

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Final appraisal determination

**Sipuleucel-T for treating asymptomatic or
minimally symptomatic metastatic
hormone-relapsed prostate cancer**

This guidance was developed using the single technology appraisal (STA) process.

1 Guidance

- 1.1 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.

2 The technology

- 2.1 Sipuleucel-T (Provenge, Dendreon) is an autologous cellular immunotherapy that stimulates the patient's own immune cells to identify and attack prostate cancer cells. The treatment involves collecting white blood cells from the patient, combining the cells with a protein to make sipuleucel-T, and then infusing the cells back into the patient. Sipuleucel-T has a marketing authorisation in the UK 'for the treatment of asymptomatic or minimally symptomatic metastatic (non-visceral) castrate resistant prostate cancer in male adults in whom chemotherapy is not yet clinically

indicated'. The product had not been launched for use in England when the final appraisal determination was issued.

- 2.2 The summary of product characteristics states that the most common adverse reactions after treatment with sipuleucel-T are chills, fatigue, fever, nausea, joint pain, headache and vomiting. Serious adverse reactions include acute infusion reactions, catheter sepsis, staphylococcal bacteraemia, myocardial infarction and cerebrovascular events. For full details of adverse reactions and contraindications, see the summary of product characteristics.
- 2.3 According to the company, the cost of sipuleucel-T is £16,141.33 per dose, including the costs of leukapheresis, patient tests associated with leukapheresis, manufacture and transportation, and excluding VAT. The summary of product characteristics states that the recommended course of treatment is 3 doses at approximately 2-week intervals. The cost for a course of treatment is £47,132.68, based on a mean of 2.92 doses per patient.

3 The company's submission

The Appraisal Committee (section 8) considered evidence submitted by the company that holds the marketing authorisation for sipuleucel-T and a review of this submission by the Evidence Review Group (ERG; section 9).

Clinical effectiveness

Comparison with placebo

- 3.1 The company identified 3 randomised controlled trials (RCTs) that compared sipuleucel-T with placebo. The pivotal IMPACT trial (also known as D9902B, n=512), and the supportive trials D9901 (n=127) and D9902A (n=98), were phase III randomised double-

blind placebo-controlled multicentre trials conducted in the USA and Canada. All 3 trials included patients with asymptomatic metastatic hormone-relapsed prostate cancer without visceral metastases. The IMPACT trial also recruited patients with minimally symptomatic metastatic hormone-relapsed prostate cancer, defined as not needing regular opioid analgesics and with a pain score of 3 or less out of 10 on a visual analogue scale. All 3 trials excluded patients with visceral metastases (that is, those involving the liver, lungs or brain) or an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or above. In IMPACT, 18.2% of patients had previously received chemotherapy, whereas about 6% of patients in D9901 and about 10% in D9902A had previously received chemotherapy. In each trial, the baseline patient characteristics were similar across the randomised groups.

- 3.2 In all the sipuleucel-T trials, patients were randomised in a 2:1 ratio to have either sipuleucel-T or placebo every 2 weeks for a total of 3 infusions. Patients in either treatment group could have androgen deprivation therapy with or without bisphosphonates. Treatment with corticosteroids or chemotherapy was not allowed. After disease progression, patients in both groups and their clinicians were told which treatment group the patient was in, and the patients were free to choose their subsequent treatments. For patients in the placebo group, 1 option after disease progression was to have salvage therapy with APC8015F – a product manufactured using similar specifications as sipuleucel-T but from frozen white blood cells. APC8015F was made with fewer cells than sipuleucel-T. In IMPACT, 63.7% of patients in the placebo group had salvage therapy, in D9901 it was 75.6% and in D9902A it was 66.7%. In IMPACT, 57.2% of patients in the sipuleucel-T group had docetaxel chemotherapy after progression and 50.3% of patients in the placebo group had docetaxel.

3.3 The primary endpoint for the IMPACT trial was overall survival. The main secondary endpoint was time to disease progression. The company originally included time to disease-related pain as an outcome measure but then removed it in a protocol amendment, so it only measured time to disease-related pain for a subset of patients. Patients remained in the IMPACT trial until death or until the time when 331 patients in the trial had died, at which point the trial stopped. The median follow-up time for the IMPACT trial was 34 months. The primary endpoint for the D9901 and D9902A trials was time to disease progression. Additional endpoints included overall survival and time to onset of disease-related pain. Patients in the D9901 and D9902A trials remained in the study until 36 months after randomisation unless they died sooner. The company did not provide the median follow-up time. For all the trials, the company collected data on the time to the start of docetaxel treatment and carried out intention-to-treat (ITT) analyses. The IMPACT protocol specified that the primary ITT analysis to determine the magnitude of effect would be adjusted for baseline serum concentration of prostate-specific antigen (PSA) and lactate dehydrogenase, as well as for the 3 variables that were used to minimise differences between the randomised groups (that is, Gleason grade, number of bone metastases and bisphosphonate use).

3.4 During the IMPACT trial, 61.6% (210/341) of patients randomised to sipuleucel-T died compared with 70.8% (121/171) of patients randomised to placebo. The IMPACT trial showed that patients randomised to sipuleucel-T survived for longer (median 25.8 months) than patients randomised to placebo (median 21.7 months), with a difference of 4.1 months. The risk of death was statistically significantly lower in the sipuleucel-T group than in the placebo group (hazard ratio [HR] 0.78, 95% confidence interval

[CI] 0.61 to 0.98, $p=0.03$). During the trial, 85.0% (290/341) of patients randomised to sipuleucel-T had disease progression compared with 82.5% (141/171) of patients randomised to placebo. The median time to disease progression was 14.6 weeks with sipuleucel-T and 14.4 weeks with placebo; there was no statistically significant difference between treatment groups (HR 0.95, 95% CI 0.77 to 1.17, $p=0.63$). The time to disease-related pain was measured in 428 patients; there was no statistically significant difference between treatment groups (HR 0.80, 95% CI 0.56 to 1.15, $p=0.23$).

- 3.5 The company conducted a retrospective (that is, not pre-specified in the statistical plan) subgroup analysis of the IMPACT trial. The subgroup was defined as the quartile of patients with the lowest baseline PSA concentration; that is, 22.1 nanogram/ml and below (noting that the trial excluded people with a PSA concentration of 5.0 nanogram/ml and below). In this subgroup of patients, there was a difference of 13.0 months in median survival between treatment groups (HR 0.51, 95% CI 0.31 to 0.85, p value not reported). In the quartile of patients with the highest baseline PSA concentration (above 134.1 nanogram/ml), there was a difference of 2.8 months in median survival between treatment groups (HR 0.84, 95% CI 0.55 to 1.29, p value not reported). The company suggested that sipuleucel-T has a delayed onset of action because it is an immunotherapy, so giving it early in the course of disease progression (as indicated by a low PSA) could provide patients with more time to benefit from sipuleucel-T.
- 3.6 The D9901 trial found a statistically significantly lower risk of death in patients randomised to sipuleucel-T than in patients randomised to placebo (HR 0.59, 95% CI 0.39 to 0.88, $p=0.01$). The D9902A trial did not find a difference between treatment groups on the

secondary outcome measure of overall survival (HR 0.79, 95% CI 0.48 to 1.28, $p=0.33$). Neither trial showed that sipuleucel-T prolonged time to disease progression or time to disease-related pain.

- 3.7 To estimate a summary measure of the effectiveness of sipuleucel-T compared with placebo, the company conducted a meta-analysis using individual patient data from the 3 sipuleucel-T trials. The outcome measures were overall survival, time to the start of docetaxel treatment, and time to disease-related pain. The meta-analysis showed that patients randomised to sipuleucel-T survived longer than patients randomised to placebo (median 25.4 months compared with 21.5 months), with a difference of 3.9 months. The risk of death was statistically significantly lower in the sipuleucel-T group than in the placebo group (HR 0.74, 95% CI 0.61 to 0.88, $p<0.001$). The median time to the start of docetaxel treatment was slightly shorter for the sipuleucel-T group (16.8 months) than for the placebo group (17.7 months); the difference between groups was not statistically significant (HR 1.10, 95% CI 0.88 to 1.38, $p=0.39$). The median time to disease-related pain was 5.6 months in the sipuleucel-T group and 5.3 months in the placebo group; the difference between groups was not statistically significant (HR 0.80, 95% CI 0.60 to 1.08, $p=0.14$).
- 3.8 The company presented a pooled analysis of adverse events in the 3 RCTs that included patients with metastatic prostate cancer (IMPACT, D9901 and D9902A) and 1 trial that included patients with non-metastatic prostate cancer (P-11). In total, the analysis included 601 patients who had sipuleucel-T and 303 patients who had placebo. Most adverse events developed within 1 day of the infusion and resolved within 2 days. The most common adverse events (experienced by at least 15% of patients) in the sipuleucel-T

group were chills, fatigue, fever, back pain, nausea, joint pain and headache. The incidence of infection was 27.5% in the sipuleucel-T group and 27.7% in the placebo group (confidence intervals and p value were not reported). The incidence of serious adverse events was similar in the sipuleucel-T group (24.0%) and the placebo group (25.1%). One reported death was considered to be possibly related to treatment with sipuleucel-T. In the IMPACT trial, 1.5% of patients in the sipuleucel-T group stopped treatment because of adverse events.

Comparison with abiraterone

3.9 To conduct an indirect treatment comparison of sipuleucel-T with abiraterone, the company used the results of the ongoing COU-AA-302 trial. This phase III randomised double-blind placebo-controlled multicentre trial recruited patients with asymptomatic or minimally symptomatic metastatic hormone-relapsed prostate cancer who had not previously received chemotherapy. Patients were randomised to have abiraterone (n=546) or placebo (n=542), both in combination with prednisone. The 2 primary endpoints were progression-free survival and overall survival. The third interim analysis showed that patients randomised to abiraterone survived for longer (median 35.3 months) than patients randomised to placebo (median 30.1 months). The risk of death was lower in the abiraterone group than in the placebo group (HR 0.79, 95% CI 0.66 to 0.95, p=0.0151), but the difference between groups was not statistically significant according to the pre-specified criterion. The third interim analysis showed that progression-free survival, the time to the start of cytotoxic therapy, and the time to the start of opioid use were all statistically significantly longer in the abiraterone group than the placebo group.

3.10 The company's indirect comparison used hazard ratios from the final results of IMPACT and the third interim analysis of COU-AA-302. The company stated that including all 3 sipuleucel-T trials in the indirect comparison would have resulted in more favourable results for sipuleucel-T compared with abiraterone. This is because, for overall survival, the treatment effect of sipuleucel-T was greater based on the meta-analysis (see section 3.7) than based on the IMPACT results alone (see section 3.4). In the IMPACT trial, 18.2% of patients had previously received chemotherapy, whereas this group of patients was excluded from COU-AA-302. Accordingly, the indirect comparison only included results from the subgroup of IMPACT patients who had not previously received chemotherapy. In this subgroup, the hazard ratio for the risk of death with sipuleucel-T compared with placebo was 0.75 (95% CI 0.58 to 0.95, p value not stated). The indirect comparison showed that sipuleucel-T and abiraterone had a similar effect on overall survival. The hazard ratio for sipuleucel-T compared with abiraterone was 0.94 (95% CI 0.69 to 1.28, p=0.70).

Evidence Review Group's comments

3.11 The ERG commented that the treatment pathways for patients in the sipuleucel-T trials may not reflect the pathways currently used in the NHS, which could limit how generalisable the results are to clinical practice. The ERG noted that 18.2% of patients in the IMPACT trial had previously received chemotherapy. The ERG queried whether these patients would fall within the marketing authorisation for sipuleucel-T, which specifies use only when chemotherapy is not yet clinically indicated. In response to clarification, the company explained that, at the time the trial started, guidelines for the use of chemotherapy in metastatic hormone-relapsed prostate cancer were not as well defined as they are now. The company stated that the patients enrolled in IMPACT

would have been unlikely to have chemotherapy under current UK treatment guidelines.

- 3.12 The ERG noted that the sipuleucel-T trials showed a benefit in overall survival but not in time to disease progression. The ERG advised that this apparent inconsistency may be due to confounding of the overall survival data because of non-randomised treatment after disease progression.
- 3.13 The ERG cautioned that the subgroup of patients in the IMPACT trial with low baseline PSA had been identified in a post-hoc analysis. It stated that, because randomisation was not stratified by baseline PSA, there may have been confounding differences (that is, differences in prognostic variables) between the sipuleucel-T and placebo groups in the low-PSA subgroup. The ERG also noted advice from clinical experts that there is no clinical significance attached to a PSA concentration of 22.1 nanogram/ml.
- 3.14 The ERG advised that the company's rationale for excluding D9901 and D9902A from the indirect comparison (see section 3.10) was based on analyses of the whole population. However, the company presented no evidence on the results of the meta-analysis for a subgroup not previously treated with chemotherapy. In response to the factual check of the ERG report, the company presented a pooled analysis of all 3 sipuleucel-T trials in the subgroup not previously treated with chemotherapy; the hazard ratio for the risk of death with sipuleucel-T compared with placebo was 0.72 (95% CI 0.59 to 0.88, p value not stated). When this pooled hazard ratio was used in the indirect comparison, the hazard ratio for the risk of death with sipuleucel-T compared with abiraterone was 0.91 (95% CI 0.70 to 1.20, p value not stated). The company stated that it adopted a conservative approach in its economic model by using

the higher hazard ratio from the indirect comparison that included only the IMPACT trial (see section 3.10).

- 3.15 The ERG commented that it was not possible to establish the adverse-event profile of sipuleucel-T compared with only best supportive care (BSC). This was because all patients in the control group had at least 1 leukapheresis and placebo infusion, and the possible adverse effects of these procedures were unknown. The placebo consisted of blood cells that had been collected, transported and infused in the same way as cells from patients in the treatment group, except the placebo cells were not cultured to create the active component of sipuleucel-T.
- 3.16 Regarding the company's indirect comparison, the ERG expressed concern that the placebo groups in the 2 trials may not have been similar because patients had prednisone in the placebo arm of COU-AA-302 but not in IMPACT. Moreover, the choice of treatment after progression may have varied between trials. The indirect comparison also assumed that hazards were proportional between arms of each trial, yet the ERG could not confirm that this assumption had been met in COU-AA-302. Because of these issues, the ERG advised that there was uncertainty in the results of the indirect comparison.

Cost effectiveness

- 3.17 The company submitted a cost-utility Markov model comparing sipuleucel-T with BSC and abiraterone for asymptomatic or minimally symptomatic metastatic hormone-relapsed prostate cancer. The model had 3 main health states: pre-docetaxel use, death, and a single state that included both docetaxel use and post-docetaxel use. The pre-docetaxel health state was split into 4 sub-states, defined by whether the patient used opioids and/or

experienced adverse events. The use of opioids served as a proxy for patients experiencing pain. Patients moved from the pre-docetaxel to the docetaxel/post-docetaxel health state when their disease was no longer adequately controlled with sipuleucel-T, BSC or abiraterone. Patients were treated with docetaxel when they entered the docetaxel/post-docetaxel health state and they remained in this health state until death. In the company's opinion, an alternative model structure based on pre- and post-progression health states would have needed sub-states to reflect different stages of care and states of health, which it suggested would have been less transparent than the chosen model structure. The company stated that the use of pre- and post-progression health states would not have provided additional insight into the cost effectiveness of sipuleucel-T. The company's model was based on a lifetime time horizon of 10 years and a cycle length of 30.42 days; it included a half-cycle correction. Both costs and utilities were discounted at 3.5% per year and the perspective was that of the NHS and personal social services.

3.18 In the base case, the modelled population was based on the ITT population of the IMPACT trial. The company also presented a subgroup analysis of patients with a baseline PSA concentration of 22.1 nanogram/ml or below (see section 3.5). The comparator for the base case and the low-PSA subgroup was BSC. For the comparison with abiraterone, the company presented a third analysis based on the subgroup of patients who had not previously received chemotherapy.

3.19 For the base case and the low-PSA subgroup, the company estimated the proportion of time that patients spent in each health state by using parametric curves fitted to the IMPACT trial data. The base-case analyses used the ITT data and the low-PSA

analyses used data from the quartile of patients with the lowest baseline PSA concentration. The company chose log-normal or log-logistic survival functions and fitted them independently to each trial arm for the outcome measures of time to opioid treatment, time to docetaxel use and overall survival. In the IMPACT trial, patients in the placebo arm could have salvage therapy with APC8015F after disease progression. The company stated that APC8015F would be unavailable outside the trial, so it assumed that patients in the BSC arm of the model had docetaxel instead. Thus, for the BSC arm, the time that patients spent in the pre-docetaxel health state was informed by trial data that showed the time to the first use of docetaxel or APC8015F or death.

3.20 In the base case, the company did not adjust the overall survival curve representing BSC to take into account the benefit of APC8015F salvage therapy (that is, treatment switching) in the IMPACT trial. However, for the low-PSA subgroup, the company used an iterative parameter estimation model to adjust for the benefit of APC8015F therapy. This means that, for the low-PSA subgroup, the BSC arm of the model estimated survival times for people who did not have APC8015F. The company assumed that APC8015F prolonged life to the same extent as sipuleucel-T.

3.21 When comparing sipuleucel-T with abiraterone, the company estimated the time in different health states in the sipuleucel-T arm of the model using curves fitted to the IMPACT data as described in section 3.19. The company used data from the subgroup of patients in IMPACT who had not previously received chemotherapy. The company then used the overall survival hazard ratio derived from the indirect comparison (see section 3.10) to estimate survival in the abiraterone arm of the model, based on survival with sipuleucel-T. In its original model, the company

assumed that the curves for time to docetaxel use and time to opioid use for abiraterone were equivalent to those for sipuleucel-T. In response to clarification, the company submitted an additional analysis that used hazard ratios derived from an indirect comparison to estimate time to docetaxel use and time to opioid use for abiraterone compared with sipuleucel-T.

- 3.22 The company did not measure health-related quality of life in the sipuleucel-T trials, so the company's model used utility values taken from published studies. The company took the utility value for the pre-docetaxel health state for individuals not taking opioids and without adverse events, 0.760, from a meta-analysis of utility values for prostate cancer (Bremner et al. 2007). In Bremner et al., the utility value of 0.760 described a health state of metastatic disease with severe sexual dysfunction. To estimate the utility values for the other 3 pre-docetaxel sub-states, the company applied disutilities associated with pain and adverse events. The company calculated the utility value for the docetaxel/post-docetaxel health state as an average of the utility while having docetaxel (0.538, taken from Sandblom et al. 2004) and after having docetaxel (0.691, assumed to be equivalent to the utility of patients before docetaxel who are taking opioids but do not experience adverse events). This average was weighted by the proportion of patients having docetaxel and by the time spent 'on and off' docetaxel, for each arm of the model. In response to clarification, the company corrected its utility calculations and provided revised estimates for the docetaxel/post-docetaxel health state; these estimates were not weighted by the proportion of patients having docetaxel. The company assumed that the utility values were constant within each health state.

- 3.23 The company's estimates of resource use were based on a systematic review and a survey of oncologists in the UK. Costs were based on the British national formulary (BNF), NHS reference costs and the Payment by Results tariff. The company calculated that sipuleucel-T had a fixed acquisition cost of £47,132.68 based on an average of 2.92 infusions, estimated from IMPACT. This cost included leukapheresis, transportation of white blood cells, and manufacture and transportation of the drug. In the base-case analysis, the company used a fixed acquisition cost of £58,600 for abiraterone, based on the BNF list price and a treatment duration of 20 months. Abiraterone is available to the NHS through a simple discount patient access scheme, for which the level of the discount is confidential and cannot be disclosed to the company that holds the marketing authorisation for sipuleucel-T. Accordingly, the company applied assumed discounts to the list price of abiraterone in a sensitivity analysis. Other drug costs in the model included docetaxel, which is offered to some patients after disease progression. The company applied the acquisition costs for sipuleucel-T, abiraterone and docetaxel once at the beginning of the model.
- 3.24 Costs in the pre-docetaxel health state included physician visits, procedures and tests, and when necessary the costs of opioids and managing adverse events. In addition, the docetaxel and post-docetaxel health state included the costs of cancer-related hospitalisations. The model included the cost of end-of-life care.

Results of the company's economic analyses

- 3.25 In the company's base-case analysis, treatment with sipuleucel-T resulted in more quality-adjusted life years (QALYs; incremental QALY gain 0.354) and higher costs (incremental costs £44,266) than BSC. The incremental cost-effectiveness ratio (ICER) for

sipuleucel-T compared with BSC was £124,875 per QALY gained. The company conducted sensitivity analyses and scenario analyses that resulted in ICERs of at least £84,823 per QALY gained for sipuleucel-T compared with BSC.

- 3.26 In the company's analysis for the subgroup with a baseline PSA concentration of 22.1 nanogram/ml or below, the ICER for sipuleucel-T compared with BSC was £48,672 per QALY gained (incremental QALY gain 0.937, incremental costs £45,620). The company conducted sensitivity analyses and scenario analyses that resulted in ICERs between £43,659 and £56,878 per QALY gained for sipuleucel-T compared with BSC.
- 3.27 In the company's analysis of sipuleucel-T compared with abiraterone for the subgroup of patients who had not previously received chemotherapy, sipuleucel-T dominated abiraterone at list price. This result means that treatment with sipuleucel-T resulted in more QALYs (incremental QALY gain 0.023) and lower costs (incremental costs £5954) than treatment with abiraterone. The company conducted sensitivity analyses applying assumed discounts to the price of abiraterone of 30% or more; these analyses resulted in ICERs for sipuleucel-T compared with abiraterone of at least £511,663 per QALY gained.
- 3.28 In response to a request for clarification, the company provided additional sensitivity analyses that altered 1 variable at a time. The analyses:
- used hazard ratios derived from an indirect comparison to estimate time to docetaxel use and time to opioid use for abiraterone compared with sipuleucel-T (see section 3.21)
 - used revised utility values for the docetaxel/post-docetaxel health state (see section 3.22)

- used a Weibull distribution for overall survival and time to docetaxel
- assumed fewer patients had docetaxel
- reduced the number of cycles of docetaxel.

For the ITT population of the IMPACT trial and the low-PSA subgroup, the sensitivity analyses generally resulted in higher ICERs than those presented in the original submission. For the ITT population, the sensitivity analyses resulted in ICERs between £130,985 and £141,330 per QALY gained for sipuleucel-T compared with BSC. For the low-PSA subgroup, the sensitivity analyses resulted in ICERs between £49,657 and £54,901 per QALY gained for sipuleucel-T compared with BSC. For the comparison with abiraterone in the subgroup of patients who had not previously received chemotherapy, the sensitivity analyses showed that sipuleucel-T dominated abiraterone at the list price.

Evidence Review Group's comments

3.29 The ERG observed that the company had not presented a fully incremental analysis to compare sipuleucel-T with both BSC and abiraterone. The ERG stated that a different model structure, based on time to progression rather than time to docetaxel use, may have altered the estimates of cost-effectiveness for sipuleucel-T. This was because the company's chosen model structure (based on time to docetaxel use) did not include any decrease in health-related quality of life, or increase in costs, associated with disease progression that occurred before treatment with docetaxel. The ERG stated that there were several months, on average, between disease progression and the start of docetaxel treatment in the IMPACT trial.

3.30 The ERG compared the estimates of time to docetaxel use from the IMPACT trial and the company's model (see section 3.19). In the trial, the median time to docetaxel use was 10.1 months in the sipuleucel-T group and the median time to either docetaxel or APC8015F use was 6.0 months in the placebo group. In the company's base-case model, the median time to docetaxel use was 12.6 months in the sipuleucel-T arm and the median time to either docetaxel or APC8015F use was 7.1 months in the BSC arm. The ERG expressed concern that patients in the placebo group of the trial may have had APC8015F before treatment with docetaxel was necessary. Accordingly, the ERG advised that the trial and the model may have underestimated time to docetaxel use for patients treated with BSC. To support this argument, the ERG referred to a publication of the IMPACT trial that showed that time to docetaxel use was longer in the placebo group than in the sipuleucel-T group (estimated median 13.9 months compared with 12.3 months), when the analysis used data on time to docetaxel use only rather than time to either docetaxel or APC8015F use. The ERG advised that time to docetaxel use was an important driver of the base-case model because 92.8% of the incremental QALY gain associated with sipuleucel-T was accrued within the pre-docetaxel health state. Overall, the ERG considered that the trial data did not support the assumption in the company's model that sipuleucel-T prolonged time to docetaxel use compared with BSC.

3.31 When the ERG fitted curves to the IMPACT data, the results were different to those presented by the company. The ERG believed that the company mistakenly used the parameter values from the log-logistic fit for the log-normal curve and vice versa. The ERG's parameters for the Weibull distribution were the same as those provided by the company. The ERG noted that the Weibull distribution provided a good fit to the overall survival data and was

used in the company's iterative parameter estimation analysis (see section 3.20). Therefore, the ERG chose a Weibull distribution for overall survival in its exploratory analyses.

- 3.32 The ERG questioned why the company had not adjusted the survival curve representing BSC in its base case to account for patients switching to salvage treatment with APC8015F. The company did adjust for treatment switching in its analyses of the low-PSA subgroup. However, the ERG noted that the company's iterative parameter estimation analysis used data for the entire ITT population and the company applied the results to analyses of the low-PSA subgroup. In the ERG's opinion it would have been preferable to conduct the iterative parameter estimation analysis using data for the low-PSA subgroup only. The ERG stated that, as a result, the company's model and the ERG's exploratory analyses may have overestimated overall survival in the BSC arm of the low-PSA subgroup.
- 3.33 When comparing sipuleucel-T with abiraterone, the company assumed that time to docetaxel use and time to opioid use for patients treated with abiraterone were the same as for patients treated with sipuleucel-T. The ERG was concerned that the company's assumptions did not reflect the trial data. The COU-AA-302 trial found that time to cytotoxic therapy and time to opioid use were longer with abiraterone than with placebo. In contrast, the sipuleucel-T trials did not find a benefit of sipuleucel-T compared with placebo in time to docetaxel use or time to opioid use. The ERG noted that the company provided a revised model in response to a clarification request. The revised model used hazard ratios derived from an indirect comparison for time to docetaxel use and time to opioid use. However, the ERG was concerned that the

hazard ratios used in the company's revised model appeared to be inconsistent with the results of IMPACT and COU-AA-302.

- 3.34 The ERG queried why the company had used the utility value of 0.76 from Bremner et al. (2007) rather than the value of 0.72 from Sullivan et al. (2007) for the pre-docetaxel health state. The ERG noted that the Bremner et al. meta-analysis included several studies that measured utility values using the time trade-off technique, which is not in the NICE reference case. In contrast, the ERG noted that the Sullivan et al. study used the EQ-5D which is in the NICE reference case. The ERG explored the impact of using the Sullivan et al. utility value in its sensitivity analyses.
- 3.35 The ERG considered that the company used an inappropriate method to calculate the utility of the docetaxel/post-docetaxel health state in its original model, because it was not necessary to weight average utility by the proportion of patients having docetaxel. The ERG preferred the company's revised utility values for the docetaxel/post-docetaxel health state (see section 3.22).
- 3.36 The ERG noted that the company's modelled duration of abiraterone treatment (19.8 months) was substantially longer than the modelled mean time to docetaxel (12.4 months). This implies that patients have treatment with abiraterone and docetaxel concurrently, which is implausible. Consequently, in the ERG's opinion, the company's model lacked face validity. The ERG reduced the duration of abiraterone treatment in its exploratory analyses to be the same as the time to treatment with docetaxel.
- 3.37 The ERG observed that the company calculated the cost of docetaxel in the BSC arm based on the proportion of patients having either docetaxel or APC8015F in IMPACT. For the company's analysis that adjusted for treatment switching to

APC8015F, the ERG considered it would have been preferable to base the cost of docetaxel on the proportion of patients having docetaxel only. The ERG also noted that the company's original model assumed 10 cycles of docetaxel treatment, whereas clinical experts advised that most patients would have 6–9 cycles. In response to clarification, the company provided sensitivity analyses that used fewer cycles of docetaxel.

Evidence Review Group's exploratory analyses

3.38 The ERG's exploratory analyses used a base case that incorporated the following changes:

- The company's revised utility values for the docetaxel/post-docetaxel health state (see sections 3.22 and 3.35).
- Overall survival curves using a Weibull instead of a log-normal distribution (see section 3.31).
- An overall survival curve for the BSC arm adjusted for treatment switching to salvage therapy with APC8015F (see section 3.32).
- The ERG's estimates of parameters for the log-normal curves for time to docetaxel use and time to opioid use (see section 3.31).
- An assumption that time to docetaxel use was the same in the BSC arm and the sipuleucel-T arm (see section 3.30).
- Basing the proportion of patients who incurred the cost of docetaxel on the proportion who had docetaxel in the BSC arm of the trial, rather than the proportion who had either docetaxel or APC8015F (see section 3.37).
- An assumption that patients treated with docetaxel had a mean of 7.3 cycles of docetaxel based on advice from clinical experts (see section 3.37) and the company's response to clarification.

3.39 In the ERG's base case, the ICER for sipuleucel-T compared with BSC was £111,417 per QALY gained. The ERG stated that the key

drivers of the cost-effectiveness results were the choice of parametric distribution for overall survival and the assumptions about docetaxel use (including the time to docetaxel use, the proportion of patients who had docetaxel and the number of cycles of docetaxel).

3.40 The ERG's analysis for the low-PSA subgroup resulted in an ICER of £61,381 per QALY gained for sipuleucel-T compared with BSC. A one-way sensitivity analysis that used a log-normal curve for overall survival resulted in an ICER for sipuleucel-T compared with BSC of £58,279 per QALY gained.

3.41 For the analyses of the subgroup of patients who had not previously received chemotherapy, the ERG used its base-case parameters and initially assumed that there was no difference between sipuleucel-T and abiraterone in time to docetaxel use and time to opioid use. The ERG reduced the duration of abiraterone treatment to be the same as time to docetaxel use. The ERG conducted an incremental analysis that included BSC, abiraterone at list price and sipuleucel-T. The results indicated that treatment with abiraterone gained more QALYs and incurred higher costs than BSC. In turn, treatment with sipuleucel-T gained more QALYs and incurred higher costs than abiraterone. The results showed that abiraterone was extendedly dominated, meaning that the ICER for abiraterone compared with BSC was higher than the ICER for sipuleucel-T compared with BSC. Treatments that are extendedly dominated are typically removed from an incremental cost-effectiveness analysis. The ICER for sipuleucel-T compared with BSC was £111,682 per QALY gained. The ERG conducted one-way sensitivity analyses that applied assumed discounts of 20% or more to the price of abiraterone. With the discounted prices, abiraterone was no longer extendedly dominated and the

ICERs for sipuleucel-T compared with abiraterone were at least £243,492 per QALY gained.

3.42 The ERG did not accept the company's assumption that there was no difference between sipuleucel-T and abiraterone in time to docetaxel use or time to opioid use. In the ERG's opinion, this assumption contradicted the trial results. However, the ERG acknowledged that an indirect comparison was not possible because there were insufficient data on outcomes for the subgroup not previously treated with chemotherapy in the IMPACT trial. The ERG conducted a one-way sensitivity analysis in which it assumed that the time to docetaxel use was equal between sipuleucel-T and BSC, and it applied the hazard ratio from the COU-AA-302 trial to estimate time to docetaxel use with abiraterone. Sipuleucel-T dominated abiraterone (at its list price) and the ICER for sipuleucel-T compared with BSC was £111,682 per QALY gained.

3.43 Full details of all the evidence are in the [committee papers](#).

4 Consideration of the evidence

The Appraisal Committee reviewed the data available on the 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. It also took into account the effective use of NHS resources.

4.1 The Committee noted that, in their submissions to NICE, patient organisations indicated that the most important benefits of sipuleucel-T were its potential to extend life, its short course of treatment and that it has few associated adverse reactions. Although the patient organisations advised that there was no

experience of using sipuleucel-T in England, they expected sipuleucel-T to reduce pain, improve mental and physical health, and offer an additional treatment option at an early stage of disease progression. The Committee noted that, in response to the appraisal consultation document, a patient group and a patient expert said that they encouraged the development of innovative treatments and that sipuleucel-T would provide a valuable additional treatment option with manageable side effects. The Committee concluded that patients would like to have the option of having treatment with sipuleucel-T within the NHS.

4.2 The Committee discussed the place of sipuleucel-T in the clinical pathway of care for people who have metastatic hormone-relapsed prostate cancer (without visceral metastases) with no or minimal symptoms for which chemotherapy is not yet indicated. The Committee noted that the treatments currently used in the NHS in England include best supportive care (BSC), abiraterone and radium-223. The clinical experts stated that, given its mechanism of action as an immunotherapy, they would prefer to use sipuleucel-T earlier in the treatment pathway before moving on to abiraterone and chemotherapy. The Committee noted that it had not been presented with evidence on the effectiveness of sipuleucel-T at different places in the treatment pathway, and it was aware that the marketing authorisations for sipuleucel-T and abiraterone are almost identical. Therefore, the Committee concluded that it could only appraise sipuleucel-T based on the evidence presented and in line with the marketing authorisation.

4.3 The Committee considered the relevant comparators for this appraisal. It noted that docetaxel was listed as a comparator in the final scope issued by NICE. It understood that the company did not present a comparison of sipuleucel-T with docetaxel because the

marketing authorisation for sipuleucel-T specifies people with metastatic hormone-relapsed prostate cancer for which chemotherapy is not yet indicated. The Committee agreed that docetaxel is not a relevant comparator. The Committee noted that people in England with prostate cancer that is not yet suitable for chemotherapy may have abiraterone through the Cancer Drugs Fund. Although the Committee was aware that the use of abiraterone in this setting is currently being appraised by NICE, and that the Cancer Drugs Fund is a special funding arrangement that is not guaranteed after 2016, it was satisfied that abiraterone is currently part of established practice in the NHS. The clinical experts stated that, although radium-223 is also available through the Cancer Drugs Fund, it is generally used for people with symptomatic disease and could not be considered a relevant comparator to sipuleucel-T. The Committee also heard from clinical experts and patient experts that some patients would have BSC that may involve radiotherapy, bisphosphonates, corticosteroids or pain relief. The Committee concluded that abiraterone and BSC are the most relevant comparators for sipuleucel-T.

Clinical effectiveness

4.4 The Committee considered the clinical effectiveness of sipuleucel-T and noted that the evidence in the company's submission came from the pivotal IMPACT trial and 2 additional trials (D9901 and D9902A) that compared sipuleucel-T with placebo. It noted that all 3 trials included patients who had previously received chemotherapy and the Committee discussed the implications of this, given that the marketing authorisation for sipuleucel-T specifies people with metastatic hormone-relapsed prostate cancer for which chemotherapy is not yet clinically indicated. The Committee heard from clinical experts that the trials were

conducted at a time when chemotherapy was the only available treatment option, and that sipuleucel-T would be used before chemotherapy in current clinical practice. The Committee accepted that the patients in IMPACT who had previous chemotherapy might not have had this treatment under current clinical care. However, it considered that previous chemotherapy could impact on the clinical effectiveness of subsequent treatments, so it was important to examine trial results for people who had not previously received chemotherapy. The Committee noted that, for the IMPACT trial, the company presented results for a pre-specified subgroup of patients who had not previously received chemotherapy, but these results were used only for the comparison with abiraterone. The Committee concluded that the subgroup of patients who had not previously received chemotherapy reflected the marketing authorisation for sipuleucel-T and was the most relevant population for this appraisal.

- 4.5 The Committee discussed the results of the randomised controlled trials of sipuleucel-T. It noted that 2 of the 3 trials showed that sipuleucel-T extended life, but none of the trials showed that sipuleucel-T prolonged time to disease progression. The Committee heard from clinical experts that the biological reasons for this pattern of results were not fully understood, but similar findings had been reported for other immunotherapies for cancer. Clinical experts also told the Committee that 1 explanation for the observed results could be that immunotherapies take some time to show their full benefit. The patient experts expressed concerns that the placebo used in the sipuleucel-T trials may have been harmful to older patients. However, the Committee noted that the European public assessment report concluded that the placebo treatment was unlikely to have adversely affected the patients in the control group. The Committee noted the Evidence Review Group's (ERG)

comments that the overall survival results may have been confounded by post-progression treatments. In particular, the post-progression use of docetaxel was more common in the sipuleucel-T group of the IMPACT trial than in the placebo group (see section 3.2) and this could mean that the trial overestimated the effectiveness of sipuleucel-T. The Committee was aware that, in all 3 trials, patients in the placebo group could have salvage therapy with APC8015F. Having heard from the clinical experts that the APC8015F salvage therapy was likely to be as effective as sipuleucel-T, the Committee considered that the trials may have underestimated the effectiveness of sipuleucel-T and therefore it was reasonable to adjust the results for treatment switching to APC8015F (see section 4.14). Based on the balance of the evidence presented, the Committee concluded that sipuleucel-T improved survival compared with placebo. The Committee also concluded that the trials did not show that sipuleucel-T delayed disease progression compared with placebo.

4.6 The Committee considered whether the results from the sipuleucel-T trials could be generalised to the population in England. It heard from the clinical experts that, although the trials were conducted in the USA and Canada, they would expect similar results to be obtained in the UK. The Committee accepted the views of the clinical experts and concluded that the results from the trials were likely to be generalisable to the population in England.

4.7 The Committee discussed the subgroup of patients with a baseline serum prostate-specific antigen (PSA) concentration of 22.1 nanogram/ml and below, noting that the company identified this subgroup retrospectively. The Committee queried why the company had chosen PSA, rather than another prognostic variable, to define a subgroup. It heard that the company built a statistical

model that predicted death in the IMPACT trial based on 6 baseline variables. The company stated that it had selected PSA to define a subgroup because baseline PSA had the lowest p value of these 6 variables. The Committee noted that the company had not provided full details of this analysis, and that a low p value did not necessarily mean that PSA had the largest effect on treatment outcomes. The Committee queried why the company had chosen an upper limit of 22.1 nanogram/ml to define the subgroup, rather than any other value. During the first Appraisal Committee meeting, the Committee heard from the company that it had conducted several analyses using different cut-offs of PSA (such as decile groups in IMPACT) and that, in its submission, it had chosen to present evidence on the subgroup that showed the greatest benefit of sipuleucel-T. This was the group with the lowest quartile of PSA values (22.1 nanogram/ml and below). The Committee considered that this method of identifying subgroups was arbitrary and scientifically inappropriate, because it increased the risk of finding statistically significant differences between treatment groups that had occurred by chance. During the second Appraisal Committee meeting, the Committee heard that the company had focused on the subgroup with the lowest quartile of PSA values because sipuleucel-T was more cost effective in this subgroup and because the quartile analysis was included in the European public assessment report and the summary of product characteristics. The company was unable to explain why it had presented the PSA quartile analysis rather than other PSA analyses (such as decile groups) to the European Medicines Agency. The Committee noted that the company did not present a statistical test of interaction (that is, a test of whether the effectiveness of sipuleucel-T varied according to a patient's baseline PSA concentration). The company was unable to confirm whether the hazard ratio for the low-PSA

subgroup was adjusted for prognostic variables, notably PSA and the variables used to minimise differences between the randomised groups. The company's response to the appraisal consultation document did not provide additional justification for the way it identified the low-PSA subgroup and for the way it conducted statistical analyses for this subgroup. The Committee concluded that the company had identified the low-PSA subgroup in an arbitrary manner. It also concluded that there was insufficient evidence to establish whether the clinical effectiveness of sipuleucel-T was different in the low-PSA subgroup compared with the rest of the population.

- 4.8 The Committee discussed the clinical relevance of the cut-off in PSA concentration of 22.1 nanogram/ml. The clinical experts were unable to identify any single PSA value that was currently used for guiding treatment decisions. The Committee also heard from clinical experts that, in clinical practice, the choice of treatment was not based on PSA alone but was influenced by several factors including: symptoms; the rate of change of PSA; the results of bone and CT scans; and patient preference. In response to the appraisal consultation document, the company advised that PSA value may be used to guide treatment decisions for new technologies such as sipuleucel-T, even if PSA values have not been used previously to guide treatment decisions. The Committee accepted this possibility. It noted that registry data could have been used to assess whether outcomes after treatment with sipuleucel-T in clinical practice were similar to those in the IMPACT trial for patients with low baseline PSA concentration. However, the company had not presented such information. The Committee heard from the company that the 'Provenge Registry for Observation, Collection and Evaluation of Experience Data' (PROCEED) is measuring outcomes for patients who have had sipuleucel-T, but the company considered that the

data are immature and cannot provide useful information on overall survival. The Committee considered that the population relevant to the appraisal comprised people who had not previously received chemotherapy, yet the company had not presented results for a low-PSA subgroup for this population. The Committee concluded that it could not rely on the company's subgroup analysis because the PSA concentration of 22.1 nanogram/ml was not currently used to guide treatment choices in clinical practice and the company's analysis included some people who had previously received chemotherapy.

- 4.9 The Committee considered the company's indirect comparison of sipuleucel-T with abiraterone, which used data from the IMPACT and COU-AA-302 trials. It noted that the point estimate for the hazard ratio for the risk of death was 0.94 (see section 3.10), suggesting that sipuleucel-T was more effective than abiraterone in prolonging overall survival. However, the difference was not statistically significant (95% confidence interval 0.69 to 1.28, $p=0.70$). The Committee was aware that the company used results from the IMPACT trial alone, rather than from the meta-analysis of sipuleucel-T trials, in the indirect comparison. The Committee heard from the company that it used the IMPACT trial alone because this trial included patients with no symptoms and those with minimal symptoms, and that this population matched the marketing authorisation for sipuleucel-T. The Committee also heard from the company that an indirect comparison based on the meta-analysis would be more favourable to sipuleucel-T (see section 3.14). The Committee noted that the other 2 sipuleucel-T trials (D9901 and D9902A) included asymptomatic patients, a population that was included in the marketing authorisation and was relevant for this appraisal. The Committee considered that the indirect comparison should include all of the relevant clinical trial

evidence and therefore it would be preferable to use the meta-analysis results. The Committee was aware that the ERG had several concerns about the indirect comparison (see section 3.16), including differences between the IMPACT and COU-AA-302 trials in the placebo group and in post-progression treatments. The Committee concluded that there was uncertainty surrounding the results of the indirect comparison, but that it would be reasonable to assume that sipuleucel-T and abiraterone had similar effectiveness in prolonging overall survival.

- 4.10 The Committee discussed the adverse events associated with treatment with sipuleucel-T. It noted that the most common adverse events in the sipuleucel-T group in the trials were chills, fatigue, fever, back pain, nausea, joint pain and headache. It also noted that most adverse events in the trials developed within 1 day of the infusion and resolved within 2 days. The Committee noted that the European public assessment report stated that sipuleucel-T is considered less toxic than other therapies (such as abiraterone, enzalutamide, docetaxel and cabazitaxel) that are currently used for treating metastatic hormone-resistant prostate cancer. The Committee concluded that the current evidence indicates that sipuleucel-T has a manageable adverse-event profile.

Cost effectiveness

- 4.11 The Committee discussed the different populations included in the company's economic analyses. It noted that the company's base case used the intention-to-treat population from IMPACT, which included patients who had previously received chemotherapy. The Committee considered that the relevant population for the appraisal comprised patients who had not received prior chemotherapy (see section 4.4). The Committee concluded that the economic analysis based on the subgroup of patients who had not received prior

chemotherapy was more relevant to the appraisal than the company's base-case analysis.

4.12 The Committee considered the structure of the company's economic model, which defined health states based on the time to treatment with docetaxel. It heard from clinical experts that the start of chemotherapy was an important event for patients, so it was reasonable to include this time point in the economic model. However, the Committee noted that it was more usual to base an economic model on states of health rather than stages of treatment. The Committee was aware of the comment from the ERG that the model did not include the disutility and costs associated with disease progression that occurs before docetaxel treatment, and it noted advice from clinical experts that quality of life usually deteriorates before docetaxel. The Committee observed that it was not clear how the model captured the disutility and costs associated with disease progression for those patients who did not have docetaxel. It heard from clinical experts that some patients stop using opioids, but this possibility was not included in the model. The Committee also considered it preferable to include time to disease progression in the economic model because this was a blinded outcome in the sipuleucel-T trials, whereas time to docetaxel was not blinded. The Committee was aware that the model did not consider any post-progression treatments other than docetaxel. The Committee concluded that the company's model structure did not adequately reflect the treatment pathway and course of disease for patients with metastatic hormone-relapsed prostate cancer, and that this added considerable uncertainty to the estimates of cost effectiveness.

4.13 The Committee discussed the data on relative effectiveness used in the economic model. The Committee was aware that the

company used data from the IMPACT trial. It considered that it would have been preferable to base the model on the meta-analysis of sipuleucel-T trials because the meta-analysis included all relevant trial evidence. The Committee discussed the distributions for overall survival used by the company (log-normal) and the ERG (Weibull). The Committee agreed that both of these curves fitted the data well, and that it was appropriate to use a Weibull curve to be consistent with the curve used in the iterative parameter estimation model. For the comparison with abiraterone, the Committee considered that there was substantial uncertainty about the results of the indirect comparison. Accordingly, the Committee agreed that it was necessary to consider sensitivity analyses that used alternative assumptions, for example, assuming that sipuleucel-T and abiraterone were equally effective in prolonging survival (that is, a hazard ratio of 1). The Committee noted that the company did not present these sensitivity analyses. The Committee also noted that the assumptions in the company's model about time to docetaxel and time to opioids with abiraterone did not reflect the trial data for abiraterone, and the assumptions favoured sipuleucel-T (see section 3.33). In summary, the Committee agreed that the company's model had excluded evidence from some sipuleucel-T trials and had not explored alternative assumptions about the relative effectiveness of sipuleucel-T and abiraterone. It concluded that it was necessary to address these issues in order to estimate a plausible incremental cost-effectiveness ratio (ICER), and it noted that the ERG had done this in its exploratory analyses.

- 4.14 The Committee considered treatment switching in the IMPACT trial. It was aware that 63.7% of patients in the placebo group had salvage therapy with APC8015F after disease progression. The Committee heard from clinical experts and the company that,

although APC8015F was made from frozen cells and a smaller number of cells, it was believed to be as effective as sipuleucel-T. The Committee agreed that APC8015F may have had a beneficial effect on overall survival. Accordingly, the Committee concluded that in the economic analyses of sipuleucel-T it was appropriate to adjust for treatment switching to APC8015F in the control arm of IMPACT. During the meeting, the company was unable to explain the method it had used to adjust for treatment switching and it could not comment on whether using an alternative method would have affected the estimates of cost effectiveness. The Committee concluded that it was appropriate to adjust for treatment switching to APC8015F in the economic analyses of sipuleucel-T, but it had not been provided with enough information to determine whether the company's method of adjustment was appropriate.

- 4.15 The Committee discussed the costs used in the company's model. It noted that the acquisition cost of sipuleucel-T included the costs of leukapheresis, patient tests associated with leukapheresis, transportation of white blood cells, and manufacture and transportation of sipuleucel-T. Because it is complex to administer sipuleucel-T, and there is no experience in the UK of using this treatment, the Committee was unsure whether the NHS would incur additional costs of using sipuleucel-T not included in the economic model. The Committee noted that the company planned to offer sipuleucel-T in a limited number of treatment centres initially. It heard from patient experts that this could make it difficult for some people to get treatment with sipuleucel-T. The Committee considered that there may be patient travel costs associated with sipuleucel-T treatment, but those costs had not been included in the model. The Committee concluded that some elements of the cost to the NHS of providing treatment with sipuleucel-T were unclear and that this added uncertainty to the estimates of cost

effectiveness. The Committee was aware that abiraterone is available to the NHS through a simple discount patient access scheme, for which the level of the discount is confidential and cannot be disclosed to the company that holds the marketing authorisation for sipuleucel-T. The Committee was aware of the true discount in the patient access scheme for abiraterone. The Committee further concluded that it was appropriate to use assumed discounts for the price of abiraterone in the economic analyses.

- 4.16 The Committee discussed the exploratory analyses conducted by the ERG: adjusting for treatment switching; using a Weibull distribution to model overall survival; assuming that docetaxel-free survival was the same in the BSC arm and the sipuleucel-T arm; and assuming a shorter duration of treatment for both docetaxel and abiraterone. The Committee noted that, in its exploratory analyses, the ERG modelled docetaxel-free survival as time to docetaxel use only, whereas the company used data on time to either docetaxel or APC8015F use. The Committee preferred the ERG's approach because APC8015F may have been provided before docetaxel was indicated and there was no evidence that sipuleucel-T prolonged time to docetaxel use compared with BSC (see sections 3.19 and 3.30). The Committee also preferred the approach of presenting fully incremental analyses for sipuleucel-T, BSC and abiraterone in the subgroup of patients who had not received prior chemotherapy. The Committee concluded that the assumptions made in the ERG's exploratory analyses were reasonable, although it noted that the ERG's analyses could not explore the effect of using a different model structure (see section 4.12).

4.17 The Committee considered whether sipuleucel-T was a cost-effective use of NHS resources for the subgroup of patients who had not received prior chemotherapy. It noted that, with a discounted price for abiraterone, the analyses resulted in an ICER of at least £512,000 (company's analyses) or at least £244,000 (ERG's analyses) per quality-adjusted life year (QALY) gained for sipuleucel-T compared with abiraterone. When abiraterone was not included in the ERG's analysis, the ICER for sipuleucel-T compared with BSC was £112,000 per QALY gained. The Committee 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.

4.18 The Committee discussed whether sipuleucel-T could be considered a cost-effective use of NHS resources for the subgroup of patients with a low baseline PSA concentration. It noted that the company had not presented economic analyses for the subgroup of patients in IMPACT with a baseline PSA below the median, even though the company stated that this subgroup was pre-specified. For the subgroup with a baseline PSA concentration of 22.1 nanogram/ml or below, the Committee noted that the company's original analyses resulted in an ICER of £48,700 per QALY gained for sipuleucel-T compared with BSC. The Committee was aware that the company's revised analyses, submitted in response to clarification, resulted in higher ICERs (see section 3.28). It noted that the ERG's exploratory analysis resulted in an ICER of £61,400 per QALY gained for sipuleucel-T compared with BSC. The Committee noted that the sensitivity analyses presented by the company and the ERG did not substantially reduce the ICER. The Committee considered these results to be

uncertain because the subgroup may have included patients who had previously received chemotherapy. It was also concerned that the company had not presented a comparison with abiraterone in this subgroup. In addition, it had strong reservations about the way the low-PSA subgroup had been selected, and whether sipuleucel-T was truly more effective in this subgroup than in the overall population (see sections 4.7 and 4.8). It also noted that all of the ICERs estimated by the company and the ERG fell substantially above the range normally considered to be cost effective.

4.19 The Committee considered advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with short life expectancy, and that are licensed for indications that affect small numbers of people with incurable illnesses. For this advice to be applied, all of the following criteria must be met:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.
- 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 treatment is licensed or otherwise indicated for small patient populations normally not exceeding a cumulative total of 7000 for all licensed indications in England.

In addition, when taking these criteria into account, the Committee must be persuaded that the estimates of extension to life are robust and the assumptions used in the reference case economic modelling are plausible, objective and robust.

4.20 The Committee discussed whether metastatic hormone-relapsed prostate cancer at this stage of therapy is associated with a mean life expectancy of less than 24 months. The Committee noted that the median overall survival in the control group of the IMPACT trial was 21.7 months in the intention-to-treat analysis and 22.0 months in the subgroup not previously treated with chemotherapy. The Committee acknowledged that patients in the placebo group in IMPACT had salvage therapy, which may have prolonged survival. It heard from the company that it was not possible to estimate mean survival in IMPACT because several patients dropped out of the study. The Committee concluded that the median survival in the control group of the IMPACT trial was less than 24 months, but the mean survival was unknown and was likely to be longer than the median.

4.21 The Committee discussed additional evidence from clinical trials about life expectancy with metastatic hormone-relapsed prostate cancer. It was aware of 2 trials that recruited a population similar to that specified in the marketing authorisation for sipuleucel-T and that reported longer overall survival than the IMPACT trial. The Committee noted that median overall survival in the group randomised to BSC (placebo) was 30 months in both the COU-AA-302 trial of abiraterone and the PREVAIL trial of enzalutamide. These trials were conducted more recently than the IMPACT trial. The Committee was aware of the company's view that the IMPACT trial reflects 'a truer representation of survival in this patient population' because patients in COU-AA-302 and PREVAIL may have benefited from post-progression therapies, such as sipuleucel-T, that are not currently available in England. However, the Committee noted that only 5% of the patients in the control group of COU-AA-302 had sipuleucel-T after disease progression. The Committee considered that patients in the

COU-AA-302 and PREVAIL trials may have survived for longer because of post-progression treatments that were unavailable at the time of the IMPACT trial but that are currently available in England, such as enzalutamide, abiraterone and cabazitaxel. The Committee was aware that the company's submission referred to additional prostate cancer trials that reported median overall survival in the control group of 17 to 22 months. The Committee considered that several of these trials were not relevant because they recruited patients who were suitable for docetaxel, and these patients were at a later stage of disease progression than the population specified in the marketing authorisation for sipuleucel-T. The Committee concluded that the survival estimates from the COU-AA-302 and PREVAIL trials of 30 months were relevant to the current appraisal.

- 4.22 The Committee discussed alternative sources of evidence about life expectancy with metastatic hormone-relapsed prostate cancer. It heard from the company that it was important not to rely on clinical trial data alone because trials recruit a highly selected group of patients. The Committee acknowledged this limitation, but noted that it had to make a decision on the basis of the evidence presented to it and most of this evidence came from clinical trials. In response to consultation, a commentator referred to a systematic review of observational studies (Kirby et al. 2011). The review found that the average life expectancy of people with 'castrate-resistant' prostate cancer was 14 months, and median survival for people with metastatic disease ranged from 9 to 13 months. The Committee was aware that the Kirby et al. review included studies that used varied definitions of 'castrate-resistant' prostate cancer, and it was not clear whether any of the definitions matched the definition used in clinical practice in England. The Committee observed that some studies in the review recruited symptomatic

patients who were at a later stage of disease progression than the population specified in the marketing authorisation for sipuleucel-T. The Committee noted that the review included 5 studies with data on mortality; 4 of the studies were conducted before 2004 and the fifth from 2005–2007. It observed that patients in these studies may not have had access to treatments currently available in England that have been shown to extend life, such as docetaxel, enzalutamide, abiraterone and cabazitaxel. The Committee considered that the population included in the Kirby et al. review did not match the population who might receive sipuleucel-T in England, and there were differences in treatment pathways between the studies in the review and NHS clinical practice. Although the Committee values evidence from observational studies, it concluded that the results of the Kirby review were unlikely to be generalisable to the NHS. It also noted that it had not been presented with a recent systematic review of observational studies. Taking all of the evidence into account, the Committee considered that the mean life expectancy for people with metastatic hormone-relapsed prostate cancer for which chemotherapy is not yet indicated was unlikely to be less than 24 months; therefore sipuleucel-T at this stage in the treatment pathway did not meet the end-of-life criterion for short life expectancy.

- 4.23 The Committee discussed whether sipuleucel-T met the other 2 criteria for end-of-life consideration. It noted that, according to the company's estimate, sipuleucel-T was licensed for a population of about 4600 patients in England. The Committee concluded that sipuleucel-T met the end-of-life criterion for population size. The Committee noted that, according to the company's estimate, sipuleucel-T was associated with a median extension to life of 4.0 months compared with BSC in the subgroup of patients who had not previously received chemotherapy. It further noted that, in

this subgroup, the company estimated that sipuleucel-T was associated with a mean extension to life of 0.8 months compared with abiraterone. The Committee concluded that sipuleucel-T met the end-of-life criterion on extension to life when compared with BSC, but not when compared with abiraterone. The Committee further concluded that not all end-of-life criteria had been met. The Committee also concluded that, even if the end-of-life criteria had been met, an unacceptably large weighting would need to be put on the QALY to bring the ICERs for sipuleucel-T into the range representative of a cost-effective treatment.

- 4.24 The Committee considered whether sipuleucel-T was innovative and whether it had demonstrable and distinctive benefits of a substantial nature not adequately captured in the reference-case measure of QALYs. The Committee was aware that sipuleucel-T is an autologous cellular immunotherapy and is the first treatment for metastatic hormone-relapsed prostate cancer that is not cytotoxic or based on hormone therapy. The Committee heard from patient experts that sipuleucel-T is novel and that they wished to encourage researchers to develop innovative therapies. The Committee concluded that sipuleucel-T was innovative, but that it had not been presented with any evidence of demonstrable and distinctive benefits that had not been captured in the reference-case measure of QALYs.
- 4.25 The Committee noted that the ICERs for sipuleucel-T were well above the range usually considered a cost-effective use of NHS resources, and that sipuleucel-T did not meet the criteria for end-of-life consideration. Therefore, the Committee could not recommend sipuleucel-T for adults with asymptomatic or minimally symptomatic metastatic (non-visceral) hormone-relapsed prostate cancer for which chemotherapy is not yet clinically indicated.

Summary of Appraisal Committee's key conclusions

TAXXX	Appraisal title: Sipuleucel-T for treating asymptomatic or minimally symptomatic metastatic hormone-relapsed prostate cancer	Section
Key conclusion		
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.		1.1
The Committee concluded that sipuleucel-T compared with placebo extended life for people with asymptomatic or minimally symptomatic metastatic non-visceral hormone-relapsed prostate cancer for which chemotherapy is not yet clinically indicated. It also concluded that the trials did not show that sipuleucel-T delayed disease progression compared with placebo.		4.5
The Committee concluded that there was uncertainty surrounding the results of the indirect comparison, but that it would be reasonable to assume that sipuleucel-T and abiraterone had similar effectiveness in prolonging overall survival.		4.9
The Committee noted that the incremental cost-effectiveness ratio (ICER) for sipuleucel-T was well above the range usually considered a cost-effective use of NHS resources, and that sipuleucel-T did not meet the criteria for end-of-life consideration.		4.25
Current practice		

<p>Clinical need of patients, including the availability of alternative treatments</p>	<p>Sipuleucel-T offers an additional treatment option at an early stage of disease progression. The treatments currently used in the NHS in England for asymptomatic or minimally symptomatic non-visceral metastatic hormone-relapsed prostate cancer, for which chemotherapy is not yet clinically indicated, include best supportive care and abiraterone (funded via the Cancer Drugs Fund).</p>	<p>4.1– 4.3</p>
<p>The technology</p>		
<p>Proposed benefits of the technology</p> <p>How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</p>	<p>The patient organisations stated that the most important benefits of sipuleucel-T are its potential to extend life, its short course of treatment and that it has few associated adverse reactions.</p>	<p>4.1</p>
	<p>Sipuleucel-T is an autologous cellular immunotherapy and is the first treatment for metastatic hormone-relapsed prostate cancer that is not cytotoxic or based on hormone therapy. The Committee concluded that sipuleucel-T was innovative but that it had not been presented with any evidence of demonstrable and distinctive benefits that had not been captured in the reference-case measure of quality-adjusted life years.</p>	<p>4.24</p>

<p>What is the position of the treatment in the pathway of care for the condition?</p>	<p>The clinical experts stated that they would prefer to use sipuleucel-T earlier in the treatment pathway, before abiraterone and chemotherapy. The Committee noted that it had not been presented with evidence on the effectiveness of sipuleucel-T at different places in the treatment pathway, and it was aware that the marketing authorisations for sipuleucel-T and abiraterone are almost identical.</p>	<p>4.2</p>
<p>Adverse reactions</p>	<p>The Committee concluded that current evidence shows that sipuleucel-T has a manageable adverse-event profile.</p>	<p>4.10</p>
<p>Evidence for clinical effectiveness</p>		
<p>Availability, nature and quality of evidence</p>	<p>The Committee noted that the evidence in the company's submission came from the pivotal IMPACT trial and 2 additional trials (D9901 and D9902A) that compared sipuleucel-T with placebo, and from an indirect comparison of sipuleucel-T with abiraterone which used data from the IMPACT and COU-AA-302 trials.</p>	<p>4.4, 4.9</p>
<p>Relevance to general clinical practice in the NHS</p>	<p>Clinical experts advised that, although the sipuleucel-T trials were conducted in the USA and Canada, they would expect similar results from trials in the UK.</p>	<p>4.6</p>

<p>Uncertainties generated by the evidence</p>	<p>The Committee noted that all 3 sipuleucel-T trials included patients who had previously received chemotherapy, yet the marketing authorisation specifies people with prostate cancer for which chemotherapy is not yet indicated. The Committee concluded that the subgroup of patients who had not previously received chemotherapy reflected the marketing authorisation for sipuleucel-T and was the most relevant population for this appraisal.</p>	<p>4.4</p>
	<p>The Committee noted that 2 of the 3 trials showed that sipuleucel-T extended life, but none of the trials showed that sipuleucel-T prolonged time to disease progression. The Committee heard from clinical experts that the biological reasons for this were not fully understood but similar findings had been reported for other immunotherapies. One explanation is that immunotherapies take time to show their full benefit.</p>	<p>4.5</p>

	<p>The Committee considered that the company's indirect comparison should include all of the relevant clinical trial evidence and so it would be preferable to use the meta-analysis results rather than data from IMPACT only. The Committee was aware that the Evidence Review Group (ERG) had several concerns about the indirect comparison, including differences between the IMPACT and COU-AA-302 trials in the placebo group and in post-progression treatments.</p>	<p>4.9</p>
<p>Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?</p>	<p>The company identified a subgroup of patients with a baseline prostate-specific antigen (PSA) concentration of 22.1 nanogram/ml and below. The Committee considered that the company's method of identifying subgroups was arbitrary. It concluded that there was insufficient evidence to establish whether the clinical effectiveness of sipuleucel-T was different in the low-PSA subgroup compared with the rest of the population. The Committee also concluded that it could not rely on the company's subgroup analysis because the PSA value of 22.1 nanogram/ml was not currently used to guide treatment choices in clinical practice and the company's analysis included some people who had previously received chemotherapy.</p>	<p>4.7, 4.8</p>

Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee concluded that sipuleucel-T compared with placebo extended life for people with asymptomatic or minimally symptomatic metastatic hormone-relapsed prostate cancer for which chemotherapy is not yet clinically indicated. The Committee also concluded that the trials did not show that sipuleucel-T delayed disease progression compared with placebo.	4.5
	The Committee concluded that there was uncertainty surrounding the results of the indirect comparison, but that it would be reasonable to assume that sipuleucel-T and abiraterone had similar effectiveness in prolonging overall survival.	4.9
Evidence for cost effectiveness		
Availability and nature of evidence	The Committee concluded that the economic analysis based on the subgroup of patients who had not received prior chemotherapy was more relevant to the appraisal than the company's base-case analysis.	4.11

<p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p>	<p>The Committee observed that it was not clear how the model captured the disutility and costs associated with different stages of disease, such as progression before docetaxel or progression for patients who do not have docetaxel. The Committee concluded that the model structure did not adequately reflect the treatment pathway and course of disease.</p>	<p>4.12</p>
	<p>The Committee considered that it would have been preferable to base the model on the meta-analysis of sipuleucel-T trials because the meta-analysis included all relevant trial evidence.</p>	<p>4.13</p>
	<p>The Committee concluded that it was appropriate to adjust for treatment switching to APC8015F in the economic analyses of sipuleucel-T, but it had not been provided with enough information to determine whether the company's method of adjustment was appropriate.</p>	<p>4.14</p>
	<p>The Committee concluded that some elements of the cost to the NHS of providing treatment with sipuleucel-T were unclear.</p>	<p>4.15</p>

<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>The Committee concluded that sipuleucel-T was innovative but that it had not been presented with any evidence of demonstrable and distinctive benefits that had not been captured in the reference-case measure of quality-adjusted life years (QALYs).</p>	<p>4.24</p>
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>The Committee considered the results for the subgroup with a low baseline PSA concentration to be uncertain because the subgroup may have included patients who had previously received chemotherapy. It was also concerned that the company had not presented a comparison with abiraterone in this subgroup. In addition, it had strong reservations about the way the low-PSA subgroup had been selected and whether sipuleucel-T was truly more effective in this subgroup than in the overall population.</p>	<p>4.18</p>

<p>What are the key drivers of cost effectiveness?</p>	<p>The ERG advised that the key drivers of cost effectiveness were the choice of parametric distribution for overall survival and the assumptions about docetaxel use (including the time to docetaxel use, the proportion of patients who had docetaxel and the number of cycles of docetaxel).</p>	<p>3.39</p>
<p>Most likely cost-effectiveness estimate (given as an ICER)</p>	<p>For the subgroup of patients who had not received prior chemotherapy and using a discounted price for abiraterone, the ICER was at least £512,000 (company's analyses) or at least £244,000 (ERG's analyses) per QALY gained for sipuleucel-T compared with abiraterone. When abiraterone was not included in the ERG's analysis, the ICER for sipuleucel-T compared with best supportive care was £112,000 per QALY gained.</p>	<p>4.17</p>
	<p>For the subgroup with a baseline PSA concentration of 22.1 nanogram/ml or below, the company's original analyses resulted in an ICER of £48,700 per QALY gained for sipuleucel-T compared with best supportive care. The company's revised analyses resulted in higher ICERs. The ERG's exploratory analysis resulted in an ICER of £61,400 per QALY gained for sipuleucel-T compared with best supportive care.</p>	<p>4.18</p>
<p>Additional factors taken into account</p>		

<p>Patient access schemes (PPRS)</p>	<p>Abiraterone, a comparator in this appraisal, is available to the NHS through a simple discount patient access scheme, for which the level of the discount is confidential and cannot be disclosed to the company that holds the marketing authorisation for sipuleucel-T. The Committee concluded that it was appropriate to use assumed discounts for the price of abiraterone in the economic analyses. The Committee was aware of the true discount in the patient access scheme for abiraterone.</p>	<p>4.15</p>
<p>End-of-life considerations</p>	<p>Median survival in the control group of the IMPACT trial was less than 24 months; the mean survival was unknown. Two more recent trials, which recruited a population similar to that specified in the marketing authorisation for sipuleucel-T, reported median overall survival in the control group of 30 months. The Committee discussed a systematic review of observational studies that reported shorter life expectancy, but it concluded that the results of this review were unlikely to be generalisable to the NHS. The Committee considered that the mean life expectancy for people with metastatic hormone-relapsed prostate cancer for which chemotherapy is not yet indicated was unlikely to be less than 24 months, so sipuleucel-T at this stage in the treatment pathway did not meet the end-of-life criterion for short life expectancy.</p>	<p>4.20– 4.22</p>

	The company estimated that sipuleucel-T was associated with a median extension to life of 4.0 months compared with best supportive care and a mean extension to life of 0.8 months compared with abiraterone. The Committee concluded that sipuleucel-T met the end-of-life criterion on extension to life when compared with best supportive care, but not when compared with abiraterone.	4.23
	The company estimated that sipuleucel-T was licensed for a population of about 4600 patients in England.	4.23
Equalities considerations and social value judgements	No equality issues relevant to the Committee's recommendations were raised.	

5 Implementation

5.1 NICE has developed tools [[link to www.nice.org.uk/guidance/TAXXX](#)] to help organisations put this guidance into practice (listed below). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing template and report to estimate the national and local savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.

- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Related NICE guidance

Details are correct at the time of consultation and will be removed when the final guidance is published. Further information is available on the [NICE website](#).

Published

- [Prostate cancer: diagnosis and treatment](#) (2014) NICE guideline CG175
- [Enzalutamide for the treatment of metastatic hormone relapsed prostate cancer previously treated with a docetaxel containing regimen](#) (2014) NICE technology appraisal guidance 316
- [Denosumab for the prevention of skeletal-related events in adults with bone metastases from solid tumours](#) (2012) NICE technology appraisal guidance 265
- [Abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen](#) (2012) NICE technology appraisal guidance 259
- [Cabazitaxel for hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen](#) (2012) NICE technology appraisal guidance 255
- [Docetaxel for the treatment of metastatic prostate cancer](#) (2006) NICE technology appraisal guidance 101

Under development

- Abiraterone for treating metastatic hormone-relapsed prostate cancer not previously treated with chemotherapy. Suspended NICE technology appraisal.

- Enzalutamide for treating metastatic, hormone-relapsed prostate cancer for people in whom chemotherapy is not yet clinically indicated. NICE technology appraisal guidance, publication expected September 2015.

7 Date for review of guidance

- 7.1 The guidance on this technology will be considered for review 3 years after publication of the guidance. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Amanda Adler

Chair, Appraisal Committee

January 2015

8 Appraisal Committee members, guideline representatives and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Amanda Adler (Chair)

Consultant Physician, Addenbrooke's Hospital

Professor Ken Stein (Vice Chair)

Professor of Public Health, University of Exeter Medical School

Dr Jeff Aronson

Reader in Clinical Pharmacology, University Department of Primary Health Care, University of Oxford

Professor John Cairns

Professor of Health Economics, Public Health and Policy, London School of Hygiene and Tropical Medicine

Mr Matthew Campbell-Hill

Lay member

Professor Imran Chaudhry

Lead Consultant Psychiatrist and Deputy Associate Medical Director,
Lancashire Care NHS Foundation Trust

Dr Lisa Cooper

Echocardiographer, Stockport NHS Foundation Trust

Dr Maria Dyban

General Practitioner, Cardiff

Mr Robert Hinchliffe

HEFCE Clinical Senior Lecturer in Vascular Surgery and Honorary Consultant
Vascular Surgeon, St George's Vascular Institute

Dr Neil Iosson

Locum General Practitioner

Mrs Anne Joshua

NHS 111 Pharmacy Lead, Patients and Information, NHS England

Dr Rebecca Kearney

Clinical Lecturer, University of Warwick

Ms Emily Lam

Lay member

Professor Ruairidh Milne

Director of Strategy and Development and Director for Public Health Research
at the National Institute for Health Research (NIHR) Evaluation, Trials and
Studies Coordinating Centre at the University of Southampton

Mr Christopher O'Regan

Head of Health Technology Assessment & Outcomes Research, Merck Sharp & Dohme

Professor Stephen Palmer

Professor of Health Economics, Centre for Health Economics, University of York

Mr Alun Roebuck

Consultant Nurse in Critical and Acute Care, United Lincolnshire NHS Trust

Mr Cliff Snelling

Lay member

Ms Marta Soares

Research Fellow, Centre for Health Economics, University of York

Mr David Thomson

Lay member

Dr Nerys Woolacott

Senior Research Fellow, Centre for Health Economics, University of York

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Dr Rosie Lovett

Technical Lead

Nwamaka Umeweni

Technical Adviser

Jeremy Powell
Project Manager

9 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by the School of Health and Related Research (SchARR), the University of Sheffield:

- Simpson EL, Davis S, Thokala P, Sipuleucel-T for the treatment of metastatic hormone relapsed prostate cancer, August 2014

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I. Company:

- Dendreon

II. Professional/specialist and patient/carer groups:

- British Uro-Oncology Group
- Cancer Research UK
- Prostate Cancer Advisory Group
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians

III. Other consultees:

- Department of Health

- NHS England
- Welsh Government

IV. Commentator organisations (did not provide written evidence and without the right of appeal):

- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Janssen
- Medicines and Healthcare Products Regulatory Agency
- National Collaborating Centre for Cancer
- Teva

C. The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They gave their expert personal view on sipuleucel-T by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Amit Bahl, Consultant Clinical Oncologist, Bristol Cancer Institute, nominated by Dendreon – clinical expert
- Dr Simon Crabb, Senior Lecturer and Honorary Consultant in Medical Oncology, University of Southampton, nominated by the Royal College of Physicians – clinical expert
- Mr David Smith, Honorary Secretary, Tackle Prostate Cancer, nominated by Tackle Prostate Cancer – patient expert
- Mr Stuart Watson, nominated by Prostate Cancer UK – patient expert

D. Representatives from the following company attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Dendreon