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Sipuleucel-T for the treatment of metastatic hormone relapsed prostate cancer: A NICE Single Technology Appraisal; an Evidence Review Group perspective

Abstract

The National Institute for Health and Care Excellence (NICE) invited Dendreon, the company manufacturing sipuleucel-T, to submit evidence for the clinical and cost-effectiveness of sipuleucel-T for asymptomatic or minimally symptomatic metastatic non-visceral hormone-relapsed prostate cancer (mHRPC) in whom chemotherapy is not yet clinically indicated, as part of NICE's single technology appraisal (STA) process. The comparator was abiraterone acetate (AA) or best supportive care (BSC). The School of Health and Related Research at the University of Sheffield was commissioned to act as the Evidence Review Group (ERG). This paper describes the company submission (CS), ERG review and subsequent decision of the NICE Appraisal committee (AC). The ERG produced a critical review of the clinical and cost-effectiveness evidence of sipuleucel-T based upon the CS.

Clinical-effectiveness data relevant to the decision problem were taken from three randomised controlled trials (RCTs) of sipuleucel-T and a placebo (PBO) comparator of antigen-presenting cells (APC) being re-infused (APC-PBO) (D9901, D9902A and D9902B), and one RCT (COU-AA-302) of AA plus prednisone versus PBO plus prednisone. Two trials reported a significant advantage for sipuleucel-T in median overall survival (OS) compared with APC-PBO: for trial D9901, an adjusted hazard ratio (HR) 0.47; (95% CI 0.29, 0.76) p<0.002; for D9902B, adjusted HR 0.78 (95% CI 0.61, 0.98) p=0.03. There was no significant difference between groups in D9902A, unadjusted HR 0.79 (95%CI 0.48, 1.28) p=0.331. Sipuleucel-T and APC-PBO groups did not differ significantly in time to disease progression, in any of the three RCTs. Most adverse events (AE) developed within one day of the infusion, and resolved within two days. The CS included an indirect comparison of sipuleucel-T (D9902B) and AA plus prednisone (COU-AA-302). As trials differed in prior use of chemotherapy, an analysis of only chemotherapy-naïve patients was included, in which the OS for sipuleucel-T and AA was not significantly different, HR 0.94 (95%CI 0.69, 1.28) p=0.699. The ERG had several concerns regarding the data and assumptions incorporated within the company's cost-effectiveness analyses and conducted exploratory analyses to quantify the impact of making alternative assumptions or using alternative data inputs. The deterministic incremental cost-effectiveness ratio (ICER) for sipuleucel-T versus BSC when using the ERG's preferred data and assumptions was £108,585 per quality adjusted life year (QALY) in the whole licensed population and £61,204/QALY in the subgroup with low prostate-specific antigen (PSA) at baseline. The ERG also conducted an incremental analysis comparing sipuleucel-T against both AA and BSC in the chemotherapy-naïve subgroup. Sipuleucel-T had a deterministic ICER of £111,682/QALY in this subgroup, when using the ERG's preferred assumptions, and AA was extendedly dominated. The ERG also concluded that estimates of costs and benefits for AA should be interpreted with caution given the limitations of the indirect comparison.

The AC noted that the ICER for sipuleucel-T was well above the range usually considered cost-effective, and did not recommend sipuleucel-T for the treatment of asymptomatic or minimally symptomatic metastatic non-visceral hormone relapsed prostate cancer.

1. Introduction

Health technologies must be shown to be clinically effective and to represent a cost-effective use of resources to be recommended for use within the National Health Service (NHS) in England. The National Institute for Health and Care Excellence (NICE) is an independent organisation responsible for providing national guidance on promoting good health and preventing and treating ill health in priority areas with significant impact. The NICE single technology appraisal (STA) process covers new technologies, within single indications, usually soon after the UK marketing authorisation.[1] Within the STA process, the company provides a written submission, alongside a mathematical model that summarises their estimates of the cost-effectiveness of the technology.[2] This submission is reviewed by an external academic organisation, the Evidence Review Group (ERG), which consults with clinical specialists to produce an ERG report. After consideration of the company submission (CS), the ERG report and testimony from experts and other stakeholders, an Appraisal Committee (AC) usually formulates their preliminary guidance, on which stakeholders are invited to comment. Following this, a subsequent appraisal consultation document may be produced or a Final Appraisal Determination (FAD) issued, which is open to appeal.

2. The clinical condition and current treatment

Sipuleucel-T is licensed for the treatment of asymptomatic or minimally symptomatic metastatic, non-visceral, hormone-refractory prostate cancer for adults in whom chemotherapy is not yet clinically indicated.[3]

Hormone-refractory prostate cancer (HRPC), often referred to as castrate-resistant prostate cancer, is an advanced disease characterised by progression after surgical or pharmaceutical castration, defined by the European Association of Urology [4] as: castrate serum levels of testosterone <50 ng/dL or <1.7 nmol/L; three consecutive rises of prostate-specific antigen (PSA), one week apart, resulting in two 50% increases over the nadir, with a PSA>2 ng/mL; antiandrogen withdrawal for at least four weeks for flutamide (six weeks for bicalutamide); PSA progression despite consecutive hormonal manipulations. In the CS, metastatic HRPC (mHRPC) was defined by documenting castrate serum testosterone levels, increases in serum PSA concentration and radiographic progression of tumour lesions. Asymptomatic or minimally symptomatic mHRPC was described as the subset of patients with no or minimal cancer-related symptoms, who do not require opioid analgesics for pain management.[2]

According to 2014 NICE prostate cancer guidelines,[5] mHRPC treatment options include second-line androgen deprivation therapy, chemotherapy with or without corticosteroids, and best supportive care (BSC). Asymptomatic patients may be treated with watchful waiting and maximised androgen deprivation therapy. Symptomatic patients may be treated with steroids and bisphosphonates. At the time of the sipuleucel-T appraisal, an appraisal for abiraterone acetate (AA) for chemotherapy-naïve mHRPC was suspended.[6]

3. The technology

Sipuleucel-T (Provenge, Dendreon) is an autologous active cellular immunotherapy product that is designed to stimulate an immune response to prostate cancer.[3] Autologous peripheral blood mononuclear cells, including antigen-presenting cells (APCs), are collected from the patient approximately three days prior to treatment, and incubated with a recombinant fusion protein to form sipuleucel-T. Sipuleucel-T is administered to the patient by infusion.[3] The recommended course is three doses at two-week intervals.

According to the CS, the cost of sipuleucel-T was £16,141.33 per dose, including the costs of leukapheresis, patient tests associated with leukapheresis, manufacture and transportation, and excluding value added tax.[7] The cost for a course of treatment was £47,132.68, based on a mean 2.92 doses per patient.[7]

4. The independent ERG review

The ERG report comprised a critical review of the evidence for the clinical and cost-effectiveness of the technology, based upon the company submission (CS) to NICE on the use of sipuleucel-T within its licensed indication. The comparators considered were BSC and AA. As part of the process the ERG and NICE had the opportunity to obtain clarification on specific points in the CS, resulting in the company's providing additional evidence.

4.1 Clinical evidence

The clinical-effectiveness data were taken from four randomised controlled trials (RCTs). There were three RCTs (D9901,[8] D9902A[9] and D9902B[10]) of sipuleucel-T. Their placebo (PBO) comparator entailed one-third of the patient's antigen-presenting cells (APC) being re-infused (APC-PBO). Salvage therapy with APC8015F (manufactured to the same specifications as sipuleucel-T, but from the two-thirds of patient APCs cryopreserved at the time of APC-PBO preparation) was available to APC-PBO patients following disease progression. There was one RCT of AA plus prednisone versus PBO plus prednisone (COU-AA-302).[11]

Two of the sipuleucel-T trials (D9901, D9902B) reported a significant advantage in overall survival (OS) compared with APC-PBO. For trial D9901, median OS was 25.9 months in the sipuleucel-T group and 21.4 months in the APC-PBO group, adjusted hazard ratio (HR) 0.47; (95% confidence interval [CI] 0.29, 0.76) p<0.002.[8] In trial D9902B, median OS was 25.8 months in the sipuleucel-T group and 21.7 months in the APC-PBO group, adjusted HR 0.78 (95% CI 0.61, 0.98) p=0.03.[10] There was no significant difference between groups in D9902A,[2] unadjusted HR 0.79 (95%CI 0.48, 1.28) p=0.33, median OS was 19.0 months for sipuleucel-T and 15.7 months for APC-PBO.

Sipuleucel-T and APC- PBO groups did not differ significantly in time to disease progression, in any of the RCTs. [2;8;10] There was no statistically significant difference between sipuleucel-T and APC-PBO groups in time to disease related pain, in a combined analysis of D9901 and D9902A, or for the D9902B patients for whom the outcome was measured.[2]

The CS included an indirect comparison of sipuleucel-T and AA plus prednisone. For this comparison one sipuleucel-T RCT (D9902B) and one AA RCT (COU-AA-302) were used. These trials differed in prior use of chemotherapy, and so an analysis of only chemotherapy-naïve patients was included. For this analysis OS was not significantly different between sipuleucel-T and AA, HR 0.94 (95%CI 0.69, 1.28) p=0.70.[2]

Adverse event (AE) data in the CS was presented pooled from four RCTs. These comprised the three sipuleucel-T RCTs that provided effectiveness data and an ongoing trial of sipuleucel-T in non-metastatic prostate cancer.[12] Most AEs developed within one day of the infusion, and resolved within two days. Common AEs in sipuleucel-T treated patients included chills, fatigue, pyrexia, back pain, nausea, arthralgia, and headache.[12]

4.1.1 The ERG's interpretation of clinical evidence

The ERG believed that all relevant trials with available data were included within the CS. For all RCTs providing effectiveness data, the populations were asymptomatic or minimally symptomatic mHRPC, reflecting the disease characteristics of the population eligible for sipuleucel-T. There may be differences between treatment pathways of trial patients and current UK practice. In the sipuleucel-T trials 6.3%-18.2% participants were not chemotherapy-naïve, and so were outside marketing authorisation criteria.

All trials were large enough to be adequately powered for primary endpoints, and provided intention to treat (ITT) analyses. All trials were appropriately randomised, and were blinded until disease progression. Time to disease progression in all trials was an outcome with a low risk of bias.

Following disease progression in the sipuleucel-T trials, risk of bias was introduced by un-blinding and the provision of non-randomised post-progression treatment, including potential salvage therapy for the APC-PBO groups. There was a lack of consistency between time to disease progression and OS outcomes. This may be due to confounding, or a delayed onset of the effect of immunotherapy may mean that full therapeutic effect was not reached prior to disease progression.

There was uncertainty in the results of the indirect comparison due to: assumed equivalence of APC-PBO and PBO plus prednisone comparator groups; salvage therapy available to the APC-PBO group of D9902B after disease progression, and in COU-AA-302 availability of AA to the PBO plus prednisone group after the second interim OS analysis; non-randomised post-progression anti-cancer therapy within both trials; exclusion of D9901 and D9902A; it was unclear if the assumption of proportional hazards between arms held for the COU-AA-302 trial.

4.2 Cost-effectiveness evidence

The CS included a systematic review to identify published cost-effectiveness analyses.[2] Although the ERG identified one additional published analysis, it concerned the US healthcare system and had limited relevance.

The company presented a de novo model based economic evaluation. The base case analysis addressed the whole population meeting the licensed indication, and was based on an ITT analysis of D9902B comparing sipuleucel-T to best supportive care (BSC). A subgroup analysis examined the cost-

effectiveness of sipuleucel-T versus BSC in the subgroup of patients with a low baseline PSA level of ≤22.1ng/mL. The rationale given being that sipuleucel-T was more effective in patients with low disease burden. A second subgroup analysis examined the cost-effectiveness of sipuleucel-T versus AA (plus prednisone) in chemotherapy-naïve patients, because the COU-AA-302 trial only enrolled chemotherapy-naïve patients.

In all three of the company's cost-effectiveness analyses, an NHS and Personal Social Services (PSS) perspective was taken, and discounting was 3.5% for costs and benefits in line with the NICE reference case. Costs were based on prices from 2013/14. A lifetime horizon was used to estimate costs and benefits, with benefits expressed using quality-adjusted life years (QALYs) gained. The care pathway in the model assumed patients received sipuleucel-T, BSC or AA until disease progression to the point of requiring docetaxel. Docetaxel usage was incorporated within the model but no other mHRPC treatments were included.

The model tracked the proportion of patients residing within various health-states over time using monthly time-cycles and was therefore similar in many ways to a Markov or state-transition model. However, the model was populated using parametric survival curves rather than the transition matrix approach usually associated with Markov/state transition models.

The model was primarily driven by parametric survival curves for OS. In the analyses for the ITT population (D9902B trial), and the low PSA subgroup, OS was based on parametric curves fitted independently to the sipuleucel-T and APC-PBO Kaplan-Meier data from D9902B. In the low PSA analysis the Kaplan-Meier data for the APC-PBO arm were first adjusted to remove the survival benefit of cross-over to post-progression salvage therapy. This was done using an iterative parameter estimation (IPE) model fitted to the whole ITT population of D9902B. In the chemotherapy-naive subgroup analysis, the OS for AA was estimated from the OS for sipuleucel-T using an indirect HR, calculated using the Bucher [13] method based on HRs from the COU-AA-302 and D9902B trials, with the latter estimated in the chemotherapy-naïve subgroup.

The period of OS in the model was partitioned into pre and post-docetaxel therapy using parametric survival curves for docetaxel-free survival. Docetaxel-free survival in the BSC arm was based on time to either salvage therapy or docetaxel in the APC-PBO arm of D9902B, on the basis that APC8015F salvage therapy would not be available if sipuleucel-T was not a treatment option.

The period of docetaxel-free survival in the model was further partitioned into periods before and after initiation of opioids using parametric survival curves for time to opioid use. The proportion of patients experiencing AEs was estimated separately for patients using or not using opioids.

Once patients progressed to docetaxel they were modelled within a single docetaxel/post-docetaxel state, with costs and utility values calculated using a weighted average according to the proportion of time spent on docetaxel and post-docetaxel. The ERG identified an error in the calculation of this weighting which was then corrected by the company. The duration of docetaxel treatment was fixed at ten cycles in the original CS model, but this was varied in sensitivity analyses following an ERG request.

Health utility values in the model were based on estimates from the literature. The utility value pre-docetaxel was based on a published meta-analysis of prostate cancer utilities.[14] Utility decrements

were applied to this for patients experiencing AEs or requiring opioids. Utility during docetaxel therapy was based on a study which measured EuroQol-5D (EQ-5D) in the year before death from prostate cancer.[15] The utility post-docetaxel therapy was set equivalent to the utility prior to docetaxel for patients requiring pain relief with opioids.

The cost of leukapheresis, manufacture and transport of sipuleucel-T was included as one figure within the model, with only the cost of the infusion procedure and physician time for administration activities incorporated separately. Drug costs for docetaxel, AA, prednisone (administered concomitantly with docetaxel and AA) and paracetamol and anti-histamine (both administered prior to sipuleucel-T) were based on current British National Formulary list prices. Resource use was included for hospitalisations to manage grade 3/4 AEs, follow-up visits with primary and secondary care healthcare professionals, imaging studies and blood tests, opioid treatment, cancer-related hospitalisations after disease progression and palliative care at the end-of-life. Most of the resource use estimates were based on a survey of UK oncologists after a systematic review identified only one study,[16] which was used to estimate hospitalisation rates.

The CS base case incremental cost-effectiveness ratio (ICER) for the population meeting the licensed indication (based on the D9902B ITT population) was £124,875/QALY for sipuleucel-T versus BSC based on the deterministic model. The range of ICERs generated by the univariate sensitivity analysis was £111,052 -£142,627/ QALY. The scenario analysis adjusting for the survival effect of salvage therapy using the IPE model provided a significantly lower ICER of £84,823/QALY. The mean ICER from the probabilistic sensitivity analysis was consistent with the deterministic base case ICER. The probabilistic sensitivity analysis suggested a very low (<1%) probability of the ICER falling below £50,000/QALY for the base case analysis.

The CS ICER for the low PSA subgroup was £48,672/QALY for sipuleucel-T versus BSC based on the deterministic model. The range of ICERs generated by the univariate sensitivity analysis was £43,659-£56,876/QALY. The mean ICER from the probabilistic sensitivity analysis was consistent with the deterministic base case ICER. The probabilistic sensitivity analysis estimated a moderate probability (53.1%) of the ICER falling below £50,000/QALY but a very low probability (<1%) of falling under £30,000/QALY.

Using the list price for AA, in the chemotherapy-naïve subgroup, the CS model estimated that sipuleucel-T dominated AA, although this comparison was subject to considerable uncertainty as variation in the duration of AA treatment resulted in an ICER of £369,810/QALY for sipuleucel-T versus AA. Whilst the mean cost savings were fairly large (£5,954 per patient), the mean QALY gains were low at 0.023. Therefore sensitivity analyses which resulted in a positive incremental cost for sipuleucel-T compared with AA also resulted in high ICERs. The probabilistic sensitivity analysis showed the cost and QALY estimates were distributed over all four quadrants of the cost-effectiveness plane. The probabilistic sensitivity analysis estimated that sipuleucel-T dominated AA in 46% of samples and the probability of the ICER falling under £30,000/QALY was 59%.

4.2.1 The ERG's interpretation of cost-effectiveness evidence

The ERG had several concerns regarding the structure of the company's model and the data and assumptions incorporated with the company's cost-effectiveness analyses. The models for the ITT population and the low PSA subgroup appeared to underestimate time to docetaxel in the BSC arm, as cross-over to salvage therapy was treated as equivalent to initiation of docetaxel. As time to docetaxel was used as a proxy for time to disease progression in the model, this biased the analysis in favour of sipuleucel-T. Time to progression observed in D9902B was not significantly different between the two arms. Assuming that patients receiving salvage therapy would instead receive docetaxel, overestimated docetaxel usage in the BSC arm, biasing the results in favour of sipuleucel-T.

The validity of time to opioid use and time to docetaxel as model inputs was questionable given that in D9902B time to opioid use was removed as a study outcome following a protocol amendment, and time to docetaxel was never an outcome.

Randomisation of D9902B was not stratified by PSA level or prior chemotherapy usage. Therefore the cost-effectiveness analyses based on these subgroups could be biased by an imbalance in unknown confounding factors.

The ERG identified the following problems with the assumptions adopted in the CS analysis.

Assuming that ten cycles of docetaxel were used in every patient, rather than six to nine cycles suggested by clinical advice, biased the results in favour of sipuleucel-T as docetaxel usage was estimated to be higher in the BSC arm of the model, except in the comparison with AA where it favoured AA.

The ERG believed that the parameter values had been mixed up for the log-normal and log-logistic parametric survival curves, and therefore had more confidence in the company-generated ICER using the Weibull survival curves. The ICER appeared to be sensitive to the choice of survival curve.

The IPE model used to adjust for the effects of cross-over to salvage therapy was estimated in the ITT population but applied in the low PSA subgroup. This approach was inconsistent with the company's assertion that sipuleucel-T was more effective for people with low PSA. Whilst the IPE model was used to adjust for the effect on OS of cross-over to salvage therapy, it did not adjust for any differential timing of docetaxel therapy between the treatment arms after unblinding. The IPE model assumed that salvage therapy given after disease progression had equivalent efficacy to sipuleucel-T given at randomisation, and the ICER was sensitive to this assumption.

The indirect comparison with AA was subject to several limitations due to the lack of a head-to-head RCT comparing these treatments. The model also assumed equivalent survival curves for time to docetaxel and time to opioid use which appeared to underestimate the benefits of AA observed in the COU-AA-302 trial and therefore potentially biased the results in favour of sipuleucel-T.[10;11] The ERG requested that an alternative method employing the HRs from the COU-AA-302 trial be used, but insufficient details were provided to validate the approach used by the company in response to this request. The mean duration of AA in the model was longer than the mean time to docetaxel suggesting that the model had little face validity. Either the duration of AA was overestimated, or duration of docetaxel-free survival underestimated, which would bias the results in favour of sipuleucel-T. The model assumed equivalent disutilities, and monthly rates, for AEs despite AA having a different treatment duration and AE profile.

The ERG identified some problems with the sampling of the parameter values for the parametric survival curves used in the probabilistic sensitivity analysis. The parameter sampling failed to take into account correlation between the parameter values (although this was later corrected by the company) and samples were limited to exclude extreme values.

An incremental analysis of sipuleucel-T compared to both AA and BSC, which would allow the most cost-effective treatment to be identified, was not provided for any of the three populations modelled.

The ERG conducted exploratory analyses for the comparison of sipuleucel-T and BSC in the ITT population and low PSA subgroup based on the ERG's preferred assumptions:

•   Included the correction to docetaxel/post-docetaxel utility values

•   Time to docetaxel in the BSC arm assumed equivalent to the sipuleucel-T arm in line with results of time to progression endpoint

•   Docetaxel usage based on proportions who actually received docetaxel in the BSC arm (rather than either docetaxel or salvage therapy)

•   Patients treated with docetaxel received a mean of 7.3 cycles of docetaxel

•   Used Weibull instead of log-normal curves for OS

•   Used log-normal curves (estimated by the ERG) for docetaxel-free survival and opioid-free survival

•   Used OS adjusted for cross-over to salvage therapy in the BSC arm

•   Incorporated the correlation between parameter values for parametric survival curves using variance-covariance matrix

•   Allowed survival parameters to be sampled from their full distribution in the probabilistic sensitivity analysis rather than bounding them at their 95% CIs.

The ICER for sipuleucel-T versus BSC when using these assumptions was £108,585/QALY. The probabilistic sensitivity analysis suggested zero probability that the ICER would fall under £50,000/QALY. For the low PSA subgroup, the ICER for sipuleucel-T versus BSC was £61,204/QALY. For the chemotherapy-naïve subgroup, the ERG's incremental analysis estimated AA (at list price) was extendedly dominated by sipuleucel-T, and that the ICER for sipuleucel-T versus BSC was £111,682/QALY. However, the mean difference in costs and QALYs between the sipuleucel-T and AA treatment strategies was small compared to the spread of incremental costs and QALYs suggesting great uncertainty in the incremental costs and QALYs.

5. Conclusions of the ERG report

None of the three sipuleucel-T RCTs found a statistically significant treatment effect on time to disease progression, whereas two RCTs reported a significant advantage in overall survival compared with APC-PBO. This lack of consistency between outcomes may be due to confounding, or may be due to a delayed treatment effect of immunotherapy. The ICER for sipuleucel-T versus BSC when using the ERG's preferred data and assumptions was £108,585/QALY in the whole licensed population and £61,204/QALY in the low PSA subgroup. The ERG's probabilistic sensitivity analysis suggested zero probability that the ICER would fall under £50,000/QALY in the ITT population, and a very low probability (<2%) that sipuleucel-T had an ICER under £50,000/QALY in the low PSA population.

There were no head-to-head trials of sipuleucel-T and abiraterone acetate, and the indirect comparison was subject to uncertainty. The ERG conducted an incremental analysis comparing sipuleucel-T against both AA and BSC in the subgroup with no prior chemotherapy. Sipuleucel-T had a deterministic ICER of £111,682/QALY versus BSC in this subgroup when using the ERG's preferred assumptions, and AA (at list price) was extendedly dominated.

6. Key methodological issues identified by the ERG

The ERG had several concerns regarding the data and assumptions incorporated with the company's cost-effectiveness analyses and conducted exploratory analyses to quantify the impact of making alternative assumptions or using alternative data inputs. Issues which appeared to have the most impact on the ICER were: adjustment for cross-over to salvage therapy; the choice of survival curve for OS; the proportion receiving docetaxel; estimation of time to docetaxel; and the number of docetaxel cycles administered.

7. NICE guidance

7.1 Key issues considered by the Appraisal Committee

The AC reviewed the data available on clinical and cost-effectiveness of sipuleucel-T, having considered evidence on the nature of prostate cancer and the value placed on the benefits of sipuleucel-T by people with the condition, those who represent them, and clinical experts.[7]

The AC noted that two of three trials showed that sipuleucel-T extended OS, but none of the trials showed that sipuleucel-T prolonged time to disease progression, and heard from clinical experts that biological reasons for this were not fully understood. The AC noted the ERG comment that OS may have been confounded by post-progression treatments. The patient experts expressed concerns that APC-PBO may have been harmful to older patients, however, the AC noted that the European public assessment report[3] concluded this was unlikely. Based on the balance of evidence presented, the AC concluded that sipuleucel-T improved OS compared with APC-PBO.

The chemotherapy-naive subgroup was considered to reflect the marketing authorisation for sipuleucel-T, and was therefore most relevant population for this appraisal. The AC concluded there was insufficient evidence to establish whether sipuleucel-T affected OS differently in the low-PSA subgroup, compared with the rest of the population, and that results for this subgroup were uncertain because it included patients with prior chemotherapy. Also the company had not presented a comparison with AA in the low PSA subgroup.

The AC considered the structure of the company's economic model, which defined states based on the time to treatment with docetaxel. It heard from clinical experts that the start of chemotherapy was an important event, although it was unusual to base an economic model on treatments rather than states of health. The AC observed that the model did not include the disutility and costs associated with disease progression that occurs before docetaxel treatment.

The AC concluded that despite uncertainty surrounding the indirect comparison, it would be reasonable to assume that sipuleucel-T and AA had similar effectiveness in prolonging OS. The AC noted that the

assumptions in the company's model about time to docetaxel and time to opioids did not reflect the trial data for AA. It concluded there should have been sensitivity analyses to address these issues.

The AC concluded that the assumptions made in the ERG's exploratory analyses were reasonable, although this could not explore the effect of using a different model structure.

The AC considered that there were areas of considerable uncertainty in the results generated by the model, and that all of the ICERs estimated by the company and the ERG fell substantially above the range normally considered cost effective; that is, £20,000 to £30,000 per QALY gained.

The Committee published preliminary recommendations for consultation and discussed the consultation comments at a second Committee meeting but no changes were made to these preliminary recommendations following consultation.

7.2 Final guidance

The final NICE guidance published in February 2015 stated that:

"Sipuleucel-T is not recommended within its marketing authorisation for treating adults who have asymptomatic or minimally symptomatic metastatic non-visceral hormone-relapsed prostate cancer for which chemotherapy is not yet clinically indicated."[7]

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