On-treatment serum prostate-specific antigen and overall survival in prostate cancer (STAMPEDE platform protocol): a post-hoc analysis of data from five phase 3 trials

Mahaz Kayani, Laura Murphy*, Peter Dutey-Magni, Sarah Howlett, Ashwin Sachdeva, Minal Padden-Modi, Hoda Abdel-Aty, Louise C Brown, Claire L Amos, Kitty Chan, Duncan C Gilbert, Ruth E Langley, Michael Brown, Matthew R Sydes, Christopher C Parker, STAMPEDE Collaborators†, William Cross, Zafar Malik, Mohini Varughese, Fabio Turco, Robin Millman, David Matheson, Silke Gillessen, Noel W Clarke, Mahesh K B Parmar, Nicholas D James, Gerhardt Attard*

Summary

Background Serum prostate-specific antigen (PSA) concentrations decrease after hormone therapy for prostate cancer, with the nadir serving as a potentially useful prognostic biomarker. To support clinical use, we evaluated the association between PSA nadir values and survival outcomes, stratified by pre-treatment metastatic volume or, in patients with non-metastatic cancer, stratified by lymph node status.

Methods As part of the STAMPEDE platform trial, patients with metastatic or very high-risk non-metastatic prostate adenocarcinoma were recruited to five randomised, controlled, phase 3 trials conducted at 126 hospitals or oncology centres in Switzerland and the UK. Patients were randomly assigned to either standard of care (androgren deprivation therapy [ADT] alone or ADT plus docetaxel) or to one of five experimental treatment groups: ADT plus docetaxel with or without zoledronic acid, ADT plus abiraterone acetate with or without enzalutamide, or ADT plus prostate radiotherapy (only patients with metastatic disease). We used trial data from these participants to perform landmark analyses to test associations of PSA at 6, 12, and 24 weeks after randomisation with overall survival. Only patients with a PSA value were included in each landmark analysis. The Kaplan–Meier method was used to estimate 96-month overall survival rates and the corresponding 95% CIs for patients categorised by either metastatic volume or lymph node status. The STAMPEDE protocol platform is registered with ClinicalTrials.gov (NCT00268476), EUDRACT (2004-000193-31), and ISRCTN (ISRCTN78818544).

Findings This study included 7129 patients from the STAMPEDE platform, who were recruited between Oct 5, 2005, and Sept 2, 2016; 4438 had metastases and 2691 had very high-risk non-metastatic disease. Among patients with metastasis and volumetric assessment, 2211 (55·9%) of 3956 had high-volume metastases, and among those with non-metastatic disease, 1033 (38·4%) were lymph node positive. A PSA concentration of 0·2 ng/mL or less was less frequent at 6 weeks or 12 weeks, but was associated with equivalent survival rates, compared with a PSA of 0·2 ng/mL or less at 24 weeks. Survival rates of PSA subcategories (≤0·2 ng/mL, >0·2 to 1·0 ng/mL, >1·0 to 3·0 ng/mL, and >3·0 ng/mL) differed by metastatic volume or, in patients with non-metastatic disease, by nodal status. Survival was longest for patients allocated to abiraterone with or without enzalutamide. Among patients with metastatic disease in the abiraterone with or without enzalutamide group who had a PSA of 0·2 ng/mL or less at 24 weeks, 96-month overall survival in patients with low-volume metastatic disease (64·1% [95% CI 57·8–69·8]) was higher than in patients with high-volume metastatic disease (44·6% [37·1–51·9]), but lower than in patients with non-metastatic, node-positive disease (79·4% [73·8–83·9]). 96-month overall survival was highest for patients with non-metastatic, node-negative disease (82·8% [95% CI 78·7–86·1]).

Interpretation Metastatic volume or nodal status influence survival rates associated with on-treatment serum PSA categories, including for undetectable PSA. Radiological features and serum PSA could be combined to better predict survival. PSA at 24 weeks showed strongest associations with overall survival, although a PSA concentration of 0·2 ng/mL or less at any timepoint predicted favourable outcome. These findings could inform prognosis and warrant evaluation for treatment selection in clinical trials.

Funding Cancer Research UK, Prostate Cancer UK, UK Medical Research Council, and John Black Charitable Foundation.

Introduction

Prostate cancer is a major cause of cancer-related deaths, accounting for 400 000 deaths globally in 2022.[1] Over the past two decades, outcomes for patients presenting with advanced prostate cancer have improved substantially, in part due to treatment intensification strategies alongside

Lancet Oncol 2026; 27: 625–36

See Comment page 531

*Contributed equally

†The full list of STAMPEDE collaborators is included in the appendix (pp 40–240)

UCL Cancer Institute, University College London, London, UK (M Kayani MBBS, S Howlett MBBS, Prof G Attard PhD); **MRC Clinical Trials Unit at UCL, Institute of Clinical Trials and Methodology, University College London, London, UK** (M Kayani, L Murphy PhD, P Dutey-Magni PhD, H Abdel-Aty MD(Res), Prof L C Brown PhD, C L Amos PhD, K Chan BSc, D C Gilbert PhD, R E Langley PhD, Prof M R Sydes MSc, R Millman, D Matheson PhD, Prof M K B Parmar DPhil); **Department of Oncology, University College London Hospitals, London, UK** (M Kayani, S Howlett, Prof G Attard); **Division of Cancer Sciences, University of Manchester, Manchester, UK** (A Sachdeva PhD FRCS, M Brown PhD, Prof N W Clarke ChM); **Department of Surgery, Christie NHS Foundation Trust, Manchester, UK** (A Sachdeva, Prof N W Clarke); **Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, London, UK** (M Padden-Modi MBBS, H Abdel-Aty, Prof C C Parker MD, Prof N D James PhD); **St James's University Hospital, Leeds, UK** (W Cross PhD); **Clatterbridge Cancer Centre NHS Foundation Trust, Wirral, UK** (Z Malik FRCR); **Royal Devon University Healthcare NHS Foundation Trust and University of Exeter, UK** (M Varughese FRCR); **Institute of Oncology of Southern Switzerland, Ente Ospedaliero Cantonale,**

Bellinzona, Switzerland and Faculty of Biosciences, University of Southern Switzerland, Lugano, Switzerland (F Turco MD, Prof S Gillessen MD); **Department of Urology, Salford Royal Hospital, Northern Care Alliance NHS Foundation Trust, Manchester, UK** (Prof N W Clarke)

Correspondence to: Prof Gerhardt Attard, UCL Cancer Institute, University College London, London, UK
g.attard@ucl.ac.uk

See Online for appendix

Research in context

Evidence before this study

We searched PubMed for clinical trials published in English between database inception and Oct 2, 2025, using the terms "prostate cancer", "prostate-specific antigen", "hormone-sensitive" or "castration-sensitive", "response", and "clinical trial". We identified 12 post-hoc analyses from phase 3 randomised controlled trials and one meta-analysis in patients with metastatic disease, and two post-hoc analyses plus one meta-analysis in patients with non-metastatic disease. These studies consistently showed that a lower on-treatment prostate-specific antigen (PSA) concentration is associated with improved overall survival, with the most common threshold investigated being a concentration of 0·2 ng/mL or less. However, most analyses assessed PSA at 6–7 months after treatment initiation, and the optimal timing of PSA measurement and threshold of PSA concentration have not been validated prospectively. No study has evaluated the prognostic role of PSA concentration in patients receiving androgen receptor pathway inhibitors for high-risk non-metastatic disease. Similarly, it is unclear whether combining PSA response with other clinical markers, such as CHAARTED metastatic volume or nodal status for patients with non-metastatic disease, could improve prognostic accuracy.

Added value of this study

This is the largest analysis of PSA nadir within a randomised controlled trial framework. We showed that PSA measured as early as 6 weeks or 12 weeks is associated with long-term survival, alongside the established 24-week timepoint. To our knowledge, we show for the first time the prognostic value of PSA in patients with very high-risk non-metastatic disease treated with an androgen receptor pathway inhibitor. On-treatment PSA values combined with metastatic volume or nodal status improve estimation of 8-year survival estimates.

Implications of all the available evidence

On-treatment serum PSA is a robust prognostic marker, with improved survival prediction when combined with conventional imaging-derived features. Future clinical trials should evaluate use of on-treatment PSA concentration combined with metastatic burden to personalise treatment intensification or de-intensification.

androgen deprivation therapy (ADT). These treatments include androgen receptor pathway inhibitors (ARPIs; eg, abiraterone acetate with prednisone [hereafter referred to as abiraterone]), or androgen receptor antagonists (eg, enzalutamide, apalutamide, or darolutamide),[2–7] docetaxel chemotherapy for patients with metastatic disease, radiotherapy to the primary tumour for patients with low-volume metastatic disease, and PARP inhibitors for *BRCA*-mutated prostate cancer.[8–12] However, prostate cancer is a heterogeneous disease with variable outcomes. Some patients might benefit from multi-therapy or multimodal approaches, whereas others might have similar outcomes with less intense regimens that are less toxic. This range of outcomes has driven the search for reliable prognostic biomarkers to support personalised management. One such biomarker is metastatic disease burden at the start of ADT. The CHAARTED trial used a now widely adopted definition of high-volume disease: presence of visceral metastases or at least four bone lesions with at least one beyond the vertebral bodies and pelvis.[12]

In parallel, several post-hoc analyses have shown that serum prostate-specific antigen (PSA) concentrations after treatment initiation are associated with long-term outcomes.[13–16] The SWOG9346 trial of intermittent ADT in patients with metastatic prostate cancer categorised patients into distinct prognostic groups based on PSA values after 7 months of treatment: 0·2 ng/mL or less, higher than 0·2 ng/mL to 4·0 ng/mL, and higher than 4·0 ng/mL.[16] These categories are now being considered in prospective adaptive trial designs, although they have not been recommended for use to change treatment by any guidelines.[17,18]

We aimed to study how metastatic volume and on-treatment serum PSA can be used together to improve prediction of patient survival. We performed a post-hoc analysis of on-treatment PSA concentrations and their associations with overall survival in patients included in any of five individually powered phase 3 trials conducted in the STAMPEDE (Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy) platform protocol.

Methods

Study design and participants

The STAMPEDE platform protocol has been previously described.[19] All patients had prostate adenocarcinoma (requiring histological confirmation from protocol version 8.0, Sept 2, 2011), with intention to treat with ADT, WHO performance score of 0–2, neutrophil count higher than $1·5\times10^9$ cells per L, platelet count higher than 100×10^9 per L, and estimated glomerular filtration rate higher than 30 mL/min per 1·73 m², and were randomly assigned within 12 weeks of initiating ADT. Patients were stratified according to the presence or absence of metastatic disease, confirmed by imaging, including CT of the pelvis and abdomen (with chest CT or a chest x-ray) or whole-body bone scintigraphy or equivalent. Non-metastatic disease was defined as no evidence of distant metastases on conventional imaging. Patients were eligible if they had node-positive disease or, if node negative, had either high-risk newly diagnosed disease (defined as at least two of: tumour stage T3–T4,

Gleason score 8–10, or PSA ≥40 ng/mL) or relapsing disease with high-risk features (≤12 months of previous ADT, an interval of ≥12 months off treatment, and either PSA ≥4 ng/mL with a doubling time <6 months or PSA ≥20 ng/mL). Pelvic radiotherapy was administered according to local guidelines for untreated non-metastatic disease. Palliative radiotherapy was permitted for symptom control in patients with metastatic disease. Docetaxel was allowed as standard of care in addition to ADT after implementation of a protocol amendment (version 13; Dec 17, 2015). Where imaging was available for central review, patients with metastatic disease were classified (after completion of accrual) as having high-volume or low-volume disease based on the CHAARTED trial definition.[12] Nodal status was determined locally by CT or MRI of the pelvis and was a stratification factor. The primary outcome of the STAMPEDE platform trials was overall survival. Survival data up to February, 2024, 19 years after the start of accrual to the included trials, were used for the analysis.

There was no difference in efficacy or overall survival between the docetaxel and docetaxel plus zoledronic acid trials or between the abiraterone and abiraterone plus enzalutamide trials.[2,20–22] Consequently, patients were grouped into docetaxel-treated or abiraterone-treated groups for analysis. Patients within the STAMPEDE platform were also randomly assigned to receive zoledronic acid with or without celecoxib, but were excluded from this analysis because these treatments are not part of the current standard of care.

The study was approved by the institutional review board at each participating site and was conducted in accordance with the International Council for Harmonisation of Good Clinical Practice guidelines, the Declaration of Helsinki, and local regulations regarding the conduct of clinical research. All patients provided written informed consent. The STAMPEDE protocol platform is registered with ClinicalTrials.gov (NCT00268476), EUDRACT (2004-000193-31), and ISRCTN (ISRCTN78818544).

Procedures

Treatment details have been reported in the primary manuscripts.[2,8,20,21,23] Briefly, patients enrolled in the abiraterone trials were randomly assigned (1:1) to ADT (consisting of medical castration with luteinising hormone-releasing hormone agonists or antagonists, or surgical castration [bilateral orchidectomy]), ADT plus oral abiraterone 1000 mg and oral prednisolone 5 mg daily, or ADT plus abiraterone, prednisolone, and oral enzalutamide 160 mg daily. These trials recruited patients sequentially and did not share control patients, but did share patients with metastatic disease with a parallel trial evaluating radiotherapy to the primary tumour (appendix p 1). ADT, abiraterone, and enzalutamide were planned to continue life-long for patients with metastatic disease and for 3 years (ADT) or 2 years (abiraterone and enzalutamide) for patients with non-metastatic disease who received curative-intent radiotherapy. Patients assigned to docetaxel in the docetaxel trials received treatment at 75 mg/m² intravenously for six three-weekly cycles with prednisolone (10 mg) daily and standard premedication before each injection. Patients with newly diagnosed metastatic disease were randomly assigned (1:1) to standard of care alone or standard of care plus radiotherapy to the primary tumour (external beam to the prostate given as one of two schedules nominated before random assignment: 36 Gy in six consecutive weekly fractions of 6 Gy or 55 Gy in 20 daily fractions of 2·75 Gy over 4 weeks). There was no blinding to treatment allocation.[8,20–24] Information on post-progression therapies were collected by local sites and reported in the trials.[8,20–23]

Outcomes

This analysis used data from the STAMPEDE platform and is not a primary trial report. We aimed to test the association between serum PSA concentrations and overall survival, defined as the time from the landmark timepoint (6, 12, and 24 weeks after randomisation) to death from any cause. As reported in the primary manuscripts, most patients in both the metastatic and high-risk non-metastatic cohorts died from prostate cancer as opposed to other causes. Data on serum PSA concentrations were collected locally using trial case report forms. All patients with a PSA value were included in each landmark analysis, and the PSA value at that timepoint was used rather than the lowest PSA reached at any point. Patients were excluded if no PSA value was available.

Baseline characteristics and death status were obtained from the datasets used for previous trial publications.[2,8,20–23] To improve completeness, overall survival data for patients in England and Wales were supplemented through linkage with the Civil Registration of Death dataset in a process that has been previously described.[25] Patients not linked to the civil registrations of deaths were censored on the last date they were known to be alive from the trial case report forms. Patients who withdrew consent to long-term follow-up were censored at the date of withdrawal.

Statistical analysis

To evaluate the association between PSA and overall survival, we fitted multivariable Cox proportional hazards models, which was prespecified in a statistical analysis plan (appendix pp 21–39).

PSA at 24 weeks was modelled as a continuous variable using a fractional polynomial approach, with the hazard of death estimated relative to a reference value of 0·2 ng/mL. PSA was also considered as a categorical variable; hazard ratios (HRs) and 95% CIs were reported to quantify the association between PSA categories

(≤0·2 ng/mL, >0·2 to 1·0 ng/mL, >1·0 to 3·0 ng/mL, and >3·0 ng/mL, with the latter three categories chosen to create approximately balanced group sizes) and the hazard of death, using the PSA of 0·2 ng/mL or less group as the reference. Models were adjusted for treatment allocation and key baseline covariates, including log-transformed PSA before starting ADT (ng/mL); time from ADT initiation to randomisation; age (continuous); Gleason score (≤7 *vs* 8–10); WHO performance status (0 *vs* 1–2); regular use of aspirin or non-steroidal anti-inflammatory drugs (a minimisation factor in STAMPEDE[26]); nodal stage (node negative N0 *vs* node positive N1); tumour stage (T0–T2, T3, or T4); previous local therapy; enrolment period (to account for changes in post-progression therapy), and metastatic volume (low *vs* high). For the multivariable Cox models, we used a complete case approach. Therefore, patients with missing values for any adjustment covariate (eg, nodal status, tumour stage, or Gleason score) were excluded from the multivariable models but remained in the univariable analyses.

Similarly, we conducted three prespecified landmark analyses: the primary analysis at 24 weeks post randomisation and additional landmark analyses at 6 weeks and 12 weeks. The Kaplan–Meier method was used to estimate the 96-month overall survival of both the overall cohort divided by metastatic status (metastatic *vs* non-metastatic) and then by CHAARTED volume (metastatic cohort) or nodal status (non-metastatic cohort). 95% CIs were computed using the Greenwood formula. Survival time was measured from the date of randomisation, not the landmark timepoint to aid comparison between the three analyses, unless stated otherwise.

In a post-hoc exploratory analysis, we fitted a Cox model for 24-week PSA categories that additionally adjusted for both 6-week and 12-week PSA category. To assess robustness of the overall survival findings, we also

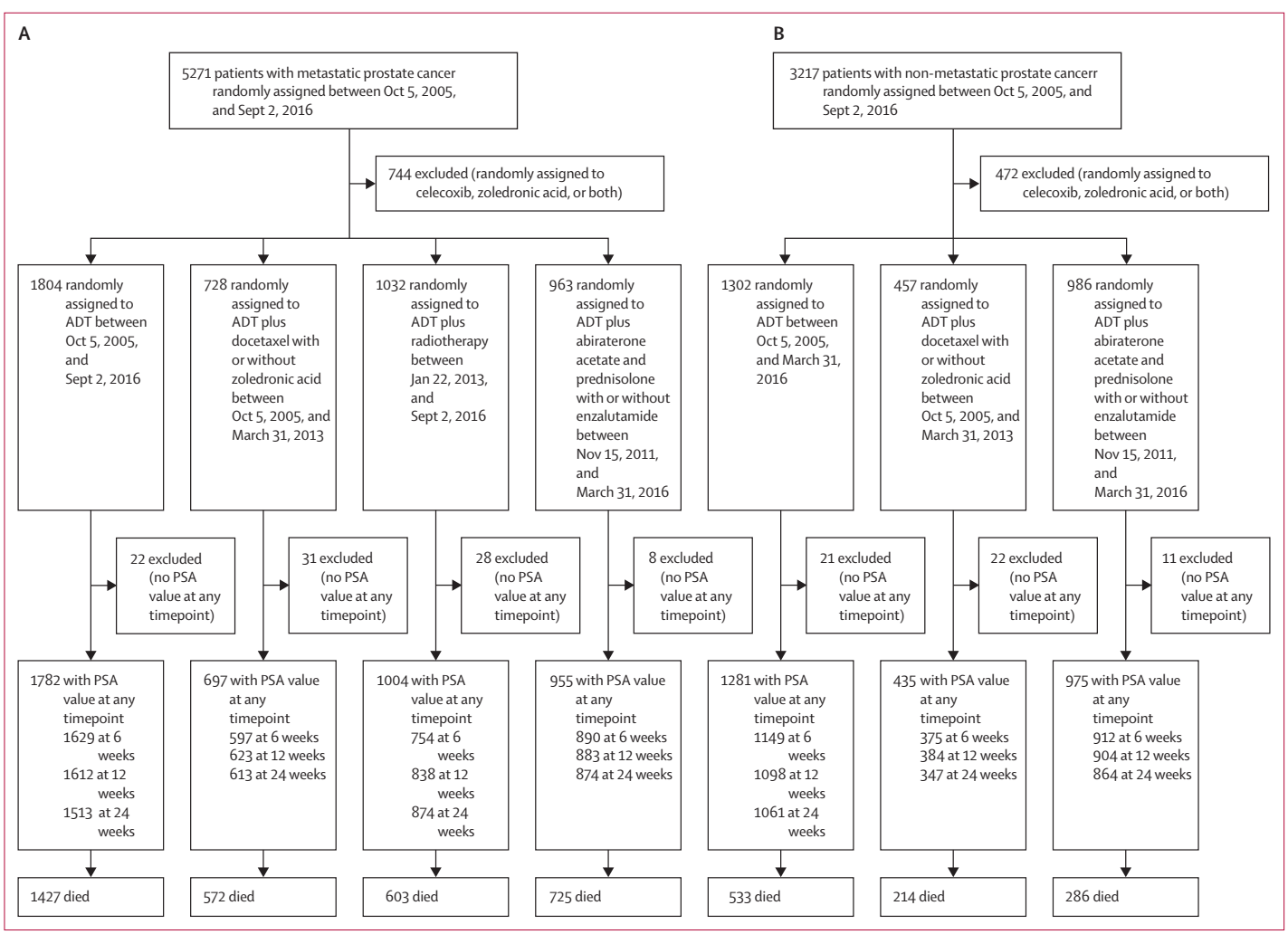


Figure 1: **Study flow**
Patient disposition split by treatment assignment and metastatic status: metastatic disease (A) or non-metastatic disease (B). ADT=androgen deprivation therapy. PSA=prostate-specific antigen.

undertook an exploratory post-hoc analysis (not prespecified in the statistical analysis plan), to evaluate prostate cancer-specific survival using Fine–Gray competing-risks regression at the 24-week landmark, reporting subdistribution HRs across PSA categories. We considered p values of less than 0·05 to indicate significance.

Analyses were performed using STATA (version 18) by two UK Medical Research Council Clinical Trials Unit statisticians (LM and PDM).

Results

Between Oct 5, 2005, and Sept 2, 2016, the STAMPEDE platform protocol randomly assigned 8488 patients to eight phase 3 trials (figure 1). For this analysis, we excluded 1216 patients who were randomly assigned to celecoxib, zoledronic acid, or a combination of both drugs. A further 143 patients with no PSA values at any of the three landmark timepoints were excluded. This left 7129 patients who were randomly assigned in a relevant trial and had at least one PSA value. Of these patients, 3063 were randomly assigned to receive standard-of-care comprising ADT (n=2631) or ADT plus docetaxel (n=432). Research treatments added to the standard of care were docetaxel or docetaxel plus zoledronic acid (n=1132), abiraterone or abiraterone plus enzalutamide (n=1930), and radiotherapy to the prostate (n=1004, patients with metastatic disease only). Among 3956 patients with metastatic disease who had volume assessment, 2211 (55·9%) had high-volume metastases (appendix p 3), and among 2691 patients with non-metastatic disease, 1033 (38·4%) were lymph node positive (appendix p 4).

The median time from starting ADT to randomisation was 50 days (IQR 30–69) in the metastatic cohort and 43 days (21–64) in the non-metastatic cohort. For patients who started specific research treatments, median time from randomisation to the initiation of docetaxel was 16 days (IQR 11–23), to initiation of abiraterone with or without enzalutamide was 11 days (6–19), and to initiation of radiotherapy (for patients with metastatic disease) was 35 days (28–62; appendix p 5). In the non-metastatic cohort, the median time to starting radiotherapy was 191 days (IQR 147–not reached [NR]; appendix p 6). Median follow-up was 9·6 years (IQR 8·3–11·4; appendix p 6 shows the split by treatment assignment). We identified that 3327 (75·0%) of 4438 patients with metastatic disease and 1033 (38·4%) of 2691 patients with non-metastatic disease had died. 121 (1·7%) of 7129 eligible patients withdrew consent and were censored at the date of withdrawal.

We evaluated 24-week PSA as a continuous variable and identified that log transformation fitted the best model in both the metastatic and non-metastatic cohorts (figure 2A, B). Increasing PSA concentrations were associated with steep rises in the relative hazard of death, with the slope of this association reducing at PSA values above approximately 1·5 ng/mL in the non-metastatic cohort and above 3 ng/mL in the metastatic cohort (global p<0·0001). Adjustment for known prognostic variables did not materially alter the association between on-treatment PSA concentration and overall survival (appendix pp 7–8).

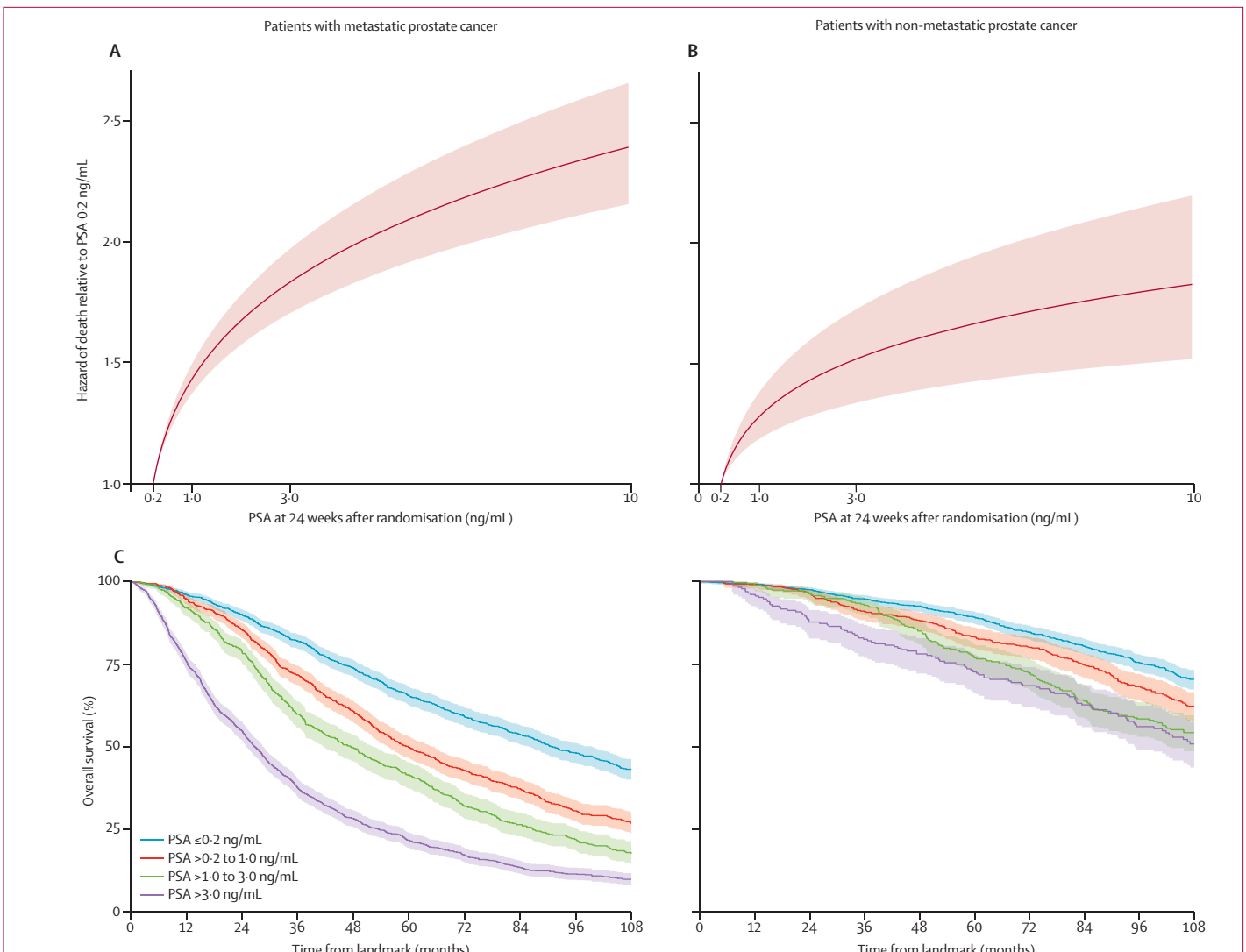
Next, we considered PSA as a categorical variable (figure 2C, D). There was a progressive decline in overall survival with increasing PSA categories. A similar trend was observed in the non-metastatic cohort, but, as predicted by the non-linear model, 96-month overall survival rates did not differ between the two highest categories (60·1% [95% CI 54·7–65·1] for PSA >1·0 to 3·0 ng/mL and 60·2% [53·4–66·3] for PSA >3·0 ng/mL; appendix pp 11–12).

Assessment of the proportional hazards assumption using Schoenfeld residuals indicated evidence of non-proportionality for some PSA categories, particularly in the metastatic cohort (appendix p 9). Early hazard differences between PSA categories were more pronounced and attenuated over longer follow-up.

We next evaluated PSA concentration at 24 weeks according to treatment allocation. Among patients with metastatic disease, the proportion with a PSA of 0·2 ng/mL or less was lowest in the standard-of-care group (253 [16·7%] of 1513) and highest in the abiraterone group (479 [54·8%] of 874). The proportion who had a PSA of 0·2 ng/mL or less was similar for patients in the docetaxel group (173 [28·2%] of 613) and those in the radiotherapy group (259 [29·6%] of 874). Among patients with a PSA of 0·2 ng/mL or less at 24 weeks, 96-month overall survival also differed by treatment group: 56·3% (95% CI 51·6–60·7) for patients in the abiraterone group compared with 40·4% (32·9–47·8) for patients in the docetaxel group (appendix pp 11–12).

In the non-metastatic cohort, the proportion of patients who had a PSA of 0·2 ng/mL or less at 24 weeks was also lowest in the standard-of-care group (329 [31·0%] of 1061) and highest in the abiraterone group (679 [78·6%] of 864). Consistent with previous trial efficacy reports,[22] a similar proportion of patients with non-metastatic disease in the docetaxel group had a PSA of 0·2 ng/mL or less (131 [37·8%] of 347) as in the standard-of-care group.

We then evaluated serum PSA at 6 weeks and 12 weeks. In the metastatic cohort, a PSA of 0·2 ng/mL or less was observed in 1164 (30·0%) of 3874 patients at 24 weeks compared with 793 (20·0%) of 3956 patients at 12 weeks and 482 (12·5%) of 3870 patients at 6 weeks. Once patients had reached a PSA of 0·2 ng/mL or less, they were unlikely to experience a rise. For example, of 899 patients with a PSA of 0·2 ng/mL or less at 6 weeks and a value at 24 weeks, only 83 (9·2%) had a subsequent rise higher than 0·2 ng/mL at 24 weeks (all other combinations of PSA values are listed in the appendix pp 18–20). Patients with a PSA in categories greater than 0·2 ng/mL at 6 weeks or 12 weeks who subsequently had



Number at risk (censored)																				
PSA ≤0·2 ng/mL	1164 (0)	1113 (7)	1041 (9)	945 (12)	837 (27)	726 (44)	635 (65)	560 (82)	400 (191)	247 (309)	1139 (0)	1122 (8)	1101 (10)	1066 (12)	1039 (16)	976 (42)	895 (74)	825 (100)	602 (276)	354 (492)
PSA >0·2 to 1·0 ng/mL	910 (0)	861 (2)	770 (8)	644 (11)	536 (21)	432 (30)	361 (41)	299 (57)	196 (112)	131 (156)	552 (0)	543 (4)	526 (6)	495 (7)	481 (7)	443 (18)	419 (25)	381 (36)	276 (109)	182 (182)
PSA >1·0 to 3·0 ng/mL	594 (0)	547 (0)	469 (1)	355 (1)	293 (3)	238 (9)	179 (15)	142 (21)	102 (39)	64 (59)	352 (0)	346 (2)	336 (3)	322 (5)	294 (6)	261 (11)	239 (18)	207 (22)	165 (47)	114 (88)
PSA >3·0 ng/mL	1206 (0)	910 (6)	656 (9)	447 (12)	333 (15)	251 (21)	193 (28)	145 (34)	102 (57)	71 (75)	229 (0)	220 (0)	200 (1)	188 (1)	177 (2)	159 (8)	144 (14)	128 (18)	102 (31)	72 (53)

Figure 2: **Association of 24-week serum PSA with overall survival of patients with metastatic or non-metastatic prostate cancer**
Hazards of death, with reference to survival in patients with a PSA of 0·2 ng/mL and metastatic disease (A) or non-metastatic disease (B). Kaplan–Meier curves for overall survival of patients with metastatic disease (C) or non-metastatic disease (D) split by serum PSA categories. Survival time was measured from the landmark of 24 weeks after randomisation. Shading represents 95% CIs. PSA=prostate-specific antigen.

a decline to 0·2 ng/mL or less at 24 weeks most commonly had a PSA concentration between 0·2 and 1·0 ng/mL, although there were also some declines from higher PSA categories. Similarly, in the non-metastatic cohort, a PSA of 0·2 ng/mL or less was observed in 1139 (50·1%) of 2271 patients at 24 weeks compared with 843 (35·3%) of 2386 patients at 12 weeks and 538 (22·1%) of 2436 patients at 6 weeks. A Sankey plot illustrating the relationships between PSA values from individual patients across the three timepoints is shown in figure 3A.

On-treatment PSA concentrations were associated with overall survival in the metastatic cohort as early as 6 weeks after randomisation (figure 3B). Among patients with metastatic disease, the 96-month overall survival rate for those with a PSA of 0·2 ng/mL or less was 47·9% (95% CI 43·2–52·4) at 6 weeks and was 50·2% (46·6–53·8) at 12 weeks, both of which were similar to the overall survival rate for a PSA of 0·2 ng/mL or less at 24 weeks (50·3% [47·3–53·2]). However, when higher PSA categories (>0·2 to 1·0 ng/mL, >1·0 to 3·0 ng/mL,

and >3·0 ng/mL) were considered, survival rates estimated using week 6 or week 12 PSA values were higher than those based on week 24 PSA values. Notably, a PSA higher than 3·0 ng/mL was associated with a 96-month overall survival rate of 21·1% (95% CI 19·2–23·1) at 6 weeks versus 16·2% (14·3–18·2) at 12 weeks and 12·2% (10·4–14·2) at 24 weeks (figure 3B; appendix pp 11–16).

In the non-metastatic cohort, patients with a PSA of 0·2 ng/mL or less at 6 weeks had a 96-month overall survival rate of 77·3% (95% CI 73·4–80·7), similar to patients at 12 weeks (75·7% [72·6–78·5]) and 24 weeks (78·0% [75·4–80·4]). A PSA higher than 3·0 ng/mL was associated with similar 96-month overall survival when measured at 6 weeks, 12 weeks, or 24 weeks (appendix pp 11–16).

In a post-hoc exploratory analysis, we fitted a Cox model for 24-week PSA categories that additionally adjusted for both 6-week and 12-week PSA category. The HRs for increasing PSA categories relative to PSA of

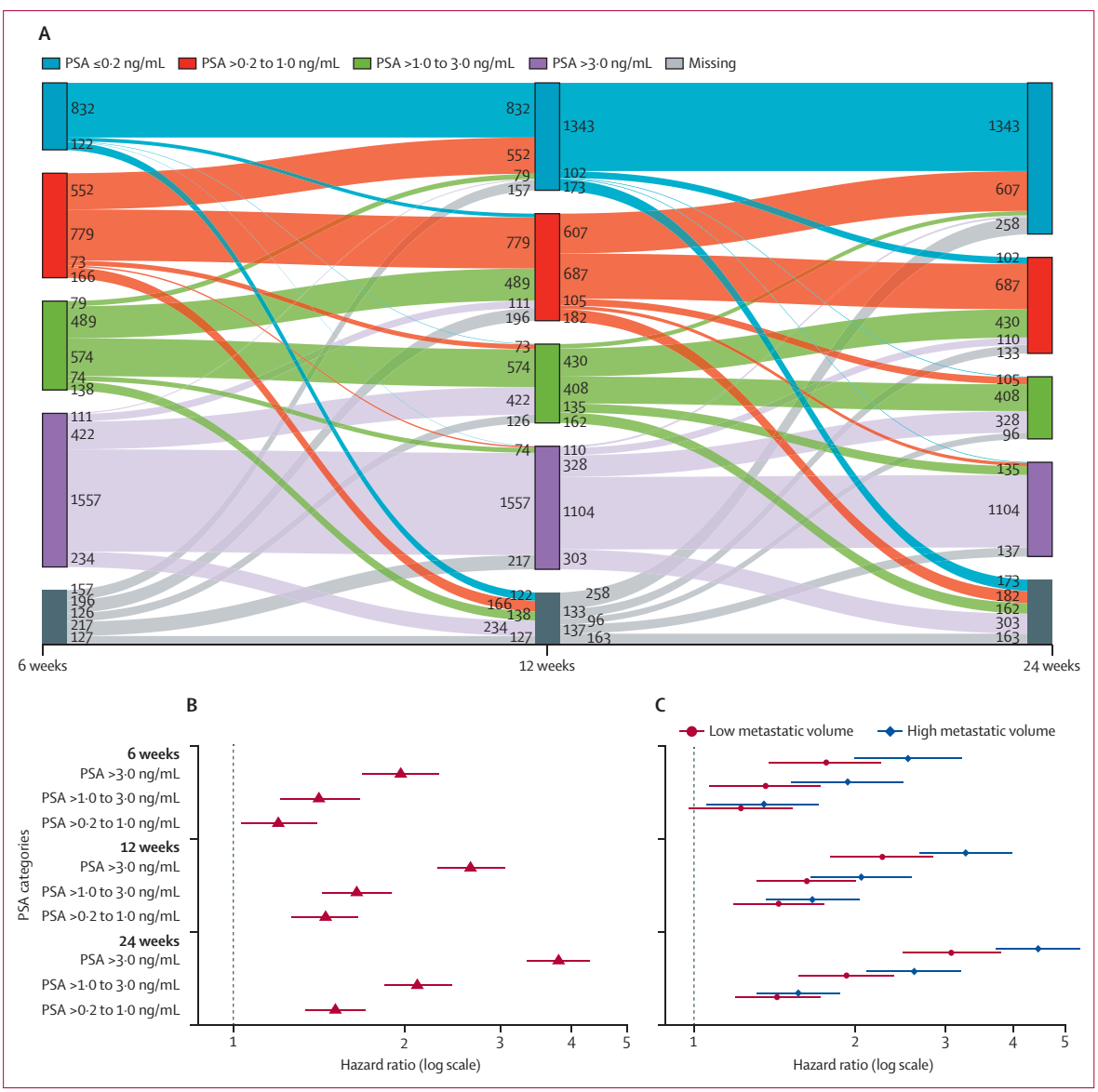


Figure 3: **Serum PSA at 6 weeks, 12 weeks, and 24 weeks after randomisation**

(A) Sankey diagram showing the number of patients in each PSA category at 6 weeks, 12 weeks, and 24 weeks after randomisation. The width of each ribbon is proportional to the number of patients in the specific PSA category at that timepoint. Values <70 are not shown for readability. See the appendix (p 19) for patterns of PSA category transitions. (B) Forest plots of adjusted hazard ratios of death compared with the reference value of ≤0·2 ng/mL at 6 weeks, 12 weeks, and 24 weeks after randomisation in patients with metastatic disease. (C) Forest plots of adjusted hazard ratios of death compared with the reference value of ≤0·2 ng/mL at 6 weeks, 12 weeks, and 24 weeks after randomisation with additional separation by low-volume or high-volume metastatic disease. Survival time was measured from the landmark time. The x-axis represents the hazard ratio on a logarithmic scale, where 1 indicates no difference. Error bars indicate 95% CIs. PSA=prostate-specific antigen.

0·2 ng/mL or less became 1·51 (95% CI 1·25–1·82), 2·78 (2·21–3·51), and 5·17 (4·05–6·60), all with p values less than 0·0001 (data not shown).

We then evaluated overall survival outcomes in PSA subcategories, split by metastatic volume, or nodal status in the non-metastatic cohort. A PSA decline to 0·2 ng/mL or less at 24 weeks was significantly more frequent in patients with low-volume metastatic disease (620 [39·9%] of 1554) than in those with high-volume metastatic disease (428 [22·6%] of 1890). In the non-metastatic cohort, PSA decline to 0·2 ng/mL or less at 24 weeks was also more frequent, with a smaller difference between patients with node-negative disease (719 [52·3%] of 1376) versus those with node-positive disease (417 [46·7%] of 819]; appendix p 11–12). Across all timepoints, within each PSA category, overall survival rates were greater in low-volume metastatic cohorts than in high-volume metastatic cohorts (figure 3C).

Among patients with low-volume metastatic disease who reached a PSA of 0·2 ng/mL or less at 24 weeks, the 96-month overall survival rate was 57·1% (95% CI 53·0–61·0]) compared with 39·8% (35·0–44·5) for patients with high-volume metastatic disease (figure 4; appendix p 11). 96-month overall survival of patients with non-metastatic disease and a PSA of 0·2 ng/mL or less was higher than in patients with low-volume metastatic disease. Among patients who had a 24-week PSA of 0·2 ng/mL or less in the non-metastatic cohort, the

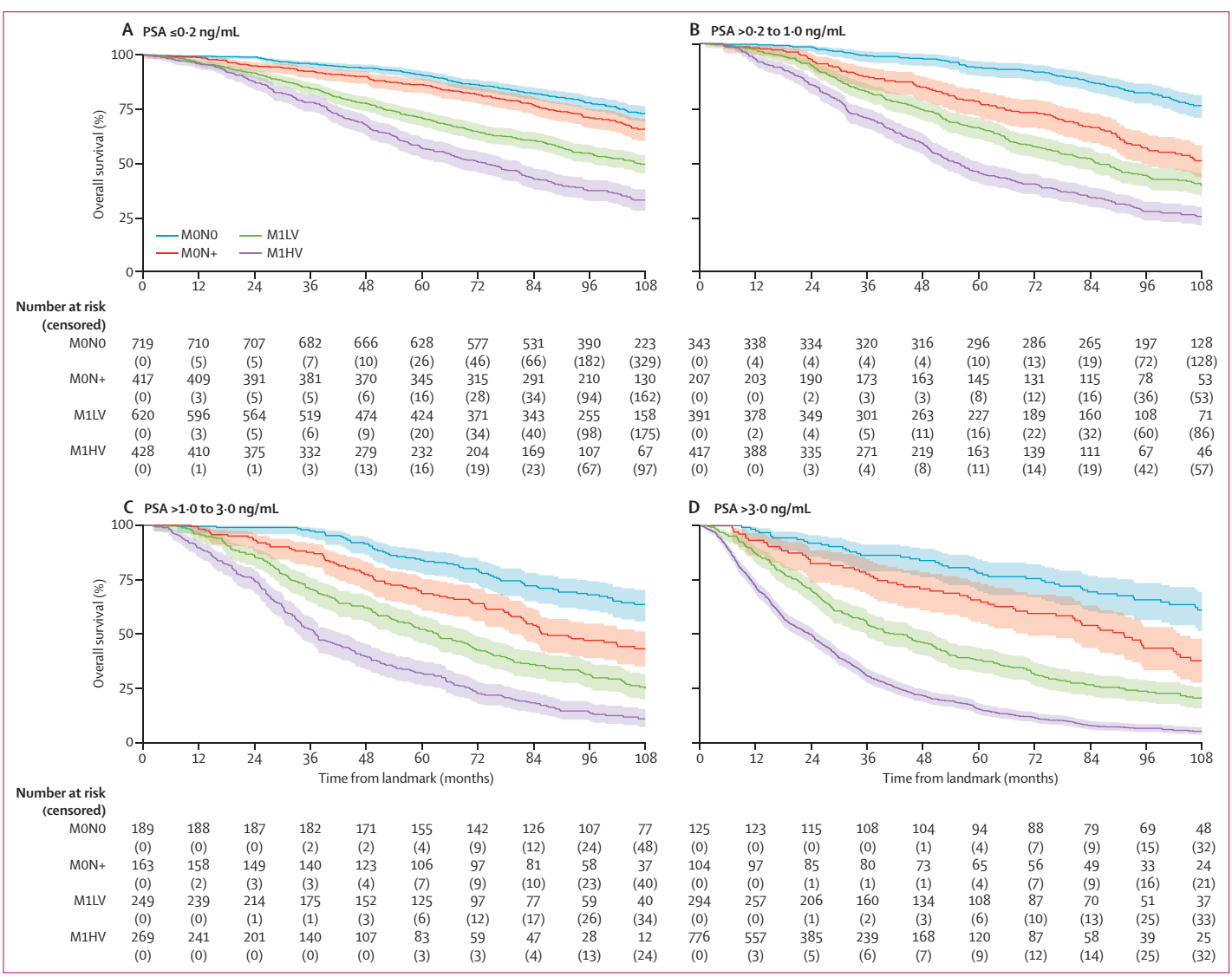


Figure 4: **Overall survival for patients categorised by 24-week serum PSA and disease burden**

Kaplan–Meier curves showing overall survival for patients categorised by 24-week serum PSA ≤0·2 ng/mL (A), >0·2 to 1·0 ng/mL (B), >1·0 to 3·0 ng/mL (C), and >3·0 ng/mL (D) and by disease burden. Survival time was measured from the landmark of 24 weeks after randomisation. Shading represents 95% CIs. M0N0=non-metastatic node-negative disease. M0N+=non-metastatic node-positive disease. M1LV=metastatic low-volume disease. M1HV=metastatic high-volume disease. PSA=prostate-specific antigen.

estimated 96-month overall survival was 80·3% (95% CI 77·1–83·1) for node-negative disease and 73·9% (69·3–77·9) for node-positive disease.

ADT plus ARPI is now the standard-of-care treatment backbone. Therefore, we finally focused on overall survival outcomes among patients assigned to an abiraterone regimen. Similarly, predicted survival by 24-week PSA of patients treated with ADT and an abiraterone regimen was different based on metastatic volume, and for non-metastatic disease based on lymph node status (appendix p 2). A PSA of 0·2 ng/mL or less at 24 weeks was more likely to be observed in patients with low-volume metastatic disease (253 [66·9%] of 378) than in patients with high-volume disease (117 [43·4%] of 409; appendix p 11). Among patients with a PSA of 0·2 ng/mL or less at 24 weeks, 96-month overall survival rate was higher in patients with low-volume metastatic disease (64·1% [95% CI 57·8–69·8]) than in those with high-volume metastatic disease (44·6% [37·1–51·9]; figure 5). A smaller difference in the 96-month overall survival rate was observed in the non-metastatic cohort between patients with node-negative disease (82·8% [95% CI 78·7–86·1]) and those with node-positive disease (79·4% [73·8–83·9]).

A post-hoc exploratory analysis of prostate cancer-specific survival using a competing risks framework showed patterns consistent with overall survival (appendix p 17). Across metastatic and non-metastatic cohorts, higher 24-week PSA categories were associated with progressively worse prostate cancer-specific survival. In patients with metastatic disease, adjusted subdistribution HRs were 1·70 (95% CI 1·44–2·00) for PSA higher than 0·2 to 1·0 ng/mL, 2·72 (2·28–3·25) for PSA higher than 1·0 to 3·0 ng/mL, and 4·72 (4·02–5·55) for PSA higher than 3·0 ng/mL; corresponding estimates in patients with non-metastatic disease were 1·90 (1·38–2·61), 2·91 (2·09–4·05), and 3·56 (2·34–5·41; all p<0·0001).

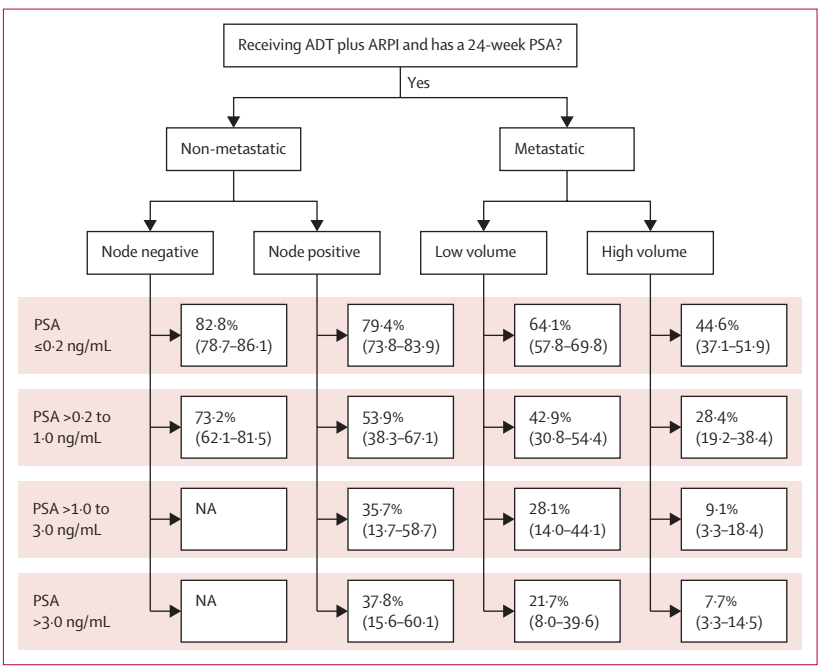


Figure 5: **Flowchart to estimate 96-month overall survival rates based on imaging and on-treatment PSA (≤0·2 ng/mL at 24 weeks) for patients treated with ADT and abiraterone**
Data are overall survival (95% CI) at 96 months. NA indicates that there were ten or fewer patients in this category. ADT=androgen deprivation therapy. ARPI=androgen receptor pathway inhibitor. NA=not applicable. PSA=prostate-specific antigen.

Discussion

With follow-up of up to 19 years, this study provides robust 96-month overall survival estimates and, combined with the large sample size, enables several novel discoveries. First, to our knowledge, this is the first analysis to show the prognostic significance of on-treatment PSA for patients with non-metastatic prostate cancer treated with ADT and an ARPI. Second, across all three landmark timepoints, patients who reached a PSA concentration of 0·2 ng/mL or less at 6 weeks or 12 weeks had long-term survival similar to those reaching this threshold at 24 weeks, in both metastatic and non-metastatic cohorts. However, because PSA decline is often gradual, a value higher than 0·2 ng/mL before 24 weeks did not necessarily indicate poor prognosis. Many patients with higher PSA at 6 weeks or 12 weeks subsequently reached 0·2 ng/mL or less by 24 weeks. Consequently, survival estimates for PSA categories higher than 0·2 ng/mL at earlier landmarks were more favourable than at 24 weeks, reflecting ongoing response rather than treatment failure. Third, the 96-month overall survival rates predicted by each PSA category are treatment specific, with consistently superior outcomes for patients receiving abiraterone. Furthermore, we found evidence of non-proportionality for some PSA categories, which probably reflects time-varying treatment effects and changes in disease biology. However, although this deviation from proportional hazards could reduce model efficiency, it does not alter the direction of effect. These remain clinically interpretable despite non-proportional hazards. Finally, fewer patients with high-volume metastatic disease had a PSA of 0·2 ng/mL or less at 24 weeks, but, intriguingly, their survival was worse than patients who had low-volume metastases and who had a PSA decline to the same category. We hypothesise that a PSA of 0·2 ng/mL or less reflects similar androgen receptor signalling suppression in both groups, but patients with high-volume disease might carry a larger burden of residual tumour that does not secrete PSA. This residual disease could contribute to poorer outcomes. Although this hypothesis cannot currently be confirmed without more sensitive imaging or molecular analyses, our findings support using both metastatic volume and on-treatment PSA category to guide monitoring and treatment intensification.

This study has some limitations. First, the STAMPEDE trial recruited patients before the widespread adoption of next-generation imaging modalities, such as PET and MRI; therefore, metastatic status was determined using conventional imaging alone. Although some patients classified as having non-metastatic disease might have had metastases detectable using more sensitive imaging, and volume assessment differs by imaging modality, the long-term prognostic relevance of discordant results between conventional and next-generation imaging remains under investigation.[27] Second, the analysis is limited to patients who survived long enough to provide PSA measurements at the specified timepoints. Patients without PSA data were more likely to have died or experienced disease progression. As a result, individuals with particularly aggressive prostate cancer biology, who were either progressing rapidly before PSA assessment or were ineligible for the trial due to early progression, are under-represented in this analysis. Third, treatment options for castration-resistant prostate cancer have expanded significantly during the trial period, potentially influencing overall survival outcomes, so this study might underestimate survival rates. Fourth, the lower limit of PSA recorded was 0·2 ng/mL, reflecting the sensitivity of clinical assays used during the accrual period. Recent studies suggest that ultra-low PSA concentrations (<0·01 ng/mL) might also have prognostic utility, which could be evaluated further in combination with metastatic status.[28] Finally, additional information could be obtained at baseline, such as digital pathology multi-modal artificial intelligence scores or molecular classifiers,[29,30] that might improve prognostication when combined with serum PSA dynamics. This study prioritised including all patients with a PSA value, and future work could integrate more biomarker information across subsets of patients.

When applying these findings in clinical practice, the landmark timepoints used in this analysis (measured from randomisation) can be considered broadly equivalent to time from initiation of ARPI, as abiraterone began a median of 10 days after randomisation. The interval from starting ADT to ARPI was variable, but was approximately a median of 60 days, which reflects typical clinical pathways. Fewer than 4% of patients presented with metachronous disease; therefore, these results primarily apply to synchronous presentations. To aid clinical decision making, we provide a practical flow chart for estimating survival probabilities. Future research should validate these estimates in external datasets and develop a nomogram to support personalised treatment strategies. Although the inclusion of both metastatic and very high-risk non-metastatic disease, together with multiple treatment strategies, introduces substantial clinical heterogeneity, this reflects real-world practice and strengthens the relevance of our findings.

In conclusion, we report clinically relevant long-term survival data categorised by standard imaging and on-treatment PSA concentrations from a large, prospective platform trial. These findings could inform patient counselling, follow-up schedules, and treatment decision making at the start of ADT. Several clinical trials have recently initiated that prospectively investigate, for example, using on-treatment PSA for treatment de-escalation (DE-ESCALATE [NCT05974774], LIBERTAS [NCT05884398]) or intensification (TRIPLE SWITCH [NCT06592924], PEACE6-Poor Responders [NCT06496581]). We report excellent outcomes that support the potential for de-intensification strategies in specific subgroups of patients, most notably for those with low-volume metastatic disease treated with abiraterone and reaching a PSA of 0·2 ng/mL or less, whereas treatment intensification should be considered for patients with higher PSA values, most notably for those who had high-volume metastatic disease at presentation.

Contributors

MK, LM, NDJ, GA, LCB, FT, and SG were involved in study conceptualisation. LM, MK, PD-M, AS, and MB contributed to data curation. LM and PD-M did the formal analysis. GA, NDJ, SG, AS, MKBP, and NWC were involved in funding acquisition. MK, LM, GA, LCB, FT, SG, and MRS contributed to methodology. CLA, KC, PD-M, LCB, RM, DM, and MKBM were involved in project administration. All authors contributed to the investigation and managed resources. GA, DCG, and LCB supervised the study. MK, LM, PD-M, GA, and LCB verified the data used in the study. MK, LM, PD-M, GA, and LCB made the figures. MK, LM, PD-M, GA, and LCB wrote the original draft of the report. All authors reviewed and edited the report. RM and DM are the patient and public involvement representatives in the Trial Management Group. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

LM reports support for the present manuscript from Cancer Research UK and research funding to her institution for the STAMPEDE trial from Janssen, Astellas, Novartis, Sanofi, and Clovis. AS reports grants or contracts from Cancer Research UK, The Urology Foundation, the Prostate Cancer Foundation, the Engineering and Physical Sciences Research Council, and Prostate Cancer UK; consulting fees from Veracyte and Novartis; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Ipsen and Gedeon Richter; support for attending meetings or travel from Janssen; participation on a data safety monitoring board or advisory board for Act-ResoLUTE, Veracyte, and Janssen; and a leadership role as an associate member of the European Association of Urology Prostate Cancer Guidelines Panel. REL reports support for the present manuscript from UK Research and Innovation–Medical Research Council core funding. MRS reports support for the present manuscript from UK Research and Innovation–Medical Research Council through part of his employment in a previous role; grants or contracts from Astellas, Janssen, and Sanofi-Aventis to his previous institution for research elsewhere within the STAMPEDE research platform; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Eisai, Eli Lilly, and Janssen; support for attending meetings or travel from the Health Research Board (Ireland), the Trials Research Methodology Network (Ireland), and the National Cancer Grid (India); and participation on independent data monitoring committees for academic sponsors, none of which are paid. CCP reports participation on an advisory board for Janssen (payment to institution); consultancy for Novartis (payment to institution); and participation on an independent data monitoring committee for Telix Pharmaceuticals. WC reports payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Bayer, Johnson & Johnson, and Ipsen; support for attending meetings or travel from Bayer, Johnson & Johnson, and Ipsen; and a

leadership role as a clinical adviser for the UK National Institute for Health and Care Excellence clinical adviser. MV reports payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Astellas, and support for attending meetings or travel from Astellas. FT reports payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Silvio Grasso Consulting, the Swiss Group for Clinical Cancer Research, Merck, and Novartis (payment to institution), and from Bayer and MSD (personal); support for attending meetings or travel from Bayer; and participation on a data safety monitoring board or advisory board for Bayer and Telix Pharmaceuticals. SG reports consulting fees from Ipsen and Avalere Health; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Silvio Grasso Consulting, Peer Voice, the European Society for Medical Oncology, Meister ConCept, the Swiss Group for Clinical Cancer Research, American Society of Clinical Oncology Genitourinary, AdMeTech Foundation, EPG Health, Intellisphere, Orikata, Medtoday Switzerland, UroPratica Group in São Paulo, Swiss Infomed Organisation, Swiss Cancer Institute, Emirates Oncology, Symposia Congressi, and ideA-Z Project in progress; support for attending meetings or travel from Bayer, Intellisphere, Gilead, and Johnson & Johnson; patents planned, issued, or pending for prostate cancer biomarkers (WO2009138392); participation on data safety monitoring boards or advisory boards for MSD, Bayer, Bristol Myers Squibb, Daiichi Sankyo, Boehringer Ingelheim, Innomedica, Macrogenics, Astellas, Novartis, Amgen, Merck, and GSK; leadership or fiduciary roles in other boards, societies, committees, or advocacy groups for Pfizer, the ALPINE Prostate Cancer Committee, LinkinVax, and the University of Applied Sciences and Arts of Southern Switzerland (Manno, Switzerland); and other financial or non-financial interests from ASCO, Unicancer, AstraZeneca, Pfizer, and Bayer. NWC reports support for the present manuscript through STAMPEDE trial funding; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Bayer, AstraZeneca, Janssen, and Astellas; participation on a data safety monitoring board or advisory board for the CAPItello-281 trial; and a leadership role as Clinical Lead of the National Prostate Cancer Audit for England and Wales. MKBP reports support for the present manuscript from the UK Medical Research Council through core funding to the Clinical Trials Unit. NDJ reports support for the present manuscript from Cancer Research UK and the UK Medical Research Council; study funding and provision of study drug from Sanofi, Astellas, and Janssen; grants or contracts from the Prostate Cancer Foundation; consulting fees from Johnson & Johnson and AstraZeneca; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Astellas; patents planned, issued, or pending related to an AI pathology tool licensed to ArteraAI; and participation on a data safety monitoring board as a member of the VISION trial. GA reports grants or contracts from Janssen, Astellas Pharma, Novartis, and Agilent; royalties or licenses through the Institute of Cancer Research Rewards to Discoverers Scheme; support for attending meetings or travel and personal fees from Janssen, Astellas Pharma, Pfizer, Ipsen, Novartis/AAA, Abbott Laboratories, Ferring, ESSA Pharmaceuticals, Bayer Healthcare Pharmaceuticals, Beigene, Blue Earth Therapeutics, Takeda, Veracyte, AstraZeneca, and Sanofi-Aventis; and patents planned, issued, or pending for blood-based methylation markers (GB1915469.9). All other authors declare no competing interests.

Data sharing

Individual participant data are available upon request to the corresponding author and after deidentification, as per the moderated access approach of the UK Medical Research Council Clinical Trials Unit at University College London (London, UK).

Acknowledgments

The STAMPEDE protocol was funded by Cancer Research UK's Clinical Research Committee (formerly the Clinical Trials Advisory Awards Committee; CRUK_A12459) with educational grants from Novartis, Sanofi-Aventis, Pfizer, Janssen Pharma, Astellas, and Clovis Oncology. Sanofi-Aventis, and Janssen, and Novartis provided free drugs for the conduct of the trials included in this study. The Clinical Trials Unit at University College London receives core funding from the UK Medical Research Council (grant codes MC_UU_12023/25 and MC_UU_00004/01). These analyses were supported by Prostate Cancer UK (MA-PM16-001) and the John Black Charitable Foundation. We thank all patients who participated and their families, the site staff and investigators and the STAMPEDE oversight committees. The majority of patients in the STAMPEDE trial were recruited in the UK, and recruiting sites receive funding for delivery of clinical research within the National Health Service from the Nation Institutes for Health and Care Research (NIHR) Clinical Research Network funded by the UK Department of Health. The views expressed in this Article are those of the authors and not necessarily those of the National Health Service, the NIHR, or the Department of Health.

References

1 James ND, Tannock I, N'Dow J, et al. The *Lancet* Commission on prostate cancer: planning for the surge in cases. *Lancet* 2024; **403:** 1683–722.
2 James ND, de Bono JS, Spears MR, et al. Abiraterone for prostate cancer not previously treated with hormone therapy. *N Engl J Med* 2017; **377:** 338–51.
3 Davis ID, Martin AJ, Stockler MR, et al. Enzalutamide with standard first-line therapy in metastatic prostate cancer. *N Engl J Med* 2019; **381:** 121–31.
4 Fizazi K, Tran N, Fein L, et al. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. *N Engl J Med* 2017; **377:** 352–60.
5 Chi KN, Agarwal N, Bjartell A, et al. Apalutamide for metastatic, castration-sensitive prostate cancer. *N Engl J Med* 2019; **381:** 13–24.
6 Armstrong AJ, Szmulewitz RZ, Petrylak DP, et al. ARCHES: a randomized, phase III study of androgen deprivation therapy with enzalutamide or placebo in men with metastatic hormone-sensitive prostate cancer. *J Clin Oncol* 2019; **37:** 2974–86.
7 Saad F, Vjaters E, Shore N, et al. Darolutamide in combination with androgen-deprivation therapy in patients with metastatic hormone-sensitive prostate cancer from the phase III ARANOTE trial. *J Clin Oncol* 2024; **42:** 4271–81.
8 Parker CC, James ND, Brawley CD, et al. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. *Lancet* 2018; **392:** 2353–66.
9 Smith MR, Hussain M, Saad F, et al. Darolutamide and survival in metastatic, hormone-sensitive prostate cancer. *N Engl J Med* 2022; **386:** 1132–42.
10 Fizazi K, Foulon S, Carles J, et al. Abiraterone plus prednisone added to androgen deprivation therapy and docetaxel in de novo metastatic castration-sensitive prostate cancer (PEACE-1): a multicentre, open-label, randomised, phase 3 study with a 2×2 factorial design. *Lancet* 2022; **399:** 1695–707.
11 Attard G, Agarwal N, Graff JN, et al. Niraparib and abiraterone acetate plus prednisone for HRR-deficient metastatic castration-sensitive prostate cancer: a randomized phase 3 trial. *Nat Med* 2025; **31:** 4109–18.
12 Sweeney CJ, Chen Y-H, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. *N Engl J Med* 2015; **373:** 737–46.
13 Chowdhury S, Bjartell A, Agarwal N, et al. Deep, rapid, and durable prostate-specific antigen decline with apalutamide plus androgen deprivation therapy is associated with longer survival and improved clinical outcomes in TITAN patients with metastatic castration-sensitive prostate cancer. *Ann Oncol* 2023; **34:** 477–85.
14 Matsubara N, Chi KN, Özgüroğlu M, et al. Correlation of prostate-specific antigen kinetics with overall survival and radiological progression-free survival in metastatic castration-sensitive prostate cancer treated with abiraterone acetate plus prednisone or placebos added to androgen deprivation therapy: post hoc analysis of phase 3 LATITUDE study. *Eur Urol* 2020; **77:** 494–500.
15 Tripathi A, Chen Y, Jarrard DF, et al. Ten-year survival rates by PSA nadir in patients with metastatic hormone-sensitive prostate cancer: long-term survival analysis from the ECOG-ACRIN 3805 (CHAARTED) trial. *Ann Oncol* 2025; **36:** 1409–13.
16 Hussain M, Tangen CM, Higano C, et al. Absolute prostate-specific antigen value after androgen deprivation is a strong independent predictor of survival in new metastatic prostate cancer: data from Southwest Oncology Group Trial 9346 (INT-0162). *J Clin Oncol* 2006; **24:** 3984–90.

17 Azad A, Badillo MA, Dong Q, et al. Apalutamide (APA) plus intermittent versus continuous androgen-deprivation therapy (ADT) in participants (pts) with metastatic castration-sensitive prostate cancer (mCSPC): LIBERTAS phase 3 study design. *Proc Am Soc Clin Oncol* 2024; **42** (suppl)**:** TPS236 (abstr).

18 Grisay G, Turco F, Patrikidou A, et al. EORTC GUCG 2238 De-escalate: a pragmatic trial to revisit intermittent androgen-deprivation therapy in metastatic hormone-naïve prostate cancer in the era of new AR pathway inhibitors. *Proc Am Soc Clin Oncol* 2024; **42** (suppl)**:** TPS232 (abstr).

19 Sydes MR, Parmar MK, James ND, et al. Issues in applying multi-arm multi-stage methodology to a clinical trial in prostate cancer: the MRC STAMPEDE trial. *Trials* 2009; **10:** 39.

20 Attard G, Murphy L, Clarke NW, et al. Abiraterone acetate plus prednisolone with or without enzalutamide for patients with metastatic prostate cancer starting androgen deprivation therapy: final results from two randomised phase 3 trials of the STAMPEDE platform protocol. *Lancet Oncol* 2023; **24:** 443–56.

21 James ND, Sydes MR, Clarke NW, et al. 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. *Lancet* 2016; **387:** 1163–77.

22 James ND, Ingleby FC, Clarke NW, et al. Docetaxel for nonmetastatic prostate cancer: long-term survival outcomes in the STAMPEDE randomized controlled trial. *JNCI Cancer Spectr* 2022; **6:** pkac043.

23 Attard G, Murphy L, Clarke NW, et al. Abiraterone acetate and prednisolone with or without enzalutamide for high-risk non-metastatic prostate cancer: a meta-analysis of primary results from two randomised controlled phase 3 trials of the STAMPEDE platform protocol. *Lancet* 2022; **399:** 447–60.

24 Morgans AK, Roy S, Jia AY, et al. Age and treatment intensification in metastatic hormone-sensitive prostate cancer. *NEJM Evidence* 2025; **4:** EVIDoa2500109.

25 Murray ML, Love SB, Carpenter JR, et al. Data provenance and integrity of health-care systems data for clinical trials. *Lancet Digit Health* 2022; **4:** e567–68.

26 Mason MD, Clarke NW, James ND, et al. Adding celecoxib with or without zoledronic acid for hormone-naïve prostate cancer: long-term survival results from an adaptive, multiarm, multistage, platform, randomized controlled trial. *J Clin Oncol* 2017; **35:** 1530–41.

27 Gillessen S, Turco F, Davis ID, et al. Management of patients with advanced prostate cancer. report from the 2024 Advanced Prostate Cancer Consensus Conference (APCCC). *Eur Urol* 2025; **87:** 157–216.

28 Merseburger AS, Agarwal N, Bjartell A, et al. Targeted Investigational Treatment Analysis of Novel Anti-androgen (TITAN) study: ultralow prostate-specific antigen decline with apalutamide plus androgen-deprivation therapy. *BJU Int* 2024; **134:** 982–91.

29 Grist E, Dutey-Magni P, Parry MA, et al. Tumor transcriptome-wide expression classifiers predict treatment sensitivity in advanced prostate cancers. *Cell* 2025; **188:** 5717–34.

30 Parker CTA, Mendes L, Liu VYT, et al. External validation of a digital pathology-based multimodal artificial intelligence-derived prognostic model in patients with advanced prostate cancer starting long-term androgen deprivation therapy: a post-hoc ancillary biomarker study of four phase 3 randomised controlled trials of the STAMPEDE platform protocol. *Lancet Digit Health* 2025; **7:** 100885.