IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A14-38

Sipuleucel-T – Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Sipuleucel-T – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 23 December 2014). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Sipuleucel-T – Benefit assessment according to §35a Social Code Book V

Commissioning agency:
Federal Joint Committee

Commission awarded on:
2 October 2014

Internal Commission No.:
A14-38

Address of publisher:
Institute for Quality and Efficiency in Health Care
Im Mediapark 8 (KölnTurm)
50670 Cologne
Germany

Tel.: +49 (0)221 – 35685-0
Fax: +49 (0)221 – 35685-1
E-Mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice:

- Gerhard Jakse, Rhine-Westphalian Technical University (RWTH) Aachen, Aachen, Germany

IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

IQWiG employees involved in the dossier assessment[2]:

- Ulrike Mikulić
- Andreas Gerber-Grote
- Wolfram Groß
- Marco Knelangen
- Alexander Mensch
- Regine Potthast
- Christoph Schürmann
- Volker Vervölgyi

Keywords: sipuleucel-T, prostatic neoplasms – castration-resistant, benefit assessment

[2] Due to legal data protection regulations, employees have the right not to be named.

Table of contents

List of tables[3]

Page

[3] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
ADT	androgen deprivation therapy
AE	adverse event
APC	antigen-presenting cell
CHMP	Committee for Medicinal Products for Human Use
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GM-CSF	granulocyte-macrophage colony-stimulating factor
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LH-RH	luteinizing hormone-releasing hormone
PAP	prostatic acid phosphatase
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug sipuleucel-T. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 2 October 2014.

Research question

The aim of the present report was to assess the added benefit of sipuleucel-T versus the appropriate comparator therapy (ACT) for 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 G-BA specified the following treatments as possible ACTs:

- watchful waiting while maintaining ongoing conventional androgen deprivation therapy (ADT)

or, if applicable,

- combined maximal androgen blockade with a non-steroidal anti-androgen (flutamide, bicalutamide)

or

- abiraterone acetate while maintaining ongoing ADT

The company concurred with the G-BA's specification and chose watchful waiting while maintaining ongoing conventional ADT as comparator therapy.

The present benefit assessment was conducted in comparison with the G-BA's ACT. The assessment was conducted based on patient-relevant outcomes and on randomized controlled trials (RCTs).

Results

3 relevant studies, IMPACT, D9901, and D9902A, were available for the benefit assessment. These were randomized, double-blind, multicentre approval studies, in which sipuleucel-T was compared with sham treatment. Asymptomatic (D9901 and D9902A) or asymptomatic and minimally symptomatic patients (IMPACT) with metastatic (non-visceral) castrate-resistant prostate cancer were enrolled. ADT with surgical or medical castration had to be continued in all study arms.

In the studies, 512 (IMPACT), 127 (D9901), and 98 (D9902A) patients were randomly assigned in a ratio of 2:1 to the intervention or control arm. Antigen-presenting cells were collected from the patients by means of leukapheresis in both study arms. For the intervention arm, the cells were activated with a recombinant fusion protein and then reinfused to the patients. The activated cells are called sipuleucel-T. In the control arm, one part of the cells was reinfused to the patients without activation (sham treatment). At a later time point, a product analogous to sipuleucel-T could be manufactured from the remaining cells to allow patients of the control arm to switch to the intervention. Each of the patients in both arms received a total of 3 infusions (sipuleucel-T or sham treatment). On confirmed disease progression, the patients were unblinded and received treatment at the physician's discretion. Patients in the control arm could additionally switch to sipuleucel-T treatment. The risk of bias of all 3 studies at study level was rated as low. There was a high risk of bias for all available outcomes, however. For the outcome "overall survival", such a relevant bias was conceivable that the results were considered to be not evaluable.

There was a high risk of bias for the outcome "time to disease-related pain" and for the outcomes on adverse events (AEs) because more than 2 thirds of the patients switched from sham treatment to sipuleucel-T after progression. In addition, treatment after progression was no longer blinded. Furthermore, the outcomes on AEs were only completely recorded until disease progression or up to study week 16. Thereafter, only those events were documented that the investigator determined to be related to the treatment.

For the outcome "overall survival", the available results could not be interpreted in a meaningful way. Whereas the patients in the sipuleucel-T arm switched to further treatment at the choice of the treating physician, patients in the sham treatment group of all 3 studies mainly (approximately 67%) started treatment with sipuleucel-T after progression. For a large part of the patients in the sipuleucel-T arm, further treatment consisted of docetaxel, which is proven to have an effect on overall survival. Since the use of docetaxel in the control group in median (presumably) started later than in the intervention group (2.4 months later in the IMPACT study, no information for the studies D9901 and D9902A), effective treatment was withheld from these patients for longer. Assuming that sipuleucel-T has no effect on overall survival, this can cause a relevant disadvantage of the control group (difference in median survival times in the IMPACT study: 4.1 months). It cannot be excluded that the effect in overall survival observed in the studies can be attributed to this alone.

The outcome "overall survival" was also critically discussed in the approval process of sipuleucel-T, particularly regarding the different subsequent therapies on disease progression and the lack of differences in progression-free survival between the study arms. This led to a deviating vote from some of the members of the Committee for Medicinal Products for Human Use (CHMP).

Mortality

Overall survival

There were no evaluable data for the outcome "overall survival". An added benefit of sipuleucel-T in comparison with the ACT is not proven for the outcome.

Morbidity

Time to disease-related pain

For the outcome "time to disease-related pain", there were data for asymptomatic patients in the 3 studies IMPACT, D9901, and D9902A. The meta-analysis showed no statistically significant difference between the treatment arms. An added benefit of sipuleucel-T in comparison with watchful waiting while maintaining ongoing conventional ADT is therefore not proven for this outcome.

Health-related quality of life

Data on health-related quality of life were not recorded in the 3 studies. An added benefit of sipuleucel-T in comparison with watchful waiting while maintaining ongoing conventional ADT is therefore not proven for this outcome.

Adverse events

Serious adverse events

For the outcome "serious adverse events (SAEs)", the meta-analysis of the 3 studies IMPACT, D9901, and D9902A showed no statistically significant difference between the treatment arms. Greater or lesser harm from sipuleucel-T in comparison with watchful waiting while maintaining ongoing conventional ADT is therefore not proven for this outcome.

Severe adverse events (CTCAE grade ≥ 3)

For the outcome "severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)", the meta-analysis of the studies IMPACT, D9901, and D9902A showed no statistically significant difference between the respective treatment arms. Greater or lesser harm from sipuleucel-T in comparison with watchful waiting while maintaining ongoing conventional ADT is therefore not proven for the outcome.

Discontinuation due to adverse events

Results on discontinuation due to AEs were only available for the IMPACT study. There was no statistically significant difference between the treatment arms in this study. Greater or lesser harm from sipuleucel-T in comparison with watchful waiting while maintaining ongoing conventional ADT is therefore not proven for the outcome.

Fever

The meta-analysis showed important heterogeneity for the outcome "fever". In all 3 studies (IMPACT, D9901, and D9902A), there was a statistically significant difference between the

treatment groups to the disadvantage of sipuleucel-T, the effects were therefore clearly in the same direction. There was an outcome-specific high risk of bias for each of the 3 studies. Hence, there was an indication of greater harm from sipuleucel-T in comparison with watchful waiting while maintaining ongoing conventional ADT for this outcome.

Headache

The meta-analysis of the 3 studies IMPACT, D9901 and D9902A showed a statistically significant difference to the disadvantage of sipuleucel-T for the outcome "headache". There was an outcome-specific high risk of bias for all 3 studies. This resulted in an indication of greater harm from sipuleucel-T in comparison with watchful waiting while maintaining ongoing conventional ADT.

Chills

The meta-analysis of the studies IMPACT, D9901 and D9902A showed a statistically significant difference to the disadvantage of sipuleucel-T for the outcome "chills". There was an outcome-specific high risk of bias for each of the 3 studies. This resulted in an indication of greater harm from sipuleucel-T in comparison with watchful waiting while maintaining ongoing conventional ADT.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

On the basis of the results presented, the extent and probability of the added benefit of the drug sipuleucel-T compared with the ACT is assessed as follows:

Overall, only negative effects of sipuleucel-T remain at outcome level on the basis of the available results. The negative effects consist of an indication of greater harm with the extent "considerable" (headache, chills), and an indication of greater harm, the extent of which is "non-quantifiable" (fever).

In the overall weighing of benefits and harms, these exclusively negative effects do not result in lesser benefit of sipuleucel-T. Instead, the lack of evaluable and informative results for the outcome "overall survival" overall resulted in such a high uncertainty that a conclusive weighing of the results on added benefit is not possible.

Overall, the added benefit of sipuleucel-T versus the ACT, watchful waiting while maintaining ongoing conventional ADT, is not proven for patients with asymptomatic or

[4] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data), see [1]. The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, no added benefit, or less benefit), see [2].

minimally symptomatic metastatic (non-visceral) castrate-resistant prostate cancer in whom chemotherapy is not yet clinically indicated.

Table 2 presents a summary of the extent and probability of the added benefit of sipuleucel-T.

Table 2: Sipuleucel-T – extent and probability of added benefit

Therapeutic indication	**ACT**[a]	**Extent and probability of added benefit**
Treatment of asymptomatic or minimally symptomatic metastatic (non-visceral) castrate-resistant prostate cancer in male adults in whom chemotherapy is not yet clinically indicated	▪ **watchful waiting while maintaining ongoing conventional ADT** or, if applicable, ▪ combined maximal androgen blockade with a non-steroidal anti-androgen (flutamide, bicalutamide) or ▪ abiraterone acetate while maintaining ongoing ADT	Added benefit not proven
a: Presentation of the ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold. ACT: appropriate comparator therapy; ADT: androgen deprivation therapy; G-BA: Federal Joint Committee		

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report was to assess the added benefit of sipuleucel-T versus the ACT for 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 G-BA specified the following treatments as possible ACTs for the company:

- watchful waiting while maintaining ongoing conventional ADT

or, if applicable,

- combined maximal androgen blockade with a non-steroidal anti-androgen (flutamide, bicalutamide)

or

- abiraterone acetate while maintaining ongoing ADT

The company concurred with the G-BA's specification and chose watchful waiting while maintaining ongoing conventional ADT as comparator therapy from the options mentioned. The present benefit assessment was conducted in comparison with the G-BA's ACT.

The assessment was conducted based on patient-relevant outcomes and on RCTs.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information.

Sources of the company in the dossier:

- study list on sipuleucel-T (studies completed up to 6 August 2014)
- bibliographical literature search on sipuleucel-T (last search on 25 August 2014)
- search in trial registries for studies on sipuleucel-T (last search on 23 September 2014)

To check the completeness of the study pool:

- search in trial registries for studies on sipuleucel-T (last search on 17 October 2014)

No additional relevant study was identified from the check.

2.3.1 Studies included

The studies listed in the following table were included in the benefit assessment.

Table 3: Study pool – RCT, direct comparison: sipuleucel-T + ADT vs. sham treatment + ADT

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
D9902B (IMPACT)[b]	Yes	Yes	No
D9901	Yes	Yes	No
D9902A	Yes	Yes	No

a: Study for which the company was sponsor, or in which the company was otherwise financially involved.
b: Hereinafter, this study is referred to as "IMPACT study".
ADT: androgen deprivation therapy; RCT: randomized controlled trial; vs.: versus

The study pool for the benefit assessment of sipuleucel-T corresponds to that of the company.

Section 2.6 contains a reference list for the studies included.

2.3.2 Study characteristics

Table 4 and Table 5 describe the studies used for the benefit assessment.

Table 4: Characteristics of the studies included – RCT, direct comparison: sipuleucel-T + ADT vs. sham treatment + ADT

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
IMPACT	RCT, double-blind, parallel	Adult men with asymptomatic or minimally symptomatic mCRPC and life expectancy of at least 6 months	Sipuleucel-T + ADT (N = 341) sham treatment + ADT (N = 171)	Treatment every 2 weeks[b] (week 0, 2 and 4) follow-up[c] until death or until data cut-off for final analysis data cut-off for primary analysis: 18 Jan 2009	75 centres in Canada and United States 8/2003–4/2009	Primary outcome: overall survival Secondary outcomes: time to disease-related pain[d], adverse events
D9901	RCT, double-blind, parallel	Adult men with asymptomatic mCRPC and life expectancy of at least 16 weeks	Sipuleucel-T + ADT (N = 82) sham treatment + ADT (N = 45)	Treatment at 2 week intervals[b] (week 0, 2 and 4) follow-up[c] until death or until 36 months after start of treatment data cut-off for primary analysis: 30 April 2002	19 centres in United States 1/2000–9/2004	Primary outcome: time to disease progression Secondary outcomes: overall survival, time to disease-related pain, adverse events
D9902A	RCT, double-blind, parallel	Adult men with asymptomatic mCRPC and life expectancy of at least 16 weeks	Sipuleucel-T + ADT (N = 65) sham treatment + ADT (N = 33)	Treatment at 2 week intervals[b] (week 0, 2 and 4) follow-up[c] until death or until 36 months after start of treatment	27 centres in United States 5/2000–5/2005	Primary outcome: time to disease progression Secondary outcomes: overall survival, time to disease-related pain, adverse events

a: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes exclusively contain information on the relevant available outcomes for this benefit assessment.
b: Infusions should be administered at 2 week intervals, deviations were allowed however.
c: On disease progression, patients could receive treatment at the physician's choice; patients of the sham treatment arm could also receive treatment with sipuleucel-T.
d: Data were only recorded for patients who had been included before Amendment 7 of the study protocol. After Amendment 7, this outcome was no longer recorded.
ADT: androgen deprivation therapy; mCRPC: metastatic castrate-resistant prostate cancer; N: number of randomized patients; RCT: randomized controlled trial; vs.: versus

Table 5: Characteristics of the interventions – RCT, direct comparison: sipuleucel-T + ADT vs. sham treatment + ADT

Study	Intervention	Comparison	Pretreatment and concomitant treatment
IMPACT	Sipuleucel-T IV 3 x approx. 60 min infusion at an interval of approx. 2 weeks (week 0, 2 and 4) Dose per infusion: total sipuleucel-T that could be prepared from a single leukapheresis procedure, at least 20 x 10^6 CD54+ cells, activated with PAP-GM-CSF	Sham treatment IV 3 x approx. 60 min infusion at an interval of approx. 2 weeks (week 0, 2 and 4) Dose per infusion: approx. 1/3 of inactive APCs that could be prepared from a single leukapheresis procedure	Pretreatment: ▪ chemotherapy (including docetaxel) up to 2 cycles if this treatment had been conducted ≥ 6 months before the start of the study Concomitant treatment: ▪ leukapheresis procedure 2–3 days before each infusion ▪ before infusion: acetaminophen and antihistamine (e.g. diphenhydramine) ▪ ADT: surgical or medical castration with LH-RH agonists ▪ steroids; bisphosphonates were allowed if treatment had been started 28 days before the start of the study and the dose remained stable ▪ supportive care: transfusion of blood and blood products, antibiotics, antiemetics
D9901	Sipuleucel-T IV 3 x approx. 30 min infusion at an interval of approx. 2 weeks (week 0, 2 and 4) Dose: total sipuleucel-T that could be prepared from a single leukapheresis procedure, at least 3 x 10^6 CD54+ cells, activated with PAP-GM-CSF	Sham treatment IV 3 x approx. 30 min infusion at an interval of approx. 2 weeks (week 0, 2 and 4) Dose per infusion: approx. 1/3 of inactive APCs that could be prepared from a single leukapheresis procedure	Concomitant treatment: ▪ leukapheresis procedure 2–3 days before each infusion ▪ before infusion: acetaminophen and antihistamine (e.g. diphenhydramine) ▪ ADT: surgical or medical castration with LH-RH agonists ▪ steroids; bisphosphonates were allowed if treatment had been started 30 days before the start of the study ▪ supportive care: transfusion of blood and blood products, antibiotics, antiemetics
D9902A	Sipuleucel-T IV 3 x approx. 30 min infusion at an interval of approx. 2 weeks (week 0, 2 and 4) Dose: total sipuleucel-T that could be prepared from a single leukapheresis procedure, at least 3 x 10^6 CD54+ cells, activated with PAP-GM-CSF	Sham treatment IV 3 x approx. 30 min infusion at an interval of approx. 2 weeks (week 0, 2 and 4) Dose: approx. 1/3 of inactive APCs that could be prepared from a single leukapheresis procedure	Concomitant treatment: ▪ leukapheresis procedure 2–3 days before each infusion ▪ before infusion: acetaminophen and antihistamine (e.g. diphenhydramine) ▪ ADT: surgical or medical castration with LH-RH agonists ▪ steroids; bisphosphonates were allowed if treatment had been started 30 days before the start of the study ▪ supportive care: transfusion of blood and blood products, antibiotics, antiemetics

ADT: androgen deprivation therapy; APC: antigen-presenting cell; CD: cluster of differentiation; IV: intravenous; PAP-GM-CSF: prostatic acid phosphatase fused with granulocyte-macrophage colony-stimulating factor; RCT: randomized controlled trial; vs.: versus

The 3 included studies IMPACT, D9901 and D9902A were randomized, double-blind, multicentre approval studies with patients with metastatic (non-visceral) castrate-resistant prostate cancer. The patients included received sipuleucel-T, in each case in comparison with sham treatment. ADT with surgical or medical castration with luteinizing hormone-releasing hormone (LH-RH) agonists had to be continued in all treatment arms until objective disease progression (IMPACT) or end of the study (D9901 and D9902A).

The studies D9901 and D9902A had a comparable study design. Asymptomatic patients with a life expectancy of at least 16 weeks were included. Study D9902A was conducted as part A of protocol D9902. The IMPACT study (D9902B) constituted the second part of protocol D9902 (part B) and started with Amendment 5 (May 2003). According to information provided by the company, publications at this time point suggested that disease progression and survival rates for minimally symptomatic patients were similar to those of asymptomatic castrate-resistant prostate cancer patients. For the D9902A study, recruitment of patients was stopped after inclusion of 98 patients because of this. For the IMPACT study, both minimally symptomatic and asymptomatic patients were eligible for study inclusion after Amendment 7 of the protocol (October 2005). In contrast to the studies D9002A and D9901, this study also included patients with a life expectancy of at least 6 months. Severity grades were classified by means of a pain scale ranging from 0 (no pain) to 10 (worst imaginable pain). Patients who had no tumour-related pain and who also needed no regular analgesics for tumour-related pain were considered to be asymptomatic in the 3 studies. Patients with a pain score < 4 were considered to be minimally symptomatic, they were not allowed to have received opioid analgesics within 21 days before registration (IMPACT study).

Patients who already had received chemotherapy were also included in all 3 studies. Since their proportion was below 20% in each of the 3 studies, the results of the total populations were used for the assessment of the added benefit of sipuleucel-T for the studies.

In the studies, 512 (IMPACT), 127 (D9901), and 98 (D9902A) patients were randomly assigned in a ratio of 2:1 to the treatment or control arm. In the IMPACT study, the allocation process was designed to minimize the degree of imbalance between the treatment groups for certain covariables (Gleason score, number of bone metastases, and bisphosphonate use). Patients in both arms received 3 infusions at 2 week intervals, each preceded by a leukapheresis procedure. The leukapheresis procedure served to harvest peripheral blood mononuclear cells, including antigen-presenting cells (APCs), from the patients. For patients in the intervention arm, all APCs collected in a leukapheresis procedure were activated with a recombinant fusion protein and then reinfused. These activated APCs are called sipuleucel-T. The fusion protein consisted of the prostate-specific antigen prostatic acid phosphatase (PAP) fused with the cytokine granulocyte-macrophage colony-stimulating factor (GM-CSF) and is also called PA2024. Patients in the sham treatment arm were reinfused with only one third of the harvested cells (APCs), but without prior activation. The remaining 2 thirds of the non-activated APCs were cryopreserved. To prevent infusion-related symptoms, all patients received standard treatment with acetaminophen and an antihistamine prior to the infusions.

According to the approval, the required minimum number of cells per infusion is $50x10^6$ cells [3]. In all 3 studies, the minimum number of cells specified in the respective study protocols was below this limit ($3x10^6$ cells in studies D9902A and D9901; $20x10^6$ cells in the IMPACT study). However, the study documents showed that the number of cells actually administered was notably higher than specified in the protocol and was also 10 to 80 times higher than required by the approval (median per infusion: 0.45 to 0.62 x 10^9 cells [IMPACT]; 4 x 10^9 cells [D9901]; 1.9 x 10^9 cells [D9902A]). Hence the approval requirement was not fulfilled in any of the 3 studies.

According to the approval, the duration of the infusion should be approximately 60 minutes. In the study documents of the studies D9901 and D9902A, the duration is specified with only approximately 30 minutes. It is assumed, however, that the speed of the infusion had no relevant influence on the study results. Further explanations can be found in Section 2.7.2.4.1 of the full dossier assessment.

The patients were initially observed until the occurrence of confirmed disease progression. In the IMPACT study, this was defined by disease progression shown by imaging techniques and confirmed by an independent central radiology committee. In the studies D9901 and D9902A, both clinical events and events measurable with imaging techniques could represent disease progression.

When progression was an event shown by imaging techniques, it had to be confirmed by an independent central radiology committee. In case of confirmed disease progression, the patients could be unblinded. The patients of the sipuleucel-T arm received treatment at the physician's discretion. The patients in the sham treatment arm could additionally receive a product analogous to sipuleucel-T, which was manufactured from the 2 thirds of the cryopreserved cells (conducted as a one-arm salvage study). In the 3 studies, approximately 2 thirds of the patients of the sham treatment arm chose the option to switch to the intervention (IMPACT: 63.7%; D9901: 75.6%; D9902A: 66.7%). However, these patients' data were included in the available analyses of the 3 studies IMPACT, D9901 and D9902A. For the patients who switched from the control treatment to the intervention, administration of docetaxel treatment was delayed because of this. In the IMPACT study, the first administration of docetaxel treatment was conducted 2.4 months later (difference of the medians). The results on overall survival could therefore not be interpreted in a meaningful way for the present benefit assessment (see Section 2.4.2 and Section 2.7.2.4.2 of the full dossier assessment).

Time to disease progression was the primary outcome in the studies D9902A and D9901. Overall survival and time to disease-related pain were secondary outcomes. In the IMPACT study, overall survival was recorded as primary outcome. Originally, the time to disease-related pain was primary outcome of this study, but was eliminated from the study protocol with Amendment 7 and no longer recorded after this time point. Hence only data for the

patients who were included in the study before Amendment 7 were available for this outcome. No outcomes on health-related quality of life were recorded in any of the 3 studies.

In the studies D9902A and D9901, follow-up was conducted until death, or until 36 months at the most, or until discontinuation of the study. In the IMPACT study, the patients were followed up until death, or until the final data cut-off, or until study discontinuation. The primary analysis of the IMPACT study for all outcomes was conducted on 18 January 2009 (first data cut-off), another analysis was conducted after the end of the study, on 30 April 2009 (second data cut-off). Deaths and AEs were continued to be recorded between the primary and the final analysis. An analysis of the data of the second data cut-off was only available for the outcome "overall survival".

Table 6 shows the planned duration of follow-up of the patients for the individual outcomes.

Table 6: Planned duration of follow-up – RCT, direct comparison: sipuleucel-T + ADT vs. sham treatment + ADT

Study outcome	**Planned follow-up**
IMPACT	
Overall survival	▪ until death
Disease-related pain	▪ no data[a]
Health-related quality of life	▪ not recorded
Adverse events	▪ until death (only the AEs related to treatment and all cerebrovascular events were recorded after disease progression, however)
D9901	
Overall survival	▪ 36 months after randomization or until death
Disease-related pain	▪ until disease progression; 4 weeks of follow-up for patients without pain at this time point
Health-related quality of life	▪ not recorded
Adverse events	▪ 3 years after randomization or until death (only the AEs related to treatment were documented after 16 weeks or after disease progression, however[b])
D9902A	
Overall survival	▪ 36 months after randomization or until death
Disease-related pain	▪ until disease progression; 4 weeks of follow-up for patients without pain at this time point
Health-related quality of life	▪ not recorded
Adverse events	▪ 3 years after randomization or until death (only the AEs related to treatment were documented after 16 weeks or disease progression, however[b])

a: Data were only recorded for patients who had been included before Amendment 7 of the protocol. After Amendment 7, this outcome was no longer recorded.
b: It was not clear from the study documents whether all AEs that occurred under treatment were recorded until disease progression or until week 16, or from what time point only the AEs related to the treatment were recorded (week 16 or disease progression).
ADT: androgen deprivation therapy; AE: adverse event, RCT: randomized controlled trial; vs.: versus

In D9901 and D9902A, the outcome “time to disease-related pain” was recorded until disease progression. If no disease-related pain had occurred until this time point, this was followed by a 4-week follow-up phase. In the IMPACT study, the occurrence of pain for the patients registered before Amendment 7 was recorded until the time point of this change to the protocol.

AEs in the IMPACT study were recorded until disease progression, irrespective of whether they were related to the treatment or not. Thereafter, only those AEs were recorded that the investigator determined to be related to the treatment, as well as all cerebrovascular events. It was not clear from the study documents of the studies D9901 and D9902A whether all AEs that occurred under treatment were recorded until disease progression or until treatment week 16, or from what time point only AEs related to the treatment were recorded.

Table 7 shows the characteristics of the patients in the studies included.

Table 7: Characteristics of the study populations – RCT, direct comparison: sipuleucel-T + ADT vs. sham treatment + ADT

Study	**IMPACT**		**D9901**		**D9902A**	
characteristics category	**Sipuleucel-T N = 341**	**Sham treatment N = 171**	**Sipuleucel-T N = 82**	**Sham treatment N = 45**	**Sipuleucel-T N = 65**	**Sham treatment N = 33**
Age [years]						
mean (SD)	71 (9)	70 (9)	72 (8)	71 (8)	70 (8)	71 (8)
Ethnicity, n (%)						
white	305 (89.4)	156 (91.2)	73 (89.0)	42 (93.3)	59 (90.8)	31 (93.9)
black or Afro-American	23 (6.7)	7 (4.1)	8 (9.8)	1 (2.2)	2 (3.1)	2 (6.1)
Asian	2 (0.6)	2 (1.2)	0 (0)	0 (0)	0 (0)	0 (0)
Hispanic	10 (2.9)	6 (3.5)	1 (1.2)	1 (2.2)	1 (1.5)	0 (0)
other	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
unknown	0 (0)	0 (0)	0 (0)	1 (2.2)	3 (4.6)	0 (0)
ECOG, n (%)						
0	280 (82.1)	139 (81.3)	62 (75.6)	37 (82.2)	51 (78.5)	23 (69.7)
1	61 (17.9)	32 (18.7)	20 (24.4)	8 (17.8)	14 (21.5)	10 (30.3)
Gleason score sum, n (%)						
≤ 6	37 (10.9)	15 (8.8)	22 (26.8)	7 (15.6)	15 (23.1)	9 (27.3)
7	220 (64.5)	114 (66.7)	28 (34.1)	18 (40.0)	29 (44.6)	8 (24.2)
≥ 8	84 (24.6)	41 (24.0)	32 (39.0)	20 (44.4)	20 (30.8)	16 (48.5)
missing	0 (0)	1 (0.6)	0 (0)	0 (0)	1 (1.5)	0 (0)
Number of bone metastases, n (%)						
0–5	146 (42.8)	73 (42.7)	36 (43.9)	21 (46.7)	24 (36.9)	18 (54.5)
6–10	49 (14.4)	25 (14.6)	12 (14.6)	12 (26.7)	6 (9.2)	2 (6.1)
> 10	146 (42.8)	73 (42.7)	34 (41.5)	12 (26.7)	31 (47.7)	12 (36.4)
missing	0 (0)	0 (0)	0 (0)	0 (0)	4 (6.2)	1 (3.0)

(continued)

Table 7: Characteristics of the study populations – RCT, direct comparison: sipuleucel-T + ADT vs. sham treatment + ADT (continued)

Study	**IMPACT**		**D9901**		**D9902A**	
characteristics	**Sipuleucel-T**	**Sham treatment**	**Sipuleucel-T**	**Sham treatment**	**Sipuleucel-T**	**Sham treatment**
category	**N = 341**	**N = 171**	**N = 82**	**N = 45**	**N = 65**	**N = 33**
Bisphosphonate use						
yes	164 (48.1)	82 (48.0)	3 (3.7)	3 (6.7)	8 (12.3)	3 (9.1)
no	177 (51.9)	89 (52.0)	79 (96.3)	42 (93.3)	57 (87.7)	30 (90.9)
Time since diagnosis [years], median (min; max)	7.1 (0.8; 24.5)	7.1 (0.9; 21.5)	7.6 (0.8; 17.3)	6.8 (1.6; 18.6)	5.5 (1.4; 12.8)	6.2 (1.0; 11.3)
LDH [U/L], median (min; max)	194.0 (84.0; 637.0)	193.0 (101.0; 1662.0)	173.5 (119.0; 533.0)	172.0 (108.0; 453.0)	187.0 (101.0; 1730.0)	179.0 (116.0; 730.0)
Prior prostate cancer therapy, n (%)						
chemotherapy[a]	67 (19.6)	26 (15.2)	3 (3.7)	4 (8.9)	7 (10.8)[b]	3 (9.1)
docetaxel	53 (15.5)	21 (12.3)	1 (1.2)	1 (2.2)	1 (1.5)	0 (0)
radiotherapy	185 (54.3)	91 (53.2)	41 (50.0)	18 (40.0)	41 (63.1)[b]	18 (54.5)
radical prostatectomy	121 (35.5)	59 (34.5)	37 (45.1)	13 (28.9)	22 (33.8)	10 (30.3)
orchiectomy	32 (9.4)	13 (7.6)	22 (26.8)	11 (24.4)	12 (18.5)	4 (12.1)
combined androgen blockade	279 (81.8)	141 (82.5)	76 (92.7)[c]	42 (93.3)	56 (86.2)	30 (90.9)
Study discontinuations, n (%)	ND[d]	ND[d]	6 (7.3)	6 (13.3)	13 (20.0)	2 (6.1)

a: Including docetaxel.
b: Deviating data between CSR and Module 4 A. Since the percentages in the CSR (11.1% for 7 of 65, and 65.1% for 41 of 65) did not appear to be plausible, the data were taken from Module 4 A.
c: Combined androgen blockade alone or in combination with other treatments.
d: 28 (8.2%) patients in the sipuleucel-T arm and 12 (7.0%) patients in the sham treatment arm did not receive all 3 infusions in the study.

ADT: androgen deprivation therapy; CSR: clinical study report; ECOG: Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase; max: maximum; min: minimum; N: number of randomized patients, values that are based on other patient numbers are marked in the corresponding column if the deviation is relevant (> 10%); n: number of patients in the category; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The characteristics of the study populations were largely comparable both between the studies and between the treatment arms. The mean age was 71 years. The majority of the patients were white (89% to approximately 94%). Exclusively patients with an Eastern Cooperative Oncology Group (ECOG) status of 0 or 1 were included in all studies; a larger proportion of patients had status 0 in all studies (between approximately 70% and approximately 82%).

Regarding bisphosphonate use it was notable that, in the IMPACT study, approximately half the patients were taking bisphosphonates, whereas these patients were fewer than 10% in both other studies, although the inclusion criteria of the studies were similar in respect of this parameter.

Regarding the number of bone metastases and the classification by Gleason score, there were partly differences of the patient populations both between the studies and within the studies between the treatment arms (see Table 7).

If the presentation of the meta-analyses showed heterogeneity between the studies, this was considered with regard to the differences in the patient characteristics of the studies described.

Table 8 shows the median treatment duration of the patients and the follow-up period for individual outcomes.

Table 8: Information on the course of the study – RCT, direct comparison: sipuleucel-T + ADT vs. sham treatment + ADT

Study **treatment duration/observation period**	**Sipuleucel-T + ADT** **N**	**Sham treatment + ADT** **N**
IMPACT	341	171
median treatment duration[a] [months], (Q1, Q3)	ND	ND
median observation period[b] [months], (Q1, Q3)	20.6 (ND)	19.3 (ND)
D9901	82	45
median treatment duration[c] [months], (Q1, Q3)	ND	ND
median observation period [months], (Q1, Q3)	ND	ND
D9902A	65	33
median treatment duration[d] [months], (Q1, Q3)	ND	ND
median observation period [months], (Q1, Q3)	ND	ND

a: There were no data on the median treatment duration. 91.8% (sipuleucel-T) and 92.2% (sham treatment) of the patients received all 3 infusions.
b: The data refer to the outcome "overall survival". There were no data for the other outcomes.
c: There were no data on median treatment duration. 93.9% (sipuleucel-T) and 95.6% (sham treatment) of the patients received all 3 infusions.
d: There were no data on median treatment duration. 84.6% (sipuleucel-T) and 81.8% (sham treatment) of the patients received all 3 infusions (Institute's calculation).
ADT: androgen deprivation therapy; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; vs.: versus

No data on median treatment duration were available in any of the 3 studies. However, in both study arms of the 3 studies, treatment duration was determined with 3 infusions at intervals of approximately 2 weeks. It could be inferred from the study documents that the proportion of patients who received all 3 infusions was comparable between the treatment groups in all 3 studies. It could therefore not be assumed that there were relevant differences between the study arms regarding treatment duration.

There were no data on the actual observation periods in the studies D9901 and D9902A and on possible differences between the study arms. In the IMPACT study, these were comparable for the outcome "overall survival" with 20.6 and 19.3 months. There were no data for the other outcomes.

When recording AEs, differences in observation periods can result in bias to the disadvantage of the arm with the longer observation period in the consideration of the raw proportions of the patients with event. Overall, no relevant influence of different observation periods on the results was assumed for the present studies. The reasons for this are as follows: In the

IMPACT study, all AEs were recorded until disease progression. Subsequently, only those events were documented that the investigator determined to be related to the treatment originally assigned, as well as all cerebrovascular events. In the studies D9901 and D9902A, only treatment-related AEs were recorded from a certain time point as well. It was not clear from the study documents whether this was the case after disease progression or after treatment week 16.

For all 3 studies it could be inferred from the study documents that disease progression occurred after approximately the same time in both study arms (medians, sipuleucel-T versus sham treatment: 14.6 weeks versus 14.4 weeks [IMPACT]; 11.7 weeks versus 10.0 weeks [D9901]; 10.9 weeks versus 9.9 weeks [D9902A]). Hence for the AE outcomes, no difference in observation periods between the respective treatment arms was assumed. This would also be the case in the studies D9901 and D9902A if the time point from which only treatment-related AEs were recorded had been treatment week 16 because then the observation period would have been exactly the same in both study arms.

It can be assumed that the proportion of AEs that were recorded after progression or after week 16 was comparably low and that most AEs were attributable to acute treatment-related events (see 2.7.2.4.1 of the full dossier assessment) so that, overall, no relevant influence of different observation periods on the results on AE outcomes was assumed.

Table 9 shows the risk of bias at study level.

Table 9: Risk of bias at study level – RCT, direct comparison: sipuleucel-T + ADT vs. sham treatment + ADT

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
IMPACT	Yes	Yes	Yes	Yes	Yes	Yes	Low
D9901	Yes	Yes	Yes	Yes	Yes	Yes	Low
D9902A	Yes	Yes	Yes	Yes	Yes	Yes	Low
ADT: androgen deprivation therapy; RCT: randomized controlled trial; vs.: versus							

The risk of bias at study level was rated as low for all studies. This concurs with the company's assessment.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were considered in this assessment (for reasons, see Section 2.7.2.4.3 of the full dossier assessment):

- Mortality
  - overall survival
- Morbidity
  - time to disease-related pain
- Health-related quality of life
- Adverse events
  - severe AEs (CTCAE grade ≥ 3)
  - serious adverse events (SAEs)
  - treatment discontinuations due to AEs
  - fever
  - headache
  - chills

The choice of patient-relevant outcomes deviates from that of the company (see Section 2.7.2.4.3 of the full dossier assessment). The overall rate of AEs is presented as additional information in the present benefit assessment, but was not used for the derivation of an added benefit. Specific AEs were additionally considered, which were chosen on the basis of their frequency and notable differences between the study arms.

Table 10 shows for which outcomes data were available in the studies included.

Table 10: Matrix of outcomes – RCT, direct comparison: sipuleucel-T + ADT vs. sham treatment + ADT

Study	Outcomes								
	Overall survival	Time to disease-related pain	Health-related quality of life	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)	Fever	Headache	Chills
IMPACT	No[a]	Yes	No[b]	Yes	Yes	Yes	Yes	Yes	Yes
D9901	No[a]	Yes	No[b]	Yes	No[c]	Yes	Yes	Yes	Yes
D9902A	No[a]	Yes	No[b]	Yes	No[c]	Yes	Yes	Yes	Yes

a: No evaluable results available. For reasons, see Section 2.7.2.4.2 of the full dossier assessment.
b: Outcome was not recorded.
c: According to information provided by the company in Module 4 A of the dossier, this outcome was not systematically recorded. No data were available.
ADT: androgen deprivation therapy; AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

Except for the outcomes “overall survival” (no evaluable data) and “health-related quality of life” (not recorded), data were available in at least one study for all outcomes chosen. No meaningful interpretation of the results was possible for the outcome “overall survival” because of the high proportion of patients who switched from the control treatment to the intervention.

2.4.2 Risk of bias

Table 11 shows the risk of bias for these outcomes.

Table 11: Risk of bias at study and outcome level – RCT, direct comparison: sipuleucel-T + ADT vs. sham treatment + ADT

Study	Study level	Outcomes								
		Overall survival	Time to disease-related pain	Health-related quality of life	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)	Fever	Headache	Chills
IMPACT	L	-[a]	H[b]	-	H[b]	H[b]	H[b]	H[b]	H[b]	H[b]
D9901	L	-[a]	H[b]	-	H[b]	-	H[b]	H[b]	H[b]	H[b]
D9902A	L	-[a]	H[b]	-	H[b]	-	H[b]	H[b]	H[b]	H[b]

a: No evaluable data available. For reasons, see Section 2.7.2.4.2 of the full dossier assessment.
b: Unblinding of the patient and of the treating physician at the time point of disease progression. Additionally, important differences regarding subsequent treatments: Different beginnings of treatment with docetaxel regarding time (medians, IMPACT: 7.2 months (intervention) vs. 9.6 months (control); ND for D9901 and D9902A) and high proportion of patients in the sham treatment arm who received the intervention treatment after progression (IMPACT: 63.7%; D9901: 75.6%; D9902A: 66.7%).

ADT: androgen deprivation therapy; AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; H: high; L: low; ND: no data; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

The risk of bias was rated as high for all outcomes, for the outcome "overall survival" to such an important extent that the results were considered to be not evaluable.

For the outcome "overall survival", this was mainly caused by the patients' possibility in the control arm to switch from the control treatment to the intervention after confirmed progression. Whereas the patients in the sipuleucel-T arm switched to further treatment at the choice of the treating physician, patients in the sham treatment group of all 3 studies mostly (approximately 67%) started treatment with sipuleucel-T after progression. For a large part of the patients in the sipuleucel-T arm, further treatment consisted of docetaxel, which is proven to have an effect on overall survival. Since the use of docetaxel in the control group in median (presumably) started later than in the intervention group (2.4 months later in the IMPACT study, no information for the studies D9901, D9902A), effective treatment was withheld from these patients for longer. Assuming that sipuleucel-T has no effect on overall survival, this can cause a relevant disadvantage of the control group (difference in median survival times in the IMPACT study: 4.1 months). It cannot be excluded that the effect in overall survival observed in the studies can be attributed to this alone. Overall, the uncertainty of these results was so large that they were not evaluable for the present benefit assessment (see Section 2.7.2.4.2 of the full dossier assessment).

For the outcome “time to disease-related pain”, the high risk of bias was mainly caused by the unblinding of the patients and of the treating physician, which was possible when progression occurred. Since the outcome was continued to be observed also after progression, the events on this outcome were at least partly recorded in an unblinded study situation. In addition, there was also the large proportion of patients in the control group who switched to the intervention.

For the outcomes on AEs, the number of any treatment-emergent AEs is relevant. In the 3 studies, however, AEs were only completely recorded until the time point of disease progression (IMPACT study) or until observation week 16 or disease progression (unclear information for the studies D9901 and D9902A). Events that occurred later were only recorded if the unblinded investigator determined that they were treatment-related. However, only summarizing analyses on all AEs were available for all 3 studies, i.e. including the treatment-related AEs. The influence of these events on the result on the individual outcomes on AEs considered was unclear. It also remained unclear whether events were considered that occurred in the control arm after a possible switch to sipuleucel-T. For these reasons, the results on all outcomes on AEs have a high risk of bias.

The assessment of the high risk of bias for all outcomes deviates from the company’s assessment, which derived a low risk of bias for all outcomes.

2.4.3 Results

Table 12 and Table 13 summarize the results on the comparison of sipuleucel-T and watchful waiting in patients with metastatic (non-visceral) castrate-resistant prostate cancer in whom chemotherapy is not yet clinically indicated. Where necessary, the data from the company’s dossier were supplemented by the Institute’s calculations. The figures of the meta-analyses can be found in Appendix A of the full dossier assessment.

Table 12: Results (time analyses) – RCT, direct comparison: sipuleucel-T + ADT vs. sham treatment + ADT

Outcome study time point	Sipuleucel-T + ADT		Sham treatment + ADT		Sipuleucel-T + ADT vs. sham treatment + ADT	
	N	Median time to event in months [95% CI]	N	Median time to event in months [95% CI]	HR [95% CI]	p-value
Mortality						
Overall survival						
IMPACT				No evaluable data		
D9901				No evaluable data		
D9902A				No evaluable data		
Total					Not applicable	
Morbidity						
Time to disease-related pain						
IMPACT	135	4.3 [2.8; 5.5]	68	4.0 [2.5; 5.4]	0.80 [0.56; 1.15]	0.227
D9901	82	NC [6.3; NC]	45	5.5 [3.0; 11.9]	0.68 [0.37; 1.25]	0.210
D9902A	65	7.2 [2.7; 17.4]	33	7.8 [5.9; NC]	1.39 [0.65; 2.97]	0.390[a]
Total					0.84 [0.62; 1.15]	0.280[b]

a: Slightly deviating information from the CSR.
b: Institute's calculation from meta-analysis.

ADT: androgen deprivation therapy; CI: confidence interval; CSR: clinical study report; HR: hazard ratio; N: number of analysed patients: NC: not calculable; RCT: randomized controlled trial; vs.: versus

Table 13: Results (AEs) – RCT, direct comparison: sipuleucel-T + ADT vs. sham treatment + ADT

Outcome study	Sipuleucel-T + ADT		Sham treatment + ADT		Sipuleucel-T + ADT vs. sham treatment + ADT
	N	Patients with events n (%)	N	Patients with events n (%)	RR [95% CI]; p-value
Adverse events					
AEs					
IMPACT	338	334 (98.8)	168	162 (96.4)	
D9901	82	82 (100.0)	45	44 (97.8)	
D9902A	65	63 (96.9)	31	29 (93.5)	
SAEs					
IMPACT	338	82 (24.3)	168	40 (23.8)	1.02 [0.73; 1.42]; > 0.999
D9901	82	22 (26.8)	45	8 (17.8)	1.51 [0.73; 3.11]; 0.282
D9902A	65	13 (20.0)	31	9 (29.0)	0.69 [0.33; 1.44]; 0.436
Total					1.02 [0.75; 1.39]; 0.895[a]
Discontinuation due to AEs					
IMPACT	338	5 (1.5)	168	1 (0.6)	2.49 [0.29; 21.10]; 0.447[b]
D9901		ND		ND	ND
D9902A		ND		ND	ND
Total					ND
Severe AEs (CTCAE grade ≥ 3)					
IMPACT	338	107 (31.7)	168	59 (35.1)	0.9 [0.7; 1.17][c]; ND
D9901[d]	82	27 (32.9)	45	12 (26.7)	1.23 [0.70; 2.19]; 0.548
D9902A[d]	65	21 (32.3)	31	9 (29.0)	1.11 [0.58; 2.14]; 0.817
Total					0.97 [0.77; 1.22]; 0.773[a]
Fever					
IMPACT	338	99 (29.3)	168	23 (13.7)	2.14 [1.41; 3.24][c]; < 0.001[b]
D9901	82	28 (34.1)	45	2 (4.4)	7.68 [1.92; 30.77][c]; < 0.001
D9902A	65	19 (29.2)	31	3 (9.7)	3.02 [0.97; 9.44][e]; 0.035
Total					heterogeneity[a]: Q = 3.29; df = 2; p = 0.193; I^2 = 39.1%
Headache					
IMPACT	338	54 (16.0)	168	8 (4.8)	3.36 [1.63; 6.89][c]; ND
D9901	82	14 (17.1)	45	2 (4.4)	3.84 [0.91; 16.15][c]; 0.050
D9902A	65	14 (21.5)	31	3 (9.7)	2.23 [0.69; 7.18][c]; ND
Total					3.12[a] [1.77; 5.47]; < 0.001[a]

(continued)

Table 13: Results (AEs) – RCT, direct comparison: sipuleucel-T + ADT vs. sham treatment + ADT (continued)

Outcome study	Sipuleucel-T + ADT		Sham treatment + ADT		Sipuleucel-T + ADT vs. sham treatment + ADT
	N	Patients with events n (%)	N	Patients with events n (%)	RR [95% CI]; p-value
Chills					
IMPACT	338	183 (54.1)	168	21 (12.5)	4.33 [2.87; 6.54][c]; ND
D9901	82	51 (62.2)	45	4 (8.9)	7.00 [2.70; 18.10][c]; < 0.001
D9902A	65	34 (52.3)	31	2 (6.5)	8.11 [2.08; 31.60][c]; < 0.001
Total					4.86[a] [3.38; 7.00]; < 0.001[a]

a: Institute's calculation from meta-analysis.
b: Institute's calculation, unconditional exact test (CSZ method [4]).
c: Institute's calculation, asymptotic.
d: This outcome was operationalized as "The incidence of AEs grade 3 (serious) and 4 (life-threatening), classified according to version 2.0 of the NCI CTCAE" in the dossier. The data presented there correspond to the information from the CSR on patients with an AE of severity grade 3–5.
e: Institute's calculation, asymptotic; discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods.

ADT: androgen deprivation therapy; AE: adverse event; CI: confidence interval; CSR: clinical study report; CSZ: convexity, symmetry, z score; CTCAE: Common Terminology Criteria for Adverse Events; N: number of analysed patients; n: number of patients with event; ND: no data; NCI: National Cancer Institute; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

Mortality

Overall survival

There were no evaluable data for the outcome "overall survival" (see Section 2.4.2). Hence there is no proof of added benefit of sipuleucel-T in comparison with the ACT. This deviates from the company's assessment, which derived proof of added benefit from the available data.

Morbidity

Time to disease-related pain

For the outcome "time to disease-related pain", there were only data for asymptomatic patients in the 3 studies IMPACT, D9901, and D9902A. For the IMPACT study, only data of those patients were included in the analyses who were included into the study before Amendment 7. The meta-analysis showed no statistically significant difference between the treatment arms. An added benefit of sipuleucel-T in comparison with watchful waiting while maintaining ongoing conventional ADT is therefore not proven for this outcome. This concurs with the company's assessment.

Health-related quality of life

No data on health-related quality of life were recorded in any of the 3 studies. An added benefit of sipuleucel-T in comparison with watchful waiting is therefore not proven for this outcome.

Adverse events

SAEs

For the outcome "SAEs", the meta-analysis of the 3 studies IMPACT, D9901, and D9902A showed no statistically significant difference between the treatment arms. Greater or lesser harm from sipuleucel-T in comparison with watchful waiting while maintaining ongoing conventional ADT is therefore not proven for this outcome. This assessment concurs with that of the company.

Severe adverse events (CTCAE grade ≥ 3)

For the outcome "severe AEs (CTCAE grade ≥ 3)", the meta-analysis of the studies IMPACT, D9901, and D9902A showed no statistically significant difference between the respective treatment arms. Greater or lesser harm from sipuleucel-T in comparison with watchful waiting while maintaining ongoing conventional ADT is therefore not proven for the outcome. This assessment concurs with that of the company.

Discontinuation due to adverse events

Results on discontinuation due to AEs were only available for the IMPACT study. According to the company, discontinuations due to AEs were not systematically recorded in the 2 other studies. There was no statistically significant difference between the treatment arms in this study. Greater or lesser harm from sipuleucel-T in comparison with watchful waiting while maintaining ongoing conventional ADT is therefore not proven for the outcome. This assessment concurs with that of the company.

Fever

The meta-analysis showed important heterogeneity for the outcome "fever". In the 3 individual studies, there was a statistically significant difference between the treatment groups to the disadvantage of sipuleucel-T, overall the effects were therefore clearly in the same direction. There was an outcome-specific high risk of bias for all 3 studies. Hence, there was an indication of greater harm from sipuleucel-T in comparison with watchful waiting while maintaining ongoing conventional ADT for this outcome. The company did not present the outcome in the dossier.

Headache

The meta-analysis of the studies IMPACT, D9901 and D9902A showed a statistically significant difference to the disadvantage of sipuleucel-T for the outcome "headache". There was an outcome-specific high risk of bias for all 3 studies. An indication of greater harm from

sipuleucel-T in comparison with watchful waiting while maintaining ongoing conventional ADT can be derived from this. The company did not present this outcome in the dossier.

Chills

The meta-analysis of the studies IMPACT, D9901 and D9902A showed a statistically significant difference to the disadvantage of sipuleucel-T for the outcome "chills". There was an outcome-specific high risk of bias for all 3 studies. An indication of greater harm from sipuleucel-T in comparison with watchful waiting while maintaining ongoing conventional ADT can be derived from this. The company did not present this outcome in the dossier.

2.4.4 Subgroups and other effect modifiers

Subgroups on the following characteristics were considered for the present benefit assessment: age (≤ median versus > median), ethnicity (white versus Afro-American versus other; non-white versus white), disease localization (bone and soft tissue versus bone only or soft tissue only) and number of bone metastases (0–5 versus 6–10 versus > 10).

Except for the cut-off of the characteristic "age" by medians, all subgroup characteristics and cut-offs considered were prespecified. The median age was between 71 and 73 years, depending on the study, and therefore provided a more meaningful cut-off than the pre-specified classification > 65 and < 65 years, particularly with regard to the fact that metastatic castrate-resistant prostate cancer often occurs at an advanced age.

Overall, there were no evaluable data for the outcome "overall survival" in the 3 studies (see Section 2.4.2). Hence the subgroup analyses presented by the company on this outcome were not used for the present benefit assessment.

For the outcome "time to disease-related pain" and for the outcomes of the complex "AEs", only subgroup analyses on the characteristic "age" (≤ median versus > median) were available.

The prerequisite for proof of different subgroup effects is a statistically significant interaction ($p \leq 0.05$). A p-value between 0.05 and 0.2 provides an indication of an effect modification.

The interaction tests were conducted for the total study pool, if possible. There was no indication or proof of an interaction between treatment effect and characteristic for any subgroup characteristic. For the outcome "discontinuation due to AEs", evaluable data were only available for one study (IMPACT). There was no indication or proof of an interaction between treatment effect and characteristic for this outcome either.

2.5 Extent and probability of added benefit

The derivation of extent and probability of added benefit is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.5.1 Assessment of added benefit at outcome level

The data presented in Section 2.4 resulted in no proof of an added benefit for the outcomes “overall survival” and “time to disease-related pain”, and in an indication of greater harm for the outcomes “headache”, “chills” and “fever”. No data on health-related quality of life were recorded.

The extent of the respective added benefit at outcome level was estimated from these results (see Table 14).

Table 14: Extent of added benefit at outcome level: sipuleucel-T + ADT vs. watchful waiting + ADT

Outcome category **outcome**	**Sipuleucel-T vs. watchful waiting** **quantile of time to event or proportion of events** **effect estimate [95% CI]** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	No evaluable data	
Morbidity		
Time to disease-related pain[c]	4.3–7.2 vs. 4.0–7.8 months[d,e] HR: 0.84 [0.62; 1.15] p = 0.280[f]	Lesser benefit/added benefit not proven
Health-related quality of life		
	Outcome not recorded	
Adverse events		
SAEs	20.0–26.8% vs. 17.8–29.0%[d] RR: 1.02 [0.75; 1.39] p = 0.895[f]	Lesser/greater harm not proven
Severe AEs (CTCAE grade ≥ 3)	31.7–32.9% vs. 26.7–35.1%[d] RR: 0.97 [0.77; 1.22] p = 0.773[f]	Lesser/greater harm not proven
Discontinuation due to AEs[g]	1.5 vs. 0.6% RR: 2.49 [0.29; 21.10] p = 0.447[h]	Lesser/greater harm not proven
Fever	29.2–34.1% vs. 4.4–13.7%[d] heterogeneity, effects clearly in the same direction probability: "indication"	Outcome category: non-serious/non-severe AEs greater harm, extent: "non-quantifiable"
Headache	16.0–21.5% vs. 4.4–9.7%[d] RR: 3.12 [1.77; 5.47][f] RR: 0.32 [0.18; 0.56][i] p < 0.001[f] probability: "indication"	Outcome category: non-serious/non-severe AEs $CI_u \leq 0.80$ greater harm, extent: "considerable"
Chills	52.3–62.2% vs. 6.5–12.5%[d] RR: 4.86 [3.38; 7.00][f] RR: 0.21 [0.14; 0.30][i] p < 0.001[f] probability: "indication"	Outcome category: non-serious/non-severe AEs $CI_u \leq 0.80$ greater harm, extent: "considerable"

(continued)

Table 14: Extent of added benefit at outcome level: sipuleucel-T + ADT vs. watchful waiting + ADT (continued)

a: Probability provided if statistically significant differences were present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Only information for asymptomatic patients was available for this outcome. Hence no conclusions can be drawn for minimally symptomatic patients on this outcome.
d: Minimum and maximum proportions of events or quantiles of the time to event in each treatment arm in the studies included.
e: The value was not calculable for the intervention arm in the D9901 study.
f: Institute's calculation from meta-analysis.
g: Data only available for the IMPACT study.
h: Institute's calculation, unconditional exact test (CSZ method according to [4]).
i: Institute's calculation: reversed direction of effect to enable direct use of limits to derive added benefit.
ADT: androgen deprivation therapy; AE: adverse event; CI: confidence interval, CI_u: upper limit of CI; CSZ: convexity, symmetry, z score; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; RR: relative risk; SAE: serious adverse event; vs.: versus

2.5.2 Overall conclusion on added benefit

Table 15 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 15: Positive and negative effects from the assessment of sipuleucel-T compared with watchful waiting

Positive effects	Negative effects
–	Indication of greater harm – extent: "considerable" (non-serious/non-severe adverse events: headache)
	Indication of greater harm – extent: "considerable" (non-serious/non-severe adverse events: chills)
	Indication of greater harm – extent: "non-quantifiable" (non-serious/non-severe adverse events: fever)

Overall, only negative effects of sipuleucel-T remain at outcome level on the basis of the available results. The negative effects consist of an indication of greater harm with the extent "considerable" (headache, chills), and an indication of greater harm, the extent of which is "non-quantifiable" (fever).

In the overall weighing of benefits and harms, these exclusively negative effects do not result in lesser benefit of sipuleucel-T. Instead, the lack of evaluable and informative results for the outcome "overall survival" overall resulted in such a high uncertainty that a conclusive weighing of the results on added benefit is not possible.

Overall, the added benefit of sipuleucel-T versus the ACT, watchful waiting while maintaining ongoing conventional ADT, is not proven for patients with asymptomatic or

minimally symptomatic metastatic (non-visceral) castrate-resistant prostate cancer in whom chemotherapy is not yet clinically indicated.

This deviates from the company's approach, which considered no specific AEs, and, based on the data on overall survival, derived proof of considerable added benefit of sipuleucel-T versus the ACT.

The result of the assessment of the added benefit of sipuleucel-T in comparison with the ACT is summarized in Table 16.

Table 16: Sipuleucel-T – extent and probability of added benefit

Therapeutic indication	**ACT**[a]	**Extent and probability of added benefit**
Treatment of asymptomatic or minimally symptomatic metastatic (non-visceral) castrate-resistant prostate cancer in male adults in whom chemotherapy is not yet clinically indicated	▪ **watchful waiting while maintaining ongoing conventional ADT** or, if applicable, ▪ combined maximal androgen blockade with a non-steroidal anti-androgen (flutamide, bicalutamide) or ▪ abiraterone acetate while maintaining ongoing ADT	Added benefit not proven
a: Presentation of the ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee;		

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.6 List of included studies

IMPACT

Dendreon. Provenge (sipuleucel-T) active cellular immunotherapy treatment of metastatic prostate cancer after failing hormone therapy: full text view [online]. In: ClinicalTrials.gov. 2 September 2010 [accessed: 28 October 2014]. URL: http://ClinicalTrials.gov/show/NCT00065442.

Dendreon. Provenge (sipuleucel-T) active cellular immunotherapy treatment of metastatic prostate cancer after failing hormone therapy: study results [online]. In: ClinicalTrials.gov. 2 September 2010 [accessed: 28 October 2014]. URL: http://clinicaltrials.gov/ct2/show/results/NCT00065442.

Dendreon. A randomized, double blind, placebo-controlled phase 3 trial of immunotherapy with autologous antigen presenting cells loaded with PA2024 (Provenge, sipuleucel-T, APC8015) in men with metastatic androgen independent prostatic adenocarcinoma: study D9902B; clinical study report [unpublished]. 2013.

Dendreon. A randomized, double blind, placebo-controlled phase 3 trial of immunotherapy with autologous antigen presenting cells loaded with PA2024 (Provenge, sipuleucel-T, APC8015) in men with metastatic androgen independent prostatic adenocarcinoma: study D9902B; clinical study report addendum [unpublished]. 2011.

Dendreon. SAS output: German submission [unpublished]. 2014.

Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010; 363(5): 411-422.

Schellhammer PF, Chodak G, Whitmore JB, Sims R, Frohlich MW, Kantoff PW. Lower baseline prostate-specific antigen is associated with a greater overall survival benefit from sipuleucel-T in the Immunotherapy for Prostate Adenocarcinoma Treatment (IMPACT) trial. Urology 2013; 81(6): 1297-1302.

D9901

Dendreon. A randomized, double blind, placebo-controlled trial of immunotherapy with autologous antigen-loaded dendritic cells (Provenge, APC8015) for asymptomatic, metastatic, hormone refractory prostate cancer: study D9901; clinical study report [unpublished]. 2006.

Dendreon. Vaccine therapy in treating patients with metastatic prostate cancer that has not responded to hormone therapy: full text view [online]. In: ClinicalTrials.gov. 8 October 2010 [accessed: 28 October 2014]. URL: http://ClinicalTrials.gov/show/NCT00005947.

Dendreon. Vaccine therapy in treating patients with metastatic prostate cancer that has not responded to hormone therapy: study results [online]. In: ClinicalTrials.gov. 8 October 2010 [accessed: 28 October 2014]. URL: http://clinicaltrials.gov/ct2/show/results/NCT00005947.

Dendreon. SAS output: German submission [unpublished]. 2014.

Lee D. Autologous dendritic cells pulsed with prostatic acid phosphatase (APC8015) for patients with hormone-refractory prostate cancer with a Gleason score ≤ 7. Clin Prostate Cancer 2003; 2(2): 81-83.

Small EJ, Schellhammer PF, Higano CS, Redfern CH, Nemunaitis JJ, Valone FH et al. Placebo-controlled phase III trial of immunologic therapy with sipuleucel-T (APC8015) in patients with metastatic, asymptomatic hormone refractory prostate cancer. J Clin Oncol 2006; 24(19): 3089-3094.

D9902A

Dendreon. Immunotherapy with APC8015 (sipuleucel-T, provenge) for asymptomatic, metastatic, hormone-refractory prostate cancer: full text view [online]. In: ClinicalTrials.gov. 2 September 2014 [accessed: 28 October 2014]. URL: http://ClinicalTrials.gov/show/NCT01133704.

Dendreon. Immunotherapy with APC8015 (sipuleucel-T, provenge) for asymptomatic, metastatic, hormone-refractory prostate cancer: study results [online]. In: ClinicalTrials.gov. 2 September 2014 [accessed: 28 October 2014]. URL: http://clinicaltrials.gov/ct2/show/results/NCT01133704.

Dendreon. A randomized, double blind, placebo-controlled trial of immunotherapy with autologous antigen-loaded dendritic cells (Provenge, APC8015) for asymptomatic, metastatic, hormone refractory prostate cancer: study D9902A; clinical study report [unpublished]. 2006.

Dendreon. SAS output: German submission [unpublished]. 2014.

References for English extract

Please see full dossier assessment for full reference list.

1. Institute for Quality and Efficiency in Health Care. General Methods: version 4.1 [online]. 28 November 2013 [accessed: 1 August 2014]. URL: https://www.iqwig.de/download/IQWiG_General_Methods_Version_%204-1.pdf.

2. Institute for Quality and Efficiency in Health Care. Ticagrelor: benefit assessment according to §35a Social Code Book V; extract; commission no. A11-02 [online]. 29 September 2011 [accessed: 5 May 2012]. URL: https://www.iqwig.de/download/A11-02_Extract_of_dossier_assessment_Ticagrelor.pdf.

3. European Medicines Agency. Provenge: European public assessment report; product information [German] [online]. 3 October 2013 [accessed: 14 March 2014]. URL: http://www.ema.europa.eu/docs/de_DE/document_library/EPAR_-_Product_Information/human/002513/WC500151099.pdf.

4. Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Computat Stat Data Anal 1994; 17(5): 555-574.

The full report (German version) is published under https://www.iqwig.de/de/projekte-ergebnisse/projekte/arzneimittelbewertung/a14-38-sipuleucel-t-nutzenbewertung-gemaess-35a-sgb-v-dossierbewertung.6454.html.