

Cost-effectiveness of zoledronic acid and strontium-89 as bone protecting treatments in addition to chemotherapy in patients with metastatic castrate-refractory prostate cancer: results from the TRAPEZE trial (ISRCTN 12808747)

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Objective

To evaluate the cost-effectiveness of adding zoledronic acid or strontium-89 to standard docetaxel chemotherapy for patients with castrate-refractory prostate cancer (CRPC).

Patients and methods

Data on resource use and quality of life for 707 patients collected prospectively in the TRAPEZE 2 × 2 factorial randomised trial (ISRCTN 12808747) were used to assess the cost-effectiveness of i) zoledronic acid versus no zoledronic acid (ZA vs. no ZA), and ii) strontium-89 versus no strontium-89 (Sr89 vs. no Sr89). Costs were estimated from the perspective of the National Health Service in the UK and included expenditures for trial treatments, concomitant medications, and use of related hospital and primary care services. Quality-adjusted life-years (QALYs) were calculated according to patients' responses to the generic EuroQol EQ-5D-3L instrument, which evaluates health status. Results are expressed as incremental cost-effectiveness ratios (ICERs) and cost-effectiveness acceptability curves.

Results

The per-patient cost for ZA was £12 667, £251 higher than the equivalent cost in the no ZA group. Patients in the ZA group had on average 0.03 QALYs more than their counterparts in no ZA group. The ICER for this comparison was £8 005. Sr89 was associated with a cost of £13 230, £1365 higher than no Sr89, and a gain of 0.08 QALYs compared to no Sr89. The ICER for Sr89 was £16 884. The probabilities of ZA and Sr89 being cost-effective were 0.64 and 0.60, respectively.

Conclusions

The addition of bone-targeting treatments to standard chemotherapy led to a small improvement in QALYs for a modest increase in cost (or cost-savings). ZA and Sr89 resulted in ICERs below conventional willingness-to-pay per QALY thresholds, suggesting that their addition to chemotherapy may represent a cost-effective use of resources.

Keywords

castrate-refractory prostate cancer, cost-effectiveness analysis, quality of life, bone protecting treatments, zoledronic acid, Sr89

Introduction

Prostate cancer is one of the commonest types of cancer and a major health problem around the world. In 2012, >1.1

million men were diagnosed with prostate cancer making this the second most common male cancer worldwide, accounting for ~15% of all newly diagnosed male cancers [1]. In the UK, prostate cancer is the commonest form of cancer, with

~42 000 men being diagnosed with the disease and almost 11 000 men dying from it annually [2].

Prostate cancer typically presents as local disease, but a significant proportion of patients progress despite initial treatment. Hormone therapy has been the main treatment for relapsed prostate cancer [3], leading to responses typically lasting for 12–24 months. The period after failure of initial androgen-deprivation therapy is now termed castrate-resistant prostate cancer (CRPC) [4]. Following two landmark trials, chemotherapy with docetaxel and prednisolone (DP) is considered the bedrock of therapy for metastatic CRPC [5,6].

In patients with metastatic disease, the commonest site of spread is bone. Two treatments approved for bone disease are zoledronic acid (ZA) [7,8] and strontium-89 (Sr89) [9,10]. A pre-docetaxel era trial combined chemotherapy with Sr89 in a small randomised trial and suggested a survival advantage in patients allocated to Sr89 [11]. ZA is approved on the basis of reductions in skeletal-related events (SRE), a composite endpoint including symptomatic fractures, surgeries, and radiotherapy to bone.

There is considerable uncertainty as to whether the cost of adding bone-protecting treatments, such as ZA or Sr89, to standard chemotherapy would be warranted by improved quality of life (QoL) and reduced use of healthcare resources, possibly due to fewer SREs. This question is particularly pertinent as ZA is now available as a generic product, at a considerably lower price than its branded counterpart.

Given this, we sought to assess the cost effectiveness of adding bone-protecting treatments to docetaxel chemotherapy for patients with CRPC, using prospectively collected data from the TRAPEZE 2 × 2 factorial randomised controlled trial (ISRCTN 12808747). Two relevant comparisons were explored in the trial: i) ZA in addition to standard chemotherapy vs no ZA and ii) Sr89 in addition to standard chemotherapy vs no Sr89.

Patients and methods

The TRAPEZE trial design is described in detail elsewhere [12, 13]. Briefly, this was a randomised open label phase III study using a 2 × 2 factorial design aiming to compare ZA vs no ZA (stratified for Sr89) and Sr89 vs no Sr89 (stratified for ZA). The trial recruited 757 patients with progressive metastatic CRPC according to the following eligibility criteria: age ≥ 18 years, Eastern Cooperative Oncology Group (ECOG) score ≤ 2, and adequate haematological, renal, and hepatic function. Participants were randomised to one of four arms: i) DP arm: docetaxel 75 mg/m² 3-weekly and oral prednisolone 10 mg daily for up to 10 cycles; ii) DP+ZA arm: DP plus ZA 4 mg 3-weekly during chemotherapy then 4-weekly until disease progression; iii) DP+Sr89 arm: DP for six cycles, Sr89 150 MBq then further DP up to total of 10

cycles; iv) DP+ZA+Sr89 arm: DP plus both Sr89 and ZA as above. Ethical approval was received from the Multicentre Research Ethics Committee and regulatory approval was granted by the UK Medicines and Healthcare Regulatory Agency.

The primary outcome of the clinical analysis was clinical progression-free survival, defined as the number of days from randomisation to the first occurrence of a symptomatic SRE, pain progression, or death. The main outcome of the cost-effectiveness analysis is cost per quality-adjusted life-year (QALY). Responses to EuroQol EQ-5D-3L (a generic instrument for describing and evaluating health status; each dimension uses three levels of severity corresponding to no problems, some problems, and extreme problems), needed for calculating QALYs and, thereby, cost-effectiveness in this trial were available for 707 (93%) of the 757 patients. This was a representative subgroup of the trial patients (Table S1). Patient characteristics are given in Table 1.

Resource use and cost

Data on healthcare resource use were collected prospectively through case report forms (CRFs) and patient-completed questionnaires. Relevant resource use fell under three main categories: i) trial treatments; ii) concomitant treatments, and iii) use of other related hospital and primary care services. The cost of trial treatments was calculated according to patient-specific doses and number of treatment cycles provided, taking into account the cost of drug administration. The cost of care or medications provided concomitantly with trial treatment (radiotherapy, abiraterone, cabazitaxel, mitoxantrone, blood transfusions, additional docetaxel, Sr89, ZA, and surgical procedures) was obtained by weighting their respective use recorded in CRFs by unit costs available from national sources (Table 1) [14–17]. Outpatient appointments, inpatient stay, and GP visits were drawn from CRFs, while post-treatment hospital stay and visits were obtained from patient-completed questionnaires. Questionnaire data were missing for 126 patients and were imputed using multiple imputation by chained equations [18].

QoL and QALYs

QALY scores were derived by translating responses to the EQ-5D-3L health status instrument [19] into preference-based (utility) scores using a standard value set [20]. The EQ-5D-3L was collected 3-weekly during treatment, then monthly for 3 months, and 3-monthly until death. QALYs were calculated as the area under the curve connecting utility scores available at different time points. For patients who were known to have died, a utility of zero was assigned on the date of death [21]. For patients still alive at the time of analysis, their last known EQ-5D-3L score was carried forward to the date last seen.

Table 1 Unit cost prices and sources.

Item	Cost, £	Source
Docetaxel	155 for 1 mL vial (20 mg)	British National Formulary [14]
Prednisolone	0.64/day	British National Formulary [14]
ZA	58 for 4mg	NHS Commercial Medicines Unit [17]
Sr89	1710 per fraction of 150 mBq	Nuclear Medicine Department, University Hospital Birmingham.
Abiraterone	98/day	British National Formulary [14]
Cabazitaxel	3696/cycle	British National Formulary [14]
Mitoxantrone	100/cycle	British National Formulary [14]
Radiotherapy	813 cost of radiotherapy preparation plus 118 cost of radiotherapy fraction	NHS Reference Costs [16]
Blood	123/unit plus i.v. cannula (£1) and blood giving set (£4)	NHS Blood and Transplant
Administration of DP, ZA (standalone), mitoxantrone	245	NHS Reference Cost [16]
Administration cabazitaxel	144	NHS Reference Cost [16]
Administration of Sr89	443	Nuclear Medicine Department, University Hospital Birmingham
Blood transfusion	172	NHS Reference Cost [16]
Decompression for spinal cord compression	9573	NHS Reference Cost [16]
Laminectomy	6893	NHS Reference Cost [16]
Intramedullary nailing	4995	NHS Reference Cost [16]
Hip replacement	8038	NHS Reference Cost [16]
Fracture	3888	NHS Reference Cost [16]
Spinal cord compression	7816	NHS Reference Cost [16]
Inpatient stay	680	NHS Reference Cost [16]
Outpatient appointment	135	Personal Social Services Research Unit [15]
GP consultation	63	Personal Social Services Research Unit [15]

Cost-effectiveness analysis

Analyses were conducted from the perspective of the NHS in the UK. Consistent with recommendations, costs and benefits accruing beyond 12 months were discounted at a rate of 3.5% per year [22]. A total cost and a total number of QALYs were calculated for each patient, with 95% CIs around mean values obtained through 1000 bias-corrected and accelerated (BCa) bootstrap replications [23,24]. Given the short expected survival time of patients with metastatic CRPC and the long-term follow-up of patients in the trial, lifetime costs and effects were largely observed and so extrapolation beyond the trial was unnecessary. In the comparison between ZA and no ZA, the main analysis was based on the fact that, as of 2013, ZA has been available as a generic product, at a price significantly lower than its branded counterparts. Additional analyses were conducted on the basis of the proprietary product.

Differences in mean total costs and QALYs between the compared options were presented as incremental cost-effectiveness ratios (ICERs), a measure reflecting the additional cost associated with a gain of an additional QALY [25]. To account for uncertainty in the results, nonparametric bootstrapping was used to replicate the joint distribution of the differences in cost and QALYs [26]. This generated 5000 paired estimates of incremental costs and QALYs, which were

subsequently used to derive cost-effectiveness acceptability curves [27]. Cost-effectiveness acceptability curves show the probability of each option being cost-effective across a range of possible values of willingness to pay (ceiling ratio) for an additional QALY [28]. The impact of alternative assumptions and uncertain values on the results were explored in additional sensitivity analyses.

Results

Comparison of ZA vs no ZA

Cost by resource use category, total costs and total QALYs for the comparison between ZA and no ZA are given in (Table 2). The most substantial difference in costs was due to the use of ZA itself provided as protocol and follow-up treatment in the ZA group. With the exception of ZA, patients in the ZA group presented lower use of additional care and medications. Notably, there were differences in the use of radiotherapy and surgery, reflective of the fact that patients in the ZA group had fewer SREs. The difference in total costs between ZA and no ZA was £251 (BCa 95% CI: -£1099 to £1602); this difference was contingent on the acquisition cost of ZA. In relation to health benefits, patients in the ZA group had an average of 0.91 QALYs, reflecting a gain of 0.03 QALYs (BCa 95% CI: -0.07 to 0.13) over their counterparts in the no ZA group.

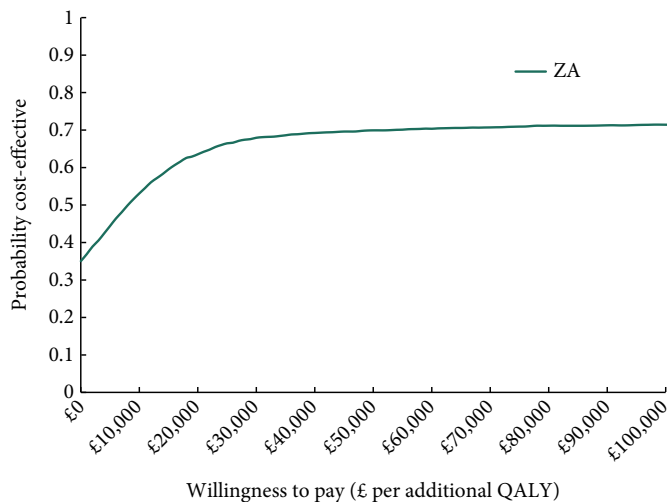
Table 2 Mean per-patient cost and QALYs for ZA vs no ZA.

	ZA (n = 350)	No ZA (n = 357)	Difference (ZA vs no ZA)		
	Mean (SD)	Mean (SD)	Mean difference	Lower 95% CI*	Upper 95% CI*
Trial treatment, £					
DP	2502 (760)	2441 (749)	60	-49	169
ZA	346 (151)	0	346	330	361
Sr89	769 (1033)	724 (1018)	45	-107	197
ZA as follow-up treatment	837 (1358)	3 (48)	834	692	977
Concomitant medications and treatments, £					
Radiotherapy	764 (1093)	1021 (1264)	-257	-429	-85
Abiraterone	1811 (4198)	2150 (4478)	-339	-993	316
ZA as concomitant medication	235 (801)	101 (492)	134	36	230
Sr89 as concomitant medication	98 (476)	132 (539)	-34	-109	41
Blood units	23 (150)	19 (125)	4	-16	24
Cabazitaxel	301 (1710)	293 (2230)	8	-288	304
Docetaxel as concomitant medication	372 (1543)	433 (2049)	-61	-338	216
Mitoxantrone	51 (245)	26 (179)	25	-6	56
Surgery	116 (988)	377 (1974)	-261	-495	-27
Outpatient appointments and inpatient stay, £					
Hospital outpatient appointment	672 (1015)	591 (804)	81	-51	213
Hospital inpatient stay	3494 (6216)	3786 (6562)	-292	-1217	632
GP appointments	278 (319)	319 (384)	-42	-95	12
Total Cost, £	12667 (8795)	12417 (9433)	251	-1099	1602
Total QALYs	0.908 (0.683)	0.876 (0.693)	0.031	-0.07	0.133

*Obtained using the bias corrected and accelerated bootstrap method (1000 replications).

Combining differences in costs and QALYs resulted in an ICER of £8005 per QALY. At the commonly cited lower willingness-to-pay ratio of £20 000 per QALY in the UK [22, 29–33], the probability of ZA being cost-effective is 0.64 (Fig. 1). For prices of ZA between £0 and £31, the total per-patient cost of ZA is lower than that of no ZA and, given the fact that ZA is associated with a slight increase in QALYs, this treatment option dominates its comparator. For prices between £31 and £98, ZA results in ICERs up to £20 000 per QALY, and it is thus cost-effective at this willingness-to-pay value.

Fig. 1 Cost-effectiveness acceptability curve showing the probability of ZA being cost-effective at different values of willingness to pay per additional QALY.



Most of the alternative assumptions explored in additional sensitivity analyses (e.g. different prices of concomitant medications, no discounting etc.) had a small, proportional effect on the additional cost and benefits of each treatment option, and, thus, they had a minimal impact on the resulting ICER (Table S2). The only exception was the adjustment of QALYs for baseline imbalances in EQ-5D-3L scores, which resulted in a very small, non-significant difference in QALYs in favour of no ZA (0.0006 QALYs, 95% CI: -0.096 to 0.094). For ZA prices up to £28, ZA is less costly and less effective, but overall more cost-effective than no ZA (at £20 000 per QALY foregone), and it is more costly and less effective (i.e. dominated) above this price (Fig. S1).

Comparison of Sr89 vs no Sr89

The most prominent difference in mean costs between the Sr89 and no Sr89 groups was due to the use of Sr89 itself. Apart from the higher cost for Sr89, the Sr89 group was associated with greater cost for docetaxel and ZA given as protocol treatments, higher cost for cabazitaxel and docetaxel provided as concomitant medications, and increased cost due to surgeries. On the other hand, the Sr89 group was associated with fewer radiotherapies, lower use of abiraterone, ZA, and Sr89 as concomitant medications, and fewer inpatient days, outpatient appointments, and GP visits (Table 3). The analysis showed mean total costs per person of £13 230 and £11 865 for Sr89 and no Sr89 respectively, resulting in a mean difference of £1365 (BCa 95% CI: -£12 to £2742). For the comparison between Sr89 vs no Sr89, patients who received Sr89 showed a gain of 0.08 QALYs (BCa 95% CI: -0.019 to 0.181) over those in the no Sr89 group.

Table 3 Mean per-patient cost and QALYs for Sr89 vs no Sr89.

	Sr89 (n = 350)	No Sr89 (n = 357)	Difference (Sr89 vs no Sr89)		
	Mean (SD)	Mean (SD)	Mean difference	Lower 95% CI*	Upper 95% CI*
Trial treatment, £					
DP	2497 (738)	2445 (771)	52	-61	165
ZA	174 (203)	168 (203)	6	-23	35
Sr89	1507 (988)	0	1507	1407	1608
ZA as follow-up treatment	391 (965)	440 (1114)	-49	-197	100
Concomitant medications and treatments, £					
Radiotherapy	803 (1033)	983 (1318)	-180	-349	-11
Abiraterone	1905 (4279)	2058 (4408)	-153	-814	508
ZA as concomitant medication	148 (625)	187 (704)	-39	-139	61
Sr89 as concomitant medication	110 (527)	120 (492)	-9	-85	66
Blood units	21 (150)	21 (124)	0	-20	21
Cabazitaxel	375 (2192)	221 (1765)	154	-134	443
Docetaxel as concomitant medication	415 (2057)	390 (1545)	25	-233	283
Mitoxantrone	39 (218)	39 (211)	0	-32	31
Surgery	325 (1954)	172 (1064)	153	-84	390
Outpatient appointments and inpatient stay, £					
Hospital outpatient appointment	609 (889)	653 (940)	-44	-178	89
Hospital inpatient stay	3630 (6294)	3653 (6491)	-23	-950	903
GP appointments	281 (350)	316 (357)	-35	-86	16
Total Cost, £	13230 (9105)	11865 (9091)	1365	-12	2742
Total QALYs	0.933 (0.725)	0.852 (0.648)	0.081	-0.019	0.181

*Obtained using the bias corrected and accelerated bootstrap method (1000 replications).

Overall, Sr89 was associated with a higher total per-patient cost and a greater mean number of QALYs compared to no Sr89. Given these differences, the point estimate ICER for Sr89 was calculated at £16 884 per additional QALY. At a willingness-to-pay value of £20 000 for an additional QALY, the probability that Sr89 is cost-effective is 0.6 (Fig. 2). The ICER for Sr89 remains below £20 000 per QALY for prices of Sr89 up to £2120.

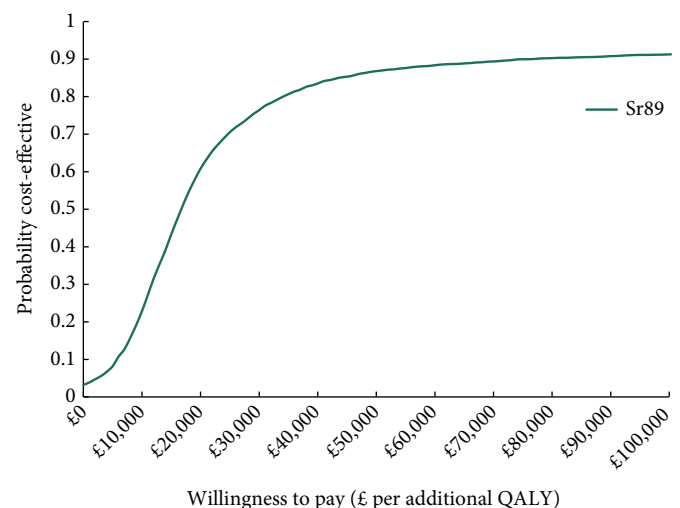
Most of the alternative scenarios explored in sensitivity analyses had a limited impact on the magnitude of the results and did not change the baseline conclusion for this comparison (Table S2). An exception was the analysis using different prices for Sr89: a lower price of Sr89 gives an ICER of £13 182 per QALY, whereas a higher price resulted in an ICER of £20 585 per QALY.

Discussion

The present study uses patient-level data collected in the TRAPEZE trial to determine whether the addition of ZA or Sr89 bone-protecting therapies to standard chemotherapy represents a cost-effective use of healthcare resources.

The comparison between ZA and no ZA showed ZA to be associated with a small additional cost for a slight improvement in QALYs. This additional cost was relatively modest, owing to the low additional cost for ZA and the fact that this cost was largely counterbalanced by reduced use of other healthcare resources (e.g. fewer radiotherapies and surgeries). Prevention of serious events such as fracture, surgery, and cord compression is seen as a desirable outcome

Fig. 2 Cost-effectiveness acceptability curve showing the probability of Sr89 being cost-effective at different values of willingness to pay per additional QALY.



for the NHS [34]; therefore, a predictable, outpatient therapy with modest net acquisition costs may be attractive to providers if it prevents emergency, unpredictable visits. In the likely case that the NHS pays less than £31 for a dose of ZA, ZA is the dominant option, being less costly and more effective than no ZA.

The magnitude of the additional cost in the ZA group is to a great extent dependent on the acquisition cost of ZA. Since 2013, ZA is available as a generic product, at a price

markedly lower than the equivalent proprietary products (Zometa[®] and Aclasta[®]). Given the average price paid by NHS hospitals for ZA in the UK, the additional cost of ZA was low, at £251, resulting in an attractive ICER of about £8000 per QALY. In the likely case that the NHS pays less than £31 for a dose of ZA, ZA is the dominant option (i.e. less costly and more effective, in terms of QALYs, than no ZA).

The Sr89 group was associated with an increase in cost and an improvement in QALYs, which translated into an ICER of £16 900 per QALY. However, these results will need to be seen in light of the fact that several new treatments licenced in the last few years have now emerged, including abiraterone, enzalutamide, cabazitaxel and, of particular relevance to this study, radium-223.

For both the comparison between ZA vs no ZA and Sr89 vs no Sr89, the calculated CIs of the differences in QALYs overlapped zero, suggesting that the observed improvements in QALYs are not statistically significant. However, given the fact that the TRAPEZE trial was not powered to detect statistically significant differences in QALYs, the observed results should not be interpreted as conclusive evidence of presence or absence of a significant difference. Consistent with recommendations, the interpretation of the results is based on the outcome of the ICERs and the uncertainty surrounding them [25,35].

To our knowledge, this is the first economic evaluation based on prospectively collected data aiming to assess the cost-effectiveness of providing patients with CRPC with ZA and Sr89 in addition to standard chemotherapy. A major strength of the present study lies in the fact that data were obtained from a large pragmatic randomised controlled trial. In line with guidance in conducting economic evaluations, costs were estimated by weighting prospectively collected patient-level resource use by unit costs drawn from national sources, health benefits were measured using a widely used preference-based measure, and analyses of the collected data were performed using recommended statistical methods [24,36–38]. While the analysis was carried out from the perspective of the NHS in the UK, the fact that the care pathway for CRPC is similar across developed countries makes the findings pertinent to other healthcare systems.

Despite this, the study presents certain methodological challenges. First, ZA appeared to have a minimal effect on QoL, which did not tally with the marked change in the number and severity of SREs. Given that events such as pain leading to radiotherapy, fracture, and spinal cord compression must certainly impair QoL, it is possible that temporary drops in QoL due to unpredictable SREs may have not been captured. This may be explained by the fact that the EQ-5D-3L forms are typically completed at predetermined points after randomisation, which are likely to fall either before

SREs or after problems are resolved. Failure to capture temporary declines in QoL due to SREs indirectly penalises groups associated with fewer SREs, in this case, the ZA group. Secondly, similarly to all trials, prospectively collected data are bound to be incomplete. In particular, final terminal phase SREs, resource use and benefits are difficult to capture, as patients are generally less likely to attend trial clinics in that period [39,40]. Last, while the trial protocol made provisions for six cycles of docetaxel chemotherapy plus an additional four cycles ‘off study’, the National Institute for Health and Care Excellence (NICE) in the UK recommended that up to 10 cycles of docetaxel chemotherapy should be administered in one treatment block. Given the intended pragmatic nature of this trial, adopting the NICE recommendation ensured that treatment arms reflected the true ‘standard of care’. Owing to the fact that docetaxel chemotherapy was provided across all treatment groups, this change is not expected to impact on a particular treatment group over another.

Further research in the area would be valuable. Despite the patient-level evidence obtained from the trial, more detailed estimates of QoL associated with SREs and use of healthcare resources would be useful. The latter is typically accessible via the Hospital Episode Statistics (HES) database, which contains details of all admissions, outpatient appointments, and emergency attendances at NHS hospitals [41]. Further analyses using HES will give the opportunity to corroborate the present study findings. In addition, it would be interesting to obtain insights into the clinical effectiveness and cost-effectiveness of both ZA and Sr89 as compared to neither treatment. While the TRAPEZE trial was not designed to investigate such comparisons, this could be pursued in a future study specifically designed to assess the particular treatment options.

In conclusion, the present findings suggest that the addition of bone-targeting treatments to standard chemotherapy lead to a small positive change in QALYs for a small additional cost (or cost-savings), resulting in an ICER below the threshold of £20 000 per QALY. These cost-effectiveness results, coupled with the treatments’ positive impact on SRE prevention, suggest that supplementation of chemotherapy with bone-protecting treatments is likely to represent a cost-effective use of the available healthcare resources.

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Conflicts of Interest

Nicholas James reports consultancy work and lecture fees from Sanofi Aventis Pharma and Novartis (directly related) and consultancy work and lecture fees from Bayer, Amgen, Janssen, Astellas, Affinity (related to prostate cancer but not drugs in this study). Ann Pope reports grants payable to investigation sites from Sanofi Aventis on the recruitment of patients, provision of Zometa[®] during the phase II trial and later a trial specific discount for sites the purchase of trial drug from Novartis and a trial specific discount for sites from GE Healthcare for the purchase of trial drug, during the conduct of the study. Chris Parker reports personal fees from Bayer, BNIT, Astellas, Janssen, Sanofi Aventis and Takeda, outside the submitted work. Andrew Stanley reports that TEVA supported his attendance at ESMO, he received personal fees from CALGENE, and AMGEN supported part of his attendance at BOPA, outside the submitted work. Janet Brown reports personal fees and non-financial support from Novartis, outside the submitted work. Lucinda Billingham reports personal fees from Eli Lilly, personal fees from Pfizer, outside the submitted work. Lazaros Andronis, Ilias Goranitis, Sharon Beesley, Alison Birtle, Stuart Collins, Duncan McLaren, Joe O'Sullivan, Emilio Porfiri, John Staffurth, James Wylie, Prabir Chakraborti, Syed Hussain, Martin Russell, Daren Barton, Adam Daunton and Sarah Pirrie report no conflicts of interest.

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Abbreviations: BCa, bias-corrected and accelerated; CRF, case report form; CRPC, castrate-refractory prostate cancer; DP, docetaxel and prednisolone; ECOG, Eastern Cooperative Oncology Group; HES, Hospital Episode Statistics; ICER, incremental cost-effectiveness ratio; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life-year; QoL, quality of life; SRE, skeletal-related events; ZA, zoledronic acid.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Graph showing ICER for ZA vs no ZA at different prices of ZA, after adjusting for baseline imbalances in EQ-5D-3L.

Table S1. Summary characteristics of participants included in the economic evaluation ($n = 707$) and all study participants ($n = 757$).

Table S2. Results of sensitivity analyses for ZA vs no ZA and Sr89 vs no Sr89.