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

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Summary

Background Current standard of care for metastatic castration-sensitive prostate cancer supplements androgen deprivation therapy with either docetaxel, second-generation hormonal therapy, or radiotherapy. We aimed to evaluate the efficacy and safety of abiraterone plus prednisone, with or without radiotherapy, in addition to standard of care.

Methods We conducted an open-label, randomised, phase 3 study with a 2×2 factorial design (PEACE-1) at 77 hospitals across Belgium, France, Ireland, Italy, Romania, Spain, and Switzerland. Eligible patients were male, aged 18 years or older, with histologically confirmed or cytologically confirmed de novo metastatic prostate adenocarcinoma, and an Eastern Cooperative Oncology Group performance status of 0–1 (or 2 due to bone pain). Participants were randomly assigned (1:1:1:1) to standard of care (androgen deprivation therapy alone or with intravenous docetaxel 75 mg/m² once every 3 weeks), standard of care plus radiotherapy, standard of care plus abiraterone (oral 1000 mg abiraterone once daily plus oral 5 mg prednisone twice daily), or standard of care plus radiotherapy plus abiraterone. Neither the investigators nor the patients were masked to treatment allocation. The coprimary endpoints were radiographic progression-free survival and overall survival. Abiraterone efficacy was first assessed in the overall population and then in the population who received androgen deprivation therapy with docetaxel as standard of care (population of interest). This study is ongoing and is registered with ClinicalTrials.gov, NCT01957436.

Findings Between Nov 27, 2013, and Dec 20, 2018, 1173 patients were enrolled (one patient subsequently withdrew consent for analysis of his data) and assigned to receive standard of care (n=296), standard of care plus radiotherapy (n=293), standard of care plus abiraterone (n=292), or standard of care plus radiotherapy plus abiraterone (n=291). Median follow-up was 3·5 years (IQR 2·8–4·6) for radiographic progression-free survival and 4·4 years (3·5–5·4) for overall survival. Adjusted Cox regression modelling revealed no interaction between abiraterone and radiotherapy, enabling the pooled analysis of abiraterone efficacy. In the overall population, patients assigned to receive abiraterone (n=583) had longer radiographic progression-free survival (hazard ratio [HR] 0·54, 99·9% CI 0·41–0·71; p<0·0001) and overall survival (0·82, 95·1% CI 0·69–0·98; p=0·030) than patients who did not receive abiraterone (n=589). In the androgen deprivation therapy with docetaxel population (n=355 in both with abiraterone and without abiraterone groups), the HRs were consistent (radiographic progression-free survival 0·50, 99·9% CI 0·34–0·71; p<0·0001; overall survival 0·75, 95·1% CI 0·59–0·95; p=0·017). In the androgen deprivation therapy with docetaxel population, grade 3 or worse adverse events occurred in 217 (63%) of 347 patients who received abiraterone and 181 (52%) of 350 who did not; hypertension had the largest difference in occurrence (76 [22%] patients and 45 [13%], respectively). Addition of abiraterone to androgen deprivation therapy plus docetaxel did not increase the rates of neutropenia, febrile neutropenia, fatigue, or neuropathy compared with androgen deprivation therapy plus docetaxel alone.

Interpretation Combining androgen deprivation therapy, docetaxel, and abiraterone in de novo metastatic castration-sensitive prostate cancer improved overall survival and radiographic progression-free survival with a modest increase in toxicity, mostly hypertension. This triplet therapy could become a standard of care for these patients.

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed from Jan 1, 1984, to Dec 31, 2012, for papers in English, using the terms "prostate cancer", "metastases", and "phase 3 trial", and found 16 studies. When the PEACE-1 trial began in 2013, androgen deprivation therapy (ADT) had for several decades been the standard of care for men with metastatic castration-sensitive prostate cancer (mCSPC). All randomised trials conducted before the mid-2010s had not shown improvement in outcomes with new therapies compared with ADT. During recruitment for the PEACE-1 trial (2013–18), overall survival of patients with de novo mCSPC was shown to be improved by combining ADT with either docetaxel or one of the second-generation androgen receptor axis inhibitors (abiraterone, apalutamide, or enzalutamide) and radiotherapy to the primary tumour, in men with low metastatic burden. It had not yet been shown whether combining some of these new therapies with ADT in triple therapy could provide further clinical benefits.

Added value of this study

To our knowledge, PEACE-1 is the first trial to show that a triple systemic therapy—consisting of ADT, docetaxel, and a second-generation androgen signalling inhibitor (abiraterone, combined with prednisone)—improves both radiographic progression-free survival and overall survival in patients with de novo mCSPC, without excessively increasing toxicity (mostly hypertension and aminotransferase increase).

Implications of all the available evidence

The findings from the PEACE-1 trial, combined with the evidence from other studies, add weight to the concept that systemic treatment intensification provides clinical benefit for men with mCSPC and illustrate that early treatment intensification is more effective than identical or similar treatments being used sequentially when the disease has become castration-resistant. At a minimum, patients with mCSPC with a high metastatic burden who are fit enough to be treated with docetaxel should be considered for this triple systemic therapy.

Introduction

After several decades with no substantial progress, the treatment of de novo (synchronous) metastatic prostate cancer has drastically evolved in the past 10 years with the addition of diverse treatments to androgen deprivation therapy (ADT), the former standard of care (SOC). The prognosis for men with de novo metastatic castration-sensitive prostate cancer (mCSPC) has been improved by using ADT concomitantly with either docetaxel[1–5] or one of the second-generation androgen receptor axis inhibitors (abiraterone,[6–8] apalutamide,[9] or enzalutamide[10,11]). In 2018, radiotherapy to the primary tumour was also shown to extend the overall survival of patients with low-volume metastatic burden.[12] The benefits of these various combinatory therapies were confirmed by meta-analyses[13–15] and have helped to shape the current guidelines for the treatment of mCSPC.[16–18]

Nevertheless, it remains to be established whether merging some of these new therapies could provide further clinical benefits and, if so, what combination might be most suitable for de novo mCSPC.[19] Conducted by a European consortium (PEACE),[20] this study aimed to evaluate the efficacy and safety of abiraterone plus prednisone, with or without radiotherapy, in addition to SOC (ADT with or without docetaxel).

Methods

Study design and participants

We conducted an open-label, randomised, active-controlled, phase 3 study with a 2×2 factorial design (PEACE-1) at 77 sites across seven European countries (Belgium, France, Ireland, Italy, Romania, Spain, and Switzerland). The complete list of inclusion and exclusion criteria is provided in the appendix (pp 5–6). Briefly, male patients aged 18 years or older with histologically confirmed or cytologically confirmed prostate adenocarcinoma documented as de novo metastatic by bone scan, CT, or MRI (according to Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1 criteria) and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1 (or 2 due to bone pain) were eligible for inclusion, provided they had received ADT for no more than 3 months before randomisation and had at least 6 weeks between the initiation of ADT and the first docetaxel dose. Patients with a pure small-cell carcinoma, or previous prostate cancer treated by a definitive local treatment were not eligible. All participants provided written informed consent before any study-specific procedures or randomisation were initiated.

The initial protocol was reviewed and first approved on July 10, 2013, by the French Independent Ethics Committee (Comité de Protection des Personnes Ile de France VII). The protocol complied with the ethical principles of the Declaration of Helsinki and was approved by Institutional Review Boards at each study site. The trial conformed with the International Conference on Harmonization and Good Clinical Practice guidelines, and applicable regulatory requirements. Steering and Independent Data Monitoring Committees roles and members are described in the appendix (pp 3–4).

Two major protocol amendments were made during the accrual period, to account for the evolution of SOC for men with mCSPC. Although ADT alone was the SOC when the trial began recruitment in 2013, the protocol was amended on Oct 5, 2015 (273 patients had already been accrued), to allow for docetaxel use in SOC worldwide, after ADT with docetaxel had shown improvement in overall survival.[2,3] Then, in 2017, ADT plus abiraterone was also shown to improve overall

survival compared with ADT alone.[6,7] Thereby, an additional amendment was filed on Aug 10, 2017, to make docetaxel mandatory for the remainder of the patients to be accrued, so that the trial could evaluate the addition of abiraterone to ADT with docetaxel (given that the evaluation of ADT plus abiraterone compared with ADT alone had already been addressed by other trials). Further details on the amendments to the protocol and statistical analysis plan are provided in the appendix (pp 7–8). Evolution of the sample size and allocation of patients according to these key amendments is depicted in the appendix (pp 9–10).

Randomisation and masking

Eligible patients were centrally randomly assigned in the Alea Clinical Portal), in a 1:1:1:1 ratio, to SOC, SOC plus radiotherapy, SOC plus abiraterone (abiraterone plus prednisone), or SOC plus radiotherapy plus abiraterone. This randomisation process was performed via the Tenalea autonomous software, solely accessed by the trial data manager within the Epidemioloy and Biostatistics facility of the Gustave Roussy Center in Villejuif, France until 2015, then by each investigator.

Randomisation was done using a minimisation algorithm, stratified by study site, ECOG performance status (0 *vs* 1–2), type of ADT (gonadotropin-releasing hormone agonist *vs* antagonist *vs* bilateral orchiectomy), planned administration of docetaxel (yes *vs* no), and disease extent or burden based on metastatic status (lymph node metastases only *vs* bone metastases [with or without lymph node metastases] *vs* visceral metastases). A similar weight was given to each of the five stratification factors, with 80% probability to minimise imbalance in the number of patients assigned to each treatment group. As the case report form gathered information for patient stratification according to high-volume versus low-volume metastatic burden classification (as defined in the CHAARTED study[2] [high volume was defined as the presence of visceral metastases or at least four bone lesions with one beyond the vertebral bodies and pelvis]), this later classification was retained to enable inter-trial comparisons. No masking was performed in this study.

Procedures

In all patients in the study, ADT was planned to be continuously maintained by either a gonadotropin-releasing hormone agonist or antagonist, or bilateral orchiectomy. Patients assigned to receive docetaxel as part of SOC with continuous ADT were to receive six cycles of intravenous docetaxel (75 mg/m² per cycle; maximum dose of 150 mg per cycle), to be administered every 3 weeks (plus or minus 3 days). Granulocyte colony-stimulating factor (G-CSF) injections after each docetaxel cycle were recommended until the protocol amendment on Jan 22, 2018, made G-CSF prophylaxis mandatory for patients who received docetaxel. The first docetaxel cycle had to be administered within 14 days after randomisation and be at least 6 weeks after ADT initiation. Patients assigned to receive abiraterone received 1000 mg of abiraterone (four 250 mg tablets, orally) once daily plus prednisone 5 mg orally twice daily, starting within 6 weeks after ADT initiation. PEACE-1 began accrual in 2013, before the LATITUDE[6] and the STAMPEDE[7] abiraterone trials were reported and before abiraterone was approved for mCSPC, which is why we used 10 mg of prednisone, similar to what is approved for metastatic castration-resistant prostate cancer (mCRPC). Abiraterone and prednisone (hereafter referred to as abiraterone) were administered until disease progression to castration resistance, withdrawal of consent, unacceptable toxicity, or death. Patients assigned to receive radiotherapy (74 Gy in 37 fractions administered over 7–8 weeks) were planned to start radiotherapy at least 3 weeks after docetaxel completion (but no more than 8 weeks after completion). Treatments given after disease progression followed common practice, and investigators were able to change therapy as they thought was most appropriate, on the basis of prostate-specific antigen (PSA) concentration variation or clinical progression, even in absence of radiographical evidence. The treatment flow chart is depicted in the appendix (p 10).

For more on the **Alea Clinical Portal** see https://www.aleaclinical.eu

Every enrolled patient was to be followed-up for a duration of 10 years. The complete list of assessments performed at each visit and follow-up intervals are detailed in the appendix (pp 12–13). Survival status data were gathered within 3 months of the cutoff date for 97% of patients.

Outcomes

The coprimary endpoints were radiographic progression-free survival and overall survival. Radiographical progression of soft-tissue lesions was evaluated by either CT or MRI, on the basis of RECIST version 1.1. Progression of bone lesions was assessed by bone scan according to the adapted version of Prostate Cancer Working Group 2 criteria,[21] with no secondary bone scan required to confirm progression. Radiographic progression-free survival was defined as the time between randomisation and the occurrence of radiographical progression or death from any cause. Overall survival was defined as the time between randomisation and death from any cause. Patients without events were censored at the date of last follow-up.

The secondary endpoints were castration-resistant prostate cancer (CRPC)-free survival, serious-genito-urinary-event-free survival, prostate-cancer-specific survival, time to next skeletal-related event, PSA response rate, prognostic study of serum PSA measured 6–8 months after initiation of systemic therapy, time to pain progression, time to chemotherapy for CRPC, quality of life, changes in bone mineral density, correlation of biomarkers with outcome, event rate per 100 person-years of treatment analysis, and toxicity. CRPC-free survival was defined as

the time between randomisation and CRPC or death from any cause. CRPC was defined as either radiographical progression or a confirmed PSA rise (based on three independent measurements: A, B, and C, with A<B<C, and C≥0·50 ng/mL), with a serum testosterone within castrated range (<0·50 ng/mL). Prostate-cancer-specific survival was defined as the time from randomisation to the occurrence of death from prostate cancer. The event rate per 100 person-years of treatment was the number of adverse events divided by the amount of person-time observed (ie, 100 patients experiencing any adverse event over a 1-year period of exposure, with an exposure time from randomisation to CRPC or last follow-up). Adverse events were graded on the basis of the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Safety analysis was based on the highest grade adverse event recorded during the period spanning from treatment initiation to CRPC. Apart from CRPC-free survival, prostate-cancer-specific survival, event rate per 100 person-years, and toxicity, secondary endpoint results were still under investigation at the time this manuscript was submitted and so are not reported here.

Statistical analysis

The initial protocol in 2013 planned for a sample size of 916 patients. However, due to a change in the SOC and the knowledge gained from the LATITUDE and STAMPEDE trial results published in late 2017, the planned sample size was increased to 1173 and the coprimary study aims were revised (appendix pp 7–8). Because PEACE-1 was the only phase 3 trial to date that could determine abiraterone efficacy in patients with mCSPC receiving ADT plus docetaxel as SOC, the timing of the final analyses was based on this population (population of interest). Sample size calculation was performed with East software (Cytel; Cambridge, MA, USA), on the basis of the assumption that no significant interaction would take place between radiotherapy and abiraterone, to allow for a 2×2 factorial analysis of abiraterone efficacy. For abiraterone efficacy evaluation, 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 abiraterone to ADT plus docetaxel would improve overall survival by 30% over a median of 53 months and progression-free survival by 40% over 30 months. Hence, with 355 patients assigned to ADT with docetaxel plus abiraterone (with or without radiotherapy) and 355 patients assigned to ADT with docetaxel without abiraterone (with or without radiotherapy), 249 deaths would give an 80% power to detect an overall survival hazard ratio (HR) of 0·70 at a two-sided α level of 0·049. With the same group allocation, 262 radiographic progression events or deaths were predicted to have an 80% power to detect a radiographic progression-free survival HR of 0·60 at a two-sided α level of 0·001.

This trial had a factorial design, based on the assumption that there would be no interaction between abiraterone and radiotherapy. Before analysing the various outcomes, the presence of such an interaction for both coprimary endpoints was tested by analyses of maximum likelihood estimates using a Cox model adjusted for stratification factors (ECOG performance status [0 *vs* 1–2], ADT type [gonadotropin-releasing hormone agonist *vs* antagonist *vs* bilateral orchiectomy], metastatic burden [low *vs* high; as defined in the Randomisation and masking section],[2] and docetaxel [no docetaxel before amendment *vs* no docetaxel after amendment *vs* with docetaxel after amendment]). In the absence of a qualitative interaction (p>0·05) between abiraterone and radiotherapy, the groups were to be combined two by two on the basis of abiraterone administration, regardless of radiotherapy, before sequentially assessing abiraterone efficacy first in the overall population and then in the ADT with docetaxel population (assuming the significance level was reached in first instance). As the preplanned number of progression-free survival and overall survival events had not been reached in the study population at the time this paper was written, the efficacy of radiotherapy remains to be analysed (appendix p 16). The coprimary endpoint results presented here correspond to the final planned analysis; no interim analysis was conducted. All efficacy analyses were conducted in the intention-to-treat population, defined as all patients who were randomly assigned to a treatment group. Safety analyses were conducted in the safety population, according to the treatment actually received by the patients (those who did not receive any investigational treatment were not included in the safety analyses).

The median follow-up was estimated by the inverse Kaplan-Meier method. Time-to-event endpoints were estimated by the Kaplan-Meier method. The Cox proportional hazards model adjusted for radiotherapy and stratification factors provided significances and an estimate of the abiraterone effect (p value and HR with CIs adjusted to match adjustment made to significance levels in the corresponding test [ie, 99·9% for radiographic progression-free survival, 95·1% for overall survival, and 95% for secondary endpoints]). The assumption of proportional hazards was evaluated on the basis of the weighted Schoenfeld residuals. The heterogeneity of the effect of abiraterone in the predefined stratification subgroups was evaluated using Cox proportional hazards models adjusted for radiotherapy and stratification factors and including an interaction term between abiraterone and the studied stratification variable. These analyses are illustrated using forest plots. Notably, we analysed the efficacy of abiraterone in the ADT with docetaxel population by disease burden. Non-parametric CIs for the median survival differences between groups were analysed by the bootkm function of the R Hmisc package

(5000 repeats). Statistical analyses were performed with SAS (version 9.4) and R (version 4.0.2).

This study is ongoing and is registered with ClinicalTrials.gov, NCT01957436.

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 (one patient subsequently withdrew consent for analysis of his data) and assigned to receive SOC (n=296), SOC plus radiotherapy (n=293), SOC plus abiraterone (n=292), or SOC plus radiotherapy plus abiraterone (n=291; figure 1). SOC was ADT alone in 462 patients and ADT with docetaxel in 710 patients (table 1).

For radiographic progression-free survival and overall survival, the median follow-up periods were longer in the overall population (3·5 years [IQR 2·8–4·6] and 4·4 years [3·5–5·4], respectively) than in the ADT with docetaxel population (3·0 years [2·1–3·8] and 3·8 years [2·9–4·5], respectively). Regardless of the population and survival outcome considered, the median follow-up periods did not differ between the groups who did or did not receive abiraterone. For the radiographic progression-free survival analyses, the median follow-up periods from randomisation to the cutoff date of Sept 1, 2020, were 3·53 years for the overall population (3·52 years for the SOC without abiraterone groups and 3·56 years for the SOC plus abiraterone groups; log-rank p=0·86) and 2·99 years for the ADT with docetaxel population (3·00 years and 2·97 years; log-rank p=0·93). For the overall survival analyses, the median follow-up periods from randomisation to the cutoff date of June 1, 2021, were 4·41 years for the overall population (4·44 years for the SOC without abiraterone groups and 4·39 years for the SOC plus abiraterone groups; log-rank p=0·98) and 3·81 years for the ADT with docetaxel population (3·75 years and 3·85 years; log-rank p=0·95).

In the overall population (n=1172), no interaction between abiraterone and radiotherapy was found for radiographic progression-free survival (p=0·64), overall survival (p=0·86), CRPC-free survival (p=0·56), or prostate-cancer-specific survival (p=0·54), after adjusting for the four stratification factors. Likewise, in the ADT with docetaxel population (n=710), no interaction between abiraterone and radiotherapy was

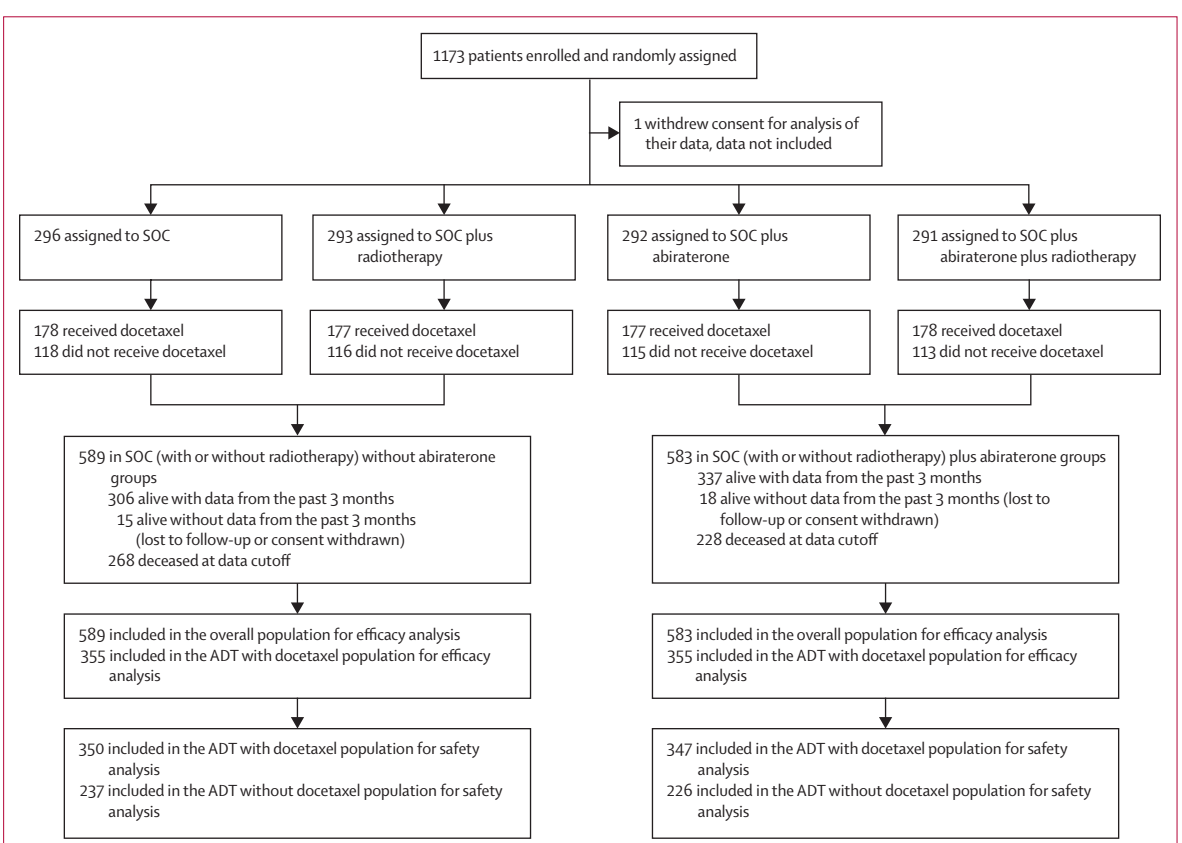


Figure 1: **Trial profile**
ADT=androgen deprivation therapy. SOC=standard of care.

found for radiographic progression-free survival (p=0·94), overall survival (p=0·85), CRPC-free survival (p=0·75), or prostate-cancer-specific survival (p=0·98), after adjusting for ECOG performance status, ADT type, and disease burden. Consequently, the comparative evaluation of abiraterone efficacy on survival outcomes was conducted by pooling the groups two by two (SOC without abiraterone [with or without radiotherapy] groups *vs* SOC plus abiraterone [with or without radiotherapy] groups).

	Overall population (n=1172)		ADT with docetaxel population (n=710)*	
	SOC plus abiraterone groups (with or without radiotherapy; n=583)	SOC without abiraterone groups (with or without radiotherapy; n=589)	SOC plus abiraterone groups (with or without radiotherapy; n=355)	SOC without abiraterone groups (with or without radiotherapy; n=355)
Assigned to receive radiotherapy	291 (50%)	293 (50%)	178 (50%)	177 (50%)
Country				
Belgium	29 (5%)	25 (4%)	16 (5%)	16 (5%)
France	458 (79%)	462 (78%)	278 (78%)	280 (79%)
Ireland	30 (5%)	30 (5%)	17 (5%)	13 (4%)
Italy	1 (<1%)	3 (1%)	0	0
Romania	4 (1%)	5 (1%)	0	0
Spain	55 (9%)	56 (10%)	38 (11%)	39 (11%)
Switzerland	6 (1%)	8 (1%)	6 (2%)	7 (2%)
Age, years				
Median	67 (61–72)	66 (59–72)	66 (60–70)	66 (59–70)
Range	37–94	43–87	37–85	44–84
ECOG performance status				
0	412 (71%)	412 (70%)	250 (70%)	246 (69%)
1–2	171 (29%)	177 (30%)	105 (30%)	109 (31%)
T stage				
T1	23 (4%)	23 (4%)	10 (3%)	13 (4%)
T2	109 (19%)	94 (16%)	64 (19%)	45 (13%)
T3	287 (51%)	310 (53%)	167 (49%)	189 (55%)
T4	98 (17%)	99 (17%)	68 (20%)	65 (19%)
Tx	45 (8%)	54 (9%)	32 (9%)	35 (10%)
Missing data	21 (4%)	9 (2%)	14 (4%)	8 (2%)
N stage				
N1	307 (55%)	325 (57%)	198 (58%)	207 (60%)
N0	186 (33%)	174 (30%)	99 (29%)	97 (28%)
NX	69 (12%)	76 (13%)	43 (13%)	39 (11%)
Missing data	21 (4%)	14 (2%)	15 (4%)	12 (3%)
Time from diagnosis, months				
Median	2·3 (1·6–3·2)	2·3 (1·4–3·1)	2·2 (1·6–3·0)	2·2 (1·4–2·9)
Missing data	10 (2%)	10 (2%)	6 (2%)	7 (2%)
Metastatic localisation				
Bone†	472 (81%)	475 (81%)	287 (81%)	279 (79%)
Lymph node only	47 (8%)	52 (9%)	27 (8%)	29 (8%)
Visceral‡	64 (11%)	62 (11%)	41 (12%)	47 (13%)
Metastatic burden§				
High burden	331 (57%)	336 (57%)	224 (63%)	232 (65%)
Low burden	252 (43%)	253 (43%)	131 (37%)	123 (35%)

(Table 1 continues on next page)

In the overall population, the addition of abiraterone to SOC (with or without docetaxel and with or without radiotherapy) decreased the number of radiographic progression events or deaths from 371 to 252, improved the median progression-free survival from 2·22 years (IQR 1·09–6·03) to 4·46 years (1·72–not reached), and reduced the relative risk of radiographic progression or death by 46% compared with patients who did not receive abiraterone (adjusted HR for radiographic progression-free survival 0·54, 99·9% CI 0·41–0·71; p<0·0001; figure 2A, table 2). The addition of abiraterone to SOC (with or without docetaxel and with or without radiotherapy) decreased the number of deaths from 268 to 228, improved the median overall survival from 4·72 years (IQR 2·59–not reached) to 5·72 years (2·72–not reached), and reduced the risk of death from any cause by 18% (adjusted HR for overall survival 0·82, 95·1% CI 0·69–0·98; p=0·030; figure 2C, table 2). In the overall population, the effect of abiraterone on radiographic progression-free survival and overall survival showed a high consistency across most of the predefined subgroups, except for the under-represented subgroup of patients who had bilateral orchiectomy and those who did not receive docetaxel based on the investigator's decision (figures 3A, 3C). For overall survival only, the effect of the addition of abiraterone was pronounced in patients with high-volume metastatic burden (figure 3C).

As SOC plus abiraterone showed a superior efficacy compared with SOC without abiraterone that met the required predefined significance level (type I error of 0·049 for overall survival and 0·001 for radiographic progression-free survival) within the overall population, abiraterone efficacy was further investigated within the more restricted ADT with docetaxel population to assess the preplanned coprimary endpoints. In this population, compared with SOC (including docetaxel) without abiraterone, the addition of abiraterone decreased the number of radiographic progression events or deaths from 211 to 139, improved the median radiographic progression-free survival from 2·03 years (IQR 1·09–not reached) to 4·46 years (1·90–not reached), and reduced the relative risk of radiographic progression or death by 50% (adjusted HR for radiographic progression-free survival 0·50, 99·9% CI 0·34–0·71; p<0·0001; figure 2B, table 2). Similarly, compared with SOC (including docetaxel) without abiraterone, the addition of abiraterone reduced the number of deaths from 151 to 121, improved the median overall survival from 4·43 years (IQR 2·47–not reached) to not reached, and reduced the relative risk of death from any cause by 25% (adjusted HR for overall survival 0·75, 95·1% CI 0·59–0·95; p=0·017; figure 2D, table 2).

By analysing the ADT with docetaxel population according to the disease burden, we observed that compared with SOC (including docetaxel) without abiraterone, the addition of abiraterone decreased the number of radiographic progression events or deaths

from 55 to 41 and from 156 to 97, and reduced the relative risk of radiographic progression or death by 42% and 53%, in patients with low metastatic burden and patients with high metastatic burden, respectively (low-volume burden median not reached *vs* 2·7 years; adjusted HR 0·58, 99·9% CI 0·29–1·15; p=0·0061; high-volume burden median 4·1 years *vs* 1·6 years; adjusted HR 0·47, 99·9% CI 0·30–0·72; p<0·0001; appendix p 10, table 2). Median overall survival in patients with high metastatic burden improved from 3·47 years with SOC without abiraterone to 5·14 years when abiraterone was added, corresponding to a 28% reduction in relative risk of death from any cause (adjusted HR 0·72, 95·1% CI 0·55–0·95; p=0·019; figure 2F, table 2). As the data were not mature, no conclusive response in overall survival could be shown for patients with low metastatic burden (figures 2E, 3D, table 2).

In the ADT with docetaxel population, compared with SOC without abiraterone, the addition of abiraterone delayed castration resistance (median CRPC-free survival 1·45 years *vs* 3·21 years; HR 0·38, 95% CI 0·31–0·47; p<0·0001; table 2, appendix p 11). Among patients in the ADT with docetaxel population who developed castration resistance and were alive at the data cutoff date, 221 (84%) of 263 patients were subsequently treated by at least one life-prolonging therapy and 213 (81%) of 263 by at least one next-generation hormonal therapy in the SOC without abiraterone groups, compared with 104 (74%) of 141 and 65 (46%) of 141, respectively, in the SOC plus abiraterone groups (appendix p 14). Prostate-cancer-specific survival was also improved by the addition of abiraterone in the ADT with docetaxel population (median 4·72 years *vs* not reached; HR 0·69, 95% CI 0·53–0·90; p=0·0062; table 2, appendix p 11).

Adding abiraterone to ADT with docetaxel (with or without radiotherapy) had no effect on the number of docetaxel cycles administered (median 6 [IQR 6–6] in both groups). 138 (61%) of 226 patients in the ADT with docetaxel population and 183 (53%) of 347 in the ADT without docetaxel population had abiraterone treatment discontinued, including 29 (21%) of 138 and 32 (17%) of 183 due to toxicity, respectively (appendix p 14). Overall, the median abiraterone treatment duration before discontinuation was 33·2 months (95% CI 25·5–43·2) in the ADT without docetaxel population and 34·1 months (30·0–43·5) in the ADT with docetaxel population.

In the ADT with docetaxel safety population, 217 (63%) of 347 patients who received abiraterone versus 181 (52%) of 350 who did not receive abiraterone had at least one severe adverse event (grade 3 or worse) and seven (2%) versus three (1%) had a fatal adverse event (table 3, appendix p 14). In the ADT without docetaxel population, 149 (66%) of 226 patients who received abiraterone had at least one severe adverse event and eight (4%) had a fatal adverse event (table 2). Therefore, the addition of docetaxel to abiraterone did not increase the incidence of severe or fatal adverse events. In the ADT with docetaxel population, 49 severe adverse events occurred per 100 person-years in patients who received abiraterone compared with 55 per 100 person-years in patients who did not receive abiraterone (appendix p 14). The incidence of frequent severe adverse events (grade 3 or worse adverse events that were reported in ≥5% of patients) was similar between patients who received abiraterone and patients who did not in the ADT with docetaxel population, except for hypertension (76 [22%] of 347 patients *vs* 45 [13%] of 350) and hepatotoxicity with increased aminotransferases (20 [6%] of 347 *vs* two [1%] of 350), which were more frequent among those who received abiraterone (table 3). Although the incidence of severe hypertension and hepatotoxicity were similar in patients who received abiraterone in the ADT with docetaxel and ADT without docetaxel populations, there was a difference, as expected, in the incidence of severe neutropenia, which occurred in 34 (10%) of 347 patients versus none of 226, respectively (appendix p 15). Although severe fatigue and peripheral neuropathy events did not reach the frequency cutoff of 5% in the ADT with docetaxel population, ten (3%) of 347 patients who received abiraterone and 15 (4%) of 350 who did not receive abiraterone had at least one event of severe fatigue, and four (1%) and six (2%) had at least one severe peripheral neuropathy event (table 3).

	Overall population (n=1172)		ADT with docetaxel population (n=710)*	
	SOC plus abiraterone groups (with or without radiotherapy; n=583)	SOC without abiraterone groups (with or without radiotherapy; n=589)	SOC plus abiraterone groups (with or without radiotherapy; n=355)	SOC without abiraterone groups (with or without radiotherapy; n=355)
(Continued from previous page)				
Gleason score				
≤7	145 (25%)	133 (23%)	79 (23%)	71 (20%)
8–10	429 (75%)	441 (77%)	270 (77%)	276 (80%)
Missing data	9 (2%)	15 (3%)	6 (2%)	8 (2%)
PSA at randomisation, ng/mL				
Median	14 (3–62)	11 (3–55)	14 (2–59)	12 (3–60)
Missing data	2 (<1%)	4 (1%)	0	2 (<1%)
Medical history				
Hypertension	270 (47%); N=574	241 (43%); N=562	156 (44%); N=352	148 (43%); N=344
Type 2 diabetes	62 (11%); N=566	80 (14%); N=556	33 (9%); N=351	56 (16%); N=344
High cholesterol	229 (40%); N=568	229 (41%); N=556	136 (39%); N=351	130 (38%); N=343

Data are n (%) or median (IQR) unless otherwise stated. All numbers are rounded to the nearest integer. Ethnicity-related information are not presented, as French laws forbid the collection of such data. SOC in the overall population was ADT with or without docetaxel. SOC in the ADT with docetaxel population was ADT with docetaxel. ADT=androgen deprivation therapy. ECOG=Eastern Cooperative Oncology Group. PSA=prostate-specific antigen. SOC=standard of care. *The median number of docetaxel cycles was 6 (IQR 6–6) in both the SOC with abiraterone and SOC without abiraterone groups. †Without visceral metastases. ‡With or without lymph node and bone metastases. §The metastatic burden was classified as reported by Sweeney and colleagues (2015), with a high burden characterised by four or more bone metastases with one or more outside the vertebral bodies or pelvis, or visceral metastases, or both; all other assessable situations were classified as low burden.

Table 1: **Baseline characteristics in the intention-to-treat population**

Discussion

To our knowledge, this is the first trial to show that a triple systemic therapy, consisting of ADT, docetaxel, and a second-generation androgen signalling inhibitor (abiraterone), extends radiographic progression-free survival and overall survival in patients with de novo mCSPC.

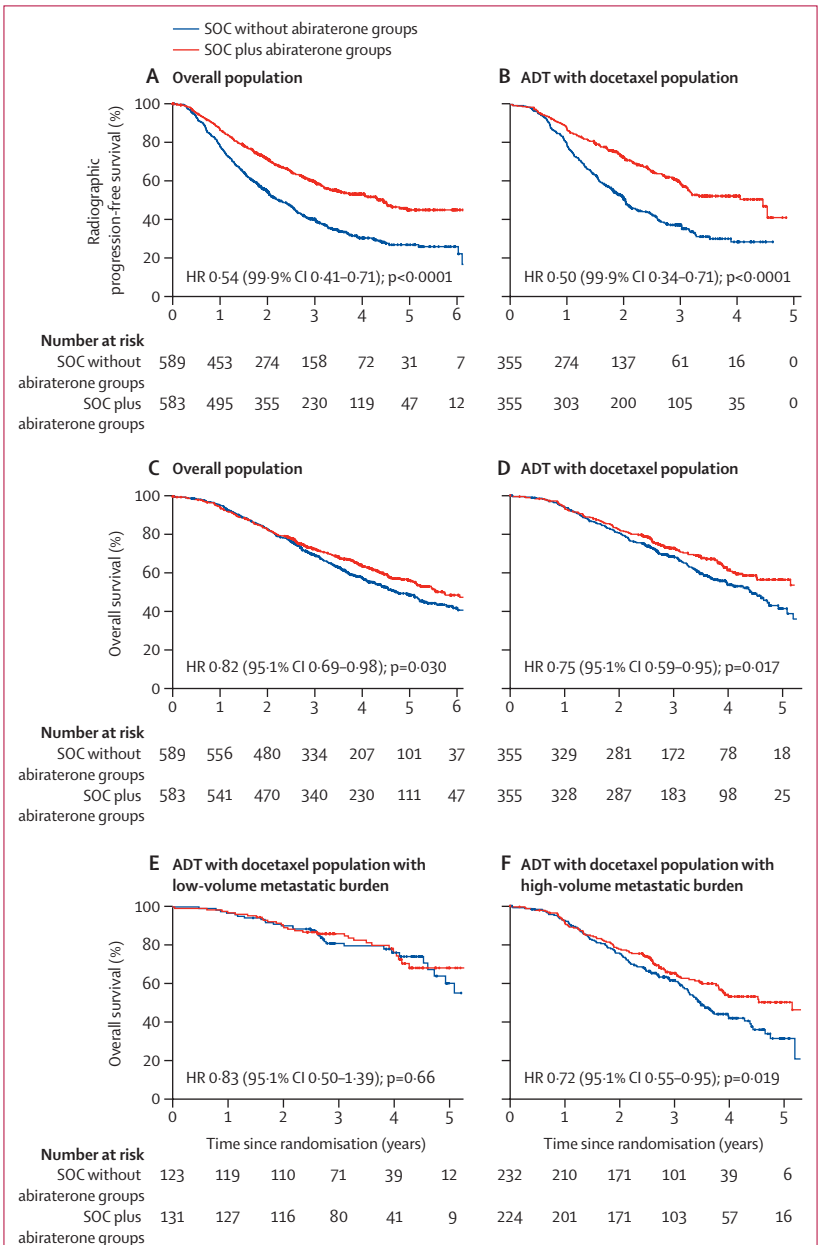


Figure 2: **Kaplan-Meier estimates of radiographic progression-free survival and overall survival in the overall population and ADT with docetaxel population**

Time-to-event curves are presented for radiographic progression-free survival (A) and overall survival (C) in the overall population, radiographic progression-free survival (B) and overall survival (D) in the ADT with docetaxel population, and overall survival in the ADT with docetaxel population in patients with low-volume metastatic burden (E) and high-volume metastatic burden (F). SOC in the overall population was ADT with or without docetaxel. SOC in the ADT with docetaxel population was ADT with docetaxel. ADT=androgen deprivation therapy. SOC=standard of care (with or without radiotherapy).

Whether the systemic treatment of high-volume disease (ie, extended metastatic spread) should differ from that of low-volume disease has been extensively debated. The benefit of ADT with docetaxel has been clearly shown for patients with mCSPC with high-volume disease,[4,22] but data collected from larger populations support a similar benefit across high-volume and low-volume disease.[3] This discrepancy might result from different ratios of patients with de novo versus relapsing low-volume disease being included in these trials, because recurrences favour better prognoses.[23] Second-generation androgen receptor axis inhibitors have shown overall survival benefits in patients with mCSPC regardless of the disease volume considered.[5,9,10] In this trial, the mature data for men with high-volume disease indicate a clear improvement in both radiographic progression-free survival and overall survival when abiraterone is added to ADT with docetaxel. Even though the data on overall survival were immature for patients with low-volume disease, an abiraterone-mediated benefit in radiographic progression-free survival was already apparent. Thus, ADT with docetaxel plus abiraterone should be proposed as a new SOC for patients presenting with high-volume disease who are fit for docetaxel prescription. However, for patients with low-volume disease, the decision of whether to use two or three agents should be carefully considered by both the patients and their oncologists, to determine whether a major benefit in radiographic progression-free survival (HR 0·58) is sufficient to justify a treatment intensification in a context of immature overall survival data. It would also depend on whether an overall survival benefit is required. Long-term data and consensus conferences will allow for clinical practice guidance refinement.

As abiraterone can inhibit CYP3A4 in vitro,[24] and as CYP3A4 is involved in docetaxel elimination,[25] the concomitant administration of these two drugs could potentially increase docetaxel exposure and thereby its toxicity. However, no increase in chemotherapy-related side-effects occurred in reaction to this concomitance, which might suggest an absence of substantial drug–drug interactions between abiraterone and docetaxel. This finding is consistent with the observation that abiraterone and docetaxel have similar pharmacokinetic behaviour when administered alone or in combination.[26] Similarly, abiraterone did not affect the clearance of another taxane, cabazitaxel, by CYP3A.[27] We also did not observe an increase in haematological toxicity when abiraterone was added to ADT with docetaxel, contrary to a phase 2 trial in patients with mCRPC.[28] The most frequent high-grade adverse event reported among patients who received abiraterone in this trial was hypertension (22% of patients who received abiraterone *vs* 13% of those who did not). This expected adverse event was carefully monitored and managed to prevent the onset of cardiovascular events, which were not seen in excess in this trial. In the ENZAMET trial,[10] hypertension was also two times as frequent among patients with

	Patients assessed, n		Median, years		Median difference, years	Hazard ratio	p value
	SOC with abiraterone groups	SOC without abiraterone groups	SOC with abiraterone groups	SOC without abiraterone groups			
Primary outcomes in the overall population							
Overall survival	583	589	5·7	4·7	0·9 (95·1% CI 0·0–2·0)	0·82 (95·1% CI 0·69–0·98)	0·030
Radiographic progression-free survival	583	589	4·5	2·2	2·1 (99·9% CI 0·7–2·9)	0·54 (99·9% CI 0·41–0·71)	<0·0001
Secondary outcomes in the overall population							
CRPC-free survival	583	589	3·8	1·5	2·3 (95% CI 1·6–3·0)	0·40 (95% CI 0·35–0·47)	<0·0001
Prostate-cancer-specific survival	583	589	NR	5·8	NA	0·75 (95% CI 0·61–0·91)	0·0038
Primary outcomes in the ADT with docetaxel population							
Overall survival	355	355	NR	4·4	NA	0·75 (95·1% CI 0·59–0·95)	0·017
Radiographic progression-free survival	355	355	4·5	2·0	2·2 (99·9% CI 0·6–2·8)	0·50 (99·9% CI 0·34–0·71)	<0·0001
Secondary outcomes in the ADT with docetaxel population							
Overall survival in patients with low-volume metastatic burden	131	123	NR	NR	NA	0·83 (95·1% CI 0·50–1·39)	0·66
Overall survival in patients with high-volume metastatic burden	224	232	5·1	3·5	1·1 (95·1% CI 0·2–1·9)	0·72 (95·1% CI 0·55–0·95)	0·019
Radiographic progression-free survival in patients with low-volume metastatic burden	129	122	NR	2·7	NA	0·58 (99·9% CI 0·29–1·15)	0·0061
Radiographic progression-free survival in patients with high-volume metastatic burden	225	231	4·1	1·6	2·2 (99·9% CI 0·6–3·2)	0·47 (99·9% CI 0·30–0·72)	<0·0001
CRPC-free survival	355	355	3·2	1·4	2·0 (95% CI 1·5–3·1)	0·38 (95% CI 0·31–0·47)	<0·0001
Prostate-cancer-specific survival	355	355	NR	4·7	NA	0·69 (95% CI 0·53–0·90)	0·0062

ADT=androgen deprivation therapy. CRPC=castration-resistant prostate cancer. NA=not available. NR=not reached. SOC=standard of care (with or without radiotherapy).

Table 2: **Efficacy outcomes in the intention-to-treat population**

mCSPC who received enzalutamide in addition to ADT with docetaxel compared with those who did not receive enzalutamide. However, with enzalutamide addition, higher incidences of fatigue, syncope, and therapy discontinuation were reported, whereas we did not observe a rise in such events in PEACE-1 with the addition of abiraterone to ADT with docetaxel. Aminotransferase increase, a common side-effect of abiraterone, was observed in this trial (6% of patients who received abiraterone *vs* 1% of those who did not), but occurred at a similar frequency with or without docetaxel. This aminotransferase increase had no detectable clinical consequences, as recommended management was followed.[29] Notably, the addition of abiraterone to ADT with docetaxel did not affect severe neutropenia incidence (10% of patients who received abiraterone *vs* 9% of those who did not). The impact of toxicity on participants will be better understood after the formal analysis of quality-of-life data, at which time the triplet therapy oncological benefits might still outweigh the adverse effect of the additional toxicity.

Aside from the limitations inherently associated with open-label trials, the rapid clinical practice evolution for mCSPC that took place during the conduct of this trial prompted the sequential amendment of the PEACE-1 protocol and statistical analysis plan to reflect those changes, answer meaningful questions, and implement the best treatment options to all participants (appendix pp 7–8). In particular, as an overall survival benefit for patients with mCSPC treated with abiraterone combined with ADT alone was shown in 2017, accrual was then restricted to patients receiving ADT with docetaxel as SOC, and our pre-established statistical analysis was revised to specifically include the assessment of the efficacy of abiraterone in terms of survival outcomes in the ADT with docetaxel population. De facto, further allocating men to ADT only would have been unethical, given that the ADT plus abiraterone combination was already known to improve overall survival.

Our findings show that combining abiraterone with ADT and docetaxel improves both radiographic progression-free survival and overall survival compared

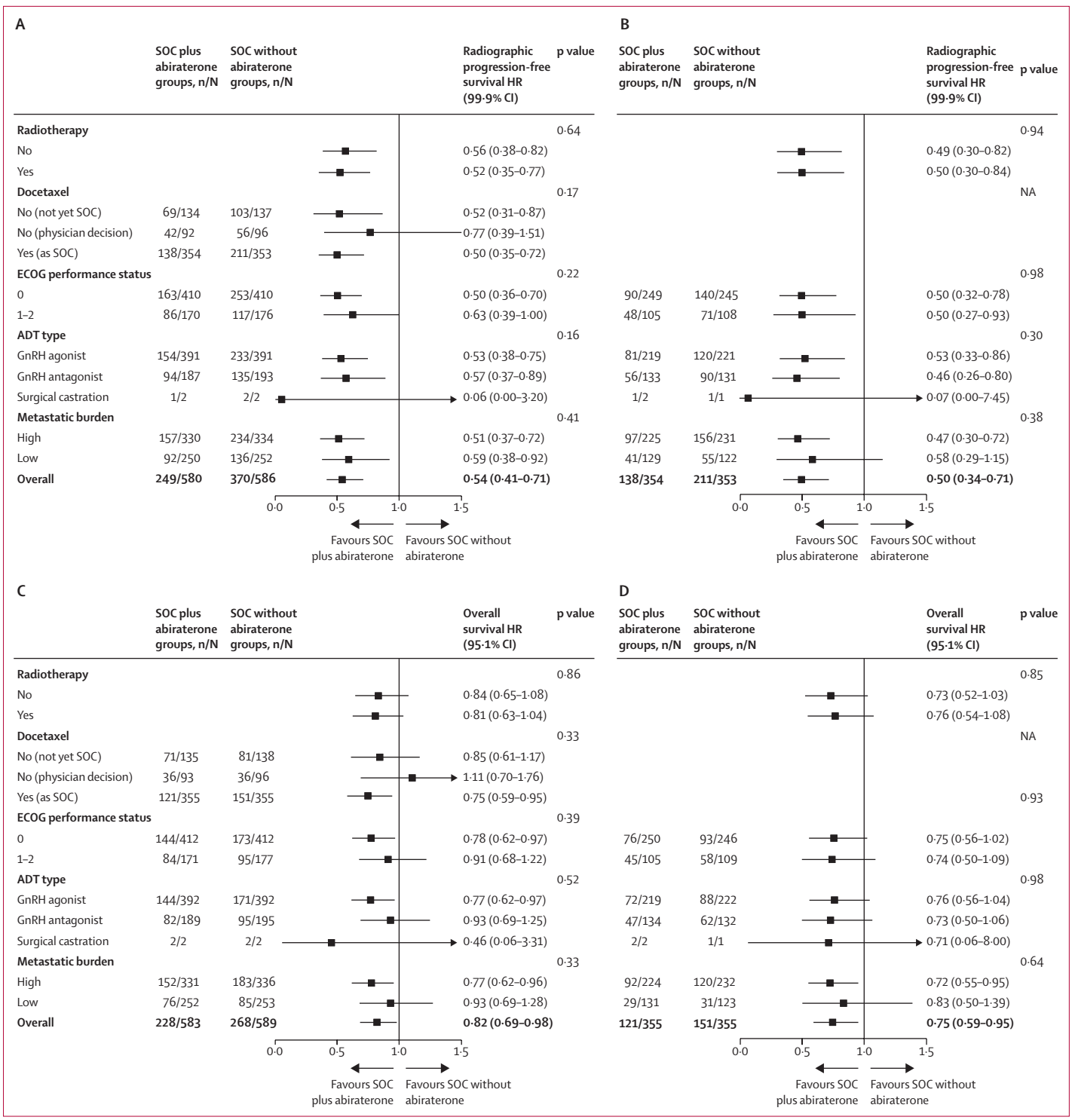


Figure 3: **HRs for radiographic progression-free survival and overall survival by predefined stratification factors in the overall population and ADT with docetaxel population**
(A) Radiographic progression-free survival in the overall population. (B) Radiographic progression-free survival in the ADT with docetaxel population. (C) Overall survival in the overall population. (D) Overall survival in the ADT with docetaxel population. n/N represents events/patients. The number of events per patients in the radiotherapy subgroup analysis is not presented as the efficacy of radiotherapy is still under investigation. HRs are plotted on a linear scale. At time of the radiographic progression-free survival analysis, metastatic burden data were not available for six patients who were excluded from the Cox model. Overall survival analysis by predefined stratification factors was conducted in the intention-to-treat population. ADT=androgen deprivation therapy. ECOG=Eastern Cooperative Oncology Group. GnRH=gonadotropin releasing hormone. HR=hazard ratio. NA=not applicable. SOC=standard of care (with or without radiotherapy).

with ADT and docetaxel without abiraterone. Indeed, docetaxel and abiraterone have distinct mechanisms of action. In addition, they do not display absolute cross-resistance, as abiraterone improves overall survival after docetaxel treatment and docetaxel retains some activity after abiraterone failure.[30,31] Collectively, these observations provide a rationale for the survival benefits resulting from their combination in this trial. However, this study did not answer whether this triple combination yields clinical advantages over ADT plus a second-generation androgen receptor axis inhibitor. Indeed, at the time when this trial was conducted (2013–18), combining ADT with such an inhibitor had not been approved for mCSPC, thereby precluding such a comparison within the trial. Incidentally, the ongoing phase 3 ARASENS (NCT02799602) and ENZAMET (NCT02446405) trials are also testing the combined efficacy of second-generation androgen receptor axis inhibitors (darolutamide and enzalutamide, respectively) with ADT and docetaxel, and their upcoming overall survival results will put the benefits of abiraterone in perspective.

Reaching treatment synergy and preventing acquired resistance despite tumour clonal heterogeneity are cardinal aspects of mCSPC management that require an optimisation of the treatment framework. In PEACE-1, significant survival benefits were obtained when abiraterone was added to ADT with docetaxel. Remarkably, these benefits were observed even though more than 80% of the SOC without abiraterone group eventually received a second-generation androgen receptor axis inhibitor (mostly abiraterone or enzalutamide) to address cancer progression. Indeed, by contrast with previous trials, PEACE-1 investigators were allowed to prescribe early salvage treatments to the control group patients who showed evidence of cancer progression. To this end, a PSA minimum value of just 0·50 ng/mL was used to define mCRPC, even in the absence of radiographic progression. Collectively, these observations suggest that the upfront combination implemented in this trial is superior to the sequential administration of these (or similar) agents as occurred in the control group. Of note, abiraterone is approved for metastatic prostate cancer in many countries and is close to becoming a worldwide generic drug.

In conclusion, this trial not only confirms that combining abiraterone with SOC improves outcomes in men with de novo mCSPC, but it shows that combining abiraterone with ADT and docetaxel improves overall and radiographic progression-free survival and other efficacy endpoints with little toxicity increase. Nonetheless, as PEACE-1 only included patients with de novo mCSPC, it is still unclear whether this triple therapy might benefit patients with metachronous mCSPC. Our findings cannot directly address whether this triplet systemic combination is superior to ADT and abiraterone. Longer follow-up is required to answer whether combining such an intensive first line systemic treatment with radiotherapy to the primary tumour might provide further clinical benefits for patients with mCSPC. This upcoming analysis will be performed when the preplanned number of radiographic progression-free survival and overall survival events is reached in the population of men presenting with low-volume metastatic dissemination.

	ADT with docetaxel population		ADT without docetaxel population	
	SOC plus abiraterone groups (with or without radiotherapy; n=347)	SOC without abiraterone groups (with or without radiotherapy; n=350)	SOC plus abiraterone groups (with or without radiotherapy; n=226)	SOC without abiraterone groups (with or without radiotherapy; n=237)
Any adverse events	346 (100%)	349 (100%)	226 (100%)	233 (99%)
Severe (grade ≥3) adverse events	217 (63%)	181 (52%)	149 (66%)	97 (41%)
Fatal (grade 5) adverse events	7 (2%)	3 (1%)	8 (4%)	5 (2%)
Frequent severe adverse events				
Hypertension	76 (22%)	45 (13%)	66 (29%)	38 (16%)
Neutropenia	34 (10%)	32 (9%)	0	0
Hepatotoxicity	20 (6%)	2 (1%)	14 (6%)	3 (1%)
Febrile neutropenia	18 (5%)	19 (5%)	2 (1%)	1 (<1%)
Gamma-glutamyl transferase increase	17 (5%)	14 (4%)	6 (3%)	4 (2%)
Erectile dysfunction	7 (2%)	5 (1%)	12 (5%)	13 (5%)
Blood alkaline phosphatase increase	15 (4%)	12 (3%)	6 (3%)	13 (5%)
Other severe adverse events				
Fatigue	10 (3%)	15 (4%)	3 (1%)	0
Peripheral neuropathy	4 (1%)	6 (2%)	1 (<1%)	0

Data are n (%). As the patients were not randomly assigned according to docetaxel prescription, toxicities recorded in the ADT without docetaxel and ADT with docetaxel populations are not directly comparable. Percentages are rounded to the nearest integer. The safety population includes patients who actually received the assigned treatment. Severe adverse events (grade ≥3) were considered frequent if they occurred in at least 5% of patients in either group and are reported in decreasing order of occurrence according to the Medical Dictionary for Regulatory Affairs Preferred Term classification. ADT=androgen deprivation therapy. SOC=standard of care.

Table 3: **Adverse events in the safety population**

Contributors

KF, AB, and SF conceived and designed the study. KF, JC, GR, RM, AF, BT, SS, DB, PR, GK, GG, FC, J-FB, AH, MS, AT-V, IL, LM, BL, SA-L, EM, CEK, AE, AR, NM, FS, FP, M-EC-F, SVF, MJ, and AB were investigators who conducted the study and collected data. KF, IR, and SF directly accessed and verified the underlying data. KF, JC, GR, RM, DB, FB, BT, GK, GG, AT-V, and SF contributed to data analysis or data interpretation. All authors contributed to data interpretation and writing, review, and approval of the manuscript for submission.

Declaration of interests

KF reports consulting fees from Amgen, AstraZeneca, Astellas, Bayer, CureVac, Janssen, Novartis, Orion, Pfizer, and Sanofi; honoraria from AstraZeneca, Astellas, Bayer, Janssen, Novartis, and Sanofi; and participation on a Data Safety Monitoring Board for Lilly. JC reports grants from AB Science, Aragon Pharmaceuticals, Arog Pharmaceuticals, Astellas Pharma, AstraZeneca, Aveo Pharmaceuticals, Bayer, Blueprint Medicines Corporation, BN Immunotherapeutics, Boehringer Ingelheim, Esperia, Bristol Myers Squibb, Clovis Oncology, Cougar Biotechnology, Deciphera Pharmaceuticals, Exelixis, F Hoffmann-La Roche, Genentech,

GlaxoSmithKline, Incyte Corporation, Janssen-Cilag, Karyopharm Therapeutics, Laboratoires Leurquin Mediolanum, Lilly, Medimmune, Millennium Pharmaceuticals, Nanobiotix, Novartis Farmacéutica, Pfizer, Puma Biotechnology, Sanofi-Aventis, SFJ Pharma, and Teva Pharma; consulting fees from Astellas Pharma, AstraZeneca, Bayer, Bristol Myers Squibb, Johnson & Johnson, MSD Oncology, Novartis, Pfizer, Roche, and Sanofi; honoraria from Bayer, Johnson & Johnson, and Astellas Pharma; payment for expert testimony from Astellas Pharma, AstraZeneca, Bayer, Bristol Myers Squibb, Johnson & Johnson, MSD Oncology, Novartis, Pfizer, Roche, and Sanofi; and participation on a Data Safety Monitoring Board or Advisory Board for Astellas Pharma, AstraZeneca, Bayer, Bristol Myers Squibb, Johnson & Johnson, MSD Oncology, Novartis, Pfizer, Roche, and Sanofi. GR reports honoraria from Astellas Pharma, AstraZeneca, Janssen, Ipsen, and Sanofi; and support for attending meetings from Janssen and Ipsen. RM reports grants from Bayer; honoraria from MSD; and participation on a Data Safety Monitoring Board or Advisory Board for Bristol Myers Squibb, Clovis, Janssen, MSD, and Pfizer. AF reports honoraria from Astellas Pharma, AstraZeneca, Janssen, Novartis, and Sanofi. BT reports grants from Ferring and Bayer; personal fees from Amgen, Astellas Pharma, Ferring, Bayer, Novartis, Myovant, and Sanofi; and non-financial support from Astellas and Janssen. SS reports grants from Astellas Pharma, AstraZeneca, and Janssen; and consulting fees, honoraria, and receipt of equipment from Astellas Pharma, AstraZeneca, Bayer, Ipesen, Janssen, and Takeda. DB reports honoraria from Amgen, Astellas Pharma, Bayer, Janssen, and Novartis. GK reports grants from Astellas Pharma and Janssen; and participation on an Advisory Board and honoraria from Astellas Pharma, AstraZeneca, Janssen, and Sanofi. FC reports honoraria from Bristol Myers Squibb and MSD; and participation on an Advisory Board for AstraZeneca, Bristol Myers Squibb, MSD, Pfizer, and Ipsen. AT-V reports grants from Bayer, Ipsen, and Pfizer; and consulting fees or honoraria from Astellas Pharma, AstraZeneca, Bristol Myers Squibb, Ipsen, JNJ, Novartis, MSD, and Roche. BL reports honararia from Janssen; and support for attending meetings from Astellas Pharma, Janssen, and Pfizer. AR reports honoraria from Astellas Pharma, Bayer, and Janssen; and support for attending meetings from Astellas Pharma, Ipsen, and Janssen. NM reports honoraria from Astellas Pharma, Bayer, Ipsen, and MSD. All other authors declare no competing interests.

Data sharing

The data collected and analysed for the purpose of the present manuscript are not immediately available due to ethical and legal restrictions. However, Unicancer will grant access to all deidentified individual data underlying the published results upon written and detailed request originating from all personnel involved in cancer research, sent to peace1@unicancer.fr.

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