hospital** (*13;* J Hamilton)
- **Romford, Queen's Hospital (Romford)** (*74;* S Gibbs, R Subramaniam)
- **Salford, Salford Royal Hospital** (*48;* N Clarke, M Lau, T Elliott)
- **Scarborough, Scarborough General Hospital** (*59;* M Hingorani)
- **Sheffield, Weston Park Hospital** (*67;* C Ferguson, P Kirkbride, M Alzouebi, T Das)
- **Shrewsbury, Royal Shrewsbury Hospital** (*116;* N Srihari, R Prashant)
- **South Shields, South Tyneside District Hospital** (*5;* A Azzabi)
- **Southampton, Southampton General Hospital** (*48;* C Heath, S Crabb, M Wheater)
- **Southport, Southport and Formby District General Hospital** (*29;* N Bhalla, C Eswar, A Sivapalasuntharam)
- **St Leonards-on-Sea, Conquest Hospital** (*5;* F McKinna, K Lees, S Beesley)
- **Stevenage, Lister Hospital** (*27;* R Hughes)
- **Stockport, Stepping Hill Hospital** (*90;* J Logue, A Adeyoju)
- **Stockton-on-Tees, University Hospital of North Tees** (*10;* D Shakespeare)
- **Stoke-on-Trent, Royal Stoke Hospital** (*56;* F Adab, R Bhana)
- **Sunderland, Sunderland Royal Hospital** (*22;* A Azzabi, I Pedley)
- **Sutton, Royal Marsden Hospital (Sutton)** (*104;* D Dearnaley, C Parker, R Huddart, V Khoo)
- **Sutton Coldfield, Good Hope Hospital** (*15;* D Ford)
- **Sutton-in-Ashfield, King's Mill Hospital** (*35;* D Saunders, G Walker)
- **Swansea, Singleton Hospital** (*122;* J Wagstaff, G Bertelli, D Pudney, M Phan)
- **Swindon, Great Western Hospital** (*40;* D Cole, E Hill)
- Graham, M Varughese, M Keni, G Plat
- A Lydon, R Srinivasan)
- s, S Tolan)

Recognising more than **3,000 site staff** at more than 100 hospitals

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

STAMPEDE investigators

UNITED KINGDOM

- **Westcliff on Sea, Southend University Hospital** (*51;* D Tsang, I Ahmed, O Chan, N Sarwar)
- **Weston Super Mare, Weston General Hospital** (*12;* S Hilman)
- **Whitehaven, West Cumberland Hospital** (*1;* J Nicoll)
- **Wigan, Royal Albert Edward Infirmary** (*22;* A Tran, R Cowan)
- **Wolverhampton, New Cross Hospital, Wolverhampton** (*19;* I Sayers)
- **Worcester, Worcestershire Royal Hospital** (*19;* L Capaldi, J Bowen)
- **Worthing, Worthing Hospital** (*59;* A Nikapota, D Bloomfield, F Castell)
- **Yeovil, Yeovil District Hospital** (*3;* E Gray, G Sparrow)
-

SWITZERLAND

- **Aarau, Hirslanden Medical Centre** (*3;* R Popescu)
- **Basel, Universitätsspital Basel** (*2;* C Reutsch, B Seifest)
- **Berne, Inselspital** (*2;* G Thalmann, B Roth)
- **Chur, Kantonsspital Graubünden** (*8;* R Strebel, R Cathomas)
- **Lausanne, Centre Hospitalier Universitaire Vaudois** (*2;* D Berthold, P Jichlinski, F Herrera)
- **St Gallen, Kantonsspital St Gallen** (*5;* D Engeler, S Prensser)

Recognising more than **3,000 site staff** at more than 100 hospitals

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

STAMPEDE Trial Management Group

Trial Management Group members

Current N James (chair); G Attard, S Chowdhury, N Clarke, S Gillessen, R Langley, C Parker; W Cross, D Dearnaley, D Gilbert, R Jones, Z Malik, JM Russell; A Adler

Ex D Aebersold, J Anderson, J de Bono, M Mason A Ritchie, R Popert

Patient Public Involvement (PPI)

Current D Matheson, R Millman

Ex J Dwyer, D Hoe-Richardson, J Stansfeld

STAMPEDE oversight committees and partners

Independent Data Monitoring Committee (IDMC)

Current John Yarnold (chair), Richard Emsley, Bertrand Tombal, Ronald De Wit

Ex Chris Williams (ex-chair), Doug Altman, Reg Hall

Trial Steering Committee (TSC)

Current James Larkin (chair), Tim Clayton, Jan-Erik Damber, Alan Horwich,

Ex Jonathan Ledermann, Richard Emsley, John Fitzpatrick,

Industry partners

Astellas

Clovis Oncology

Janssen

Novartis

Pfizer

Sanofi-Aventis

STAMPEDE CTU team

MRC Clinical Trials Unit at UCL

Current M Sydes, M Parmar, C Brawley, L Brown,
A Cook, F Ingleby, L James, M Nankivell;
D Gilbert, H Rush; N Atako, C Amos, C Pugh;
M Anjum, M Buckner, J Calvert, C Murphy,
C Wanstall, S Miller; C Au, L Bergstrom,
S Khan, T Phillips, P Vaughan; D Hague,
Z Islam, N Vanlooy

Ex E Ades, S Begum, A Brown, T Fairfield, H Gardner,
C Green, Z Khan, J Latham, N Kelk, S Naylor,
J Nuttall, S Peres, O Prendiville, K Sanders,
F S
G J

Acknowledgements

Thanks to:

Adnan Ali
Alex Hoyle
Claire Amos
Chris Parker
Emily Grist
Gert Attard
David Dearnaley
Dominic Hague
Francesca Schiavone
Lindsey Masters
Louise Brown
Malcolm Mason
Max Parmar
Melissa Spears
Nafisah Atako
Nick James
Noel Clarke
Patrick Royston
Ruth Langley
Simon Chowdhury
Stephen Townsend
Zaf Malik

Special thanks to:

Everyone involved with STAMPEDE


SCT
SOCIETY FOR CLINICAL TRIALS
2017 DAVID SACKETT
TRIAL OF THE YEAR AWARD
STAMPEDE
PRESENTED
MAY 23, 2018