
Article:
Kearns, B. orcid.org/0000-0001-7730-668X, Pandor, A. orcid.org/0000-0003-2552-5260, Stevenson, M. orcid.org/0000-0002-3099-9877 et al. (5 more authors) (2016) Cabazitaxel for Hormone-Relapsed Metastatic Prostate Cancer Previously Treated With a Docetaxel-Containing Regimen: An Evidence Review Group Perspective of a NICE Single Technology Appraisal. Pharmacoeconomics. ISSN 1170-7690

https://doi.org/10.1007/s40273-016-0457-1

Cabazitaxel for hormone-relapsed metastatic prostate cancer previously treated with a docetaxel-containing regimen: An evidence review group perspective of a NICE single technology appraisal

Benjamin Kearns*[1], Abdullah Pandor[1], Matt Stevenson[1], Jean Hamilton[1], Duncan Chambers[1], Mark Clowes[1], John Graham[2], M. Satish Kumar[3]

[1]School of Health and Related Research, University of Sheffield, Sheffield, S1 4DA, UK
[2]Taunton and Somerset NHS Foundation Trust, Taunton, UK
[3]Queen's Academy India, Queen's University Belfast, Belfast, UK

*Corresponding author:
Tel: (+44) (0)114 222 6380
Fax: (+44) (0)114 222 0749
Email: b.kearns@sheffield.ac.uk

Running title: Cabazitaxel for hormone-relapsed metastatic prostate cancer

Word count (text only): 4615

Abstract

As part of its single technology appraisal (STA) process, the National Institute for Health and Care Excellence (NICE) invited the company that manufactures cabazitaxel (Jevtana®, Sanofi, UK) to submit evidence for the clinical and cost-effectiveness of cabazitaxel for treatment of patients with metastatic hormone-relapsed prostate cancer (mHRPC) previously treated with a docetaxel-containing regimen. The School of Health and Related Research Technology Appraisal Group at the University of Sheffield was commissioned to act as the independent Evidence Review Group (ERG). The ERG produced a critical review of the evidence for the clinical and cost-effectiveness of the technology based upon the company's submission to NICE. Clinical evidence for cabazitaxel was derived from a multinational randomised open-label phase III trial (TROPIC) of cabazitaxel plus prednisone or prednisolone compared with mitoxantrone plus prednisone or prednisolone, which was assumed to represent best supportive care. The NICE final scope identified a further three comparators: abiraterone in combination with prednisone or prednisolone; enzalutamide; and radium-223 dichloride for the subgroup of people with bone metastasis only (no visceral metastasis). The company did not consider radium-223 dichloride to be a relevant comparator. Neither abiraterone nor enzalutamide has been directly compared in a trial with cabazitaxel. Instead, clinical evidence was synthesised within a network meta-analysis (NMA). Results from TROPIC showed that cabazitaxel was associated with a statistically significant improvement in both overall survival and progression-free survival compared with mitoxantrone. Results from a random-effects NMA; as conducted by the company and updated by the ERG, indicated that there was no statistically significant difference between the three active treatments for both overall survival and progression-free survival. Utility data were not collected as part of the TROPIC trial, and were instead taken from the company's UK early access programme. Evidence on resource use came from the TROPIC trial, supplemented by both expert clinical opinion and a UK clinical audit. List prices were used for mitoxantrone, abiraterone and enzalutamide as directed by NICE, although commercial in confidence patient-access schemes (PASs) are in place for abiraterone and enzalutamide. The confidential PAS was used for cabazitaxel. Sequential use of the advanced hormonal therapies (abiraterone and enzalutamide) does not usually occur in clinical practice in the UK. Hence cabazitaxel could be used within two pathways of care: either when an advanced hormonal therapy was used pre-docetaxel; or when one was used post-docetaxel. The company believed that the former pathway was more likely to represent standard National Health Service (NHS) practice, and so their main comparison was between cabazitaxel and mitoxantrone, with effectiveness data from the TROPIC trial. Results of the company's updated cost-effectiveness analysis estimated a probabilistic incremental cost-effectiveness

ratio (ICER) of £45,982 per quality-adjusted life year (QALY) gained, which the committee considered to be the most plausible value for this comparison. Cabazitaxel was estimated to be both cheaper and more effective than abiraterone. Cabazitaxel was estimated to be cheaper but less effective than enzalutamide, resulting in an ICER of £212,038 per QALY gained for enzalutamide compared with cabazitaxel. The ERG noted that radium-223 is a valid comparator (for the indicated sub-group), and that it may be used in either of the two care pathways. Hence, its exclusion leads to uncertainty in the cost-effectiveness results. In addition, the company assumed that there would be no drug wastage when cabazitaxel was used, with cost-effectiveness results being sensitive to this assumption: modelling drug wastage increased the ICER comparing cabazitaxel with mitoxantrone to over £55,000 per QALY gained. The ERG updated the company's NMA and used a random effects model to perform a fully incremental analysis between cabazitaxel, abiraterone, enzalutamide and best supportive care using PASs for abiraterone and enzalutamide. Results showed that both cabazitaxel and abiraterone were extendedly dominated by the combination of best supportive care and enzalutamide. Preliminary guidance from the committee, which included wastage of cabazitaxel, did not recommend its use. In response, the company provided both a further discount to the confidential PAS for cabazitaxel and confirmation from NHS England that it is appropriate to supply and purchase cabazitaxel in pre-prepared intravenous-infusion bags, which would remove the cost of drug wastage. As a result, the committee recommended use of cabazitaxel as a treatment option in people with an eastern cooperative oncology group performance status of 0 or 1 whose disease had progressed during or after treatment with at least 225 mg/m^2 of docetaxel, as long as it was provided at the discount agreed in the PAS and purchased in either pre-prepared intravenous-infusion bags or in vials at a reduced price to reflect the average per patient drug wastage.

.

Key points for decision makers

- Cabazitaxel may be provided in pre-prepared intravenous-infusion bags; this novel purchasing arrangement shall reduce the cost of drug wastage within the National Health Service.
- Following publication of the Appraisal Consultation Document, the National Institute for Health and Care Excellence accepted a further discount to the confidential patient-access scheme for cabazitaxel in order that it could be considered cost-effective.
- Methodological issues with the network meta-analysis comparing cabazitaxel with best supportive care, abiraterone and enzalutamide (including violation of the proportional hazards assumption and differing definitions of progression free survival) meant that relative efficacies were uncertain.

1. Introduction

The UK National Institute for Health and Care Excellence (NICE) is an independent organization. A key responsibility of NICE is to provide national guidance to the National Health Service (NHS) in England on the use of selected health technologies. The NICE single technology appraisal (STA) process is designed to appraise a single health technology with a single indication, to determine the clinical effectiveness of an intervention and whether it represents a cost-effective use of NHS resources. As part of the STA process the company manufacturing the technology submits its estimates of the clinical and cost-effectiveness of the health technology. This report is then critically reviewed by an independent evidence review group (ERG), in consultation with clinical experts. The NICE Appraisal Committee (AC) considers the company's evidence, the ERG's report and testimony from experts and other stakeholders, before it develops provisional (Appraisal Consultation Document [ACD]) or final (Final Appraisal Determination [FAD]) recommendations. An ACD is usually produced if its recommendations are restrictive or if additional clarification is required from the company. All the stakeholders have an opportunity to comment on the ACD before the NICE AC meets again to produce a FAD. This article presents a summary of the ERG report for the STA of cabazitaxel (Jevtana®) for the treatment of adults with hormone-relapsed metastatic prostate cancer treated with a docetaxel-containing regimen(1).

2. The decision problem

Within the UK prostate cancer is the most common form of cancer diagnosed amongst men, accounting for a quarter of all male cancers(2). Metastatic prostate cancer occurs when the cancer spreads to other parts of the body, such as the bones or lungs. First line therapy is typically with androgen deprivation therapy Patients whose tumours progress following initial hormone therapy (with LHRH agonists or antagonists or a combination of LHRH agonist with bicalutamide) may be referred to as having either metastatic hormone-relapsed prostate cancer (mHRPC) or metastatic castrate resistant prostate cancer (mCRPC). For men who have not received the advanced hormone therapies, abiraterone or enzalutamide, the term mHRPC is more appropriate as these men have castrate levels of testosterone yet may still respond to the advanced hormone therapies. As abiraterone and enzalutamide, which are advanced hormonal therapies, were not available during the original STA submission for cabazitaxel, the terminology used was mHRPC, which is reflected in the title of this STA submission. However, it may be more appropriate to refer to the population of interest as

people with mCRPC since most men will receive either abiraterone or enzalutamide either before or after docetaxel.

There are no published data for the incidence of mCRPC. However, a report from the National Cancer Intelligence Network reveals that of the 36,287 diagnoses in England in 2013, 5836 (16%) were classified as Stage 4 (or metastatic) cancers, with a further 6661 diagnoses (18%) having an unknown stage(3). A systematic review of trials recruiting people with mCRPC estimated a median overall survival (OS) of 19 months based on 11 trials(4).

In March 2011, cabazitaxel in combination with prednisone or prednisolone received marketing authorisation within the European Union for the treatment of patients with mHRPC previously treated with a docetaxel-containing regimen(5). Cabazitaxel was previously appraised as part of the NICE STA process (TA255), with the FAD issued in January 2012(6). The Committee did not recommend treatment with cabazitaxel, as they considered that the most plausible incremental cost-effectiveness ratio (ICER) was likely to be above £87,500 per quality-adjusted life year (QALY) gained. Following this, cabazitaxel was available via the the Cancer Drugs Fund (CDF) until its removal in January 2015. It was later re-instated on the CDF in May 2015 pending the outcomes of this STA. In England, evidence from the CDF show that there were 805 notifications for cabazitaxel in 2014/15(7).

Cabazitaxel is administered intravenously once every three weeks. Dosing is by body surface area (BSA), with a recommended dose of 25 mg/m^2. Prednisone or prednisolone are taken orally, with a dose of 10 mg/day(5). The pivotal trial for cabazitaxel (TROPIC) compared it with mitoxantrone(8). As mitoxantrone use is restricted to a maximum of ten cycles, the TROPIC trial also restricted the use of cabazitaxel to 10 cycles. However, the marketing authorisation for cabazitaxel does not limit the number of cycles that may be given.

The final scope issued by NICE listed five relevant comparators: abiraterone in combination with prednisone or prednisolone; enzalutamide; mitoxantrone in combination with prednisolone; best supportive care (BSC); and radium-223 dichloride for the subgroup of people with bone metastasis only (no visceral metastasis).

3. The Independent Evidence Group (ERG) Review

The ERG provided an independent review of the company's (Sanofi's) submission to NICE. This review included a critique of the company's estimates of clinical and cost-effectiveness. As part of the STA process, the ERG were able to ask questions to clarify specific aspects of the company's submission, and the company was able to respond with additional evidence.

3.1 Clinical evidence provided by the manufacturer

Evidence on the effectiveness of cabazitaxel was taken from the TROPIC study: a multinational open-label randomised controlled trial (RCT) of cabazitaxel plus prednisone or prednisolone in men with mHRPC which had progressed during or following treatment with docetaxel(8). The comparator was mitoxantrone plus prednisone or prednisolone. Mitoxantrone is administered intravenously once every three weeks for a maximum of ten cycles. The evidence used was more mature than that available for TA255, with median follow-up increasing from 12.8 months (513 deaths) to 20.5 months (585 deaths). The primary outcome was OS, with cabazitaxel associated with a statistically significant median OS gain of 2.3 months compared with a median OS for mitoxantrone of 12.8 months ($p < 0.001$). A secondary outcome was progression-free survival (PFS), defined as time to progression as measured by a rise in prostate-specific antigen (PSA) level, tumour progression, pain progression or death. Cabazitaxel was associated with a statistically significant median PFS of 2.8 months compared with a median PFS for mitoxantrone of 1.4 months ($p < 0.001$).

In NICE TA255, the Appraisal Committee considered a subgroup of patients with an Eastern Co-operative Oncology Group (ECOG) performance score of 0 or 1 and who had received at least 225 mg/m^2 of prior docetaxel to be the most appropriate population to receive cabazitaxel in UK clinical practice(6). This population represents 83.7% (632/755) of the total TROPIC trial population. Similar effectiveness was observed for cabazitaxel compared with mitoxantrone in this sub-group for both median OS (15.6 months compared with 13.4 months, $p <0.001$) and median PFS (2.8 months compared with 1.4 months, $p = 0.001$).

Treatment emergent adverse events (AEs) of grade ≥3 were observed in 57.4% (of 371) patients in the cabazitaxel group and 39.4% (of 371) patients in the mitoxantrone group. Cabazitaxel was also associated with a higher proportion of withdrawals from the study due to AEs (18.3% compared with 8.4%). Neutropenia and its complications were the most common AEs associated with cabazitaxel of grade ≥3 requiring medical intervention when compared with mitoxantrone. Additional safety data were available from 112 patients with mCRPC receiving cabazitaxel in the UK Early Access Programme (EAP), which is part of an

open label, single-arm international phase IIIB/IV study with participants from 12 UK cancer centres(9).

The company assumed that, as mitoxantrone has not been shown to increase survival when compared with BSC(10), the two could be considered to be equivalent. The company did not consider radium-223 dichloride to be a valid comparator. This was for two main reasons: firstly evidence for radium-223 dichloride and cabazitaxel come from different patient populations, secondly the pivotal trial for radium-223 dichloride used a different definition for PFS to the pivotal trials for abiraterone and enzalutamide.

There were no head-to-head RCTs comparing cabazitaxel with either of the advanced hormonal agents (abiraterone and enzalutamide). Instead the company identified three relevant studies which were included in a network meta-analysis (NMA). These were the TROPIC trial(8), the AFFIRM study comparing enzalutamide plus placebo with placebo with or without prednisone(11), and the COU-AA-301 study comparing abiraterone plus prednisone with prednisone plus placebo(12). To enable a coherent comparison of progression-free survival across the three pivotal trials an alternative definition of radiographic PFS (rPFS) was used, with rPFS defined as the time from randomisation to the first occurrence of: tumour progression (based on RECIST criteria) or death due to any cause. For the purposes of the NMA the company assumed that the three control arms could be considered to be equivalent with regards to both OS and rPFS (and represent BSC). The company performed both fixed-effects and random-effects NMA, preferring the former, the results of which suggested that cabazitaxel, abiraterone and enzalutamide had broadly similar effects for overall survival, but that enzalutamide was more effective than cabazitaxel and abiraterone at delaying disease progression. The NMA results also indicated a significant increase in occurrences of anaemia and nausea for cabazitaxel compared with BSC, abiraterone and enzalutamide. For diarrhoea there was a statistically significantly increase in AEs for cabazitaxel compared with BSC and abiraterone.

3.1.1 Critique of clinical evidence and interpretation

The TROPIC study represents the only known RCT of cabazitaxel plus prednisone or prednisolone to have been undertaken in the relevant population. The ERG considered that the methodological quality of the TROPIC study was generally good, but that as an open-label study there was a risk of bias in the assessment of subjective outcomes such as pain and symptomatic disease progression. However, the ERG noted that OS (the primary

outcome) and tumour response are objective measures and they, along with laboratory AEs, were unlikely to have been affected by bias.

In the TROPIC trial, cabazitaxel was associated with higher rates of neutropenic complications, renal failure, and cardiac toxicity compared with mitoxantrone. However, during the previous STA the Appraisal Committee concluded that there was no evidence of an additional risk beyond that included in the Summary of Product Characteristics. Furthermore, additional safety data from a UK EAP suggest that in general cabazitaxel is well tolerated, with manageable toxicity(9).

The company noted that the results of the NMA should be treated with caution. The ERG agreed with this, and in addition considered that the NMA results presented by the company were likely to have underestimated the uncertainty in treatment effects due to the use of fixed effects models in spite of evidence of heterogeneity amongst the included trials. Although random-effects analyses were conducted by the company these were based on standard reference priors for all parameters. Due to the small number of studies in the network a weakly informative prior for the between study standard deviation (as used in the ERG analyses) was required. In addition, the company reported the output of their NMA as hazard ratios (HRs), which is only relevant if the relative treatment effects are constant over time. This assumption of proportional hazards was violated for at least one of the trials in the NMA(12). The ERG also noted that there may have been differences in patient populations between the trials, and that there was uncertainty in the assumption that control treatments are exchangeable.

The company did not consider clinical evidence pertaining to radium-223 dichloride, for the reasons previously mentioned. However, clinical advisors to the ERG, along with the expert submissions considered by the appraisal committee(13), indicated that radium-223 dichloride is a valid treatment option for the indicated sub-group. In addition, the NICE FAD for radium-223 dichloride recommends it as an option for treating adults with hormone-relapsed prostate cancer, symptomatic bone metastases and no known visceral metastases, only if: they have had treatment with docetaxel, and the company provides radium-223 dichloride with the discount agreed in the confidential patient access scheme (PAS)(14).

3.2 Cost-effectiveness evidence

The company's cost-effectiveness results were based on an updated version of the de novo model developed for TA255(6). This cohort, partitioned-survival, Markov model was developed in Microsoft Excel®, and employed a lifetime horizon with costs and QALYs estimated using an NHS and Personal Social Services perspective. The model included three health states: stable disease; progressive disease; and death. All patients start in the stable disease state, in the subsequent cycle patients could remain in that health state or transition to either progressive disease or death. Following progression the only transition possible was to death.

Three comparators to cabazitaxel were considered by the company. These were mitoxantrone (assumed to represent BSC), abiraterone and enzalutamide. Due to potential cross-resistance typically only one of the advanced hormonal therapies is used in clinical practice. The company believed that the use of abiraterone or enzalutamide typically occurred in the pre-docetaxel setting; hence the main comparison presented was between cabazitaxel and mitoxantrone, with effectiveness data from the sub-group of the TROPIC trial. In scenario analyses cabazitaxel was compared separately with each of abiraterone and enzalutamide. The effectiveness data for these two comparisons came from the company's NMA, and was based on full trial populations. Effectiveness data from TROPIC were incorporated in the economic model via parametric models. Five models (exponential, Weibull, Gompertz, log-logistic and log-normal) were considered, with the model that minimised the Akaike information criteria (a statistical measure of goodness of fit) for both mitoxantrone and cabazitaxel chosen. Evidence on the effectiveness of abiraterone and enzalutamide was incorporated using HRs from the NMA. These HRs were applied to the parametric model for cabazitaxel from the TROPIC study (for these comparisons log-logistic and log-normal models were not considered as HRs cannot be applied to these).

Data on health related quality-of-life (HRQoL) were not collected in the TROPIC study. Instead these were taken from the UK EAP (utility data were not collected outside of the UK), which included 112 patients and measured HRQoL using the EQ-5D-3L(9). No data were available which allowed comparison of HRQoL in patients undergoing treatment with mitoxantrone or any other comparator therapy. Instead, utility values were attached to the modelled health states. Data on the utility value for progressed disease came from 25 patients. Evidence on resource use came primarily from the TROPIC trial, supplemented by a UK clinical audit of five NHS Trusts and expert clinical opinion. The clinical experts were four oncologists who were selected as UK-based specialists in prostate cancer. Following instructions from NICE, list prices were used for mitoxantrone, abiraterone and enzalutamide, so that the commercial in confidence PASs for abiraterone and enzalutamide

were not revealed to the company (Sanofi). The PAS for cabazitaxel was used for all analyses. Treatment costs included the drug costs and costs due to administration, premedication, concomitant medication and adverse events. In general costs were reported for 2013/14 unless more recent cost estimates were available, such as from the June 2015 BNF(15).

The company's base-case estimated a probabilistic cost of £50,682 per QALY gained for the comparison between cabazitaxel and mitoxantrone. Cabazitaxel was estimated to dominate abiraterone, being both cheaper and more effective. Cabazitaxel was estimated to be cheaper but less effective than enzalutamide, with an ICER of £212,038 per QALY gained associated with the use of enzalutamide in preference to cabazitaxel.

3.2.1 Critique of cost-effectiveness evidence and interpretation

As with the clinical effectiveness evidence, the ERG considers radium-223 dichloride to be a relevant comparator for the indicated subgroup. Hence the exclusion of this leads to uncertainty regarding the cost-effectiveness of cabazitaxel for this subgroup. In addition, the company considered two different pathways of care, depending on if the advanced hormonal agents were used in the pre-docetaxel or post-docetaxel setting. The ERG also considers there to be uncertainty over which care pathway represents standard NHS practice, and noted that for the latter care pathway a fully incremental analysis was not performed.

Deterministic analyses performed by the company used median values from the NMA. The ERG considers the use of mean values to be more appropriate, although the results of the NMA should be treated with caution for the reasons previously provided.

3.3 Additional Work undertaken by the ERG

The ERG updated the company's NMA and used a random effects model instead of a fixed effects model. As there were insufficient studies to estimate the between-study standard deviation, a weakly informative half-normal prior was used, as recommended in the NICE technical support document(16). For this analysis a variance of 0.32^2 was employed, fuller details are provided in the ERG report(1). Results from the NMA are displayed in Table 1. For the deterministic analyses mean HRs from the NMA were used by the ERG, it is noted that for abiraterone mean values for both OS and rPFS are above one (which suggest that

abiraterone is more effective), whilst the corresponding median values are below one (which suggest that cabazitaxel is more effective). For the probabilistic analysis the ERG used samples from the predictive distributions. In the presence of unexplained heterogeneity it is recommended that the predictive distribution better represents uncertainty about comparative effectiveness for a future rollout of a particular intervention(16).

The ERG made several changes to the company's base-case analysis, as detailed in Table 2. Of these, only the change regarding drug wastage led to a noticeable change in the estimated ICER comparing cabazitaxel with mitoxantrone. For the company's base-case it was assumed that there would be no wastage of cabazitaxel. When asked for clarification, the company noted that this lack of drug wastage was because Sanofi would be able to supply patient-specific doses of cabazitaxel, in the form of compounded bags, direct to NHS hospitals. The ERG considers that there is uncertainty over the degree to which compounding represents standard NHS practice, and further that drug wastage would still occur if people did not attend their appointment. Due to this uncertainty two ERG base-case ICERs were presented; one included and one excluded drug wastage.

Table 2 also includes details of sensitivity analyses performed by the ERG to explore different assumptions regarding both utility values for progressed disease and the extrapolation of effectiveness data. Fuller descriptions of all analyses are provided in the ERG report(1). Both increases and decreases in the base-case ICER were observed, depending on the assumptions made.

The ERG performed a fully incremental analysis comparing cabazitaxel, abiraterone, enzalutamide and BSC using PAS-adjusted prices for the three active treatments, with effectiveness data from the ERG-updated NMA. It is not possible to present ICERs from this analysis as the results are commercial in confidence. Cabazitaxel was more costly and less effective than the combination of BSC and enzalutamide, and hence was extendedly dominated. Abiraterone was also extendedly dominated by this combination. However, the ERG noted that there was uncertainty in these results due to the limitations of the NMA.

The ERG was unable to formally incorporate radium-223 dichloride into assessments of cost-effectiveness. However, it was noted that radium-223 dichloride and cabazitaxel appeared to have similar levels of clinical effectiveness and so a choice between the two would likely be influenced by the relative costs of these therapies.

3.4 Conclusions of the ERG report

As with the original STA, the clinical effectiveness evidence submitted by the company suggests that cabazitaxel was more effective than mitoxantrone in prolonging both OS and PFS. Results from the NMA, updated by the ERG to provide a better characterisation of uncertainty, suggest that there was no difference between cabazitaxel, abiraterone and enzalutamide with regards to impact on both OS and rPFS. However, the results from the NMA should be viewed with caution, as the required assumption of proportional hazards was violated.

The original base-case probabilistic ICER presented by the company comparing cabazitaxel with mitoxantrone was £50,682 per QALY gained. This assumed that there would be no drug wastage; modelling of drug wastage increased the ICER to over £55,000 per QALY gained.

Using the results of the ERG-updated NMA and PAS-adjusted prices, results from a fully incremental analysis suggests that the combination of BSC and enzalutamide extendedly dominates cabazitaxel.

The ERG considers radium-223 dichloride to be a relevant comparator for the indicated sub-group. Excluding it from the estimates of cost-effectiveness leads to uncertainty over the cost-effectiveness of cabazitaxel.

4 Key Methodological Issues

The company's NMA, and its inclusion within the economic model, led to a number of methodological issues. Treatment effects were modelled as hazard ratios, which requires an assumption of proportional hazards. This assumption has been shown to be violated for abiraterone(12). The ERG noted that methods are available for incorporating HRs that vary over time(17), but were not considered for this study. The company used the results from a fixed-effects NMA. The ERG considered that the use of a random-effects NMA provides a more appropriate representation of the anticipated uncertainty in comparative treatment effects. This also reflects good practice guidance recommendations that a lack of evidence for a parameter be reflected by a broad range of potential estimates(18). However, there was a lack of evidence to inform estimates of the between-study heterogeneity. Hence, a weakly informative prior was used, based on current good practice guidance (16), and the robustness of results to alternative prior variances was assessed. For their deterministic analyses the company used median HRs, the ERG consider the use of mean HRs to be

more appropriate. It is noted that for deterministic results abiraterone is less effective than cabazitaxel based on median values, but more effective based on mean values.

There was uncertainty in how clinical effectiveness data should be extrapolated. Results from the ERG's sensitivity analyses (Table 2) show that the company's base-case probabilistic ICER (£50,682 per QALY gained) could increase by 38% (to £68,168 per QALY gained) or decrease by 17% (to £40,887 per QALY gained), depending on the extrapolation assumptions used.

The company considered two pathways of care, depending on if the advanced hormonal therapies were used before or after docetaxel. There was uncertainty over which of the two pathways constituted standard NHS practice. This was compounded by the evolving landscape of prostate cancer research and guidance: NICE STA processes for abiraterone, enzalutamide and radium-223 dichloride were ongoing at the same time as this STA, whilst results from the STAMPEDE trial (which suggest that docetaxel treatment should be initiated alongside long-term hormone therapy) were also published(19). In addition, there was uncertainty over the degree to which drug-wastage should be included in the economic modelling; this was a key driver of cost-effectiveness results.

5 National Institute for Health and Clinical Excellence Guidance

5.1 Preliminary Guidance

In February 2016, based on the available evidence, the AC produced preliminary advice that cabazitaxel in combination with prednisone or prednisolone was not recommended for the treatment of hormone-relapsed metastatic prostate cancer treated with a docetaxel-containing regimen. The AC considered that wastage of cabazitaxel should be modelled to reflect current practice, and asked the company to provide further details of the proposed arrangements. The AC also indicated that it preferred the analyses conducted by the ERG. When reaching their preliminary advice the AC considered two separate populations. For people who had not previously been treated with abiraterone or enzalutamide the committee noted that cabazitaxel was extendedly dominated by the combination of BSC and enzalutamide. For people who have not previously been treated with abiraterone or enzalutamide the committee felt that the most plausible ICER comparing cabazitaxel with mitoxantrone was over £55,000 per QALY gained. The committee concluded that even if the

maximum possible end-of-life weight were applied to the QALY, cabazitaxel would not represent a cost-effective treatment.

5.2 Final Guidance

Following the Committee's preliminary recommendation (the ACD), comments were invited from consultees and commentators in the appraisal process, and from the public. The company's response included a further discount to the confidential PAS for cabazitaxel, an updated cost-effectiveness analysis to incorporate the AC's preferred assumptions, and clarification over the supply of cabazitaxel. The ERG updated their analyses to incorporate the new PAS reduction. In April 2016 the AC produced the FAD, which recommended use of cabazitaxel as a treatment option in people with an eastern cooperative oncology group performance status of 0 or 1 whose disease had progressed during or after treatment with at least 225 mg/m2 of docetaxel, as long as it was provided at the discount agreed in the PAS and purchased in either pre-prepared intravenous-infusion bags or in vials at a reduced price to reflect the average per patient drug wastage. This section discusses the key issues considered by the AC when developing the FAD. The full list can be found in the FAD(1).

5.2.1 Drug wastage

The AC noted that in the company's economic model wastage of cabazitaxel was not included. Under current practice cabazitaxel is supplied in vials, hence drug wastage is likely to occur. The company stated that in the future they shall be able to supply cabazitaxel in a compounded intravenous bag for each patient, and so the NHS would only have to pay for the required number of milligrams. For the ACD the committee felt that the economic model should use the vial price of cabazitaxel. In response, the company provided confirmation from NHS England that it is appropriate to supply and purchase cabazitaxel in this way. Hence for the FAD the price-per milligram of cabazitaxel was used, and wastage of cabazitaxel was not modelled. Along with the further discount to the confidential PAS for cabazitaxel, this changes the committee's most plausible probabilistic ICER to £45,982 per QALY gained.

5.2.2 Results of the NMA

Effectiveness data for comparing cabazitaxel with abiraterone, enzalutamide and best supportive care came from the company's NMA (as updated by the ERG). The committee noted that the limitations of the NMA meant that there was uncertainty in the effectiveness

data. Hence results from the fully incremental cost-effectiveness analysis, which showed that cabazitaxel was extendedly dominated by enzalutamide and best supportive care, were deemed to be highly uncertain. The committee further noted that cabazitaxel was likely to be less costly than enzalutamide and abiraterone.

5.2.3 End-of-life criteria

The AC considered end-of-life criteria for two separate patient populations, depending on if abiraterone or enzalutamide were used pre-docetaxel or post-docetaxel. Three end-of-life criteria were considered:

1. The treatment is indicated for patients with a short life expectancy, normally <24 months;
2. The treatment is licensed or otherwise indicated for small patient populations; and
3. There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment. The AC has to be persuaded that this estimate is robust.

The committee was satisfied that the first two criteria were met for both patient populations. For people treated with abiraterone or enzalutamide before docetaxel, the relevant comparator for cabazitaxel was mitoxantrone, and evidence on the survival improvement was taken from the TROPIC trial. The committee concluded that all end-of-life criteria were met for this patient population. For the other patient population, best supportive care, abiraterone and enzalutamide were relevant comparators. The committee noted that results from the company's NMA showed no statistically significant difference in overall survival between cabazitaxel, abiraterone and enzalutamide. Therefore the committee concluded that the end-of-life criteria were not met for this patient population.

6 Conclusions

The committee recognised that the clinical effectiveness of cabazitaxel had been proven, and that it prolonged life. The committee further noted responses to the consultation, which had emphasised the heterogeneity of prostate cancer and the need for a variety of treatment options. The committee was aware that they had not been presented with evidence relating to the clinical and cost-effectiveness of cabazitaxel when used amongst people who had previously received docetaxel followed by abiraterone, enzalutamide or radium-223 dichloride. As a result, the committee was unable to make a recommendation on the use of cabazitaxel for these people. The final FAD states(1):

"Cabazitaxel in combination with prednisone or prednisolone is recommended as an option for treating metastatic hormone-relapsed prostate cancer in people whose disease has progressed during or after docetaxel chemotherapy, only if:

- the person has an eastern cooperative oncology group (ECOG) performance status of 0 or 1
- the person has had 225 mg/m^2 or more of docetaxel
- treatment with cabazitaxel is stopped when the disease progresses or after a maximum of 10 cycles (whichever happens first)
- the company provides cabazitaxel with the discount agreed in the patient access scheme, and
- NHS trusts purchase cabazitaxel in accordance with the commercial access agreement between the company and NHS England, either: in pre-prepared intravenous infusion bags, or in vials, at a reduced price that includes a further discount reflecting the average cost of waste per patient"

The recommendations of the FAD differed from the preliminary guidance. The two main reasons for this are further discount to the confidential PAS for cabazitaxel and the change from modelling current practice in the supply of cabazitaxel to the future compounding scheme, which will minimise drug wastage.

Funding

This Project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment Programme (Project number 15/69/13). See the HTA programme website for further project information (http://www.hta.ac.uk). This summary of the ERG report was compiled after NICE issued the FAD. All authors have commented on the submitted manuscript and have given their approval for the final version to be published. The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

Compliance with Ethical Standards

Contributors

BK drafted the final version of the manuscript and takes responsibility as the overall guarantor of the content. All authors have commented on the submitted manuscript and have given their approval for the final version to be published. BK and MS reviewed the cost-effectiveness evidence, AP and DC reviewed the clinical-effectiveness evidence, JS reviewed statistical analyses, MC reviewed search strategies. JG and M.SK provided clinical input and advice. This summary has not been externally reviewed by PharmacoEconomics.

Conflicts of interest

BK, AP, MS, JH, DC, MC, JG and M.SK have no potential conflicts of interest that are directly relevant to the content of this article.

Table 1: Results of NMA using random effects model, half-normal prior with variance 0.32^2

Overall survival, cabazitaxel vs	Hazard ratio; median	Hazard ratio; mean	95% Predictive Interval
Best supportive care	0.72	0.77	(0.26 to 1.99)
Abiraterone	0.97	1.10	(0.24 to 4.16)
Enzalutamide	1.14	1.29	(0.27 to 4.73)
Radiographic progression free survival, cabazitaxel vs	**Hazard ratio; median**	**Hazard ratio; mean**	**95% Predictive Interval**
Best supportive care	0.75	0.80	(0.28 to 2.07)
Abiraterone	0.96	1.09	(0.23 to 4.12)
Enzalutamide	1.87	2.12	(0.45 to 7.70)

NMA: Network meta-analysis.

Table 2: Overview of ERG changes to the company's model.

Individual changes made	Incremental values (Cabazitaxel – mitoxantrone)		ICER (£)
	Costs (£)	QALYS	
Company deterministic base-case	11,450	0.232	49,327
Company probabilistic base-case	11,829	0.233	50,682
Changes made			
A1) Use eMIT prices for generic drugs	11,994	0.232	51,667
A2) Discontinuation for reasons other than disease progression not modelled	11,693	0.232	50,370
A3) Reduced disutility in the last 3 months of progressive disease not modelled	11,450	0.230	49,691
A4) Post-second line treatment resource use and proportion receiving best supportive care from UK audit for all treatments.	11,353	0.232	48,908
A5) Cost of cabazitaxel and mitoxantrone based on vial cost (assuming wastage).	14,104	0.232	60,759
A6) Use of log-logistic curves for both OS and PFS.	12,627	0.309	40,887
A7) Parametric curves for OS and PFS based on lowest AIC value (no requirement for same parametric form for both arms)*	9,347	0.137	68,168
A8) Use of the 95% low confidence interval value for progressive disease utility.	11,450	0.207	55,248
A9) Use of the 95% high confidence interval value for progressive disease utility.	11,450	0.257	44,560
ERG Deterministic base-case 1 (changes A1 to A5)	14,729	0.230	63,919
ERG Probabilistic base-case 1 (changes A1 to A5)	15,064	0.231	65,213
ERG Deterministic base-case 2 (changes A1 to A4)	11,823	0.230	51,308
ERG Probabilistic base-case 2 (changes A1 to A4)	12,133	0.234	51,849

Deterministic results are reported for individual changes.

AIC: Akaikes information criteria. eMIT: Electronic market information tool. ERG: Evidence review group. ICER: Incremental cost-effectiveness ratio. OS: Overall survival. PFS: Progression-free survival. QALYS: Quality-adjusted life-years.

* For cabazitaxel the Weibull curve is used for OS and the log-logistic curve for PFS. For mitoxantrone the curves are the log-logistic and the log-normal, respectively

References.

1. National Institute for Health and Care Excellence (NICE). Cabazitaxel for hormone-relapsed metastatic prostate cancer previously treated with a docetaxel- NICE technology appraisal guidance [TA391]2015. Available from: https://www.nice.org.uk/guidance/ta391.
2. Cancer Research UK. Prostate Cancer Statistics 2015 [Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer.
3. National Cancer Intelligence Network. Survival by stage 2014 [Available from: http://www.ncin.org.uk/publications/survival_by_stage.
4. West TA, Kiely BE, Stockler MR. Estimating scenarios for survival time in men starting systemic therapies for castration-resistant prostate cancer: a systematic review of randomised trials. Eur J Cancer. 2014;50(11):1916-24.
5. European Medicines Agency (EMA). Assessment Report For Jevtana (cabazitaxel) Procedure No.: EMEA/H/C/0020182011 26 November 2015. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002018/WC500104766.pdf.
6. Kearns B, Lloyd Jones M, Stevenson M, Littlewood C. Cabazitaxel for the second-line treatment of metastatic hormone-refractory prostate cancer: a NICE single technology appraisal. Pharmacoeconomics. 2013;31(6):479-88.
7. NHS England. National Cancer Drugs Fund List Version 5.1. 2015.
8. de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Kocak I, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet. 2010;376(9747):1147-54.
9. Bahl A, Masson S, Malik Z, Birtle AJ, Sundar S, Jones RJ, et al. Final quality of life and safety data for patients with metastatic castration-resistant prostate cancer treated with cabazitaxel in the UK Early Access Programme (EAP) (NCT01254279). BJU Int. 2015.
10. Green AK, Corty RW, Wood WA, Meeneghan M, Reeder-Hayes KE, Basch E, et al. Comparative effectiveness of mitoxantrone plus prednisone versus prednisone alone in metastatic castrate-resistant prostate cancer after docetaxel failure. Oncologist. 2015;20(5):516-22.
11. Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med. 2012;367(13):1187-97.
12. Fizazi K, Scher HI, Molina A, Logothetis CJ, Chi KN, Jones RJ, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol. 2012;13(10):983-92.
13. Goddard A. Professional expert submission to the National Institute for Health and Care Excellence. Cabazitaxel for hormone-relapsed metastatic prostate cancer previously treated with a docetaxel-containing regimen (review of TA255) [ID889]. NCRI/RCP/RCR/ACP. 2015.
14. National Institute for Health and Care Excellence (NICE). Appraisal consultation document - Radium-223 dichloride for treating hormone-relapsed prostate cancer with bone metastases. 2015. NICE, London.2015 9 November 2015. Available from: https://www.nice.org.uk/guidance/GID-TAG345/documents/prostate-cancer-hormone-relapsed-bone-metastases-radium223-dichloride-id576-appraisal-consultation-document2
15. British National Formulary. BNF June 2015. 2015.
16. Dias S, Sutton AJ, Welton NJ, Ades AE. Evidence synthesis for decision making 3 heterogeneity-subgroups, meta-regression, bias, and bias-adjustment. Medical Decision Making. 2013;33(5):618-40.
17. Jansen JP. Network meta-analysis of survival data with fractional polynomials. BMC Medical Research Methodology. 2011;11(1):61.

18. Briggs AH, Weinstein MC, Fenwick EA, Karnon J, Sculpher MJ, Paltiel AD, et al. Model parameter estimation and uncertainty analysis: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force Working Group-6. Med Decis Making. 2012;32(5):722-32.
19. James ND, Sydes MR, Clarke NW, Mason MD, Dearnaley DP, Spears MR, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. The Lancet. 2016;387(10024):1163-77.