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Platinum Priority - Prostate Cancer

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Abiraterone in "High-" and "Low-risk" Metastatic Hormone-sensitive Prostate Cancer

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Abstract

Background: Abiraterone acetate received licencing for use in only "high-risk" metastatic hormone-naïve prostate cancer (mHNPC) following the LATITUDE trial findings. However, a "risk"-related effect was not seen in the STAMPEDE trial. There remains uncertainty as to whether men with LATITUDE "low-risk" M1 disease benefit from androgen deprivation therapy (ADT) combined with abiraterone acetate and prednisolone (AAP).
Objective: Evaluation of heterogeneity of effect between LATITUDE high- and low-risk M1 prostate cancer patients receiving ADT + AAP in the STAMPEDE trial.
Design, setting, and participants: A post hoc subgroup analysis of the 2017 STAMPEDE "abiraterone comparison". Staging scans for M1 patients contemporaneously randomised to ADT or ADT + AAP within the STAMPEDE trial were evaluated centrally and blind to treatment assignment. Stratification was by risk according to the criteria set out in the LATITUDE trial. Exploratory subgroup stratification incorporated the CHAARTED criteria.
Outcome measurements and statistical analysis: The primary outcome measure was overall survival (OS) and the secondary outcome measure was failure-free survival (FFS). Further exploratory analysis evaluated clinical skeletal-related events, progression-free survival (PFS), and prostate cancer-specific death. Standard Cox-regression and Kaplan-Meier survival estimates were employed for analysis.

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Results and limitations: A total of 901 M1 STAMPEDE patients were evaluated after exclusions. Of the patients, 428 (48%) were identified as having a low risk and 473 (52%) a high risk. Patients receiving ADT + AAP had significantly improved OS (low-risk hazard ratio [HR]: 0.66, 95% confidence interval or CI [0.44–0.98]) and FFS (low-risk HR: 0.24, 95% CI [0.17–0.33]) compared with ADT alone. Heterogeneity of effect was not seen between low- and high-risk groups for OS or FFS. For OS benefit in low risk, the number needed to treat was four times greater than that for high risk. However, this was not observed for the other measured endpoints.
Conclusions: Men with mHNPC gain treatment benefit from ADT + AAP irrespective of risk stratification for "risk" or "volume".
Patient summary: Coadministration of abiraterone acetate and prednisolone with androgen deprivation therapy (ADT) is associated with prolonged overall survival and disease control, compared with ADT alone, in all men with metastatic disease starting hormone therapy for the first time.

1. Introduction

Two randomised controlled trials have reported survival gains for men with metastatic hormone-naïve prostate cancer (mHNPC) treated with androgen deprivation therapy (ADT) plus abiraterone acetate and prednisolone/prednisone (AAP) compared with ADT alone [1,2]. These results have established ADT + AAP as an alternative standard of care to ADT + docetaxel in the treatment of men with mHNPC. However, there are important differences in the design of the two trials regarding inclusion of patients based on their disease burden: LATITUDE recruited only newly diagnosed metastatic (M1) patients with "high-risk" disease starting long-term ADT for the first time, whereas STAMPEDE recruited nonmetastatic (M0) and M1 patients without risk stratification. The LATITUDE trial defined high-risk disease according to a combination of poor prognostic radiological and/or pathological features. In 2018, the European Medicines Agency and the Food and Drug Administration licensed AAP for the treatment of M1 patients with "high-risk" disease only [3,4]. Uncertainty now exists regarding the treatment benefit for patients with "low-risk" M1 disease. To address this, patients in the "abiraterone comparison" of STAMPEDE underwent image-based post hoc subset analysis, stratified retrospectively by baseline staging risk to assess whether ADT + AAP is effective in low- as well as high-risk M1 disease.

2. Patients and methods

2.1. Trial design

STAMPEDE uses a multiarm multistage platform [5] design to test multiple treatment approaches against control [6–9]. All patients relevant to this comparison were randomised to ADT + AAP (trial arm G) or ADT alone (trial arm A). Patients underwent baseline imaging prior to randomisation, including computed tomography (CT) or magnetic resonance imaging (MRI) of the pelvis/abdomen, and a technetium-99 bone scan before 1:1 randomisation to ADT + AAP or ADT alone.

2.2. Cohort selection and imaging review

Patients from the "abiraterone comparison" group were excluded from this analysis only if they had incomplete information precluding classification into low or high risk. Baseline bone scintigraphic images from patients with bone metastases were reviewed centrally for risk stratification by a urologist (A.H.). Quality control was performed by independent random sample reporting by an independent consultant radiologist (H.D.) blinded to both treatment assignment and the findings of the first investigator. A random sample of 85 patients underwent such a review. The primary and secondary scan readers were blinded to treatment allocation and outcome during all scan assessments. Providing there was sufficient concordance (>90%), the primary reader's assessments would be used.

The radiological criteria for classification into low/high risk were based upon the LATITUDE trial because of its current influence in treatment registration in mHNPC [1,2]. This defined high-risk disease as having any two of the following: (1) three or more bone metastases on bone scan, (2) Gleason sum ≥8, and (3) any visceral metastases. The analysis was also applied to the same population stratified by volume criteria used in the CHAARTED trial [10], defining high-volume disease as: (1) four or more bone metastases on bone scan, including one or more outside the vertebral bodies or pelvis, and/or (2) visceral metastases [10]. The number and location of bone metastases were recorded, and then combined with documented diagnostic biopsy Gleason score and the presence of visceral metastases on CT/MRI, permitting stratification by the LATITUDE and CHAARTED criteria.

2.3. Statistical analyses

The primary outcome measure was overall survival (OS) and the secondary outcome was failure-free survival (FFS): this was defined as radiological, clinical, or prostate-specific antigen progression, or death from prostate cancer as per the predefined STAMPEDE criteria [2]. Other outcome measures evaluated were clinical skeletal-related events (SREs), progression-free survival (PFS), and prostate cancer–specific death (PCSD), defined previously [11]. Data from the published "abiraterone comparison", frozen from the trial database on 10 February 2017, were used for survival analyses [2]. The data lock date for the retrospective scan data was 1 August 2018.

Prior to analysis, we prespecified the hypothesis that there would be no difference in the treatment effect from adding AAP across the subgroups.

Kaplan-Meier methods were used to plot survival curves and Cox proportional hazard models to estimate relative treatment effects. Cox models were adjusted for randomisation stratification factors (except for randomising centre, presence or absence of metastases, type of ADT, and planned use of prostate radiotherapy) and stratified according to time periods defined by corecruiting trial arms. Proportional-hazard assumptions were checked. A hazard ratio (HR) of <1 represents evidence for ADT + AAP, and an HR of >1 represents benefit of ADT alone. Confidence intervals (CIs) are reported at 95% levels. Heterogeneity of treatment effects among M1 risk subgroups were evaluated using interaction terms in the adjusted Cox regression models. Time-to-event analyses used time from randomisation to the outcome of interest, with those not reporting the event censored at the time of last contact. Median follow-up was determined from reverse censoring from death. All analyses were performed using Stata v15 (StataCorp LP, College Station, TX, USA).

3. Results

3.1. Study cohort

Between 15 November 2011 and 17 January 2014, 990 mHNPC M1 patients were randomised to receive ADT alone or with AAP. Patients with incomplete information precluding radiological risk-based classification were excluded as follows: absent Gleason score ($n = 34$), unobtainable bone scintigraphy ($n = 41$), and bone metastases diagnosed using nonconventional imaging ($n = 14$). A total of 901 mHNPC patients underwent stratification using the LATITUDE risk criteria (Fig. 1) and, thereafter, the CHAARTED volume criteria. Baseline characteristics by LATITUDE- and CHAARTED-defined risk/volume subgroups were balanced between the two treatment arms (Table 1). In all, 428 (48%) patients were classified as having a low risk by the LATITUDE criteria and 402 (45%) using the CHAARTED criteria. High-risk disease using the LATITUDE and CHAARTED criteria was seen in 473 (52%) and 499 (55%) patients, respectively. Median follow-up of the cohort was 42 mo.

3.2. Quality control

In total, 759 patients had bone metastases. A random sample of 85 (11%) patients from this population was included in the quality control process. Concordance between the primary and independent reviewer for the volume subgroup classification was 92% (78/85).

3.3. Overall survival

Of 901 patients, 330 (195 ADT; 135 ADT + AAP) had died. When stratified according to the LATITUDE criteria for low

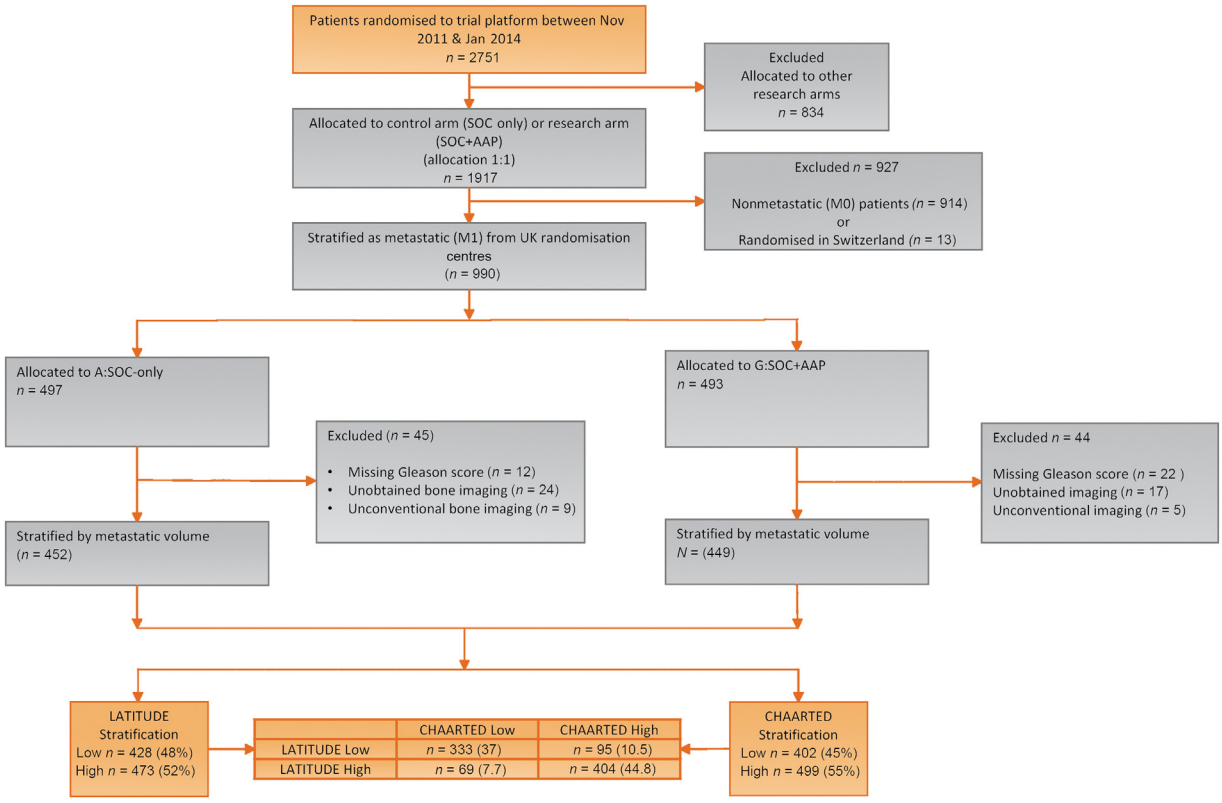

Fig. 1 – Consort diagram showing the UK M1 study cohort selection for metastatic volume stratification using CHAARTED and LATITUDE definitions. A 2 × 2 shows matched and unmatched proportions of high- and low-volume/risk patients using the LATITUDE and CHAARTED definitions. Percentages in brackets are based on the whole study population ($n = 901$). AAP = abiraterone acetate and prednisolone; SOC = standard of care.

Table 1 – Baseline patient characteristics of 901 M1 patients included and defined for LATITUDE risk and CHAARTED volume criteria.

STAMPEDE abiraterone volume analysis ($n = 901$)	LATITUDE criteria						CHAARTED criteria					
	Low risk ($n = 428$)			High risk ($n = 473$)			Low risk ($n = 402$)			High risk ($n = 499$)		
	ADT ($n = 220$)	ADT + AAP ($n = 208$)	p value	ADT ($n = 232$)	ADT + AAP ($n = 241$)	p value	ADT ($n = 196$)	ADT + AAP ($n = 206$)	p value	ADT ($n = 256$)	ADT + AAP ($n = 243$)	p value
Age at randomisation												
Median	66	66	0.37	67	67	0.75	67	66	0.14	67	68	0.36
IQR	62–72	62–71		63–72	63–71		63–72	61–71		62–72	64–72	
PSA prior to ADT												
Median	51	70	0.14	174	126	0.28	45	53	0.19	177	174	0.94
IQR	19–148	24–198		40–735	36–458		16–121	20–132		45–786	55–657	
WHO performance status												
0	174	158	0.44	163	177	0.44	155	164	0.90	182	171	0.86
1–2	46	50		69	64		41	42		74	72	
Gleason sum												
≤7	107	102	0.93	3	2	0.62	54	61	0.65	56	43	0.24
8–10	113	106		229	239		142	145		200	200	
Primary tumour stage												
≤T2	26	23	0.50	23	21	0.32	19	22	0.97	30	22	0.22
T3	133	125		116	141		120	122		129	144	
T4	54	47		68	59		46	49		76	57	
TX	7	13		25	20		11	13		21	20	
Regional node status												
N0	80	66	0.49	78	84	0.36	61	67	0.92	97	83	0.37
N+	125	130		137	131		122	127		140	134	
NX	15	12		17	26		13	12		19	26	
Eligibility												
M+, new	202	190	0.86	229	238	0.96	182	191	0.96	249	237	0.85
Previously treated	18	18		3	3		14	15		7	6	
Metastatic site												
Node	47	55	0.55	–	–	0.77	47	55	0.61	–	–	0.89
Bone	140	127		154	169		116	123		178	173	
Visceral	1	1		1	–		–	–		2	1	
Bone + node	32	24		60	52		33	28		59	48	
Bone + visceral	–	–		9	12		–	–		9	12	
Visceral + node	–	–		1	1		–	–		1	1	
Bone + node + visceral	–	1		7	7		–	–		7	8	

AAP = abiraterone acetate and prednisolone; ADT = androgen deprivation therapy; IQR = interquartile range; PSA = prostate-specific antigen.

risk, the ADT + AAP combination therapy demonstrated a survival advantage (HR: 0.66, 95% CI [0.44–0.98]): absolute 3-yr survival was 83% with ADT + AAP and 78% with ADT alone (Fig. 2A). Improvement was also seen in the high-risk disease subgroup (HR: 0.54, 95% CI [0.41–0.70]): absolute 3-yr survival was 65% with ADT + AAP and 45% with ADT (Fig. 2B). The heterogeneity of treatment effect between high- and low-risk groups was not statistically significant (p-interaction = 0.39, Fig. 3), although for OS, the number of patients needed treatment (20 vs five) to prevent one death after 3 yr in the low-risk group was four times more than that in the high-risk group.

3.4. Failure-free survival

This population included 191 FFS events with ADT + AAP and 354 with ADT alone. An absolute improvement of 44% in 3-yr FFS was observed in "low-risk" patients treated with ADT + AAP (76% ADT + AAP vs 32% ADT; HR: 0.25, 95% CI [0.17–0.33]; Fig. 2C). An absolute improvement of 33% in 3-yr FFS was also observed in high-risk patients (45% AAP vs 12% ADT; HR: 0.31, 95% CI [0.25–0.39]; Fig. 2D). There was no evidence of heterogeneity for ADT + AAP between the high- and low-risk subgroups (p-interaction = 0.29; Fig. 3).

3.5. Additional efficacy endpoints

Additional efficacy measures evaluated the impact of ADT + AAP on SREs, PFS, and PCSD within high- and low-risk subgroups. In low risk, a 12% absolute improvement in SRE-free survival at 3 yr favoured ADT + AAP treatment (91%) compared with ADT alone (79%; HR: 0.31, 95% CI [0.18–0.54]; Supplementary Fig. 1A). A further absolute improvement of 25% in low-risk 3-yr PFS favoured ADT + AAP (81%) compared with ADT alone (56%; HR: 0.33, 95% CI [0.23–0.48]; Supplementary Fig. 2A). Furthermore, a 7% absolute reduction in PCSD at 3 yr favoured ADT + AAP (89%) compared with ADT alone (82%). The competing-risk subhazard ratio for PCSD in the low-risk subgroup was 0.51 (95% CI [0.31–0.84]). Similar results were found across all these three additional endpoints in the high-risk subgroup (Supplementary Fig. 1–3). There was no evidence of heterogeneity in benefit afforded by the ADT + AAP combination between low- and high-risk subgroups for SREs, PFS, and PCSD (Fig. 3).

3.6. CHAARTED "volume" stratification

An exploratory analysis was undertaken stratifying patients by disease volume on bone scan according to the CHAARTED

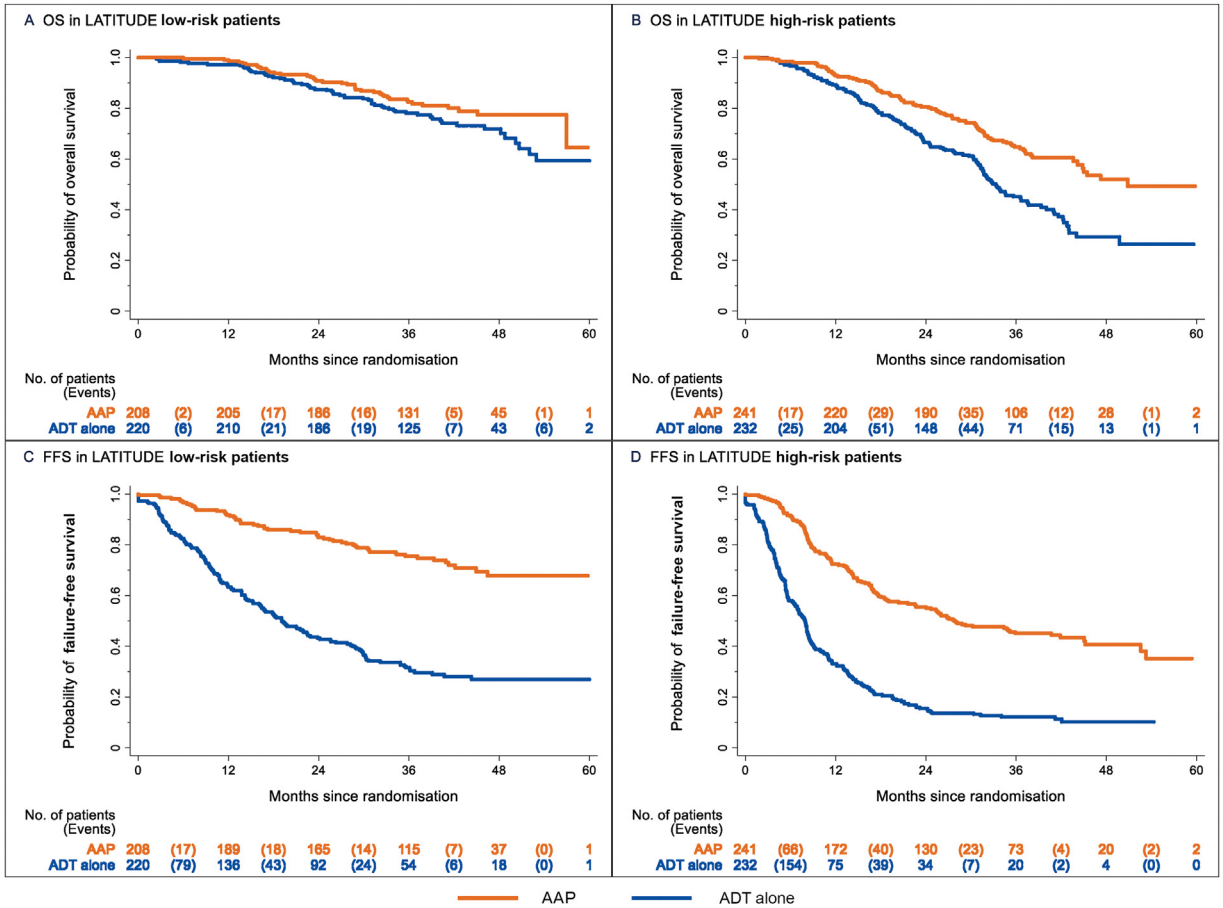

Fig. 2 – Kaplan-Meier curves according to M1 risk stratification using the LATITUDE criteria for overall survival (OS)—(A) low risk and (B) high risk, and failure-free survival (FFS)—(C) low risk and (D) high risk. AAP = abiraterone acetate and prednisolone; ADT = androgen deprivation therapy.

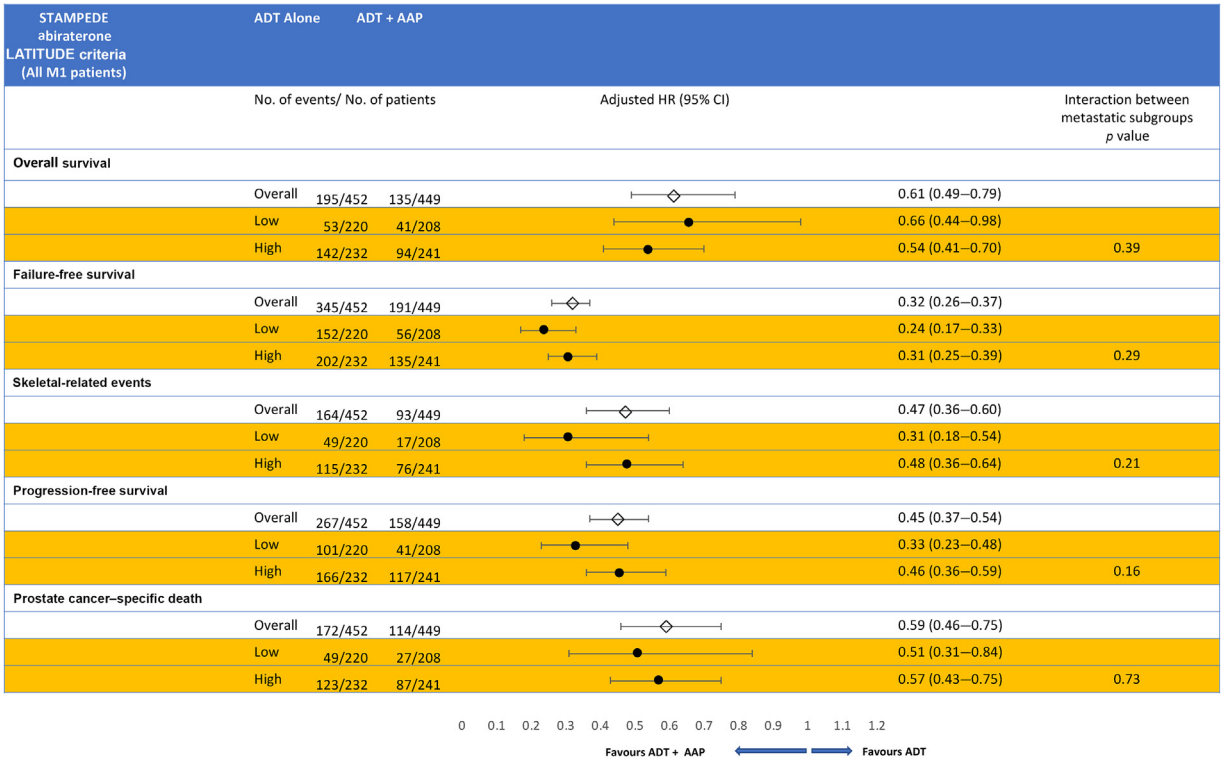

Fig. 3 – Forest plot of hazard ratios (HRs) for AAP from adjusted Cox models on overall survival, failure-free survival, skeletal-related events, progression-free survival, and prostate cancer–specific death within LATITUDE low- and high-risk subgroups. AAP = abiraterone acetate and prednisolone; ADT = androgen deprivation therapy; CI = confidence interval.

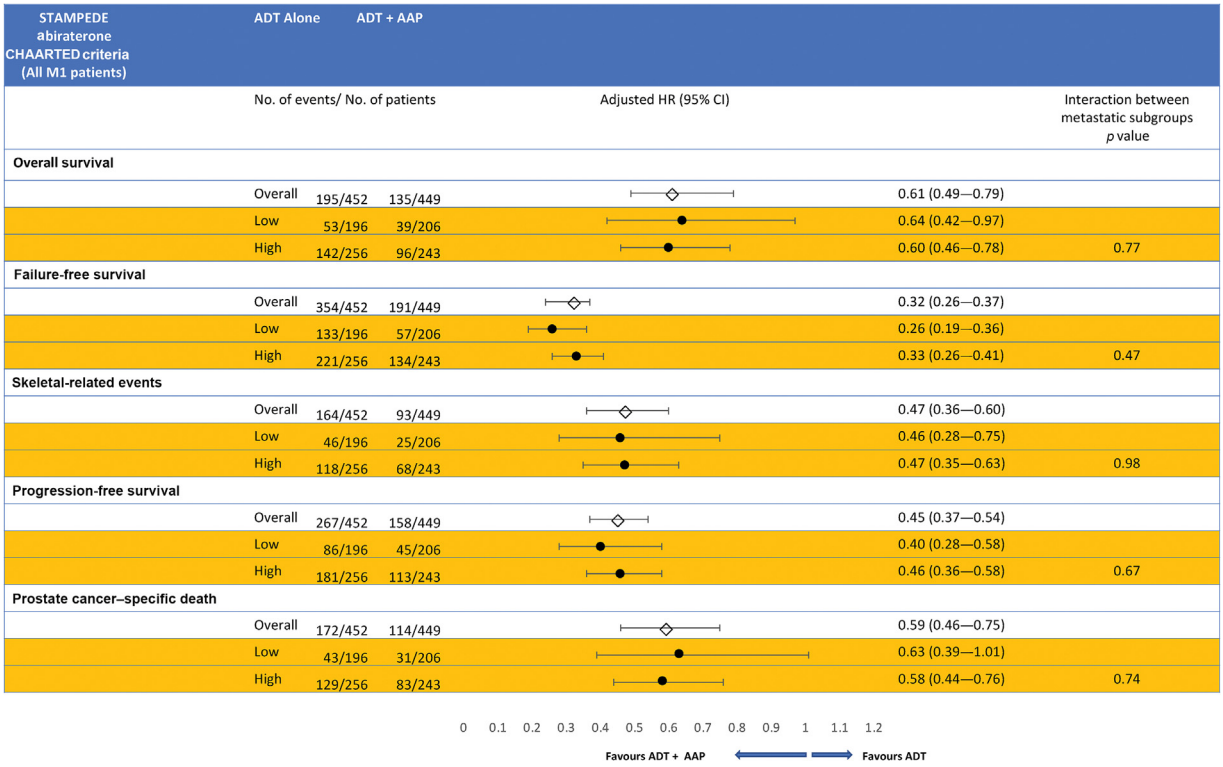

Fig. 4 – Forest plot of hazard ratios (HRs) for AAP from adjusted Cox models on overall survival, failure-free survival, skeletal-related events, progression-free survival, and prostate cancer–specific death within CHAARTED low and high-volume subgroups. AAP = abiraterone acetate and prednisolone; ADT = androgen deprivation therapy; CI = confidence interval.

trial criteria (Fig. 4). ADT + AAP conferred a significant improvement in survival of 6% (83% vs 77%) at 3 yr compared with ADT alone in low-volume disease (HR: 0.64, 95% CI [0.42–0.97]; Fig. 5). A 42% absolute gain was also seen in 3-yr FFS with ADT + AAP (74%) compared with ADT (32%) in low-volume disease (HR: 0.26, 95% CI [0.19–0.36]; Fig. 5). No evidence of heterogeneity of effect by ADT + AAP was observed for OS (p-interaction = 0.77) or FFS (p-interaction = 0.47). ADT + AAP treatment advantages were consistent throughout all additional efficacy endpoints irrespective of volume subgroup stratification (Fig. 4).

3.7. *Exploratory analysis in LATITUDE low risk and CHAARTED low volume*

LATITUDE and CHAARTED definitions differ, such that 18% (n = 164/901) of patients identified as having a low risk/volume according to one definition were stratified as having a high risk/volume by the other (Fig. 1). We therefore evaluated the efficacy of ADT + AAP in patients from lower-risk/volume categories using both LATITUDE and CHAARTED definitions. In the "double-low" subgroup of 333 patients, ADT + AAP again demonstrated significant improvements over ADT alone in OS (HR: 0.56, 95% CI [0.34–0.94]) and FFS (HR: 0.21, 95% CI [0.14–0.30]; Supplementary Table 1, and Supplementary Figs. 4 and 5).

3.8. *Sensitivity analysis of patients with de novo metastatic disease*

The analysis of STAMPEDE patients by metastatic burden may be influenced by patients with recurrent disease following previous radical treatment. Exclusion of patients receiving prior radical therapy provided a de novo cohort of 859 patients. The cohort was stratified according to the LATITUDE risk criteria (Supplementary Fig. 6) and secondarily by the CHAARTED volume criteria (Supplementary Fig. 7). Benefit of ADT + AAP over ADT alone was observed for all subgroups, irrespective of risk or volume stratification throughout all endpoints. The relative hazard for survival in de novo low-risk patients was slightly superior to the original cohort analysis (see section 3.3; HR: 0.64, 95% CI [0.42–0.97]). A similar result was seen for low-volume subgroup survival analysis (HR: 0.60, 95% CI [0.39–0.92]).

4. Discussion

The results from this STAMPEDE analysis support the use of ADT + AAP in men with mHNPC irrespective of "risk" or

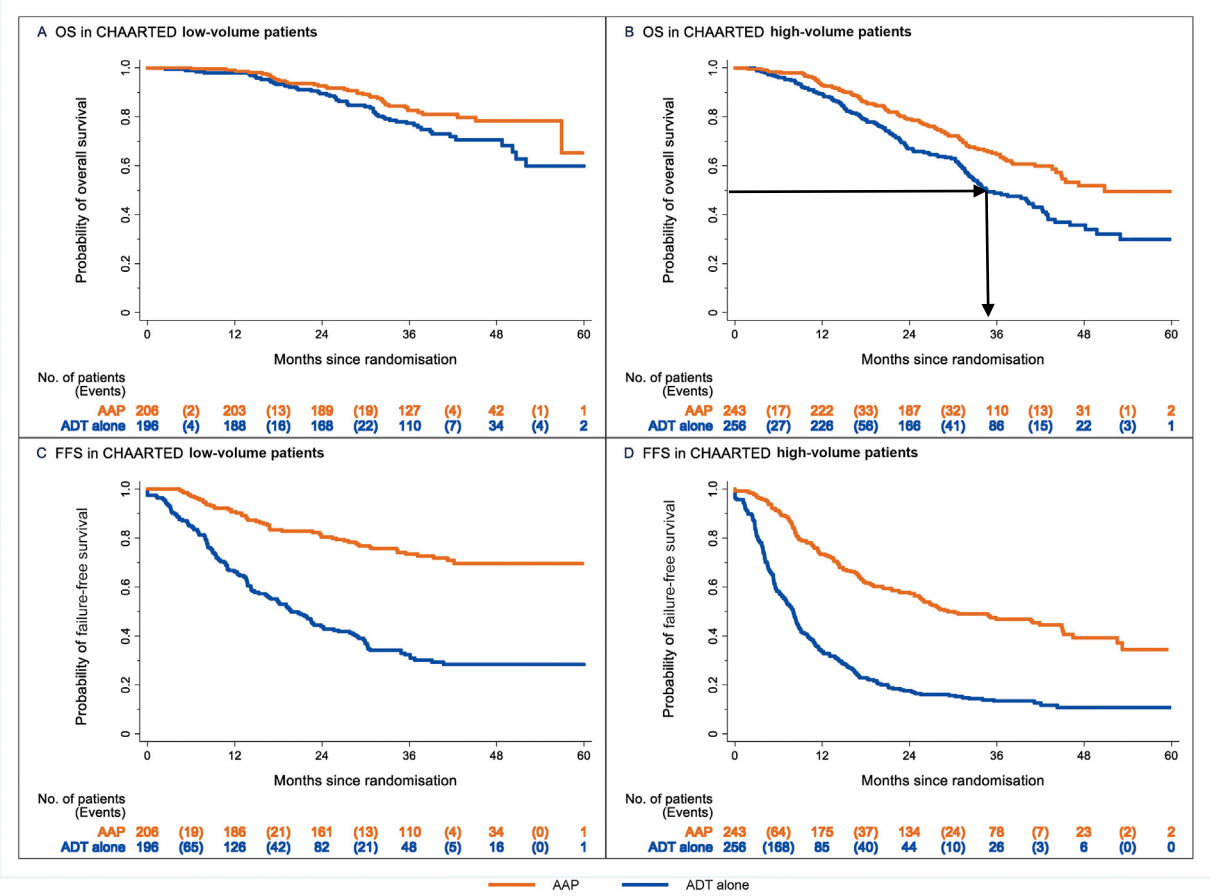

Fig. 5 – Kaplan-Meier curves according to M1 volume stratification using the CHAARTED criteria for overall survival (OS)—(A) low volume and (B) high volume, and failure-free survival (FFS)—(C) low volume and (D) high volume. AAP = abiraterone acetate and prednisolone; ADT = androgen deprivation therapy.

"volume" stratifications. The ADT + AAP benefit extended throughout all measured efficacy endpoints with a clear survival advantage in the de novo metastatic setting (HR: 0.59, 95% CI [0.47–0.74]). The survival benefit with ADT + AAP extends to the entire M1 cohort, irrespective of subgroup classification as defined by the LATITUDE or CHAARTED criteria, on each of the efficacy outcome measures. There was no evidence of subgroup interaction to support preferential subgroup ADT + AAP treatment selection. However, four times the number of low-risk patients required treatment to match the OS observed in high-risk patients. The high-risk de novo group in STAMPEDE showed a 48% relative reduction in the risk of death and a 69% relative risk reduction in treatment failure, complementing the conclusions from the LATITUDE trial [1]. However, the outcome in low-risk M1 patients had not been directly scrutinised, because such patients were not recruited in LATITUDE, and "risk"/"volume" categorisation was not applied prospectively in STAMPEDE. Image analysis subsequent to the primary report of the STAMPEDE "abiraterone comparison" demonstrates a 34% lower relative risk of death and a 76% lower relative risk of treatment failure in the "low-risk" subgroup. The improvement in outcome in this subgroup is comparable with that in the "high-risk" patients evaluated in the LATITUDE trial, which reported a 38% lower relative risk of death in the ADT + AAP group compared with the ADT group, and a 53% lower relative risk of radiological progression or death [1]. The advantages of ADT + AAP treatment in low- and high-risk disease extend throughout all exploratory outcome measures, including reductions in SREs, PFS, and PCSD. The results also show that 37% of M1 patients are identified with low-volume and low-risk mHNPC. This subgroup may potentially benefit from ADT + AAP combination therapy, yet are presently denied treatment based on the current risk-based license indications for AAP [3,4].

There are inherent limitations to a post hoc subgroup analysis of this type, including primarily the retrospective nature of its design. Despite this, the proportion of patients with evaluable scans was large, with the additional benefit of comprehensive follow-up. The metastatic burden was evaluated using conventional, as opposed to newer imaging modalities, in concordance with previously defined volume criteria. This radiological limitation was balanced by an understanding that the true utility of novel imaging modalities such as prostate-specific membrane antigen positron emission tomography scanning remains to be determined. Consequently, such imaging modalities are not currently used widely in clinical decision making in mHNPC. Interpretation of all conventional imaging is subject to interobserver variation. We endeavoured to minimise this by centralisation and reanalysis of all imaging modalities independently of the main trial team. Objectivity of results was maintained using a standardised approach to radiological interpretation, blinding reviewers to the outcome of treatment and using predefined subgroup criteria for low risk/volume as defined by other groups. Incorporation of an imaging quality control process within the study design added confidence to this centralised imaging reporting methodology. A further study limitation is reflected in the patient cohort itself. The majority of patients in our study had de novo M1 disease. Application of our results to patients who develop M1 disease after prior local therapy will require further evaluation.

Within current international practice, there is incomplete understanding and consensus for what constitutes an optimal definition of "disease burden" [12]; current definitions of risk stratification are cited [1,10,13–17]. Variations in the prevalence of "low-burden" disease across these definitions can vary between 23% and 44%, potentially influencing volume-based treatment decisions [18]. Current definitions also fail to acknowledge the poor prognostic implication of combined bone and metastatic nodal disease [19]. Emerging exploratory analysis within oligometastatic HNPC patients treated with prostatic radiotherapy suggests that nodal and/or fewer than four bone metastases stratify patients with the greatest accuracy [20]. Accepting these limitations, we incorporated subgroup radiological stratification according to LATITUDE and CHAARTED trial definitions because of their current clinical influence in guiding ADT + AAP and docetaxel treatment in mHNPC. The consistency of ADT + AAP benefit between the two stratified subgroup criteria limits the bias associated with conclusions drawn from a single stratified definition. Scrutinising the magnitude of stratified subgroup discrepancy between the LATITUDE and CHAARTED criteria revealed stratification mismatch in 18% of the trial cohort. Despite this, even when only patients with low-risk and low-volume criteria using both definitions were considered, there was significant evidence of improved OS and FFS in patients treated with ADT + AAP. International guidance should now be re-evaluated to consider altering the licenced indications to include the use of ADT + AAP in M1 patients irrespective of radiological disease burden as an alternative to ADT + docetaxel [21–23].

The treatment landscape for "low-burden" (oligometastatic) mHNPC is undergoing rapid evolution following presentation of these data and those presented in the STAMPEDE M1 radiotherapy comparison [24]. The latter demonstrated a 32% relative reduction in the risk of death (HR: 0.68, 95% CI [0.52–0.90]) in oligometastatic patients. Current speculation relating to the low-burden benefit of docetaxel in this setting will be addressed following the release of the STAMPEDE docetaxel long-term data analysis in 2019. In future, the benefit of combining focal and systemic therapy for low-burden mHNPC requires clarity, and will be addressed by the PEACE 1 trial (NCT01957436) and future STAMPEDE-based study. Metastasis-directed therapy may also provide further disease control benefits as recently demonstrated, but this requires clarification in light of developments in adjuvant therapies and novel imaging [25].

5. Conclusions

Men with mHNPC benefit from ADT + AAP irrespective of whether they have LATITUDE low/high-risk or CHAARTED

low/high-volume categorisation. The license indications for the use of this combination treatment irrespective of "risk" or "volume" classification should now be reconsidered.

Author contributions: Noel W. Clarke had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Hoyle, Ali, James, Cook, Sydes, Clarke.
Acquisition of data: Hoyle, Ali, James, Cook, Parker, de Bono, Brawley, Ingleby, Attard, Chowdhury, Cross, Dearnaley, Gillessen, Aebersold, Jones, Matheson, Mason, Ritchie, Russell, Parmar, Sydes, Clarke.
Analysis and interpretation of data: Hoyle, Ali, Cook, Brawley, Sydes, Clarke.
Drafting of the manuscript: Hoyle, Ali, Cook, Clarke.
Critical revision of the manuscript for important intellectual content: Hoyle, Ali, James, Cook, Parker, de Bono, Attard, Chowdhury, Cross, Dearnaley, Gilson, Gillessen, Aebersold, Jones, Matheson, Mason, Ritchie, Russell, Douis, Parmar, Sydes, Clarke.
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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eururo.2019.08.006.

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