JAMA Oncology | Original Investigation

Clinical Outcomes and Survival Following Treatment of Metastatic Castrate-Refractory Prostate Cancer With Docetaxel Alone or With Strontium-89, Zoledronic Acid, or Both
The TRAPEZE Randomized Clinical Trial

Nicholas D. James, PhD, FRCR, FRCP; Sarah J. Pirrie, MSc; Ann M. Pope, PhD; Darren Barton, BSc; Lazaros Andronis, PhD; Ilias Goranitis, PhD; Stuart Collins, PhD†; Adam Daunton, MBChB, MRCP; Duncan McLaren, MBBS, BSc, FRCR, FRCP(Ed); Joe O'Sullivan, MD, FRCPI, FFRRCSI, FRCR; Christopher Parker, MD, FRCR; Emilio Porfiri, MD, PhD; John Staffurth, MD, FRCR, FRCP; Andrew Stanley, MPhil; James Wylie, MBBS, MRCP, FRCR; Sharon Beesley, MBChB, MRCP, FRCR; Alison Birtle, MD, MRCP, FRCR; Janet Brown, MD; Prabir Chakraborti, MBBS, MS, FRCS, FRCR; Syed Hussain, MD, FRCS; Martin Russell, MBChB, MRCP(UK), FRCR, FRCPSG; Lucinda J. Billingham, BSc, MSc, PhD

IMPORTANCE Bony metastatic castrate-refractory prostate cancer (CRPC) has a poor prognosis and high morbidity. Zoledronic acid (ZA) is commonly combined with docetaxel in practice but lacks evidence that combining is effective, and strontium-89 (Sr89) is generally used palliatively in patients unfit for chemotherapy. Phase 2 analysis of the TRAPEZE trial confirmed combining the agents was safe and feasible, and the objectives of phase 3 include assessment of the treatments on survival.

OBJECTIVE To determine clinical effectiveness and cost-effectiveness of combining docetaxel, ZA, and Sr89, all having palliative benefits and used in bony metastatic CRPC to control bone symptoms and, for docetaxel, to prolong survival.

DESIGN, SETTING, AND PARTICIPANTS The TRAPEZE trial is a 2 × 2 factorial trial comparing docetaxel alone or with ZA, Sr89, or both. A cohort of 757 participants were recruited between February 2005 and February 2012 from hospitals in the United Kingdom. Overall, 169 participants (45%) had received palliative radiotherapy, and the median (IQR) prostate-specific antigen level was 146 (51-354). Follow-ups were performed for at least 12 months.

INTERVENTIONS Up to 10 cycles of docetaxel alone; docetaxel with ZA; docetaxel with a single Sr89 dose after 6 cycles; or docetaxel with both ZA and Sr89.

MAIN OUTCOMES AND MEASURES Primary outcomes included clinical progression-free survival (CPFS) (pain progression, skeletal-related events [SREs], or death) and cost-effectiveness. Secondary outcomes included SRE-free interval, pain progression–free interval, total SREs, and overall survival (OS).

RESULTS Overall, of 757 participants, 349 (46%) completed docetaxel treatment. Median (IQR) age was 68 (63-73) years. Clinical progression-free survival did not reach statistical significance for either Sr89 or ZA. Cox regression analysis adjusted for all stratification variables showed benefit of Sr89 on CPFS (hazard ratio [HR], 0.85; 95% CI, 0.73-0.99; $P = .03$) and confirmed no effect of ZA (HR, 0.98; 95% CI, 0.85-1.14; $P = .81$); ZA had a significant effect on SRE-free interval (HR, 0.78; 95% CI, 0.65-0.95; $P = .01$). For OS, there was no effect of either Sr89 (HR, 0.92; 95% CI, 0.79-1.08; $P = 0.34$) or ZA (HR, 0.99; 95% CI, 0.84-1.16; $P = 0.91$).

CONCLUSIONS AND RELEVANCE Strontium-89 combined with docetaxel improved CPFS but did not improve OS, SRE-free interval, or total SREs; ZA did not improve CPFS or OS but did significantly improve median SRE-free interval and reduced total SREs by around one-third, suggesting a role as postchemotherapy maintenance therapy.

TRIAL REGISTRATION isrctn.com Identifier: ISRCTN12808747

JAMA Oncol. 2016;2(4):493-499. doi:10.1001/jamaoncol.2015.5570
Published online January 21, 2016. Corrected on June 23, 2016.

Supplemental content at jamaoncology.com

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Nicholas D. James, PhD, FRCR, FRCP, University Hospital Birmingham NHS Foundation Trust, Edgbaston, Birmingham B15 2TH, United Kingdom (N.j.james.james@warwick.nhs.uk).

Prostate cancer is a major health problem worldwide and accounts for nearly one-fifth of all newly diagnosed male cancers. In the United Kingdom, approximately 35 000 men are diagnosed with prostate cancer each year, and in 2008 almost 10 000 men died from the disease.[1]

Hormone therapy has been the mainstay of treatment for relapsed prostate cancer since the seminal studies of Huggins and Hodges.[2] Responses to primary hormone therapy typically last 12 to 24 months depending on disease stage. This period after failure of initial androgen-deprivation therapy is now termed castrate-refractory prostate cancer (CRPC) with the recognition that relapsing tumors remain dependent on androgen receptor-mediated pathways reflected in the licensing of abiraterone[3] and enzalutamide.[4] Chemotherapy with docetaxel is also a mainstay of therapy for metastatic CRPC following 2 landmark trials published in 2004.[5,6] Second line chemotherapy with cabazitaxel was licensed in 2010.[7]

In patients with metastatic CRPC, bones are one of the most common sites of spread, a major cause of morbidity in men with CRPC. A number of treatments are approved for bone disease, including zoledronic acid (ZA),[8,9] denosumab,[10] strontium-89 (Sr89),[11,12] samarium-153 and, more recently, radium-223.[13] A predocetaxel era trial combined chemotherapy with Sr89 in a small randomized trial and suggested a survival advantage in patients allocated to Sr89.[14] Zoledronic acid and denosumab are approved on the basis of reductions in skeletal-related events (SREs), a composite end point. Skeletal-related events include any of the following: symptomatic pathological bone fracture; spinal cord or nerve root compression likely to be related to cancer or treatment; cancer-related surgery to bone; radiation therapy to bone (including use of radioisotopes); change of antineoplastic therapy to treat bone pain due to prostate cancer; or hypercalcemia. For this study we only collected clinically apparent SREs, and there was no attempt to identify subclinical SREs by repeat radiological examination. The trial recruited between February 2005 and February 2012, prior to the prechemotherapy licenses for abiraterone and enzalutamide. Hence, no patients received life-prolonging therapy for CRPC prior to docetaxel. Patients recruited in the later stages of the trial would have been able to receive these therapies postchemotherapy.

The TRAPEZE study sought to assess whether the addition of either Sr89, ZA, or both could offer a significant additional benefit in men receiving standard docetaxel and prednisolone in CRPC metastatic to bone. Prior therapy with bisphosphonates was permitted but should have stopped 2 months prior to study entry.

Key Points

Question What is the clinical effectiveness of docetaxel alone or with strontium-89, zoledronic acid, or both in patients with bony metastatic castrate-refractory prostate cancer?

Findings Strontium-89 combined with docetaxel improved clinical progression-free survival but did not improve overall survival, skeletal-related event–free interval, or total skeletal-related events. Zoledronic acid did not improve clinical progression-free survival or overall survival but did significantly improve median skeletal-related event–free interval and reduced total skeletal-related events by around one-third.

Meaning Strontium-89 showed modest benefits but probably has now been superseded, and zoledronic acid should be considered a component of therapy for men with progressive bony castrate-refractory prostate cancer.

Methods

Trial Design and Participants

TRAPEZE was a randomized, open-label, phase 3 trial using a 2 × 2 factorial design (eFigure 1 in Supplement 1). The trial was designed to evaluate whether additional bone targeting therapies improved clinical and health economic outcomes compared with chemotherapy alone. The trial included an initial randomized phase 2 element to assess feasibility, tolerability, and safety of the experimental arms. Phase 3 proceeded seamlessly from phase 2, and the objectives were to assess treatments within a 2 × 2 factorial design framework (ie, the trial compared ZA vs no ZA [stratified for Sr89 use] and Sr89 vs no Sr89 [stratified for ZA use]). Phase 3 had dual primary outcomes of the treatment effect on time to clinical progression-free survival (CPFS) and cost-effectiveness. Trial protocol can be found in Supplement 2. In this article, we report on treatment effect on time to CPFS; cost-effectiveness will be reported elsewhere.

We recruited patients older than 18 years with progressive metastatic CRPC, with 1 or more sclerotic bone metastases. Consenting participants had an ECOG (Eastern Cooperative Oncology Group score) of 0 to 2 and adequate hematological, renal, and hepatic function. Principal exclusions were prior chemotherapy or radionuclide therapy for CRPC, prior radiotherapy to more than 25% of bone marrow, bisphosphonate therapy within 2 months of trial entry, other malignant disease within the previous 5 years, known brain metastases, symptomatic peripheral neuropathy, and participation in any other clinical trial within 30 days of trial entry. The trial received ethical approval from the UK Multicenter Research Ethics Committee and regulatory approval from the UK Medicines and Healthcare Regulatory Agency in November 2004. In addition, each participating center obtained local institutional review board approval. Written consent was obtained from all study participants.

Interventions

Patients were randomized to 1 of 4 arms. Participants in Arm A received 3 intravenous doses of 75mg/m^2 docetaxel per week up to 10 cycles; Arm B, 3 intravenous doses of 4 mg docetaxel plus zoledronic acid (DZA) per week during chemotherapy then 4 doses per week until disease progression; Arm C, 6 cycles of docetaxel (75 mg/m^2 every 21 days) followed by a 150 MBq single dose of Sr89 (DSr89) then 4 further cycles of docetaxel; Arm D, docetaxel plus doses of both Sr89 and ZA (DSZ) previously described (eFigure 2 in Supplement 1). In phase 2, docetaxel in all arms was administered for 6 cycles with 4 further cycles at investigator discretion, but the protocol was later altered to bring all 10 cycles of chemotherapy within the primary treatment period. Patients were stratified by investigation center and ECOG performance status at trial entry in a 1:1:1:1 allocation ratio using

a computerized minimization algorithm accessed by telephone to the trials unit.

Outcome Assessment

The primary phase 3 analysis compared ZA vs no ZA (stratified for Sr89 use) and Sr89 vs no Sr89 (stratified for ZA use) in terms of CPFS defined as the number of whole days from the date of randomization to the first occurrence of a symptomatic SRE, pain progression, or death. Patients not experiencing clinical progression were censored at the date last known to be progression free. Secondary outcome measures were symptomatic SRE-free interval, pain progression–free interval, overall survival (OS), and numbers of SREs. A SRE-free interval was defined as the time in whole days from the date of randomization to the date of the first occurrence of a SRE. Patients who did not experience a SRE were censored at death or the date last known to be alive. There was no protocol-mandated radiological assessment; all SREs were clinically detected. A pain progression–free interval was defined as the time in whole days from the date of randomization to the date of clinician-determined pain progression. Overall survival was defined as the number of whole days from the date of randomization to the date of death from any cause. Additional data were collected on the number and type of SREs reported.

Statistical Analysis

Sample size calculations were based on the primary outcome measure of CPFS. The calculations were the same for both the comparison of ZA vs no ZA and Sr89 vs no Sr89. The trial aimed to detect a hazard ratio (HR) of 0.76, which would be the equivalent to 1 year CPFS rates of 30% vs 40%, assuming CPFS followed an exponential distribution. The number of events required to detect this difference in each group for either treatment comparison, using a 2-sided 5% significance level and 80% power, was 206. It was estimated that approximately 294 participants would be required in each group (ie, 588 patients in total) to observe this number of events at a 1 year follow-up. We aimed to recruit a minimum of 618 evaluable patients, which allowed for 5% dropout. Final recruitment was inflated by 20% to enable a per protocol analysis to be conducted including only those patients who remained fit to receive Sr89 following 6 cycles of docetaxel.

Factorial 2 × 2 designs assume no interaction between the 2 agents, and this assumption was investigated both graphically and by inclusion of interaction terms within a Cox model.

The first analysis of the primary outcome was an unadjusted stratified log-rank test on which the sample size was based comparing ZA vs no ZA stratified by Sr89 use and comparing Sr89 vs no Sr89 stratified by ZA use. The second analysis of the primary outcome used an adjusted Cox regression model, including both treatment comparisons and stratification factors (ie, ECOG and randomizing center). The use of stratification factors within the design leads to correlation between the treatment groups. These correlations, when not adjusted for, can lead to inflated standard error rates for treatment effects, confidence interval that are too wide, *P* values that are too high, and a subsequent reduction in power.[15] Owing to these potential implications, our primary outcome conclusions have been based on the adjusted Cox regression analysis. The use of both log-rank and Cox regression models was prespecified in the trial protocol. Graphs using the Kaplan-Meier method are presented.

Secondary outcome measures of OS, pain progression free-interval, and SRE-free interval were all analyzed using the stratified log-rank methodology with HRs and confidence intervals (CIs) taken from an associated Cox regression.

Results

Study Participants

A total of 1031 patients were assessed for study entry, and 757 consented to enter the trial between February 2005 and February 2012 and are included in the intention-to-treat analysis summarized in the CONSORT diagram (eFigure 3 in Supplement 1). Median (interquartile range [IQR]) age was 68 (63-73) years at study entry, and median (IQR) prostate-specific antigen level was 144 (51-354). Patients were evenly distributed across the arms with respect to ECOG performance status, prior radiotherapy, pain at study entry, analgesic scores, number of metastatic sites and location of metastases (**Table 1**).

Treatment

Of 757 participants, 349 (46%) completed docetaxel treatment. There were 3 main reasons participants did not complete docetaxel treatment: 118 participants (29%) had disease progression; 49 participants (12%) suffered intolerable toxic effects; and 122 participants (30%) developed another condition or occurrence that in the opinion of the treating clinician justified discontinuation of docetaxel. Of the participants randomized to receive Sr89, 253 (67%) of the patients randomized to receive Sr89 did so. The remainder did not complete therapy mainly owing to early cessation of chemotherapy. Additional details on therapy discontinuation can be seen in the CONSORT diagram (eFigure 3 in Supplement 1). Chemotherapy delivery rates were similar across all arms.

For those who received 10 cycles of docetaxel, the addition of Sr89 did not affect docetaxel doses given. In total, there were 267 docetaxel reductions affecting 6% of cycles given with no significant differences between arms. In all arms, the predominant reason for dose reduction were hematological toxic effects related to trial treatments. In total, 297 (7%) docetaxel treatment cycles were delayed with no significant differences between arms. Overall, 86 delays (29%) were owing to administrative reasons or patient choice. Of the remaining delays, 89 (30%) were owing to toxic effects, and there were 62 delays (21%) in the docetaxel alone arm, 95 (32%) in the DSr89 arm, and 107 36% in the 2 remaining arms.

Patients were able to receive additional life-prolonging treatments following clinical progression, although there was limited availability until 6 years into the trial (the final year of randomization). Of the participants who received additional life-prolonging treatments, 124 (17%) reported receiving abiraterone; 2 (0.3%), radium 223; 40 (4%), cabazitaxel; 62 (9%), rechallenged with docetaxel; 3 (0.5%), enzalutamide; and 1 (0.1%), samarium 153. In addition, 36 participants (5%) received Sr89 off-study and 136 (18%) received ZA off-study.

Table 1. Patient Baseline Characteristics

Characteristic	ZA		Sr89	
	No ZA	ZA	No Sr89	Sr89
Age, y, median (IQR)	68 (63-73)	69 (64-73)	68 (64-73)	68 (63-73)
PSA, median (IQR)	147 (51-347)	143 (51-374)	144 (54-354)	147 (48-349)
ECOG, No. (%)				
0	153 (40)	152 (40)	153 (40)	152 (40)
1	195 (51)	194 (51)	195 (52)	194 (51)
2	33 (9)	30 (9)	31 (8)	32 (9)
Prior radiotherapy, No. (%)	169 (45)	168 (45)	157 (42)	180 (48)
Daily Present Pain Index (scale 0-5), median (IQR)	1.4 (1-2)	1.5 (0.7-2)	1.6 (0.9-2)	1.4 (0.7-2)
Daily analgesic score, median (IQR)	10 (1-28)	10 (1-28)	11 (1-29)	9 (1-24)
Site of metastatic disease in addition to bone, No. (%)				
Liver	26 (7)	34 (9)	26 (7)	34 (9)
Lymph	167 (44)	159 (42)	145 (38)	181 (48)
Lung	41 (11)	38 (10)	38 (10)	41 (11)
Other soft tissue	9 (2)	17 (5)	13 (3)	13 (3)
Other	33 (7)	22 (6)	29 (8)	26 (7)
Metastatic sites, No. (%)				
1	204 (54)	216 (57)	218 (58)	202 (53)
2	111 (29)	92 (24)	97 (26)	106 (28)
3	37 (10)	34 (9)	36 (9)	35 (9)
4	6 (2)	13 (3)	7 (2)	12 (3)
5	2 (0.5)	2 (0.5)	2 (0.5)	2 (0.5)

Abbreviations: ECOG, Eastern Cooperative Oncology Group score; IQR, interquartile range; PSA, prostate-specific antigen; Sr89, strontium-89; ZA, zoledronic acid.

Toxic Effects

Overall, 493 known grade 3 or 4 adverse events[16] were reported relating to 237 patients and were equally distributed between the treatment arms. The top 5 (accounting for 42% of grade 3 to 4 adverse events) were pain, fatigue, hemoglobin changes, febrile neutropenia, and neutrophil changes. Eighteen instances of fatigue events were reported in the DSr89 arm vs 10 fatigue events in the DZS arm, 9 in the DZA arm, and 9 in the docetaxel arm. Fourteen instances of febrile neutropenia were reported in the docetaxel arm compared with 8 instances in the DZA arm, 8 in the DSr89 arm, and 6 in the DSZ arm. There were 5 Hemoglobin changes in the docetaxel arm vs 14 in the DSZ arm, 12 in the DZA arm, and 11 in the DSr89 arm, and there were only 9 instances of pain in the DZA arm vs 16 in the DSr89 arm, 13 in the docetaxel arm, and 11 in the DSZ arm. In total, 583 serious adverse events were reported, relating to 373 (49%) patients. Of these 286 (49%) were unrelated serious adverse events and 276 (47%) were serious adverse reactions. The remaining were 21 suspected unexpected serious adverse reactions, 4 in the docetaxel arm, 3 in the DZA arm, 6 in the DSr89 arm, and 8 in the DSZ arm.

Clinical Progression-Free Survival

At the time of analysis, surviving patients were followed up for a median of 22 months. In total, there were 696 clinical progression events reported. No evidence of interaction between Sr89 and ZA was found (P = .40), validating the factorial design. As shown in **Figure 1**A, the addition of ZA had no significant impact on CPFS. This is confirmed by both the unadjusted stratified log-rank test (P = .76) and the adjusted Cox regression analysis (HR, 0.98; 95% CI, 0.85-1.14; P = .81). Figure 1B shows the outcomes for Sr89, and the unadjusted stratified log-rank test did not reach statistical significance (P = .12). However, the adjusted Cox regression analysis showed evidence of a moderate effect (HR, 0.85; 95% CI, 0.73-0.99; P = .03).

OS and Pain Progression Free Interval

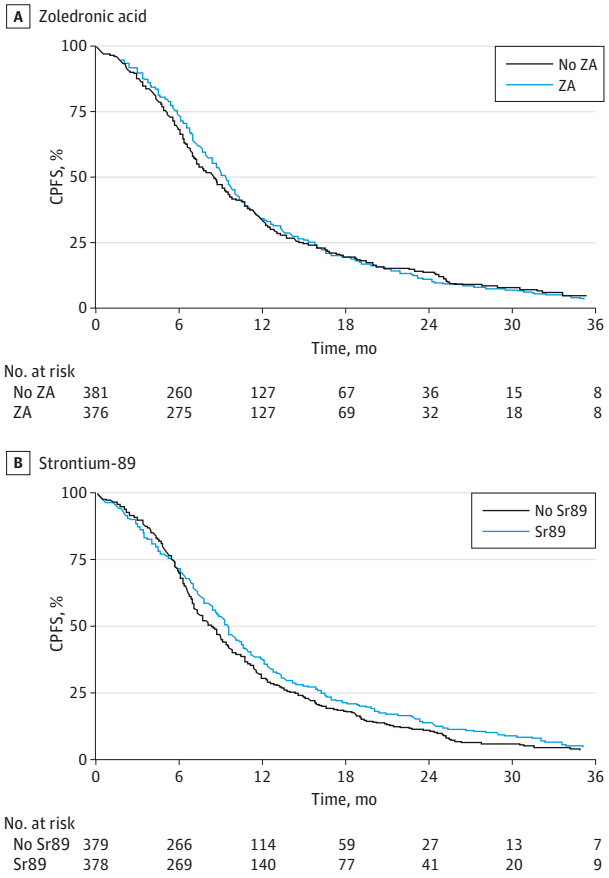
Stratified log-rank tests for secondary outcomes found no statistically significant differences in pain progression free interval (ZA: HR, 0.91; 95% CI, 0.75-1.10; P = .31 and Sr89: HR, 0.92; 95% CI, 0.76-1.11; P = .40) or OS. Median OS with and without either agent was not significantly different: 16.99 and 17.06 months for ZA (HR, 0.99; 95% CI, 0.84-1.16; P = .91) and 18.17 and 16.59 months for Sr89 (HR, 0.92; 95% CI, 0.79-1.08; P = .34).

SRE-Free Interval

In total, 437 patients experienced at least one SRE. **Figure 2**A shows the effect of ZA, which prolonged the median SRE-free interval from 11.2 to 13.6 months (HR, 0.78; 95% CI, 0.65-0.95; P = .01). Surprisingly, Sr89 did not significantly prolong the SRE-free interval (HR, 0.88; 95% CI, 0.73-1.06; P=.17), though the median SRE-free interval did increase from 11.7 to 13.0 months, suggesting a weak effect (Figure 2B). Prespecified subgroup analysis of 531 patients (70%) who were fit to receive Sr89 following completion of 6 cycles of docetaxel showed that 321 SREs occurred in total. Strontium-89 did not significantly prolong per protocol the SRE-free interval (HR, 0.85; 95% CI, 0.68-1.05; P = 0.13), though the median SRE-free interval increased from 12.75 to 14.16 month with the addition of Sr89.

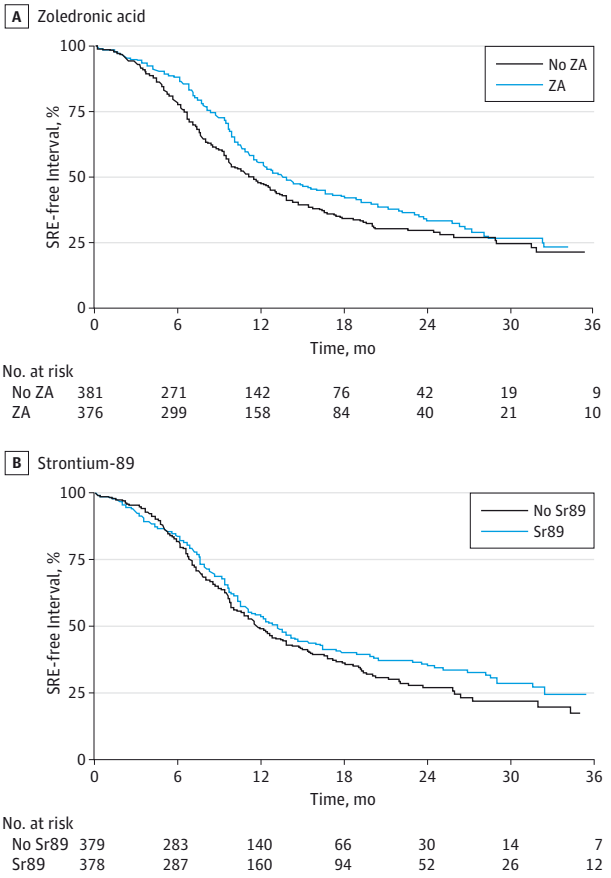
At the time of analysis, 557 participants (82%) were deceased, meaning their SRE data are complete. Surviving

Figure 1. Clinical Progression-Free Survival



A, The median CPFS in the ZA group was 9.43 months (95% CI, 8.51-9.89). B, The median CPFS in the Sr89 group was 9.56 months (95% CI, 8.74-10.25). CPFS indicates clinical progression-free survival; Sr89, strontium-89; ZA, zoledronic acid.

Figure 2. Skeletal-Related Event-Free Interval



A, The median SRE-free interval in the ZA group was 13.60 months (95% CI, 11.76-16.62). B, The median SRE-free interval in the Sr89 group was 13.04 months (95% CI, 11.14-14.69). Sr89 indicates strontium-89; SRE, skeletal-related event; ZA, zoledronic acid.

patients were equally distributed between arms. Total SREs at the time of analysis (**Table 2**) showed no effect owing to Sr89 (494 vs 535), but there was a decrease of 30% in overall SREs in participants allocated to ZA therapy (424 vs 605). In addition, the number of participants experiencing 2 or more SREs in ZA arms decreased from 154 (40%) to 103 (27%) and participants experiencing no SREs increased from 147 (39%) to 173 (46%) (eTable in Supplement 1). When the distribution of SREs was examined, the proportionate effect of ZA was greatest on those experiencing the most severe events, namely pathological fracture, surgery to bone, hypercalcemia, or spinal cord compression. There were 62 (54%) fewer instances of severe SREs in patients who received ZA, with an overall reduction of 94 instances (24%) in the use of radiotherapy for bone pain.

Discussion

There were 2 key strands to the evaluation of the trial: the clinical effectiveness of the 2 treatments and the health economic aspects that will be covered in a separate paper. As there was no interaction between the effects of the 2 therapies—Sr89 and ZA—the effects were considered separately. The recent Advanced Prostate Cancer Consensus Conference (APCCC)[17] in St Gallen strongly supported the use of chemotherapy in CRPC, but no consensus on timing was reached.[17] For bone targeting therapies, there was no consensus on whether to use these agents in some, all, or no patients with bone disease. There was also no consensus between use of ZA or denosumab. By focusing on symptomatic skeletal events, our article broadens our knowledge about the clinical value of ZA in the docetaxel era.

Strontium-89

The addition of Sr89 to chemotherapy had a favorable effect on the time to bony clinical disease progression but no effect on OS was observed. Given the previous data on Sr89,[11] there was no effect on SREs in terms of time to first SRE, total number of SREs, or distribution. Despite the positive primary outcome, it is less clear whether our findings will alter the use of Sr89 significantly for a number of reasons. First, the gain in CPFS (about a month) is likely to be seen as modest. Additionally, there was no effect on the frequency that subsequent SREs were observed. At the time of study inception, this, coupled with a modest quality-of-life gain, may have been adequate to change clinical practice.

Table 2. Skeletal-Related Events by Category

	Comparison, No.			
	ZA		Sr89	
SRE Type	No ZA	ZA	No Sr89	Sr89
Symptomatic pathological fracture	30	12	17	25
Spinal cord or nerve root compression	61	34	44	51
Cancer related surgery to bone	21	6	11	16
Hypercalcemia	2	0	0	2
Total most severe	114	52	72	94
Radiation	392	298	379	311
Change in antineoplastic therapy to treat bone pain	99	74	84	89
Total least severe	491	372	463	400
Overall total No. SREs	605	424	535	494

Abbreviations: SREs, skeletal-related events; Sr89, strontium-89; ZA, zoledronic acid.

However, we have seen a number of new treatments licensed in the last few years that improve overall survival postchemotherapy, as well as improve quality of life and SREs. These include abiraterone,[3] enzalutamide,[4] cabazitaxel[7] and, of particular relevance to this study, radium-223.[13] Radium-223, being a calcium mimetic agent, is a radioisotope with a similar uptake mechanism to Sr89. However, α emissions of radium-223 deliver a more intense and localized radiation dose than the β emissions of Sr89. The key ALSYMPCA trial of radium-223[13] showed improvements in both OS and symptomatic SREs.

Zoledronic Acid

The addition of ZA to docetaxel did not affect OS or CPFS postchemotherapy. There was, however, a substantial effect on symptomatic SREs. Defining SREs is controversial because they are a composite end point. In both the ZA and denosumab licensing trials,[18] a key component (pathological fracture) was assessed by blinded examination of serial radiographs rather than with reference to clinical symptoms. The consequence was that many SREs in the relevant trials were of uncertain clinical significance. This issue was recently reviewed by Smith et al.[18] In contrast, in our TRAPEZE study and in some other recent trials[13] in CRPC, only symptomatic SREs have been collected and makes the clinical and potentially economic consequences are much clearer. The US Food and Drug Administration (FDA) now refers to symptomatic SREs as *symptomatic skeletal events* which is a helpful and relevant distinction. We shall use this term for the remainder of the discussion. In the trial, ZA produced an increase in time to first symptomatic skeletal event (Figure 2A), a substantial decrease in symptomatic skeletal events, as well as a decrease in symptomatic skeletal events per patient (Table 2). Furthermore, when the distribution of symptomatic skeletal events by type is considered, the biggest effect of ZA was on the symptomatic skeletal events that may be considered the most severe (ie, fracture, spinal cord compression, and surgery to bone) with a 50% reduction, as compared with radiotherapy, which reduced symptomatic skeletal events by about one-third.

The prevention of serious events such as fracture, surgery, and spinal cord compression (all associated with frequent and prolonged admissions) is a high priority for clinical services with great pressures on inpatient beds. Hence, a predictable outpatient therapy may be attractive to health care providers if it prevents emergency, unpredictable resource-intense visits. We did not carry out a patient preference study; however, we believe it likely that patients would prefer a preventative treatment such as ZA to a reactive approach.

The main limitations to the data presented have been discussed herein. In particular, the development of new treatments for CRPC makes Sr89 less relevant with the advent of better radioisotope therapy in radium-223.[13] The limitations on the ZA data are more complex because the effects on symptomatic skeletal events are substantial. It is likely that these benefits are complementary to those achieved with other postdocetaxel therapies, such as abiraterone or enzalutamide. In particular, there are data that the benefit of radium-223 on symptomatic skeletal events may be increased by ZA. Improved bone protecting agents that prevent hospital visits may also alter the potential benefits of these other agents. Although denosumab was superior to ZA in CRPC using SREs or symptomatic skeletal events as an end point, there was no consensus on the use of one agent or the other in the St Gallen 2015 APCCC meeting.[17]

Although commonly prescribed in the United States, Canada, and several other countries, the use of ZA and also denosumab remains controversial in the United Kingdom and elsewhere owing to doubts about the clinical relevance of the radiological SREs in the licensing trials, particularly the question of whether additional bone protection is relevant in patients receiving life-prolonging CRPC therapy, such as chemotherapy or new generation hormone therapies. The results of our trial support the use of ZA in the context of at least 1 life-prolonging CRPC therapy (ie, docetaxel).

Conclusions

Strontium-89 showed modest benefits but probably has now been superseded with the recent license for radium-223. Zoledronic acid significantly reduced serious skeletal complications defined clinically rather than radiologically and should be considered as a component of therapy for men with progressive bony CRPC.

ARTICLE INFORMATION

†Deceased.

Accepted for Publication: November 6, 2015.

Correction: This article was corrected on June 23, 2016, to add the Open Access note.

Published Online: January 21, 2016. doi:10.1001/jamaoncol.2015.5570.

Author Affiliations: University Hospital Birmingham NHS Foundation Trust, Birmingham, England (James, Daunton, Porfiri); Cancer Research UK Clinical Trials Unit, University of Birmingham, Birmingham, England (Pirrie, Pope, Barton, Billingham); Health Economics Unit, University of Birmingham, England (Andronis, Goranitis); Cancer Research UK Clinical Trials Unit, Birmingham, England (Collins); Department of Clinical Oncology, Western General Hospital, Edinburgh, Scotland (McLaren); Northern Ireland Cancer Centre, Belfast City Hospital, Belfast, Northern Ireland (O'Sullivan); The Institute of Cancer Research & Royal Marsden NHS Foundation Trust, Sutton, England (Parker); Institute of Cancer and Genetics, Cardiff University, Cardiff, Wales (Staffurth); Department of Oncology Pharmacy, Birmingham City Hospital, Birmingham, England (Stanley); Department of Clinical Oncology, The Christie Hospital, Manchester, England (Wylie); Department of Clinical Oncology, Kent Oncology Centre, Maidstone, England (Beesley); Rosemere Cancer Centre, Royal Preston Hospital, Lancashire, England (Birtle); Cancer Research UK Clinical Centre at Leeds, University of Leeds, St James' University Hospital, Leeds, England (Brown); Department of Oncology, Royal Derby Hospital, Derby, England (Chakraborti); Institute of Translational Medicine, Department of Molecular and Clinical Cancer Medicine, University of Liverpool, Liverpool, England (Hussain); Beatson West of Scotland Cancer Centre, Glasgow, Scotland (Russell).

Author Contributions: Dr James was the chief investigator and had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: James, Barton, Collins, Parker, Stanley, Wylie, Billingham.
Acquisition, analysis, or interpretation of data: James, Pirrie, Pope, Andronis, Goranitis, Collins, Daunton, McLaren, O'Sullivan, Parker, Porfiri, Staffurth, Stanley, Beesley, Birtle, Brown, Chakraborti, Hussain, Russell, Billingham.
Drafting of the manuscript: James, Pirrie, Pope, Andronis, Daunton, McLaren, Brown.
Critical revision of the manuscript for important intellectual content: James, Pirrie, Barton, Andronis, Goranitis, Collins, Daunton, O'Sullivan, Parker, Porfiri, Staffurth, Stanley, Wylie, Beesley, Birtle, Brown, Chakraborti, Hussain, Russell, Billingham.
Statistical analysis: Pirrie, Andronis, Goranitis, Collins, Daunton, Brown.
Obtained funding: James, Barton, Billingham.
Administrative, technical, or material support: Pope, Barton, Porfiri, Stanley, Hussain.
Study supervision: James, Barton, Porfiri, Staffurth, Wylie, Birtle, Billingham.
Pharmaceutical Advice and Negotiations: Stanley.

Conflict of Interest Disclosures: Dr James has worked as a consultant and received lecture fees from Sanofi-Aventis Parma, Novartis, Bayer, Amgen, Janssen, Astellas, and Affinity. Dr Pope received grants payable to investigation sites from Sanofi-Aventis on the recruitment of patients, provisions of zoledronic acid (Zometa, Novartis Oncology) during the phase 2 trial and later a trial-specific discount for sites; the purchase of the trial drug from Novartis; and a trial-specific discount for sites from GE Healthcare for the purchase of the trial drug. Dr Parker has received personal fees from Bayer, BN ImmunoTherapeutics (Inc), Astellas, Janssen, Sanofi-Aventis, and Takeda. Dr Stanley received financial support from TEVA for his attendance at European Society for Medical Oncology; received personal fees from Calgene; and Amgen supported part of his attendance at the annual British Oncology Pharmacy Association Symposium. Dr Brown has received personal fees and nonfinancial support from Novartis. Dr Billingham has received personal fees from Eli Lilly and Pfizer. No other conflicts are reported.

Funding/Support: Sanofi Aventis and Novartis Pharmaceuticals supported the trial with educational grants and support for drug costs or trial discount for sites, respectively, and GE Healthcare also offered a trial discount to sites purchasing strontium-89. The TRAPEZE trial was an independent research project commissioned and funded by the UK National Institute for Health Research Health Technology Assessment Programme (NIHR HTA No. 06/303/205). The NIHR HTA will publish the full trial results in the Health Technology Assessment journal later in 2015; the NIHR HTA encourages publication of trial results journals but was not involved in the decision to do so here.

Role of the Funder/Sponsor: The funders/sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, MRC, CCF, NETSCC, the HTC, or the Department of Health.

Additional Contributions: We would like to thank the clinicians, research teams, and patients who participated in the trial. We would also like to thank the trial management team for the collecting and entry of trial data prior to analysis, and to Jenny Barnwell, PhD, the trial management team leader (CRCTU, University of Birmingham), for her advice during the trial and for review of this manuscript. Dr Barnwell was not compensated for her contributions.

REFERENCES

1. Cancer Research UK. Prostate Cancer Statistics. http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer. Accessed December 14, 2015.

2. Huggins C, Hodges CV. Studies on prostatic cancer. I. The effect of castration, of estrogen and androgen injection on serum phosphatases in metastatic carcinoma of the prostate. *CA Cancer J Clin*. 1972;22(4):232-240.

3. Mendenhall WM, Parsons JT, Stringer SP, Cassisi NJ, Million RR. Squamous Cell Carcinoma of the Head and Neck Treated With Irradiation: Management of the Neck. *Semin Radiat Oncol*. 1992;2(3):163-170.

4. Scher HI, Fizazi K, Saad F, et al; AFFIRM Investigators. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med*. 2012;367(13):1187-1197. Published online August 17, 2012.

5. Tannock IF, de Wit R, Berry WR, et al; TAX 327 Investigators. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med*. 2004;351(15):1502-1512.

6. Petrylak DP, Tangen CM, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med*. 2004;351(15):1513-1520.

7. de Bono JS, Oudard S, Ozguroglu M, et al; TROPIC Investigators. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet*. 2010;376(9747):1147-1154.

8. Saad F, Gleason DM, Murray R, et al; Zoledronic Acid Prostate Cancer Study Group. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *J Natl Cancer Inst*. 2002;94(19):1458-1468.

9. Saad F, Gleason DM, Murray R, et al; Zoledronic Acid Prostate Cancer Study Group. Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. *J Natl Cancer Inst*. 2004;96(11):879-882.

10. Fizazi K, Carducci M, Smith M, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. *Lancet*. 2011;377(9768):813-822.

11. Bolger JJ, Dearnaley DP, Kirk D, et al; UK Metastron Investigators Group. Strontium-89 (Metastron) versus external beam radiotherapy in patients with painful bone metastases secondary to prostatic cancer: preliminary report of a multicenter trial. *Semin Oncol*. 1993;20(3)(suppl 2):32-33.

12. Quilty PM, Kirk D, Bolger JJ, et al. A comparison of the palliative effects of strontium-89 and external beam radiotherapy in metastatic prostate cancer. *Radiother Oncol*. 1994;31(1):33-40.

13. Parker C, Nilsson S, Heinrich D, et al; ALSYMPCA Investigators. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med*. 2013;369(3):213-223.

14. Tu SM, Millikan RE, Mengistu B, et al. Bone-targeted therapy for advanced androgen-independent carcinoma of the prostate: a randomised phase II trial. *Lancet*. 2001;357(9253):336-341.

15. Kahan BC, Morris TP. Improper analysis of trials randomised using stratified blocks or minimisation. *Stat Med*. 2012;31(4):328-340.

16. Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events, Version 3.0, DCTD, NCI, NIH, SHHS, 31 March 2003. http://ctep.cancer.gov. Published June 10, 2003. Accessed December 14, 2015.

17. Gillessen S, Omlin A, Attard G, et al. Management of patients with advanced prostate cancer: recommendations of the St Gallen Advanced Prostate Cancer Consensus Conference (APCCC) 2015. *Ann Oncol*. 2015;26(8):1589-1604.

18. Smith MR, Coleman RE, Klotz L, et al. Denosumab for the prevention of skeletal complications in metastatic castration-resistant prostate cancer: comparison of skeletal-related events and symptomatic skeletal events. *Ann Oncol*. 2015;26(2):368-374.