Efficacy and safety of prostate radiotherapy in de novo metastatic castration-sensitive prostate cancer (PEACE-1): a multicentre, open-label, randomised, phase 3 study with a 2 × 2 factorial design

Alberto Bossi, Stéphanie Foulon, Xavier Maldonado, Paul Sargos, Ray MacDermott, Paul Kelly, Aude Fléchon, Bertrand Tombal, Stephane Supiot, Dominik Berthold, Philippe Ronchin, Gabriel Kacso, Naji Salem, Fabio Calabro, Jean-François Berdah, Ali Hasbini, Marlon Silva, Jihane Boustani, Hélène Ribault, Karim Fizazi, on behalf of the PEACE-1 investigators*

Summary

Background The 2×2 PEACE-1 study showed that combining androgen-deprivation therapy with docetaxel and abiraterone improved overall and radiographic progression-free survival in patients with de novo metastatic castration-sensitive prostate cancer. We aimed to examine the efficacy and safety of adding radiotherapy in this population.

Methods We conducted an open-label, randomised, controlled, phase 3 trial with a 2×2 factorial design (PEACE-1) at 77 hospitals across Europe. Eligible participants were male patients (aged ≥18 years) with de novo metastatic castration-sensitive prostate cancer confirmed by bone scan, CT, or MRI, and an Eastern Cooperative Oncology Group performance status of 0–1 (or 2 in the case of bone pain). Participants were randomly assigned (1:1:1:1) to standard of care (androgen-deprivation therapy alone or with six cycles of intravenous docetaxel 75 mg/m² every 3 weeks), standard of care plus abiraterone (oral 1000 mg abiraterone once daily plus oral 5 mg prednisone twice daily), standard of care plus radiotherapy (74 Gy in 37 fractions to the prostate), or standard of care plus radiotherapy and abiraterone. Participants and investigators were not masked to treatment allocation. The coprimary endpoints were radiographic progression-free survival and overall survival, analysed by intention to treat in patients with low-volume metastatic disease and in the overall study population. This ongoing study is registered with EudraCT, 2012-000142-35.

Findings Between Nov 27, 2013, and Dec 20, 2018, 1173 patients were enrolled and 1172 were randomly assigned to receive standard of care (n=296 [25·3%]), standard of care plus abiraterone (n=292 [24·9%]), standard of care plus radiotherapy (n=293 [25·0%]), and standard of care plus abiraterone and radiotherapy (n=291 [24·8%]). Median follow-up was 6·0 years (IQR 5·1–7·0) at the time of radiographic progression-free survival and overall survival analysis. A qualitative interaction between radiotherapy and abiraterone for radiographic progression-free survival in the population of patients with low-volume disease prevented the pooling of intervention groups for analysis (p=0·026). Adding radiotherapy to standard of care improved radiographic progression-free survival in patients with low-volume disease treated with abiraterone (median 4·4 years [99·9% CI 2·5–7·3] in the standard of care plus abiraterone group vs 7·5 years [4·0–not reached] in the standard of care plus abiraterone and radiotherapy group; adjusted hazard ratio [HR] 0·65 [99·9% CI 0·36–1·19]; p=0·019), but not in patients not treated with abiraterone (median 3·0 years [99·9% CI 2·3–4·8] in the standard of care group vs 2·6 years [1·7–4·6] in the standard of care plus radiotherapy group; 1·08 [0·65–1·80]; p=0·61). For overall survival, the predefined threshold for a statistical interaction was not reached (p=0·12); therefore, the two intervention groups receiving radiotherapy were pooled together for analysis. In patients with low-volume disease, the overall survival was not influenced by radiotherapy (median 6·9 years [95·1% CI 5·9–7·5] for standard of care with or without abiraterone vs 7·5 years [6·0–not reached] for standard of care plus radiotherapy with or without abiraterone; HR 0·98 [95·1% CI 0·74–1·28]; p=0·86). In the overall safety population, 339 (56·1%) of 604 patients who did not receive radiotherapy and 329 (58·8%) of 560 patients who received radiotherapy developed at least one severe adverse event (grade ≥3), the most common being hypertension (110 [18·2%] patients in the standard of care with or without abiraterone group and 127 [22·7%] in the standard of care plus radiotherapy with or without abiraterone group) and neutropenia (40 [6·6%] and 29 [5·2%]).

Interpretation Combining radiotherapy with standard of care plus abiraterone improves radiographic progression-free survival and castration resistance-free survival, but not overall survival in patients with low-volume de novo metastatic castration-sensitive prostate cancer. Radiotherapy reduces the occurrence of serious genitourinary events, regardless of metastatic burden and without increasing the overall toxicity, and could become a component of standard of care in patients with both high-volume and low-volume de novo metastatic castration-sensitive prostate cancer.

Funding Janssen-Cilag, Ipsen, Sanofi, and Institut National du Cancer.

Department of Radiotherapy (A Bossi MD), Department of Biostatistics and Epidemiology (S Foulon MD), and Department of Cancer Medicine (Prof K Fizazi MD), Institut Gustave Roussy, Villejuif, France; Amethyst Group, Paris, France (A Bossi, P Sargos MD); Oncostat U1018, Inserm, Labelled Ligue Contre le Cancer, Villejuif, France (S Foulon); Department of Radiotherapy, Vall d'Hebron University Hospital, Barcelona, Spain (Prof X Maldonado MD); Department of Radiotherapy, Institut Bergonie, Bordeaux, France (P Sargos); Cancer Trials Ireland, Dublin, Ireland (Prof R MacDermott MD); St Vincents University Hospital, Dublin, Ireland (Prof R MacDermott); Department of Radiotherapy, Cork University Hospital, Cork, Ireland (P Kelly BMBCh); Centre Léon Bérard, Lyon, France (A Fléchon MD); Clinique Universitaire St Luc, Brussels, Belgium (Prof B Tombal MD); Department of Radiotherapy, Institut de Cancérologie de l'Ouest René Gauducheau, Saint Herblain, France (Prof S Supiot MD); Centre Pluridisciplinaire d'Oncologie, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland (Prof D Berthold MD); Centre Azuréen Cancérologie, Mougins, France (P Ronchin MD); Amethyst Radiotherapy Center, Iuliu Hatieganu University of Medecine and Pharmacy, Cluj-Napoca, Romania (G Kacso MD); Department of Radiotherapy, Institut Paoli-Calmettes Aix-Marseille,

Marseille, France (N Salem MD);
San Camillo Forlanini Hospitals,
Rome, Italy (F Calabro MD);
Clinique Sainte Marguerite,
Hyères, France (J-F Berdah MD);
Clinique Pasteur, Brest, France
(A Hasbini MD); Centre François
Baclesse, Caen, France
(M Silva MD); Centre Georges-
Francois Leclerc, Dijon, France
(J Boustani MD); Unicancer,
Paris, France (H Ribault MD)

Correspondence to:
Dr Alberto Bossi, Department of
Radiotherapy, Institut Gustave
Roussy, Villejuif 94805, France
bossial@hotmail.com

See Online for appendix

Introduction

The treatment of patients with de novo metastatic castration-sensitive prostate cancer has drastically evolved over the past decade, leading to steady improvements in overall survival.[1–9] The STOPCAP meta-analysis reported that adding prostate radiotherapy to androgen-deprivation therapy in patients diagnosed with de novo metastatic castration-sensitive prostate cancer did not increase overall survival; however, in individuals presenting with up to four bone metastases, this therapy translated into an improvement in absolute overall survival of 7% at 3 years.[10] The active control arms of the STAMPEDE trial[6] and the HORRAD trial[11] selected in the meta-analysis consisted of androgen-deprivation therapy, with only 184 (18%) of 1029 patients in the STAMPEDE trial also receiving docetaxel in addition to androgen-deprivation therapy.

To our knowledge, PEACE-1 is the only randomised trial to date to investigate the interplay between an intensified systemic therapy consisting of androgen-deprivation therapy, docetaxel, and abiraterone plus prednisone, in addition to radiotherapy in patients diagnosed with de novo metastatic castration-sensitive prostate cancer. A previous analysis of the results from the PEACE-1 study showed that androgen-deprivation therapy, docetaxel, and abiraterone plus prednisone administered as a triple systemic therapy improved both radiographic progression-free survival and overall survival in this patient group.[7] Herein, we aimed to examine the efficacy and safety of adding radiotherapy to this intensified systemic treatment in patients with de novo metastatic castration-sensitive prostate cancer.

Methods

Study design and participants

We conducted an open-label, randomised, controlled, phase 3 trial (PEACE-1) with a 2×2 factorial design at 77 sites across Belgium, France, Ireland, Italy, Romania, Spain, and Switzerland (appendix p 2). Details of the study design and participant inclusion criteria have been published previously.[7] Briefly, male patients aged at least 18 years with newly diagnosed metastatic prostate adenocarcinoma confirmed by bone scan, CT, or MRI, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1 (or 2 in the case of bone pain) were eligible for inclusion. Patients previously treated with definitive local therapy were not eligible. A complete list of participant inclusion and exclusion criteria is provided in the appendix (pp 4–5).

Three major amendments were made during the trial period to account for the evolution of standard of care for patients with metastatic castration-sensitive prostate cancer (appendix pp 6–7). First, on Oct 5, 2015, docetaxel was allowed as a component of standard of care at the discretion of the investigators, after androgen-deprivation therapy combined with docetaxel showed an

Research in context

Evidence before this study

We searched PubMed for articles in English published between Jan 1, 1984, and Dec 31, 2012, using the terms "prostate cancer", "metastases", and "phase 3 trial". Two phase 3 randomised controlled trials (the STAMPEDE trial published in 2018 and the HORRAD trial in 2019) have studied the effect of prostate radiotherapy on outcomes in patients diagnosed with de novo metastatic castration-sensitive prostate cancer; however, radiographic progression-free survival was not assessed in either study. These trials did not find a benefit of prostate radiotherapy to overall survival, although the STAMPEDE trial reported an improvement in overall survival in a subgroup of patients presenting with low-volume metastatic disease. This improvement led to a revision in current guidelines recommending radiotherapy for this patient group. Over the past decade, an improvement in overall survival was reported following androgen-deprivation therapy with or without docetaxel and a second-generation androgen pathway inhibitor (ie, abiraterone, apalutamide, darolutamide, or enzalutamide). Both the HORRAD and the STAMPEDE trials adopted a suboptimal systemic treatment approach with androgen-deprivation therapy alone (HORRAD trial) or with androgen-deprivation therapy with or without docetaxel (STAMPEDE trial), in which docetaxel was prescribed to less than 20% of patients treated with androgen-deprivation therapy. The interplay between these current standard systemic therapies and prostate radiotherapy is yet to be evaluated.

Added value of this study

To our knowledge, the PEACE-1 study is the first randomised trial to show that radiotherapy for patients diagnosed with de novo metastatic castration-sensitive prostate cancer improves radiographic progression-free survival, delays the onset of serious genitourinary adverse events, and delays the occurrence of castration-resistant prostate cancer, regardless of metastatic burden and without increasing toxicity.

Implications of all the available evidence

Combined with previous evidence, our findings support the added value of radiotherapy in patients diagnosed with de novo metastatic castration-sensitive prostate cancer in the context of an intensified systemic treatment. Radiotherapy should be recommended for patients with metastatic castration-sensitive prostate cancer, independently of their metastatic burden.

improvement in overall survival.[1,2] Second, on Aug 10, 2017, docetaxel was made mandatory for all remaining patients after androgen-deprivation therapy plus abiraterone was shown to improve overall survival compared with androgen-deprivation therapy alone.[4,5] Third, a major amendment was made on Jan 13, 2021 following the publication of results from the HORRAD trial[11] in 2019 and the STAMPEDE trial[6] in 2018, which reported the efficacy of radiotherapy in the same settings as the PEACE-1 study. No benefit to overall survival was observed either in the HORRAD trial (hazard ratio [HR] 0·90 [95% CI 0·70–1·14]; p=0·4), which included 432 patients with metastatic castration-sensitive prostate cancer, or in the STAMPEDE trial (0·92 [0·80–1·06]; p=0·27), which included 2061 patients; however, these studies raised the possibility that survival might be improved in a subgroup of patients with low-volume metastatic disease (0·68 [0·42–1·10] in the HORRAD trial and 0·68 [0·52–0·90]; p=0·007 in the STAMPEDE trial). Considering these results, we chose to amend the protocol of the PEACE-1 study and revise our primary aim to report the efficacy of radiotherapy in patients with low-volume metastatic disease (appendix pp 6–7).

The initial protocol was reviewed and approved by the French Independent Ethics Committee of Ile de France VII and by local institutional review boards at each study site. This study was conducted in compliance with the ethical principles defined by the Declaration of Helsinki and conformed with the International Conference on Harmonization and Good Clinical Practice guidelines, as well as applicable regulatory requirements. Approval was obtained from the ethics committee of each participating centre and is available upon request. Members of the steering committee and the independent data monitoring committees are listed in the appendix (p 3). All participants provided written informed consent.

Randomisation and masking

Eligible patients were randomly assigned (1:1:1:1) to standard of care, standard of care plus abiraterone and prednisone (referred to hereafter as abiraterone), standard of care plus radiotherapy, or standard of care plus radiotherapy and abiraterone. The randomisation process was performed centrally by the Epidemiology and Biostatistics unit at Gustave Roussy (Villejuif, France) with Tenalea software. Randomisation was done by use of a minimisation algorithm and was stratified by study site, ECOG performance status score (0 vs 1–2), type of androgen-deprivation therapy (gonadotropin-releasing hormone [GnRH] receptor agonist vs GnRH receptor antagonist vs bilateral orchiectomy), planned administration of docetaxel (yes vs no), and disease extent at diagnosis based on metastatic status (lymph node metastases only vs bone metastases vs visceral metastases). Given that the case report form collected information on patient stratification according to high-volume versus low-volume metastatic disease (as defined in the CHAARTED study[2]), classification of low-volume disease was retained to enable comparisons between trials. Participants and investigators were not masked to treatment allocation.

Procedures

All randomly assigned patients received standard of care as androgen-deprivation therapy with or without docetaxel before the implementation of the Aug 10, 2017 amendment. Androgen-deprivation therapy was provided as either bilateral orchiectomy or continuous administration of a GnRH receptor agonist or antagonist. Docetaxel therapy involved six cycles of docetaxel (75 mg/m² per cycle, to a maximum dose of 150 mg per cycle) to be administered intravenously every 3 weeks (within a range of 6 days). The first docetaxel cycle had to be administered within 14 days of randomisation and at least 6 weeks after the initiation of androgen-deprivation therapy; prophylaxis with granulocyte colony-stimulating factor was initially recommended and then mandatory following two toxic deaths due to docetaxel on a site in December, 2017.

Patients allocated to standard of care plus abiraterone and prednisone were also given four tablets of abiraterone 250 mg to be taken once daily orally (1000 mg in total), in addition to prednisone 5 mg to be taken twice a day orally (10 mg in total), starting within 6 weeks of initiating androgen-deprivation therapy. Abiraterone and prednisone were administered until progression to castration-resistant prostate cancer, withdrawal of consent, unacceptable toxicity, or death, whichever occurred first.

Patients allocated to standard of care plus radiotherapy received standard of care in addition to a total radiotherapy dose of 74 Gy, delivered in 37 fractions over 7–8 weeks by intensity-modulated or three-dimensional conformal radiotherapy. The planned target volume was restricted to the prostate; however, the possibility to irradiate seminal vesicles and pelvic lymph nodes was left to the discretion of the physician in charge. Radiotherapy was to be started at least 3 weeks (but no later than 8 weeks) after completing docetaxel therapy. Patients allocated to standard of care plus radiotherapy and abiraterone received the total radiotherapy dose of 74 Gy in 37 fractions over 7–8 weeks, as well as four oral tablets of abiraterone 250 mg/day (1000 mg in total) and oral prednisone 5 mg twice daily (10 mg in total), besides standard of care.

In the case of disease progression based on a confirmed increase in prostate-specific antigen or radiographical progression, subsequent treatments were left to the discretion of the investigators. Follow-up was scheduled for a duration of 10 years; the itemised list of assessments to be performed at each follow-up visit is provided in the appendix (pp 8–9). Patients were followed up at each docetaxel cycle every 3 weeks, from day 1 of the first cycle to day 1 of the sixth cycle. After the end of chemotherapy

For more on **Tenalea software** see https://www.aleaclinical.eu

and prostate radiotherapy (if any), patients were followed up at 6 months and then at least once every 6 months for the 10-year duration. For the patients who did not receive docetaxel as standard of care, follow-up visits were scheduled at months 1, 2, 3, and 6, and then every 6 months.

Outcomes

We assessed two coprimary endpoints, radiographic progression-free survival and overall survival. Radiographic progression-free survival was defined as the time from randomisation to the occurrence of radiographic progression or death from any cause, whichever occurred first. We assessed the radiographic progression of bone lesions on bone scans according to the adapted version of the Prostate Cancer Working Group 2 criteria,[12] and evaluated the radiographic progression of soft tissue lesions using either CT or MRI based on RECIST criteria (version 1.1). Overall survival was defined as the time from randomisation to death from any cause. Patients without events were censored at the date of the last follow-up assessment.

The secondary endpoints were survival free from castration-resistant prostate cancer (herein described as castration resistance-free survival); survival free from serious genitourinary events (defined as urethral obstruction with pain or bleeding requiring an urinary catheter, double J ureteral stent, nephrostomy, transurethral resection of the prostate, radiotherapy for patients not initially assigned to radiotherapy, and palliative radical prostatectomy); survival free from prostate cancer specifically; time to next skeletal-related event; the response rate of prostate-specific antigen; a prognostic study of serum prostate-specific antigen, measured 6–8 months after the initiation of systemic therapy; time to pain progression; time to chemotherapy in patients with castration-resistant prostate cancer; quality of life; changes in bone mineral density; correlations between biomarkers (including antibodies staining luminal components, neuroendocrine features, and tumour suppressors) and outcomes (progression-free survival and overall survival); and the event rate per 100 person-years of treatment and toxicity. Castration resistance-free survival was defined as the time from randomisation to the occurrence of castration-resistant prostate cancer or death from any cause, whichever occurred first. Castration-resistant prostate cancer was defined as either radiographical progression or a confirmed increase in the concentration of prostate-specific antigen based on three independent measurements (A, B, and C, with A<B<C and C ≥0·50 ng/mL). Treatment safety was assessed through clinical examination, monitoring of haematological and biochemical findings in serum samples, and liver function tests (appendix pp 8–9). Adverse events were graded by use of the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0) and the safety analysis was based on the highest grade of adverse events recorded from the initiation of treatment to the occurrence of castration-resistant prostate cancer. We also recorded the occurrence and time to serious genitourinary events from randomisation. Herein, we report the results concerning castration resistance-free survival, time to serious genitourinary events, and toxicity given that the results of all other secondary endpoints have either been published previously[7] or were still under investigation at the time of writing.

Statistical analysis

The PEACE-1 trial had a factorial design based on the assumption that no significant interaction between abiraterone and prostate radiotherapy would take place. We calculated the size of the study population using East software (Cytel; Cambridge, MA, USA) based on this assumption to allow for a 2×2 factorial analysis of the efficacy of prostate radiotherapy. To evaluate the efficacy of prostate radiotherapy, the predetermined acceptable probability of a type I error was set at 0·05, divided between the two coprimary endpoints (0·049 for overall survival and 0·001 for radiographic progression-free survival). We hypothesised that adding prostate radiotherapy to standard of care with or without abiraterone in patients with low-volume metastatic castration-sensitive prostate cancer would improve overall survival by 32% over a median of 70 months and progression-free survival by 38% over 42 months. Hence, 213 deaths would give an 80% power to detect an HR of 0·68 for overall survival at a two-sided α level of 0·049. A total of 299 radiographic progression events or deaths were predicted to have an 80% power to detect an HR of 0·62 for radiographic progression-free survival at a two-sided α level of 0·001. The initial sample size of 916 patients specified in the 2013 protocol was subsequently increased to 1173 patients due to the change of standard of care and the results of the LATITUDE trial[5] and the STAMPEDE trial[6] in 2017.

Before analysing the outcomes, we assessed the presence of an interaction for both of the coprimary endpoints by analysing the maximum likelihood estimates for a Cox model adjusted for the following stratification factors: ECOG performance status score (0 vs 1–2); type of androgen-deprivation therapy (GnRH receptor agonist vs GnRH receptor antagonist vs bilateral orchiectomy); disease burden (low-volume vs high-volume disease) if applicable; and docetaxel (no prescription of docetaxel before the amendment vs no prescription of docetaxel after the amendment vs prescription of docetaxel after the amendment). In the absence of a qualitative interaction (p>0·05), we combined the arms two by two on the basis of prostate radiotherapy administration, regardless of abiraterone treatment prescription, before we sequentially assessed the efficacy of prostate radiotherapy first in patients with low-volume disease and then in the overall study population.
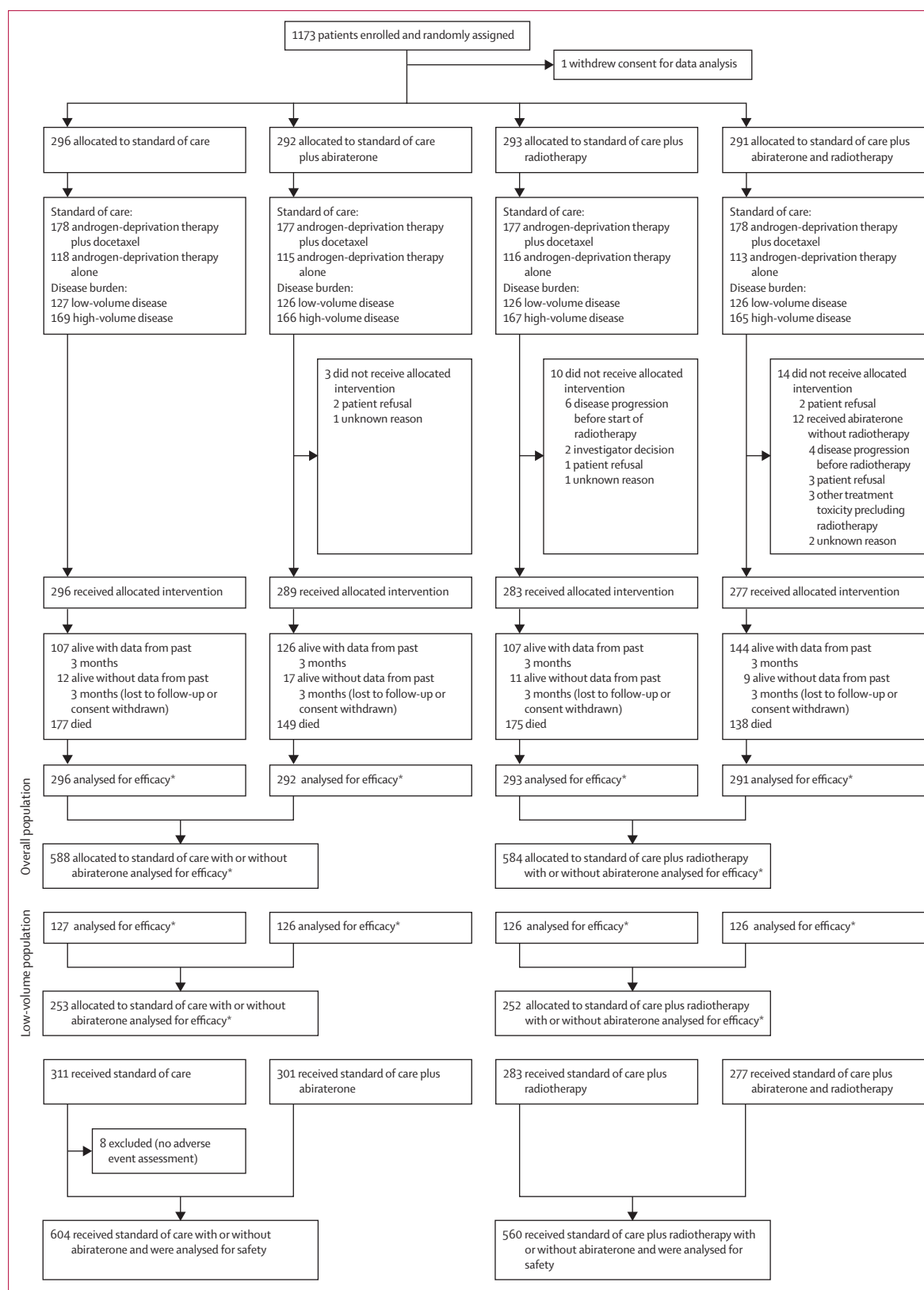
Figure 1: Trial profile
Standard of care was androgen-deprivation therapy with or without docetaxel. *The number of patients analysed for efficacy for the following endpoints: radiographic progression-free survival, overall survival, and castration resistance-free survival. For the endpoint of time to serious urinary events, the efficacy analysis was performed in the intention-to-treat population with available data (909 [77·6%] of 1172 patients).

Efficacy outcomes were analysed in the intention-to-treat population; all patients were analysed according to the treatment group to which they were randomly assigned. Safety analyses were performed in the safety population according to the treatment actually received, excluding the patients who did not receive any investigational treatment.

We estimated the median follow-up by the inverse Kaplan–Meier method and endpoints exploring time to an event with the Kaplan–Meier method. A Cox proportional hazards model, adjusting for radiotherapy, abiraterone, and stratification factors, provided statistical significance and estimates of the effect of radiotherapy (p values, HRs, and CIs adjusted to match the significance levels of the corresponding test—ie, 99·9% CIs for radiographic progression-free survival, 95·1% CIs for overall survival, and 95% CIs for secondary endpoints). The assumption of proportional hazards was evaluated on the basis of weighted Schoenfeld residuals.

All analyses were performed after the prespecified minimum number of events had been exceeded for the coprimary endpoints; 215 deaths and 305 radiographic progression-free survival events were observed in the cohort of patients with low-volume disease at data cutoff on Jan 1, 2023. All statistical analyses were performed with SAS (version 9.4). This study is ongoing and is registered with EudraCT, 2012-000142-35.

Role of the funding source
The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results
Between Nov 27, 2013, and Dec 20, 2018, 1173 patients were enrolled, of whom one patient subsequently withdrew his consent and was not included in the data analysis. Among the 1172 participants randomly assigned, 296 (25·3%) were allocated to standard of care, 292 (24·9%) to standard of care plus abiraterone, 293 (25·0%) to standard of care plus radiotherapy, and 291 (24·8%) to standard of care plus abiraterone and radiotherapy. Standard of care was prescribed as androgen-deprivation therapy alone for 462 (39·4%) patients and androgen-deprivation therapy plus docetaxel for 710 (60·6%) patients (figure 1). Overall, 505 (43·1%) patients had low-volume metastatic disease: 127 (25·1%) patients in the standard of care group, 126 (25·0%) in the standard of care plus abiraterone group, 126 (25·0%) in the standard of care plus radiotherapy group, and 126 (25·0%) in the standard of care plus abiraterone and radiotherapy group (table 1). Docetaxel was administered as part of standard of care to 355 (60·8%) of the 584 patients who received radiotherapy and 355 (60·4%) of the 588 patients who did not receive radiotherapy. Overall, 560 (95·9%) of the 584 patients who were randomly assigned to standard of care plus radiotherapy or standard of care plus abiraterone and radiotherapy received radiotherapy, 250 (44·6%) of whom had low-volume disease. The mean dose of irradiation delivered to the prostate was 73·3 Gy and 483 (93·8%) patients received the planned dose of 74 Gy. Among the 459 (78·6%) patients with available data, pelvic lymph nodes were irradiated in 49 (20·2%) of 242 patients in the standard of care plus radiotherapy group and in 58 (26·7%) of 217 patients in the standard of care plus abiraterone and radiotherapy group; this difference was not significant (p=0·10).

In the overall study population, the median follow-up period from randomisation was 6·0 years (IQR 5·1–7·0). Median follow-up was 5·9 years (5·1–7·0) for patients allocated to receive radiotherapy and 6·1 years (5·1–7·0) for those allocated to receive no radiotherapy. In the cohort of patients with low-volume disease, a qualitative significant interaction between radiotherapy and abiraterone was found for radiographic progression-free survival (p=0·026). Consequently, each intervention group was evaluated separately for this coprimary endpoint. By contrast, the prespecified threshold (p>0·05) for a qualitative statistical interaction between abiraterone and radiotherapy was not met for overall survival (p=0·12); therefore, we combined the groups

	Patients with low-volume metastatic disease		Overall study population	
	Standard of care with or without abiraterone (n=253)	Standard of care plus radiotherapy with or without abiraterone (n=252)	Standard of care with or without abiraterone (n=588)	Standard of care plus radiotherapy with or without abiraterone (n=584)
Age, years	67 (59–72)	66 (60–72)	67 (60–72)	66 (60–73)
Eastern Cooperative Oncology Group performance status score				
0	180 (71·1%)	194 (77·0%)	411 (69·9%)	413 (70·7%)
1–2	73 (28·9%)	58 (23·0%)	177 (30·1%)	171 (29·3%)
Gleason score at diagnosis				
≤7	71 (28·1%)	66 (26·2%)	142 (24·1%)	136 (23·3%)
≥8	173 (68·4%)	184 (73·0%)	429 (73·0%)	441 (75·5%)
Data missing	9 (3·6%)	2 (0·8%)	17 (2·9%)	7 (1·2%)
Time from diagnosis to randomisation, months	2·5 (1·8–3·4)	2·6 (1·7–3·5)	2·2 (1·5–3·1)	2·3 (1·5–3·2)
Metastatic volume*				
Low	253 (100·0%)	252 (100·0%)	253 (43·0%)	252 (43·2%)
High	0	0	335 (57·0%)	332 (56·8%)
Baseline prostate-specific antigen concentration, ng/mL	10·3 (3·3–31·0)	9·0 (2·3–39·1)	13·1 (3·5–57·1)	12·6 (3·0–62·4)
Received docetaxel as a component of standard of care	127 (50·2%)	127 (50·4%)	355 (60·4%)	355 (60·8%)

Data are median (IQR) or n (%), unless otherwise indicated. Standard of care comprised androgen-deprivation therapy with or without docetaxel. Ethnicity-related data are not presented, given that French laws forbid the collection of these data. *High volume was characterised by four or more bone metastases with one or more metastases outside the vertebral bodies or pelvis, or visceral metastases, or both; low volume was characterised as all other assessable situations.

Table 1: Baseline characteristics of participants in the intention-to-treat population
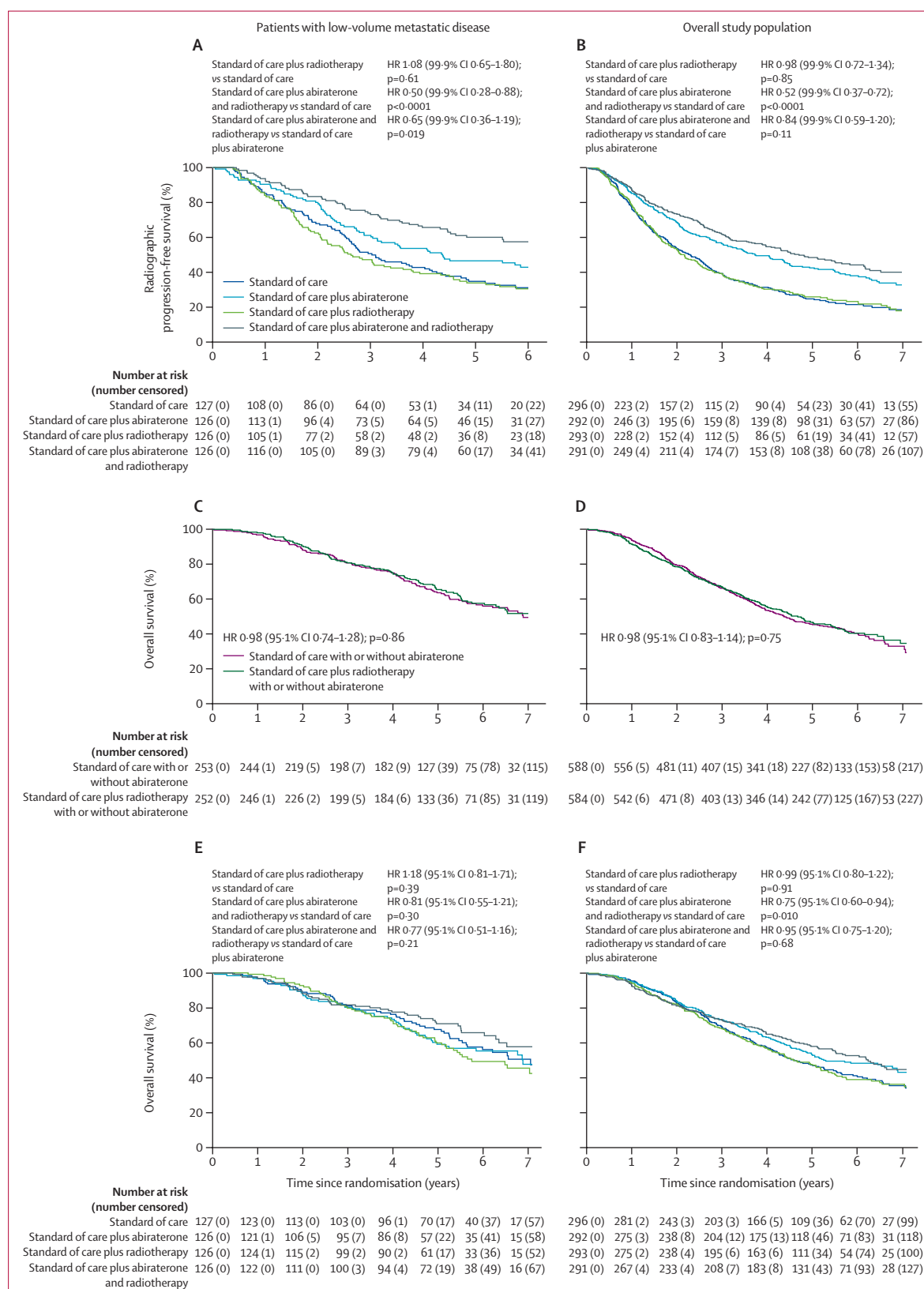
Figure 2: **Kaplan–Meier estimates of radiographic progression-free-survival and overall survival in patients with low-volume metastatic disease and the overall population**
Radiographic progression-free survival per intervention group for patients with low-volume disease (A) and for the overall population (B). Overall survival after the pooling of intervention groups allocated to radiotherapy for patients with low-volume disease (C) and for the overall population (D). Overall survival per intervention group for patients with low-volume disease (E) and for the overall population (F). Standard of care was androgen-deprivation therapy with or without docetaxel. HR=hazard ratio.

two by two on the basis of prostate radiotherapy administration for this analysis.

In the cohort of patients with low-volume disease, the addition of radiotherapy to standard of care did not decrease the number of radiographic progression events (87 of 127 patients in the standard of care group vs 89 of 126 patients in the standard of care plus radiotherapy group), nor improve radiographic progression-free survival (median 3·0 years [99·9% CI 2·3–4·8] for standard of care vs 2·6 years [1·7–4·6] for standard of care plus radiotherapy; HR 1·08 [99·9% CI 0·65–1·80]; p=0·61; figure 2A). However, adding radiotherapy to standard of care plus abiraterone decreased the number of patients with radiographic progression events (74 of 126 patients in the standard of care plus abiraterone group vs 55 of 126 patients in the standard of care plus abiraterone and radiotherapy group) and resulted in an improvement in radiographic progression-free survival of 3·1 years (median 4·4 years [99·9% CI 2·5–7·3] for standard of care plus abiraterone vs 7·5 years [4·0–not reached] for standard of care plus abiraterone and radiotherapy), with a 35% reduction in the relative risk of radiographic progression or death (adjusted HR for radiographic progression-free survival 0·65 [99·9% CI 0·36–1·19]; p=0·019; figure 2A). Furthermore, compared with standard of care alone, the number of patients with radiographic progression or death was reduced by adding radiotherapy plus abiraterone (87 of 127 patients in the standard of care group vs 55 of 126 patients in the standard of care plus abiraterone and radiotherapy group). Consequently, radiographic progression-free survival was also improved with a median radiographic progression-free survival of 3·0 years (99·9% CI 2·3–4·8) in the standard of care group compared with 7·5 years (4·0–not reached) in the standard of care plus abiraterone and radiotherapy group (HR 0·50 [99·9% CI 0·28–0·88]; p<0·0001; figure 2A).

After pooling together the two intervention groups assigned to radiotherapy, no effect of radiotherapy on overall survival was observed in the cohort of patients with low-volume disease (HR 0·98 [95·1% CI 0·74–1·28]; p=0·86). 111 deaths were reported among the 253 patients from the standard of care with or without abiraterone group, with a median overall survival of 6·9 years (95·1% CI 5·9–7·5), and 104 deaths were reported among the 252 patients from the standard of care plus radiotherapy with or without abiraterone group, with a median overall survival of 7·5 years (6·0–not reached; figure 2C). Likewise, radiotherapy had no effect on overall survival in the overall population (figure 2D). The per-arm analysis yielded similar results, with an overall absence of any radiotherapy effect on overall survival (figure 2E, F).

In the cohort of patients with low-volume disease, adding radiotherapy to standard of care with or without abiraterone significantly delayed time to the occurrence of castration-resistant prostate cancer (median 2·5 years [95% CI 2·1–2·9] in the standard of care with or without abiraterone group vs 3·4 years [2·8–4·5] in the standard of care plus radiotherapy with or without abiraterone group; HR 0·74 [95% CI 0·60–0·92]; p=0·0069; figure 3A). This effect seemed to be independent of abiraterone when the four groups were analysed separately, with a median duration of castration resistance-free survival of 3·6 years (95% CI 2·7–4·8) in the standard of care plus abiraterone group compared with 6·9 years (4·6–not reached) in the standard of care plus abiraterone and radiotherapy group (HR 0·62 [95% CI 0·44–0·87]; p=0·0056; figure 3C). Remarkably, radiotherapy had the same effect on time to the occurrence of castration-resistant prostate cancer in the overall study population (HR 0·79 [0·69–0·90]; p=0·0005; figure 3B). In the overall cohort, when the four arms were analysed separately, time to the occurrence of castration-resistant prostate cancer remained statistically shorter in the standard of care plus abiraterone group than in the standard of care plus abiraterone and radiotherapy group (median 3·1 years [95% CI 2·4–3·9] vs 4·3 years [3·3–5·5]; HR 0·79 [0·64–0·98]; p=0·028; figure 3D).

Adding radiotherapy to standard of care with or without abiraterone in the cohort of patients with low-volume disease decreased the number of serious genitourinary events from 52 to 22 and delayed the time to first serious genitourinary event (p=0·0002; table 2; figure 3E). The same effect was observed in the overall study population, with a decrease in the number of serious genitourinary events from 102 to 55 (p=0·0001 for time to first event; figure 3F). Notably, the preventive effect of radiotherapy on the occurrence of serious genitourinary events was observed across all groups, both in the cohort of patients with low-volume disease and the overall cohort (figure 3G, H). Overall, the main events justifying radiotherapy among patients in the standard of care group and the standard of care plus abiraterone group were local progression (12 patients), urinary obstruction (six patients), pain (three patients), deferred radiotherapy in a patient with a response to systemic treatment (three patients), and biological progression (two patients). The use of deferred radiotherapy in these groups was considered to be a proxy for the onset of major genitourinary events (eg, local progression, urinary obstruction, or both). A transurethral resection of the prostate was considered necessary after previous prostate irradiation in four patients only. Several baseline parameters were tested for their ability to predict the onset of serious genitourinary events. However, no meaningful clinical factor (including stage T3–T4 disease at diagnosis) was identified as a clinically significant prognostic factor for the onset of this type of event.

In the overall safety population, 339 (56·1%) of 604 patients who did not receive radiotherapy and 329 (58·8%) of 560 patients who received radiotherapy developed at least one severe adverse event (grade ≥3).
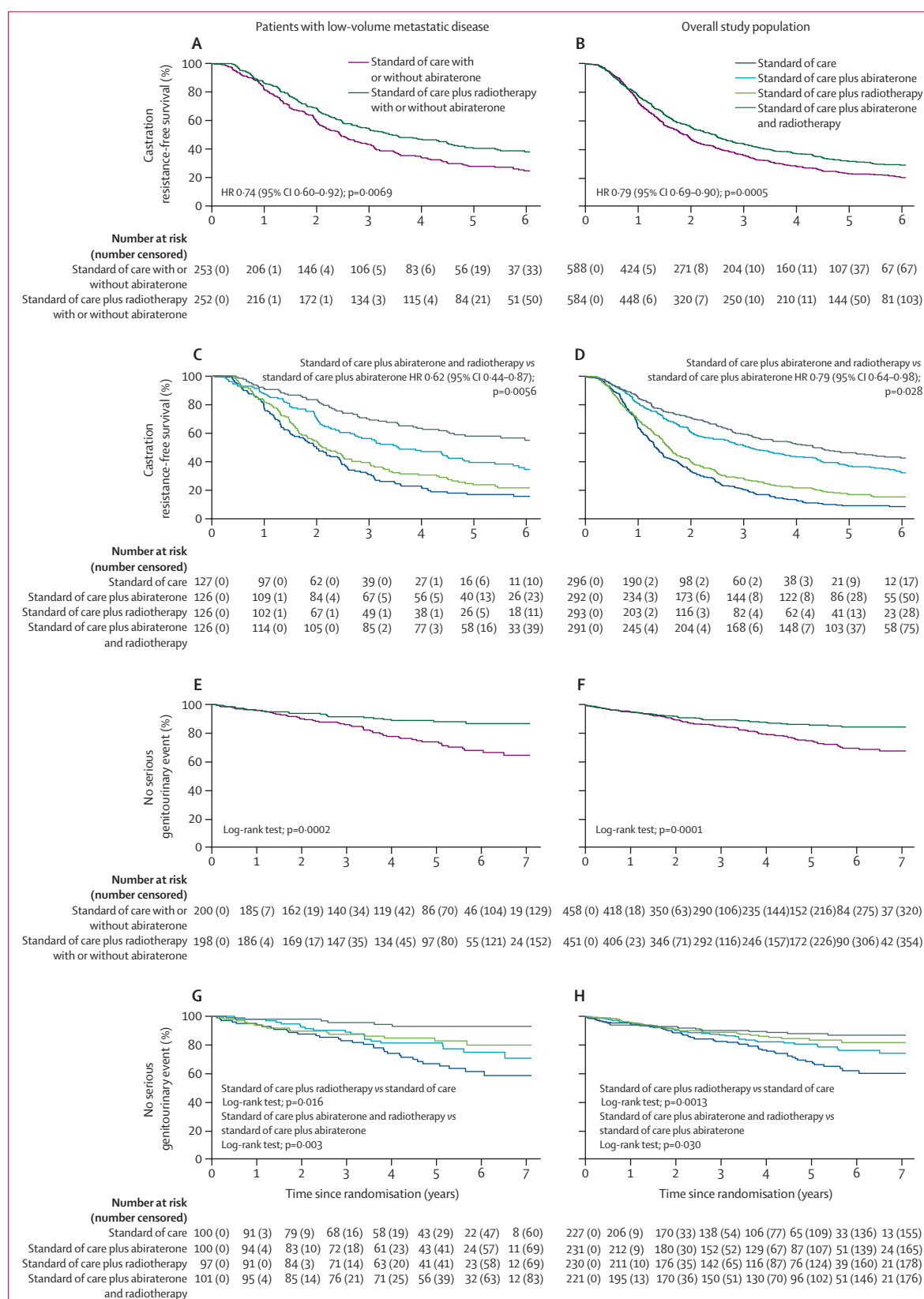
Patients with low-volume metastatic disease

A

Castration resistance-free survival (%)

- Standard of care with or without abiraterone
- Standard of care plus radiotherapy with or without abiraterone

HR 0·74 (95% CI 0·60–0·92); p=0·0069

Number at risk (number censored)

Standard of care with or without abiraterone	253 (0)	206 (1)	146 (4)	106 (5)	83 (6)	56 (19)	37 (33)
Standard of care plus radiotherapy with or without abiraterone	252 (0)	216 (1)	172 (1)	134 (3)	115 (4)	84 (21)	51 (50)

Overall study population

B

- Standard of care
- Standard of care plus abiraterone
- Standard of care plus radiotherapy
- Standard of care plus abiraterone and radiotherapy

HR 0·79 (95% CI 0·69–0·90); p=0·0005

588 (0)	424 (5)	271 (8)	204 (10)	160 (11)	107 (37)	67 (67)
584 (0)	448 (6)	320 (7)	250 (10)	210 (11)	144 (50)	81 (103)

C

Castration resistance-free survival (%)

Standard of care plus abiraterone and radiotherapy vs standard of care plus abiraterone HR 0·62 (95% CI 0·44–0·87); p=0·0056

Number at risk (number censored)

Standard of care	127 (0)	97 (0)	62 (0)	39 (0)	27 (1)	16 (6)	11 (10)
Standard of care plus abiraterone	126 (0)	109 (1)	84 (4)	67 (5)	56 (5)	40 (13)	26 (23)
Standard of care plus radiotherapy	126 (0)	102 (1)	67 (1)	49 (1)	38 (1)	26 (5)	18 (11)
Standard of care plus abiraterone and radiotherapy	126 (0)	114 (0)	105 (0)	85 (2)	77 (3)	58 (16)	33 (39)

D

Standard of care plus abiraterone and radiotherapy vs standard of care plus abiraterone HR 0·79 (95% CI 0·64–0·98); p=0·028

296 (0)	190 (2)	98 (2)	60 (2)	38 (3)	21 (9)	12 (17)
292 (0)	234 (3)	173 (6)	144 (8)	122 (8)	86 (28)	55 (50)
293 (0)	203 (2)	116 (3)	82 (4)	62 (4)	41 (13)	23 (28)
291 (0)	245 (4)	204 (4)	168 (6)	148 (7)	103 (37)	58 (75)

E

No serious genitourinary event (%)

Log-rank test; p=0·0002

Number at risk (number censored)

Standard of care with or without abiraterone	200 (0)	185 (7)	162 (19)	140 (34)	119 (42)	86 (70)	46 (104)	19 (129)
Standard of care plus radiotherapy with or without abiraterone	198 (0)	186 (4)	169 (17)	147 (35)	134 (45)	97 (80)	55 (121)	24 (152)

F

Log-rank test; p=0·0001

458 (0)	418 (18)	350 (63)	290 (106)	235 (144)	152 (216)	84 (275)	37 (320)
451 (0)	406 (23)	346 (71)	292 (116)	246 (157)	172 (226)	90 (306)	42 (354)

G

No serious genitourinary event (%)

Standard of care plus radiotherapy vs standard of care Log-rank test; p=0·016
Standard of care plus abiraterone and radiotherapy vs standard of care plus abiraterone Log-rank test; p=0·003

Time since randomisation (years)

Number at risk (number censored)

Standard of care	100 (0)	91 (3)	79 (9)	68 (16)	58 (19)	43 (29)	22 (47)	8 (60)
Standard of care plus abiraterone	100 (0)	94 (4)	83 (10)	72 (18)	61 (23)	43 (41)	24 (57)	11 (69)
Standard of care plus radiotherapy	97 (0)	91 (0)	84 (3)	71 (14)	63 (20)	41 (41)	23 (58)	12 (69)
Standard of care plus abiraterone and radiotherapy	101 (0)	95 (4)	85 (14)	76 (21)	71 (25)	56 (39)	32 (63)	12 (83)

H

Standard of care plus radiotherapy vs standard of care Log-rank test; p=0·0013
Standard of care plus abiraterone and radiotherapy vs standard of care plus abiraterone Log-rank test; p=0·030

Time since randomisation (years)

227 (0)	206 (9)	170 (33)	138 (54)	106 (77)	65 (109)	33 (136)	13 (155)
231 (0)	212 (9)	180 (30)	152 (52)	129 (67)	87 (107)	51 (139)	24 (165)
230 (0)	211 (10)	176 (35)	142 (65)	116 (87)	76 (124)	39 (160)	21 (178)
221 (0)	195 (13)	170 (36)	150 (51)	130 (70)	96 (102)	51 (146)	21 (176)

Figure 3: **Kaplan–Meier estimates of castration resistance-free survival and time to serious genitourinary events in the cohort of patients with low-volume metastatic disease and the overall cohort**
Castration resistance-free survival after the pooling of intervention groups allocated to radiotherapy for patients with low-volume disease (A) and for the overall population (B). Castration resistance-free survival per intervention group for patients with low-volume disease (C) and for the overall population (D). Time to serious genitourinary events after the pooling of intervention groups allocated to radiotherapy for patients with low-volume disease (E) and for the overall population (F). Time to serious genitourinary events per intervention group for patients with low-volume disease (G) and for the overall population (H). HR=hazard ratio.

	Patients with low-volume metastatic disease		Overall study population	
	Standard of care with or without abiraterone (n=200)	Standard of care plus radiotherapy with or without abiraterone (n=198)	Standard of care with or without abiraterone (n=458)	Standard of care plus radiotherapy with or without abiraterone (n=451)
Missing data	53/253 (20·9%)	54/252 (21·4%)	130/588 (22·1%)	133/584 (22·8%)
Total events	52 (26·0%)	22 (11·1%)	102 (22·3%)	55 (12·2%)
Urinary catheter	9 (4·5%)	7 (3·5%)	22 (4·8%)	23 (5·1%)
Suprapubic catheter	0	0	0	2 (0·4%)
Double J ureteric stent	13 (6·5%)	12 (6·1%)	28 (6·1%)	20 (4·4%)
Nephrostomy	2 (1·0%)	1 (0·5%)	6 (1·3%)	5 (1·1%)
Prostate radiotherapy	17 (8·5%)	0	27 (5·9%)	1 (0·2%)
Transurethral resection of the prostate	10 (5·0%)	1 (0·5%)	18 (3·9%)	2 (0·4%)
Radical prostatectomy	1 (0·5%)	1 (0·5%)	1 (0·2%)	2 (0·4%)

Data are n (%).

Table 2: Serious genitourinary events in patients with available data

The most common severe adverse events were hypertension (110 [18·2%] patients treated with standard of care with or without abiraterone and 127 [22·7%] treated with standard of care plus radiotherapy with or without abiraterone) and neutropenia (40 [6·6%] and 29 [5·2%]). Gastrointestinal disorders, rectal bleeding, or both were recorded in 29 (4·8%) patients treated with standard of care with or without abiraterone and 22 (3·9%) patients treated with standard of care plus radiotherapy with or without abiraterone (table 3). 40 (6·6%) patients treated with standard of care plus abiraterone and 42 (7·5%) treated with standard of care plus radiotherapy with or without abiraterone developed a second cancer during follow-up.

Discussion

This study shows that radiotherapy significantly improves radiographic progression-free survival, although no effect was observed on overall survival, in patients diagnosed with de novo metastatic castration-sensitive prostate cancer presenting with low-volume metastatic disease. We also found that radiotherapy delays the occurrence of castration-resistant prostate cancer, regardless of disease burden. Furthermore, for the first time, we show that the prevalence of serious genitourinary events is reduced by radiotherapy both in patients with low-volume metastatic disease and in the overall study population. As expected,[5] time to the occurrence of castration-resistant prostate cancer events typically preceded radiographic progression-free survival events.

Three large randomised controlled trials have investigated the relative benefits of radiotherapy in patients with metastatic castration-sensitive prostate cancer, none of which have shown any improvement in overall survival for unselected patients (no stratification based on tumour burden). However, in contrast to the HORRAD trial[11] and the current PEACE-1 study, the STAMPEDE trial[6] found a statistically significant improvement in overall survival for patients with low-volume disease. This apparent discrepancy could have several explanations. First, the metastatic burden of the patients included in the STAMPEDE trial was established retrospectively (on retrievable baseline bone scans and, thus, was not performed on all patients), whereas the disease burden (low-volume vs high-volume) was a stratification factor in the PEACE-1 trial. Additionally, the staging imaging modalities might have differed between trials, implying the well known risk of a false positive diagnosis of metastatic disease that is curable by radiotherapy (assuming only plain bone scans were used). Furthermore, and perhaps most importantly, the standard of care differed between trials. No patients in the HORRAD trial and 367 (18%) patients in the STAMPEDE trial received an intensified systemic treatment with docetaxel; however, in the PEACE-1 study, 123 (49%) patients with low-volume disease received androgen-deprivation therapy plus docetaxel as standard of care, with 131 (52%) also receiving abiraterone following randomisation. Among the patients receiving standard of care alone, this intensified systemic treatment translated into a median overall survival of 83 months (95·1% CI 70–91) in the PEACE-1 study compared with 64 months in the STAMPEDE trial. However, outcomes among patients receiving standard of care plus radiotherapy in both trials were similar, with a median overall survival of 90 months (95·1% CI 72–not reached) in the PEACE-1 study and 86 months in the STAMPEDE trial. Differences in the next-line systemic therapies that were prescribed to the patients relapsing after primary treatment might have also had some effect on these disparities.

It is well known that the local progression of uncontrolled primary prostate cancer can entail irritative and obstructive urinary symptoms, haematuria, and pain, with a subsequent need for palliative procedures, such as transurethral resection of the prostate, urinary catheters, ureteric stents, nephrostomy for the prevention or treatment of acute kidney injury, local radiotherapy, and, less frequently, prostatectomy. In two retrospective series, local symptoms were associated with additional hospital admissions and palliative procedures, which might have translated into shortened survival.[13,14] PEACE-1 is the first study showing that prostate irradiation in people with metastatic castration-sensitive prostate cancer prevents the long-term onset of serious genitourinary events. Additionally, this preventive effect was observed in patients with both low-volume and high-volume metastatic disease, irrespective of the systemic treatment received (102 events in the standard of care group vs 55 events in the standard of care plus radiotherapy group). Preventing major genitourinary events with local radiotherapy might not only positively impact the quality of life but also decrease the

global financial burden of care. No clinical factor (eg, baseline stage T3–4 disease) seemed to reliably predict the occurrence of serious genitourinary events. Furthermore, all intervention groups seemed to derive similar benefits from upfront radiotherapy, suggesting that delivering radiotherapy to all fit enough patients with de novo metastatic castration-sensitive prostate cancer, together with intensifying systemic treatment, should be considered.

PEACE-1 also shows that prostate irradiation significantly delays the onset of castration-resistant prostate cancer, independently of metastatic disease burden. This finding is no trivial issue considering that the transition to castration-resistant prostate cancer represents a significant psychological and clinical burden for patients and their families, and has been associated with a 1·9–6·2 times increase in health-care expenditure.[15,16]

Combining standard of care with abiraterone and prostate radiotherapy seems to produce a synergistic effect, leading to an improvement in radiographic progression-free survival (for patients with low-volume disease), increased time to the occurrence of serious genitourinary events (for patients with low-volume disease and the overall study population), and increased castration resistance-free survival (for patients with low-volume disease and the overall study population). A plausible explanation would be that second-generation androgen receptor pathway inhibitors might promote radio-sensitisation through the inhibition of DNA repair.[17] Importantly, this apparent synergy between treatments was not associated with any significant increase in toxicity. Indeed, the incidence of grade 3–5 gastrointestinal and genitourinary events was not greater in patients who received radiotherapy than in those who did not receive radiotherapy, further supporting that the radiotherapy regimen set up in PEACE-1 was well tolerated. Notably, the incidence of a second cancer was not greater in patients receiving radiotherapy than in those who did not.

PEACE-1 has several limitations besides the ones associated with open-label trials. For instance, the rapidly evolving landscape of treatment options for patients with metastatic castration-sensitive prostate cancer prompted the adoption of two major amendments during the accrual period. Consequently, the statistical plan had to be reviewed to implement docetaxel, making standard of care more heterogeneous. Additionally, during the inclusion period of PEACE-1, hypofractionated radiotherapy became progressively more commonly used for the management of patients with prostate cancer; however, this therapy was not permitted in this trial. Furthermore, PEACE-1 established that a triplet systemic therapy (androgen-deprivation therapy plus docetaxel and abiraterone) improved overall survival compared with a doublet therapy (androgen-deprivation therapy plus docetaxel). Nevertheless, PEACE-1 was not designed to address treatment outcomes with a standard of care

	Standard of care with or without abiraterone (n=604)		Standard of care plus radiotherapy with or without abiraterone (n=560)	
	Mild (grade 1–2)	Severe (grade ≥3)	Mild (grade 1–2)	Severe (grade ≥3)
Blood and lymphatic system disorders				
Neutropenia	49 (8·1%)	40 (6·6%)	48 (8·6%)	29 (5·2%)
Anaemia	294 (48·7%)	6 (1·0%)	301 (53·8%)	8 (1·4%)
Lymphopenia	51 (8·4%)	5 (0·8%)	75 (13·4%)	8 (1·4%)
Thrombocytopenia	44 (7·3%)	0	81 (14·5%)	2 (0·4%)
Leukopenia	20 (3·3%)	0	45 (8·0%)	0
Eosinophilia	2 (0·3%)	0	0	0
Lymphocytosis	4 (0·7%)	0	1 (0·2%)	0
Gastrointestinal disorders				
Rectal haemorrhage	13 (2·2%)	0	71 (12·7%)	5 (0·9%)
Diarrhoea	113 (18·7%)	14 (2·3%)	172 (30·7%)	1 (0·2%)
Nausea	83 (13·7%)	3 (0·5%)	68 (12·1%)	1 (0·2%)
Colitis	1 (0·2%)	1 (0·2%)	4 (0·7%)	1 (0·2%)
Haemorrhoids	16 (2·6%)	1 (0·2%)	47 (8·4%)	0
Proctitis	0	0	27 (4·8%)	0
Anal incontinence	5 (0·8%)	0	20 (3·6%)	0
Proctalgia	4 (0·7%)	0	14 (2·5%)	0
Anal inflammation	1 (0·2%)	0	12 (2·1%)	0
Anorectal discomfort	0	0	3 (0·5%)	0
Enteritis	0	0	3 (0·5%)	0
Flatulence	4 (0·7%)	0	8 (1·4%)	0
Gastrointestinal disorder	3 (0·5%)	0	4 (0·7%)	0
Gastrointestinal motility disorder	0	0	5 (0·9%)	0
Gastrointestinal toxicity	0	0	6 (1·1%)	0
Gastroesophageal reflux disease	17 (2·8%)	0	8 (1·4%)	0
Rectal tenesmus	0	0	5 (0·9%)	0
Lower abdominal pain	2 (0·3%)	0	1 (0·2%)	0
General disorders and administration site conditions				
Fatigue	301 (49·8%)	17 (2·8%)	337 (60·2%)	12 (2·1%)
Renal and urinary disorders				
Urinary tract infection	20 (3·3%)	4 (0·7%)	29 (5·2%)	6 (1·1%)
Pollakiuria	168 (27·8%)	0	327 (58·4%)	2 (0·4%)
Dysuria	108 (17·9%)	1 (0·2%)	253 (45·2%)	2 (0·4%)
Nocturia	48 (7·9%)	0	91 (16·3%)	0
Prostatitis	0	3 (0·5%)	2 (0·4%)	0
Vascular disorders				
Hypertension	245 (40·6%)	110 (18·2%)	224 (40·0%)	127 (22·7%)

Data are n (%).

Table 3: Adverse events in patients in the safety population

consisting of dual hormone therapy (ie, androgen-deprivation therapy plus contemporary androgen receptor signalling inhibitors).

In conclusion, prostate irradiation combined with an intensified systemic treatment based on abiraterone (with or without docetaxel) showed an improvement in radiographic progression-free survival, prevented the emergence of severe genitourinary events, and delayed the time to onset of castration-resistant prostate cancer, regardless of metastatic burden and without increasing

the overall toxicity in patients with de novo metastatic castration-sensitive prostate cancer. Based on these data, prostate radiotherapy could become a component of standard of care in patients with both high-volume and low-volume de novo metastatic castration-sensitive prostate cancer.

References
1 Gravis G, Fizazi K, Joly F, et al. Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2013; **14:** 149–58.
2 Sweeney CJ, Chen YH, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. *N Engl J Med* 2015; **373:** 737–46.
3 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.
4 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.
5 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.
6 Parker CC, James ND, Brawley CD, et al. Radiotherapy to the primary tumour for newly-diagnosed, metastatic prostate cancer: a randomised controlled, phase III trial (STAMPEDE). *Lancet* 2018; **392:** 2353–66.
7 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.
8 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.
9 Sweeney CJ, Martin AJ, Stockler MR, et al. Testosterone suppression plus enzalutamide versus testosterone suppression plus standard antiandrogen therapy for metastatic hormone-sensitive prostate cancer (ENZAMET): an international, open-label, randomised, phase 3 trial. *Lancet Oncol* 2023; **24:** 323–34.
10 Burdett S, Boevé LMS, Ingleby FC, et al. Prostate radiotherapy for metastatic hormone-sensitive prostate cancer: a STOPCAP systematic review and meta-analysis. *Eur Urol* 2019; **76:** 115–24.
11 Boevé LMS, Hulshof MCCM, Vis AN, et al. Effect on survival of androgen deprivation therapy alone compared to androgen deprivation therapy combined with concurrent radiation therapy to the prostate in patients with primary bone metastatic prostate cancer in a prospective randomised clinical trial: data from the HORRAD trial. *Eur Urol* 2019; **75:** 410–18.
12 Scher HI, Halabi S, Tannock I, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. *J Clin Oncol* 2008; **26:** 1148–59.
13 Patrikidou A, Brureau L, Casenave J, et al. Locoregional symptoms in patients with de-novo metastatic prostate cancer: morbidity, management and disease outcome. *Urol Oncol* 2015; **33:** e9–17.
14 Kyrdalen AE, Dahl AA, Hernes E, Småstuen MC, Fosså SD. A national study of adverse effects and global quality of life among candidates for curative treatment for prostate cancer. *BJU Int* 2013; **111:** 221–32.
15 Freedland SJ, Davis MR, Epstein AJ, Arondekar B, Ivanova JI. Healthcare costs in men with metastatic castration-resistant prostate cancer: an analysis of US Medicare fee-for-service claims. *Adv Ther* 2023; **40:** 4480–92.
16 Burbridge C, Randall JA, Lawson J, et al. Understanding symptomatic experience, impact, and emotional response in recently diagnosed metastatic castration-resistant prostate cancer: a qualitative study. *Support Care Cancer* 2020; **28:** 3093–101.
17 Wang EC, Lee WR, Armstrong AJ. Second generation anti-androgens and androgen deprivation therapy with radiation therapy in the definitive management of high-risk prostate cancer. *Prostate Cancer Prostatic Dis* 2023; **26:** 30–40.