

Optimal Treatment of Newly Diagnosed Metastatic Prostate Cancer

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ORIGINAL ARTICLE

Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer

Christopher J. Sweeney, M.B., B.S., Yu-Hui Chen, M.S., M.P.H., Michael Carducci, M.D., Glenn Liu, M.D., David F. Jarrard, M.D., Mario Eisenberger, M.D., Yu-Ning Wong, M.D., M.S.C.E., Noah Hahn, M.D., Manish Kohli, M.D., Matthew M. Cooney, M.D., Robert Dreicer, M.D., Nicholas J. Vogelzang, M.D., Joel Picus, M.D., Daniel Shevrin, M.D., Maha Hussain, M.B., Ch.B., Jorge A. Garcia, M.D., and Robert S. DiPaola, M.D.

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, parallel randomised controlled trial

Nicholas D James, Matthew R Sydes, Noel W Clarke, Malcom D Mason, David P Dearnaley, Melissa B Spears, Alastair W S Ritchie, Christopher C Parker, J Martin Russell, Gerhardt Attard, Joanne de Bono, William Cross, Rob Jones, George Thalmann, Claire Amos, David Matheson, Robin Millman, Myrona Alzouabi, Sharon Breda, Alison Birtle, Savannah Brock, Richard Cathomas, Peter Chabot, Simon Chowdhury, Audrey Cook, Tony Ellard, Joanna Gale, Stephanie Gibbs, John D Graham, John Hetherington, Robert Hughes, Robert Lester, Fiona McEneaney, Dorian M McEneaney, Joe M O'Sullivan, Clive Parke, Clive Prodd, Andrew Protheroe, Angus J Robinson, Narayanan Srihari, Rajaguru Subramanian, John Stephens, Sartham Sundar, Shaun Tolan, David Tang, John Wagstaff, Mahesh K B Parmar, for the STAMPEDE investigators*

Summary Background Long-term hormone therapy has been the standard of care for advanced prostate cancer since the 1940s. STAMPEDE is a randomised controlled trial using a multiarm, multistage platform design. It recruits men with high-risk, locally advanced, metastatic or recurrent prostate cancer who are starting first-line long-term hormone therapy. We report primary survival results for three research comparisons testing the addition of zoledronic acid, docetaxel, or their combination to standard of care versus standard of care alone.

Methods Standard of care was hormone therapy for at least 2 years; radiotherapy was encouraged for men with N0M0 disease to November 2011, then mandated; radiotherapy was optional for men with node-positive non-metastatic (N+M0) disease. Stratified randomisation (via minimisation) allocated men 2:1:1:1 to standard of care only (SOC-only; control), standard of care plus zoledronic acid (SOC+ZA), standard of care plus docetaxel (SOC+Doc), or standard of care with both zoledronic acid and docetaxel (SOC+ZA+Doc). Zoledronic acid (4 mg) was given for six 3-weekly cycles, then 4 weekly until 2 years, and docetaxel (75 mg/m²) for six 3-weekly cycles with prednisolone 10 mg daily. There was no blinding to treatment allocation. The primary outcome measure was overall survival. Pairwise comparisons of research versus control had 90% power at a 2.5% one-sided α for hazard ratio (HR) ≥ 0.75 , requiring roughly 400 control-arm deaths. Statistical analyses were undertaken using standard log-rank-type methods for time-to-event data, with hazard ratios (HRs) and 95% CIs derived from adjusted Cox models. This trial is registered at ClinicalTrials.gov (NCT00268476) and ControlledTrials.com (158CTN78818544).

Findings 2962 men were randomly assigned to four groups between Oct 5, 2005, and March 31, 2013. Median age was 65 years (IQR 60–71). 1817 (61%) men had M+ disease, 448 (15%) had N+X M0, and 697 (24%) had N0M0. 165 (6%) men were previously treated with local therapy, and median prostate-specific antigen was 65 ng/mL (IQR 23–184). Median follow-up was 43 months (IQR 30–60). There were 415 deaths in the control group (147 [14%] prostate cancer). Median overall survival was 71 months (IQR 32 to not reached) for SOC-only, not reached (32 to not reached) for SOC+ZA (HR 0.94, 95% CI 0.79–1.11; $p=0.450$), 81 months (41 to not reached) for SOC+Doc (0.78, 0.66–0.93; $p=0.006$), and 75 months (39 to not reached) for SOC+ZA+Doc (0.82, 0.69–0.97; $p=0.023$). There was no evidence of heterogeneity in treatment effect (any of the treatments) across prespecified subgroups. Grade 3–5 adverse events were reported for 399 (32%) patients receiving SOC, 197 (32%) receiving SOC+ZA, 288 (52%) receiving SOC+Doc, and 269 (52%) receiving SOC+ZA+Doc.

Interpretation Zoledronic acid showed no evidence of survival improvements and should not be part of standard of care for this population. Docetaxel chemotherapy, given at the time of long-term hormone therapy initiation, showed evidence of improved survival accompanied by an increase in adverse events. Docetaxel treatment should be part of standard of care for adequately fit men commencing long-term hormone therapy.

Funding Cancer Research UK, Medical Research Council, Novartis, Sanofi-Aventis, Pfizer, Janssen, AstraZenca, NHR Clinical Research Network, Swiss Group for Clinical Cancer Research.

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ORIGINAL ARTICLE

Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer

I.D. Davis, A.J. Martin, M.R. Stockler, S. Begbie, K.N. Chi, S. Chowdhury, X. Coskinas, M. Frydenberg, W.E. Hague, L.G. Horvath, A.M. Joshua, N.J. Lawrence, G. Marx, J. McCaffrey, R. McDermott, M. McJannett, S.A. North, F. Parris, W. Parulekar, D.W. Pook, M.N. Reaume, S.K. Sandhu, A. Tan, T.H. Tan, A. Thomson, E. Tu, F. Vera-Badillo, S.G. Williams, S. Yip, A.Y. Zhang, R.R. Zielinski, and C.J. Sweeney, for the ENZAMET Trial Investigators and the Australian and New Zealand Urogenital and Prostate Cancer Trials Group*

ABSTRACT

BACKGROUND

Enzalutamide, an androgen-receptor inhibitor, has been associated with improved overall survival in men with castration-resistant prostate cancer. It is not known whether adding enzalutamide to testosterone suppression, with or without early docetaxel, will improve survival in men with metastatic, hormone-sensitive prostate cancer.

METHODS

In this open-label, randomized, phase 3 trial, we assigned patients to receive testosterone suppression plus either open-label enzalutamide or a standard nonsteroidal antiandrogen therapy (standard-care group). The primary end point was overall survival. Secondary end points included progression-free survival as determined by the prostate-specific antigen (PSA) level, clinical progression-free survival, and adverse events.

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Davis at Level 2, 5 Arnold St., Box H18, VIC 3128, Australia, or at ian.davis@monash.edu.

*A full list of the investigators in the ENZAMET Trial is provided in the Supplementary Appendix, available at NEJM.org.

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ORIGINAL ARTICLE

Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer

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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 Gillissen, Clare Gilson, Robert 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 Doss, Chinnamani Eswar, Joanna Gale, Melissa R Gannon, Saijonnada, 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†

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. Gillissen, C.C. Parker, J.M. Russell, D.R. Berthold, C. Brawley, F. Adab, S. Aug, 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. McKinn, 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 multiarm, 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 radiologically detectable and for patients with metastatic disease

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. James at the Institute of Cancer and Genomic Sciences, University of Birmingham, Edgbaston, Birmingham B15 2TT, United Kingdom, or at mectustampede...publications@ucl.ac.uk.

*A complete list of the Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy

ORIGINAL ARTICLE

Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer

Karim Fizazi, M.D., Ph.D., NamPhuong Tran, M.D., Luis Fein, M.D., Nobuaki Matsubara, M.D., Alfredo Rodríguez-Antón, M.D., Ph.D., Boris Y. Alakseyev, M.D., Mustafa Özgüroğlu, M.D., Dingwei Ye, M.D., Susan Feyerabend, M.D., Andrew Protheroe, M.D., Ph.D., Peter De Porre, M.D., Thian Khoo, Ph.D., Youn C. Park, Ph.D., Mary B. Todd, D.O., and Kim N. Chi, M.D., for the LATITUDE Investigators*

ABSTRACT

BACKGROUND

Abiraterone acetate, a drug that blocks endogenous androgen synthesis, plus prednisone is indicated for metastatic castration-resistant prostate cancer. We evaluated the clinical benefit of abiraterone acetate plus prednisone with androgen-deprivation therapy in patients with newly diagnosed, metastatic, castration-sensitive prostate cancer.

METHODS

In this double-blind, placebo-controlled, phase 3 trial, we randomly assigned 1199 patients to receive either androgen-deprivation therapy plus abiraterone acetate (1000 mg daily, given once daily as four 250-mg tablets) plus prednisone (5 mg daily) (the abiraterone group) or androgen-deprivation therapy plus dual placebos (the placebo group). The two primary end points were overall survival and radiographic progression-free survival.

RESULTS

After a median follow-up of 30.4 months at a planned interim analysis (after 406 patients had died), the median overall survival was significantly longer in the abiraterone group than in the placebo group (not reached vs. 34.7 months) (hazard ratio for death, 0.62; 95% confidence interval [CI], 0.51 to 0.76; $P<0.001$). The median length of radiographic progression-free survival was 33.0 months in the abiraterone group and 14.8 months in the placebo group (hazard ratio for disease progression or death, 0.47; 95% CI, 0.39 to 0.55; $P<0.001$). Significantly better outcomes in all secondary end points were observed in the abiraterone group, including the time until pain progression, next subsequent therapy for prostate cancer, initiation of chemotherapy, and prostate-specific antigen progression ($P<0.001$ for all comparisons), along with next symptomatic skeletal events ($P=0.009$). These findings led to the unanimous recommendation by the independent data and safety monitoring committee that the trial be unblinded and crossover be allowed for patients in the placebo group to receive abiraterone. Rates of grade 3 hyperkalemia and hypokalemia were higher in the abiraterone group.

CONCLUSIONS

The addition of abiraterone acetate and prednisone to androgen-deprivation therapy significantly increased overall survival and radiographic progression-free survival in men with newly diagnosed, metastatic, castration-sensitive prostate cancer. Funded by Janssen Research and Development, LATITUDE ClinicalTrials.gov number, NCT01715285.

From Gustave Roussy, University of Paris Sud, Villejuif, France (K.F.); Janssen Research and Development, Los Angeles (N.T.), Bessie, Belgium (P.D.P.), San Diego, CA (T.K.), and Raritan, NJ (Y.C.P.); Instituto de Oncología de Rosario, Rosario, Argentina (L.F.); National Cancer Center Hospital East, Chiba, Japan (N.M.); 12 de Octubre University Hospital, Madrid (A.S.A.); P.A. Hertsen Moscow Cancer Research Institute, Moscow (B.Y.A.); Cerrahpaşa Medical Faculty, Istanbul University, Istanbul, Turkey (M.O.); Fudan University Shanghai Cancer Center, Shanghai, China (D.Y.); Stadelmann Urologie, Nuremberg, Germany (S.T.); Oxford University Hospitals Foundation NHS Trust, Oxford, United Kingdom (A.P.); Janssen Global Services, Raritan, NJ (M.B.T.); and BC Cancer Agency, Vancouver, Canada (K.N.C.). Address reprint requests to Dr. Fizazi at the Department of Cancer Medicine, Gustave Roussy, University of Paris Sud, 114 Rue Edouard Belin, Villejuif 94800, France, or at karim.fizazi@gustaveroussy.fr.

*A complete list of the LATITUDE investigators is provided in the Supplementary Appendix, available at NEJM.org.

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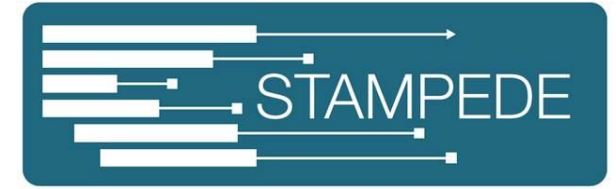
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Local and Systemic Therapy

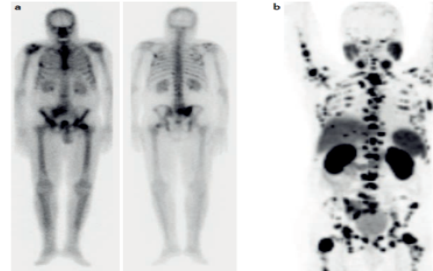
“VOLUME” “RISK” AND BENEFIT

STAMPEDE Biomedical Imaging Group (BIG)

STAMPEDE Biomedical Research Group (BRG)



- @5000 CT and Bone Scans centralised
- Treatment Response Scans currently being collected
- Aim is for >10,000
- Scans linked to outcome/pathology
- Annotated for met type/location/size



Alex Hoyle
Adnan Ali
Anie Haran
Thomas Hambrock
Hassan Douis
Noel Clarke
MRC CTU

Volume / Risk Consort Diagram for Docetaxel Analysis

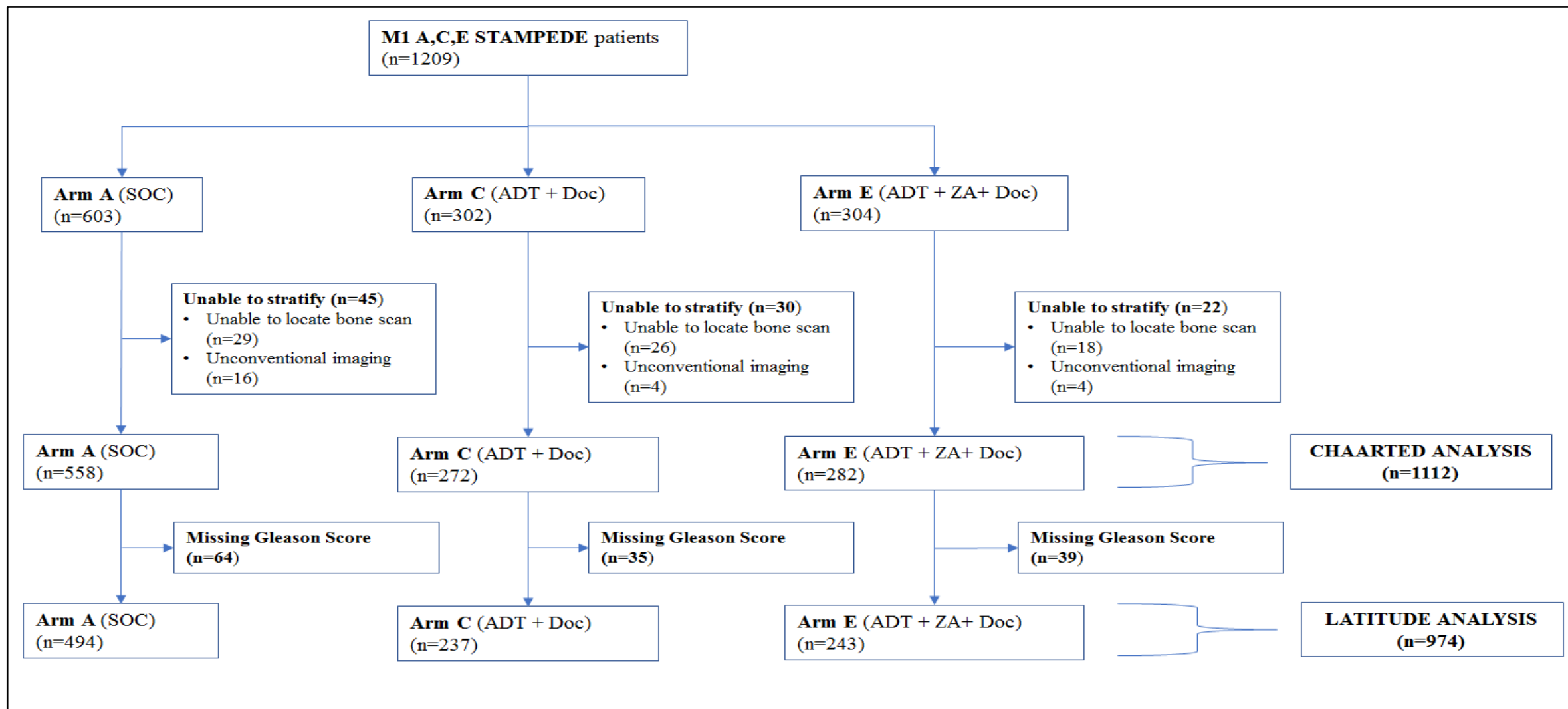
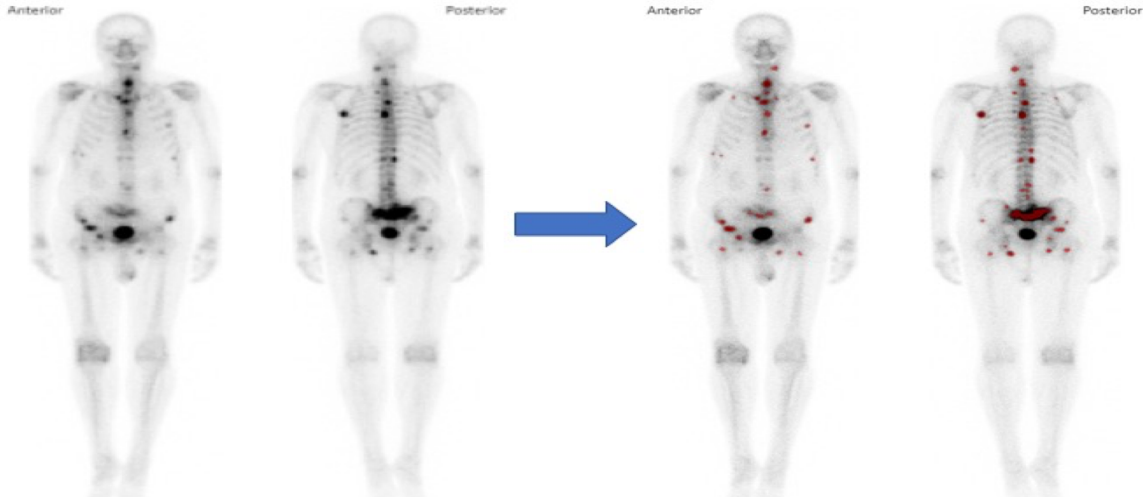


Image Analysis

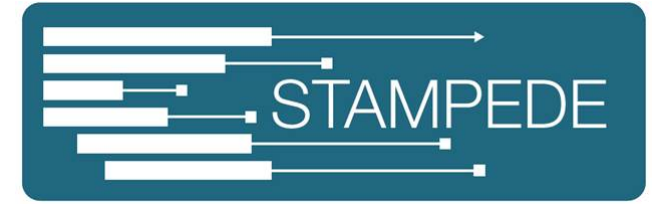


Measured Endpoint	Endpoint definition / components
Overall Survival	Time from randomisation to death of any cause
Failure Free Survival	Time from randomisation to radiological, clinical, biochemical failure or death of any cause
Skeletal Related Events	Time from randomisation to pathological fracture, spinal cord compression or prophylactic surgery/radiotherapy
Progression Free Survival	Time from randomisation until clinical, radiological or death from PCa
Prostate Cancer Specific Survival	Time from randomisation to death attributed to PCa.

Location of metastasis	Definition of radiological metastasis														
Non-Regional Lymph node metastasis (CT/MRI imaging)	<p>Royal college of radiology, Lymph node size criteria, Regional size criteria (Appendix 4) ²³⁷</p> <p>Mediastinum</p> <table> <tr> <td>Subcarinal</td><td>12mm</td></tr> <tr> <td>Retrocrural</td><td>6mm</td></tr> </table> <p>Abdomen /</p> <table> <tr> <td>Gastrohepatic ligament</td><td>8mm</td></tr> <tr> <td>Porta Hepatis</td><td>8mm</td></tr> <tr> <td>Portacaval</td><td>10mm</td></tr> <tr> <td>Coeliac axis to renal artery</td><td>10mm</td></tr> <tr> <td>Renal Artery to aortic bifurcation</td><td>12mm</td></tr> </table> <p>Differentiate in database between;</p> <p>Measurable lesion >15mm (RECIST 1.1⁷⁸)</p> <p>Non-Measurable lesion <10mm (RECIST 1.1)⁷⁸</p>	Subcarinal	12mm	Retrocrural	6mm	Gastrohepatic ligament	8mm	Porta Hepatis	8mm	Portacaval	10mm	Coeliac axis to renal artery	10mm	Renal Artery to aortic bifurcation	12mm
Subcarinal	12mm														
Retrocrural	6mm														
Gastrohepatic ligament	8mm														
Porta Hepatis	8mm														
Portacaval	10mm														
Coeliac axis to renal artery	10mm														
Renal Artery to aortic bifurcation	12mm														
Visceral metastasis (CT/MRI imaging)	<p>Any measurable abnormality within affected organ as recorded on Stampede CRF.</p> <p>Differentiate in database between;</p> <p>Measurable lesion >10mm (RECIST 1.1⁷⁸)</p> <p>Non-Measurable lesion <10mm (RECIST 1.1⁷⁸)</p>														
Bone metastasis (Bone Scintigraphy)	<p>Any area of focal asymmetrical increased tracer uptake, in the absence of clinical report to the contrary, in patients with bone metastasis as recorded within the Stampede trial CRFs.</p>														

The Management of “Low Volume” Metastatic Disease

The “Threshold” Effect for Primary Treatment Using Radiotherapy



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.

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 Langle, 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, Saijonnada, 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†*

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Stampede Arm H: RT M1 Results

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, Adrian AU, Alistair W S Ritchie, Gerhardt Altland, Simon Chowdhury, William Cross, David P Dearnaley, Silke Gillman, Clare Gilson, Robert Jones, Ruth E Langley, Zofia Malik, Malcolm D Mason, David Matheson, Robin Millman, Martin Russell, George N Thalmann, Claire J Amos, Roberto Alonz, Amit Bahl, Alioune Barte, Omar Din, Hassan Davis, Chinmoyi Eswar, Joanna Gale, Melissa R Gannon, Sajjanna, Sara Khakhar, Jason F Lester, Joe M O'Sullivan, Omi A Parkh, Ian D Preley, Delia M Pudney, Denise J Sheehan, Nanyan Nair Selvar, 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†

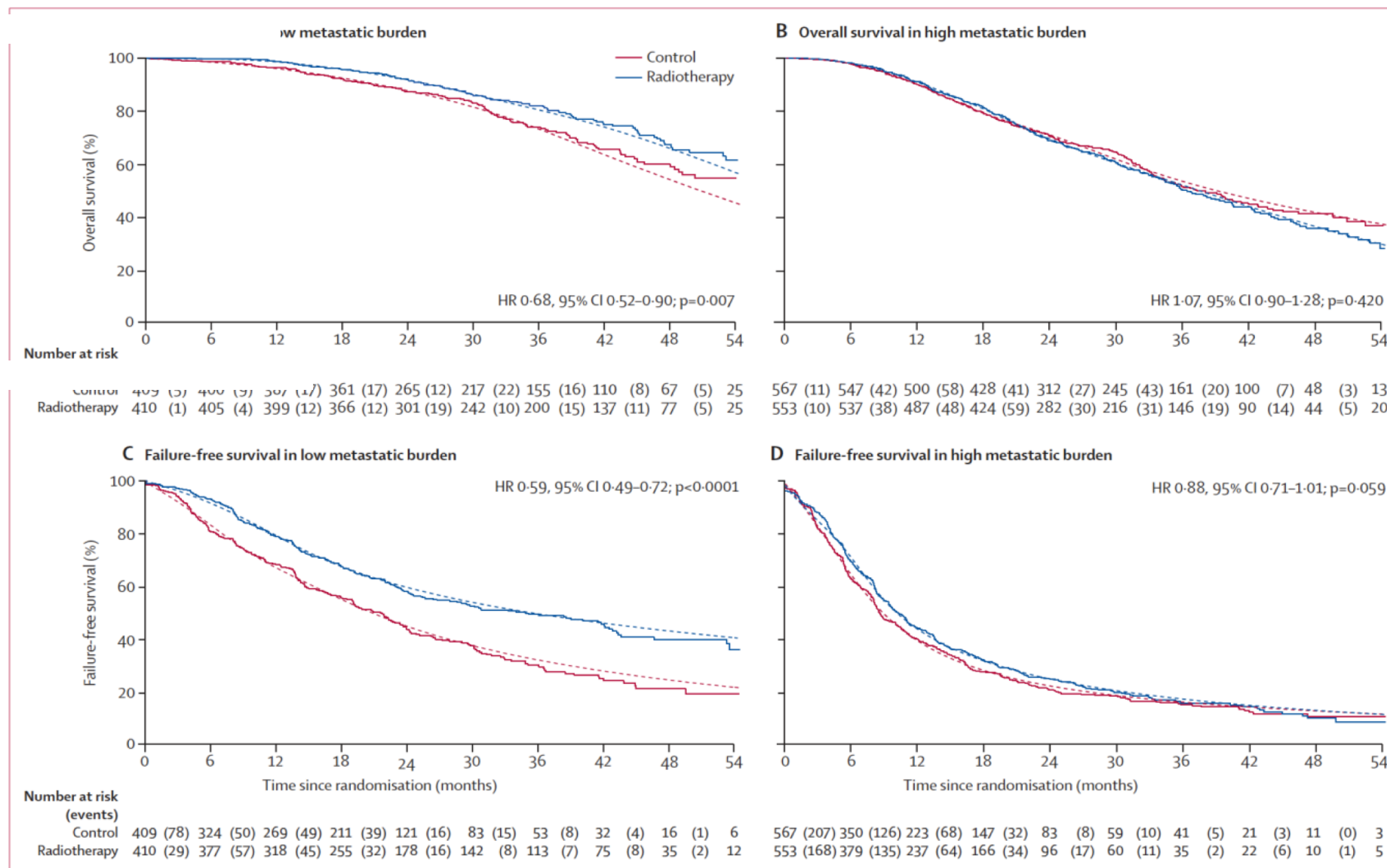


Figure 4: Overall survival and failure-free survival by treatment and metastatic burden

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Overall survival: Pre-Specified Subgroup Analysis by Metastatic Disease Burden

Subgroup	SOC-only Dths/N	SOC+RT Dths/N	Interaction p-value	Haz. Ratio (95% CI)
Metastatic burden (CHAARTED volume classification)				
Low burden	116/408	90/409	0.0098	0.68 (0.52, 0.90)
High burden	252/565	257/552		1.07 (0.90, 1.28)
Overall				0.92 (0.80, 1.06)

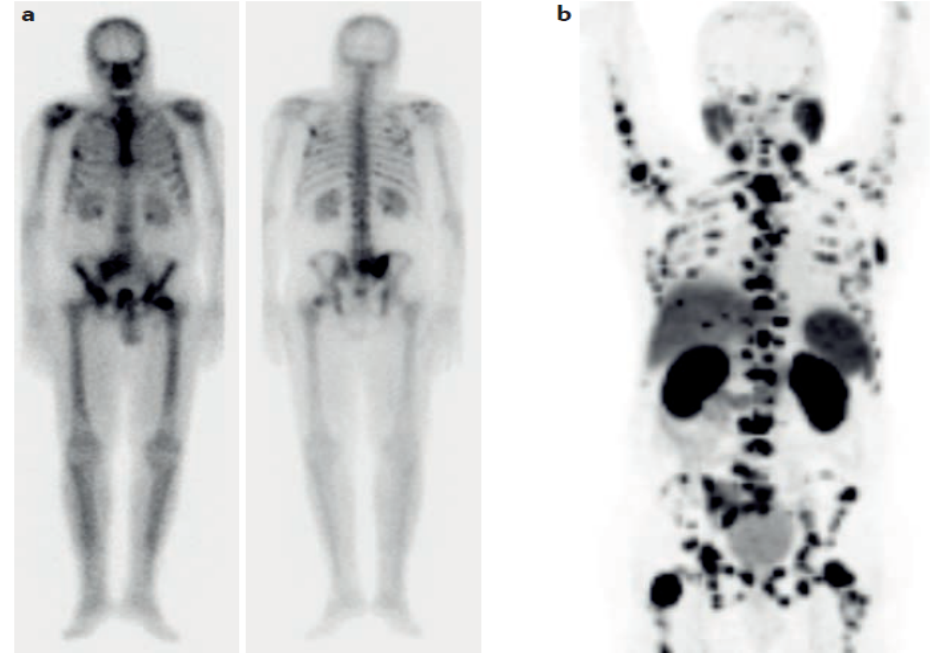
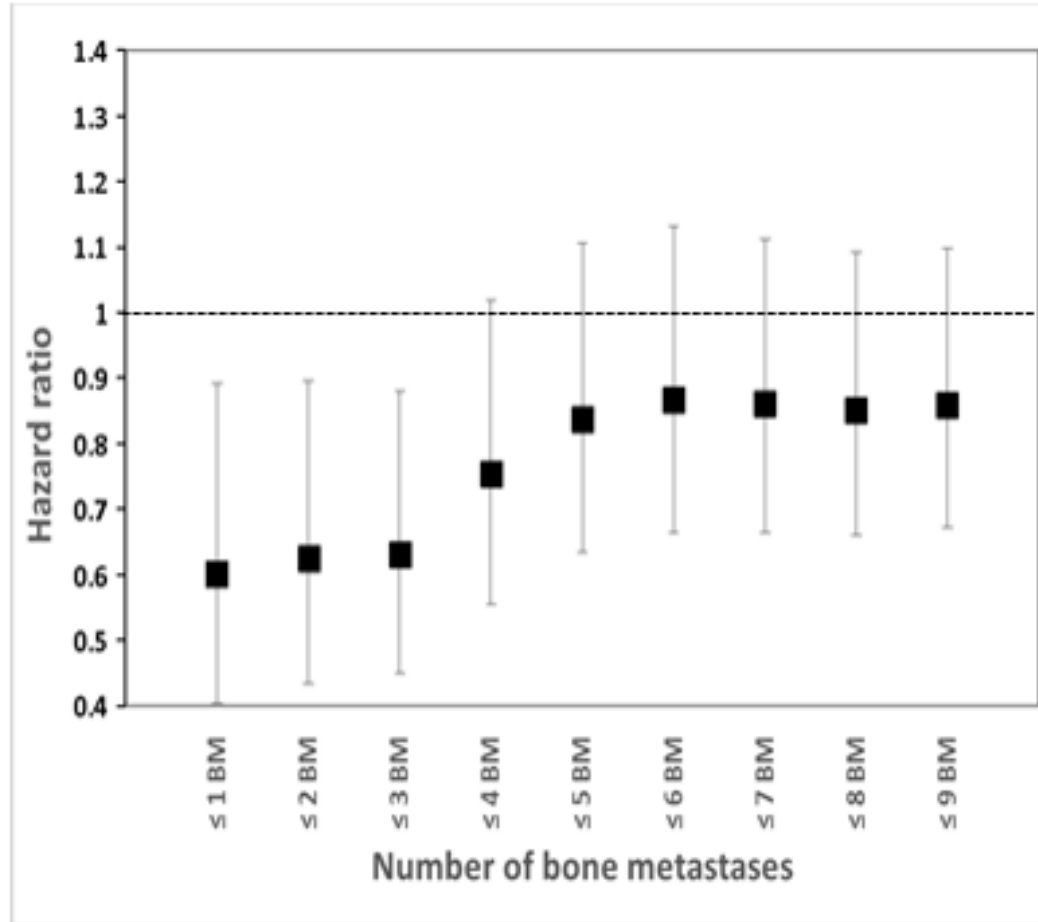
Clear evidence that effect size does differ by disease burden (p=0.0098)

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 Brouley, Noel W Clarke, Alex P Hoyle, Adrian Ali, Alastair W S Ritchie, Gerhardt Attard, Simon Choudhury, William Cross, David P Dearnaley, Silke Gillies, Clare Gilson, Robert J Jones, Ruth E Langley, Zafar M Malik, Malcolm D Mason, David Matheson, Robin Millman, J Martin Russell, George N Thalmann, Claire A. Amos, Roberto Alaraz, Ami Bahl, Alison Birtle, Omar Din, Hassan Douis, Chinmaman 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, Naryanran Nair Sathar, Anna T H Tran, Mahesh K B Parmar, Matthew S Ryder*, on behalf of the Systemic Therapy for Advanced or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) investigators†

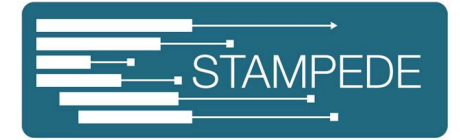
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Bone Scanning and The Threshold Effect of Disease Burden



The Bone Scan is *PREDICTIVE* of Response to Radiotherapy to the Primary Site When the Bone Metastasis Number is 4 or Less

Conclusion 1



- **At low disease burden there is a volume threshold effect whereby treatment of the primary with radiotherapy is beneficial**
- **This threshold is predicted by the conventional bone scan**



Systemic Therapy

“VOLUME” “RISK” AND BENEFIT

Volume / Risk Definitions

Source	Stratification	Content
Yossepowitch O et al Glass et al	Minimal	Nodal AND/OR Axial skeletal metastasis
	Extensive	Appendicular skeletal AND/OR Visceral metastasis
SWOG criteria	Minimal	Disease confined to spine, pelvic bones or lymph nodes
	Extensive	Ribs metastasis AND/OR long bone metastasis AND/OR Visceral metastasis
CHAARTED criteria	Low volume	<4 bone metastasis
	High Volume	≥4 bone metastasis (at least 1 outside the spine or pelvis) AND/OR Visceral metastasis
LATITUDE criteria	Low Volume	<2 of <ul style="list-style-type: none"> • >3 bone mets • Gleason score ≥8 • Visceral mets
	High volume	≥2 of the above

None are validated

Common themes

Non-Regional LN

– Low volume

Visceral Disease

– High volume



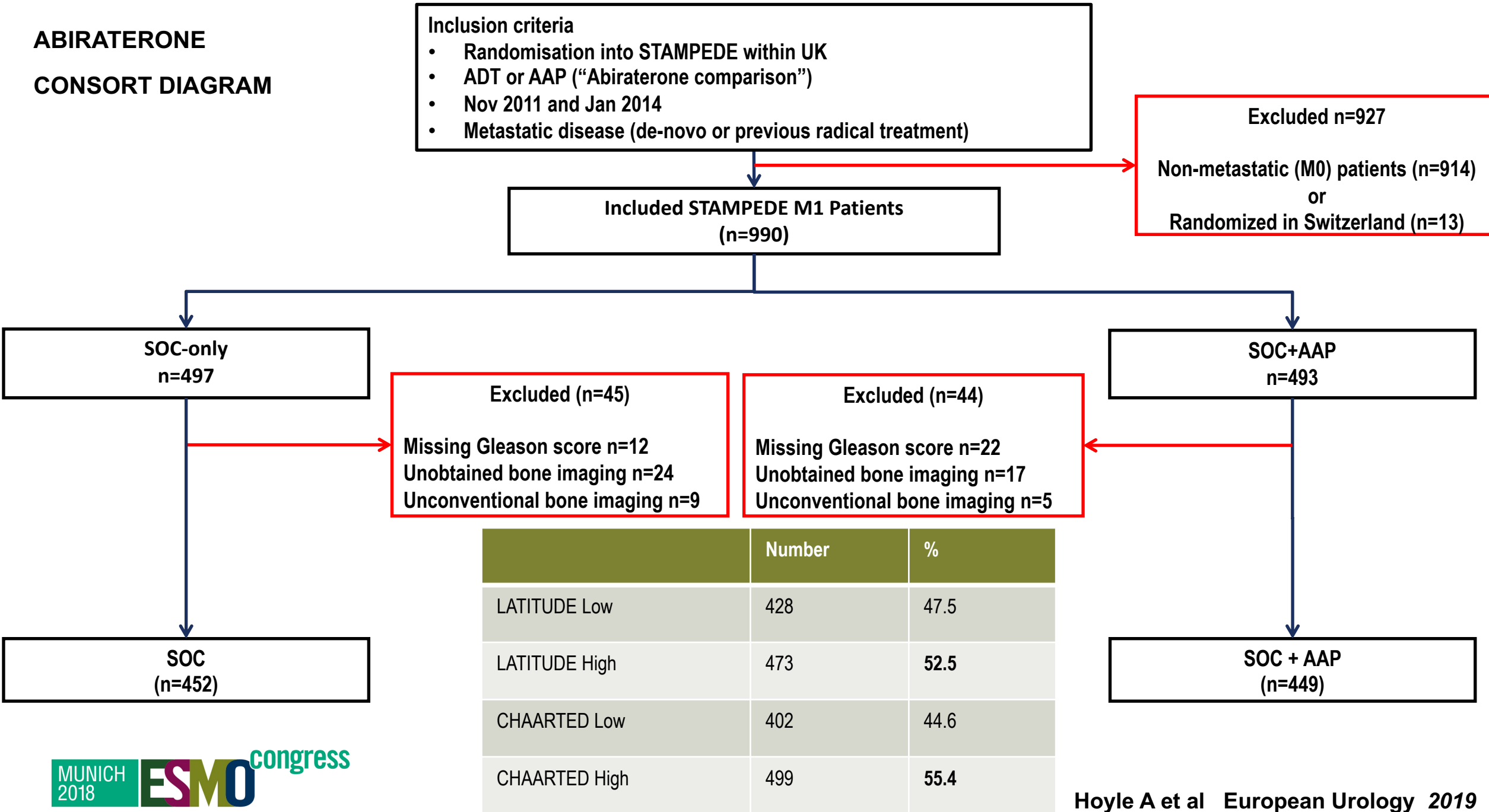
Role of Abiraterone + ADT in High and Low Risk Metastatic Hormone Naïve Prostate Cancer.

Alex Hoyle, Adnan Ali, Nick James, Chris Parker, Adrian Cook, Gert Attard, Simon Chowdhury, Bill Cross, David Dearnaley, Johann de Bono, Clare Gilson, Silke Gillesen, Rob Jones, David Matheson, Malcolm Mason, Alastair Ritchie, Martin Russell, Max Parmar, Matt Sydes, Noel W. Clarke; for the STAMPEDE trial

European Urology 2019


















**ABIRATERONE
CONSORT DIAGRAM**



RESULTS: LATITUDE RISK STRATIFICATION

	ADT alone	AAP	Adjusted HR ^a (95%CI)		p-value	Interaction by metastatic volume p-value
	No. of events/No. of patients					
Overall survival						
All patients	195/452	135/449		0.609 (0.488-0.789)	<0.001	0.385
Low risk	59/220	41/208		0.657 (0.438-0.983)	0.041	
High risk	136/232	94/241		0.536 (0.411-0.699)	<0.001	
Failure free survival						
All patients	354/452	191/449		0.316 (0.264-0.378)	<0.001	0.294
Low risk	152/220	56/208		0.238 (0.174-0.325)	<0.001	
High risk	202/232	135/241		0.313 (0.250-0.392)	<0.001	
Skeletal related events						
All patients	164/452	93/449		0.467 (0.362-0.602)	<0.001	0.207
Low risk	49/220	17/208		0.311 (0.179-0.543)	<0.001	
High risk	115/232	76/241		0.477 (0.356-0.639)	<0.001	
Progression free survival						
All patients	267/452	158/449		0.446 (0.366-0.544)	<0.001	0.159
Low risk	101/220	41/208		0.334 (0.232-0.482)	<0.001	
High risk	166/232	117/241		0.463 (0.364-0.588)	<0.001	
Prostate cancer specific death*						
All patients	172/452	114/449		0.587 (0.462-0.746)	<0.001	0.728
Low risk	49/220	27/208		0.511 (0.312-0.836)	0.008	
High risk	123/232	87/241		0.570 (0.432-0.754)	<0.001	

CHAARTED VOLUME CRITERIA

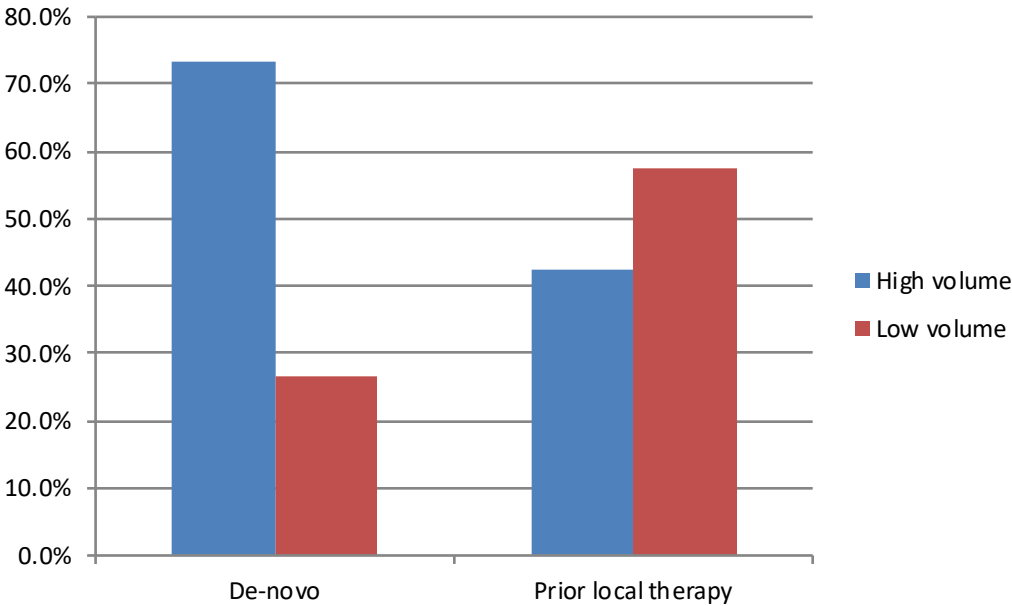
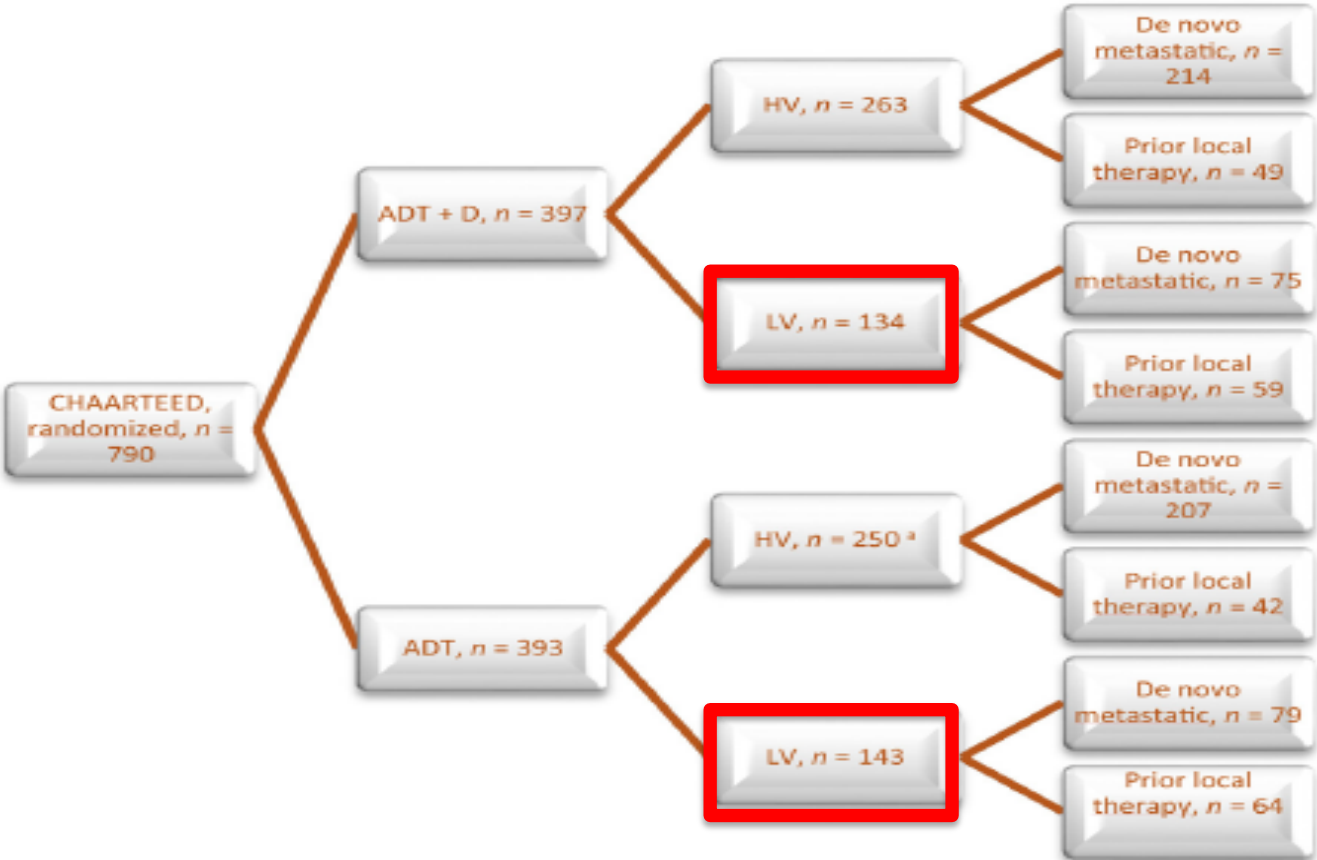
		ADT alone	AAP		Adjusted HR ^a (95%CI)	p-value	Interaction by metastatic volume p-value
		No. of events/No. of patients					
Overall survival							
	All patients	195/452	135/449		0.609 (0.488-0.789)	<0.001	0.771
	Low volume	53/196	39/206		0.637 (0.420-0.966)	0.034	
	High volume	142/256	96/243		0.601 (0.463-0.779)	<0.001	
Failure free survival							
	All patients	354/452	191/449		0.316 (0.264-0.378)	<0.001	0.472
	Low volume	133/196	57/206		0.259 (0.189-0.356)	<0.001	
	High volume	221/256	134/243		0.327 (0.263-0.408)	<0.001	
Skeletal related events							
	All patients	164/452	93/449		0.467 (0.362-0.602)	<0.001	0.981
	Low volume	46/196	25/206		0.459 (0.282-0.749)	0.002	
	High volume	118/256	68/243		0.468 (0.347-0.632)	<0.001	
Progression free survival							
	All patients	267/452	158/449		0.446 (0.366-0.544)	<0.001	0.670
	Low volume	86/196	45/206		0.401 (0.279-0.577)	<0.001	
	High volume	181/256	113/243		0.457 (0.360-0.579)	<0.001	
Prostate cancer specific death*							
	All patients	172/452	114/449		0.587 (0.462-0.746)	<0.001	0.740
	Low volume	43/196	31/206		0.627 (0.388-1.013)	0.057	
	High volume	129/256	83/243		0.579 (0.439-0.764)	<0.001	

0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1 1.1 1.2

ADT + Abiraterone + Prednisolone (AAP)
better

ADT alone better

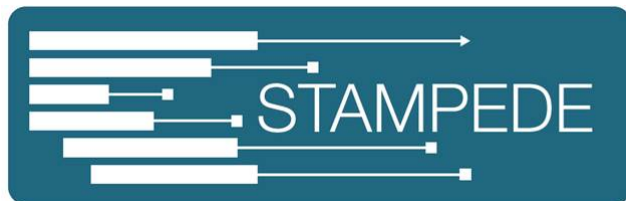
Distribution of High and Low Volume Patients in CHAARTED Stratified by M1 status at Presentation (de-novo or M1 following prior local therapy)



	ADT + D Arm		ADT Arm		Overall	
	De-novo, n(%)	Prior local therapy, n(%)	De-novo, n(%)	Prior local therapy, n(%)	De-novo, n(%)	Prior local therapy, n(%)
High volume	214 (74%)	49 (45.4%)	207 (72.4%)	42 (39.6%)	421 (73.2%)	91 (42.5%)
Low volume	75 (26%)	59 (54.6%)	79 (27.6%)	64 (60.4%)	154 (26.8%)	123 (57.5%)
Total	289 (100%)	108 (100%)	286 (100%)	106 (100%)	575 (100%)	214 (100%)

ESMO 2019 Late Breaking Abstract #8440

Docetaxel for hormone-naïve prostate cancer: results from long-term follow-up of metastatic (M1) patients in the STAMPEDE randomised trial (NCT00268476) and sub-group analysis by metastatic burden



Cohort selection



M1 patients randomized within the STAMPEDE MAMS platform to Arm A (ADT) or Arm C (ADT + Docetaxel), n =1086

M1 cohort

Arm A (n=724)

Arm C (n=362)

Excluded as bone scans
not centralized or
unconventional imaging
(n=166)

Excluded as bone scans
not centralized or
unconventional imaging
(n=90)

Burden Cohort

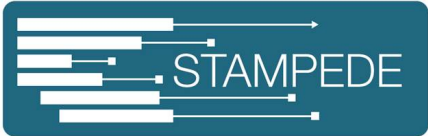
Arm A (n=558)
CHAARTED low, n = 238 (43%)
CHAARTED high , n = 320 (57%)

Arm C (n=272)
CHAARTED low, n=124 (46%)
CHAARTED high, n=148 (54%)

- Median follow-up M1 cohort -78 months
- Median follow-up burden cohort - 72 months

ESMO 2019 Abstract #844O

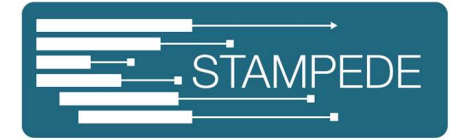
Overall survival



	Arm A	Arm C	HR* (95% CI)	Interaction p-value for low and high burden subgroups
Low burden	115/238	51/124	0.76 (0.54 – 1.07)	0.827
High burden	254/320	106/148	0.81 (0.64 – 1.02)	
Burden cohort	369/558	157/272	0.79 (0.64 – 0.94)	
M1 cohort	494/724	225/362	0.81 (0.69 – 0.95)	

* The hazard ratios and 95% confidence intervals are from Cox proportional hazards models, adjusted for age (<70 or ≥70), N stage (N0, N+ or NX), WHO PS (0 or 1-2), NSAID or aspirin use (uses either or no), RT planned and stratified by time period.

Conclusion 2



- **There is no dichotomised “volume” / “burden” related effect relating to Docetaxel**
- **Prostate Cancer patients presenting with *De Novo* M1HNPC should *all* be considered for combined systemic treatment with Docetaxel or Novel ADT combined with SOC ADT**

