IQWiG Reports – Commission No. A15-08

Sipuleucel-T (Addendum to Commission A14-38)[1]

Addendum

Commission: A15-08
Version: 1.0
Status: 2 March 2015

[1] Translation of addendum A15-08 *Sipuleucel-T (Addendum zum Auftrag A14-38*) (Version 1.0; Status: 2 March 2015). 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
(Addendum to Commission A14-38)

Commissioning agency:
Federal Joint Committee

Commission awarded on:
10 February 2015

Internal Commission No.:
A15-08

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

IQWiG employees involved in the addendum[2]:

- Volker Vervölgyi
- Christoph Schürmann
- Beate Wieseler

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

Page

List of tables

Page

List of figures

Page

List of abbreviations

Abbreviation	Meaning
ADT	androgen deprivation therapy
CI	confidence interval
FDA	Food and Drug Administration
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HR	hazard ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
SGB	Sozialgesetzbuch (Social Code Book)

1 Background

On 10 February 2015, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct a supplementary assessment for Commission A14-38 (Sipuleucel-T – Benefit assessment according to §35a Social Code Book (SGB) V [1]).

With its comment on IQWiG's dossier assessment, the pharmaceutical company (hereinafter referred to as "the company") presented further information on results for the outcome "overall survival" [2]. The G-BA therefore commissioned IQWiG with the assessment of the analysis on the outcome "overall survival" presented by the company in the dossier under consideration of the supplementary information provided in the comment.

The responsibility for the present assessment and the results of the assessment lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

In the dossier assessment, the results on the outcome "overall survival" were not interpretable in a meaningful way because the majority of the patients in the sham treatment group of all 3 studies included (67%) started treatment with sipuleucel-T after progression. In contrast, the patients in the sipuleucel-T arm switched to further treatment at the physician's choice. Because of this allowed treatment switching in the control group to the experimental intervention, the risk of bias was estimated to be so important that the results on overall survival were considered to be not evaluable.

With its comment, the company presented further analyses to support the interpretation of the results on overall survival. This was the following additional information, which is relevant for an assessment of the outcome "all-cause mortality":

- information on the time to the administration of docetaxel in the 3 included studies IMPACT (D9902B), D9901 and D9902A (including different sensitivity analyses on overall survival based on the time point of the docetaxel administration)
- sensitivity analyses on overall survival under the assumption of a positive effect of docetaxel
- sensitivity analyses on overall survival with separate analysis of patients with and without subsequent docetaxel treatment

The different analyses of the docetaxel administration after progression and of overall survival are presented in the following sections. Section 2.1 provides an overview of the result of assessment A14-38. Section 2.2 describes the different analyses presented by the company and their results. An overall assessment of the data is conducted in Section 2.3. Section 2.4 describes whether and how conclusions of the original dossier assessment A14-38 have changed.

2.1 Initial situation

Three studies (D9901, D9902A, IMPACT) were available that reported results on the outcome "overall survival" and that were used for the benefit assessment. In all studies, the patients were either assigned to treatment with sipuleucel-T or to sham treatment at the start of the study. The treatment of the patients in the 3 studies with the experimental or control intervention is described in more detail in dossier assessment A14-38 [1]. On confirmed disease progression, the patients were unblinded and received treatment at the physician's discretion (including docetaxel). Patients in the control arm could additionally switch to treatment with a product analogous to sipuleucel-T, which was manufactured from cryopreserved cells. A total of 67% of the patients in the control arms of the 3 studies received this (modified) experimental intervention on progression. Following this treatment, further therapies at the physician's discretion could be used (including docetaxel).

This possibility for the patients in the control arm to receive the experimental intervention was one of the reasons why the proportion of patients with docetaxel administration in the studies differed between the treatment groups. Since docetaxel has a positive effect on overall survival [3,4], this can lead to bias of the treatment effect of sipuleucel-T, which actually is the one of interest. A strong distorting influence from docetaxel administration in favour of sipuleucel-T could be assumed particularly for the IMPACT study because docetaxel was not only used more frequently in the verum group, but also earlier: Patients who received docetaxel in the course of the study received this drug after a median time of 7.2 months in the verum group, and after 9.6 months in the control group. There were no corresponding data for the other 2 studies. Moreover it was unclear whether treatment with docetaxel was completely withheld from some of the patients in the control arm because of the treatment switching to the experimental intervention, and how large this proportion was.

Based on the information presented by the company in the dossier it could also not be excluded overall that the observed treatment effect in overall survival was solely caused by the more frequent and earlier administration of docetaxel in the sipuleucel-T arm. The uncertainty of these results was considered to be so great in dossier assessment A14-38 that they were not evaluable for the benefit assessment.

2.2 Presentation of the analyses of the docetaxel administration after progression and of overall survival

In its comment, the company presented further information on the time course of the administration of docetaxel and analyses on the investigation of potential bias from docetaxel. These are described below.

Time to first administration of docetaxel

In its comment, the company subsequently submitted analyses on the time to the first administration of docetaxel so that this information was now available for all 3 studies. These are shown in Table 1.

Table 1: Analysis of the time to the first use of docetaxel – RCT, direct comparison: sipuleucel-T + ADT vs. sham treatment + ADT

Outcome study	Sipuleucel-T		Sham treatment		Sipuleucel-T vs. sham treatment	
	N	Events (%) median time to event in months	N	Events (%) median time to event in months	HR [95% CI][a]	p-value[b]
Time to first administration of docetaxel						
IMPACT	341	195 (57.2) 12.3	171	86 (50.3) 13.9	1.21 [0.93; 1.55]	0.150
D9901[c]	82	29 (35.4) NC	45	20 (44.4) 25.5	0.69 [0.39; 1.23]	0.208
D9902A[d]	65	22 (33.8) 29.8	33	10 (30.3) 21.0	1.06 [0.50; 2.25]	0.874

a: Cox regression model, adjusted for PSA and LDH to baseline.
b: Log-rank test.
c: No information on the docetaxel administration was available for 4 (sipuleucel-T) versus 4 (sham treatment) patients. These patients were considered as if they had received no docetaxel.
d: No information on the docetaxel administration was available for 8 (sipuleucel-T) versus 1 (sham treatment) patients. These patients were considered as if they had received no docetaxel.
ADT: androgen deprivation therapy; CI: confidence interval; HR: hazard ratio; LDH: lactate dehydrogenase; N: number of analysed patients: NC: not calculable; PSA: prostate-specific antigen; RCT: randomized controlled trial; vs.: versus

Considering the median time to the first use of docetaxel it appears that the control group received docetaxel later only in the IMPACT study. However, the results of the effect estimates indicate earlier administration of docetaxel in the sipuleucel-T arm in the studies IMPACT and (to a lesser degree) D9902A and later administration in the D9901 study. In the studies IMPACT and D9902A, the proportion of patients who received docetaxel was higher in the sipuleucel-T arms. The difference in the D9902A study was small, but it is to be noted that there was no information on docetaxel administration for 8 patients (approximately 12%) in the sipuleucel-T arm. No final conclusion can be reached in the interpretation of the data in this study. In the D9901 study, the proportion of patients who received docetaxel in the course of the study was higher in the control group.

The corresponding Kaplan-Meier curve was additionally available for the IMPACT study (see Figure 1). This also shows the earlier use of docetaxel in the sipuleucel-T arm. There were no corresponding curves for the other 2 studies.

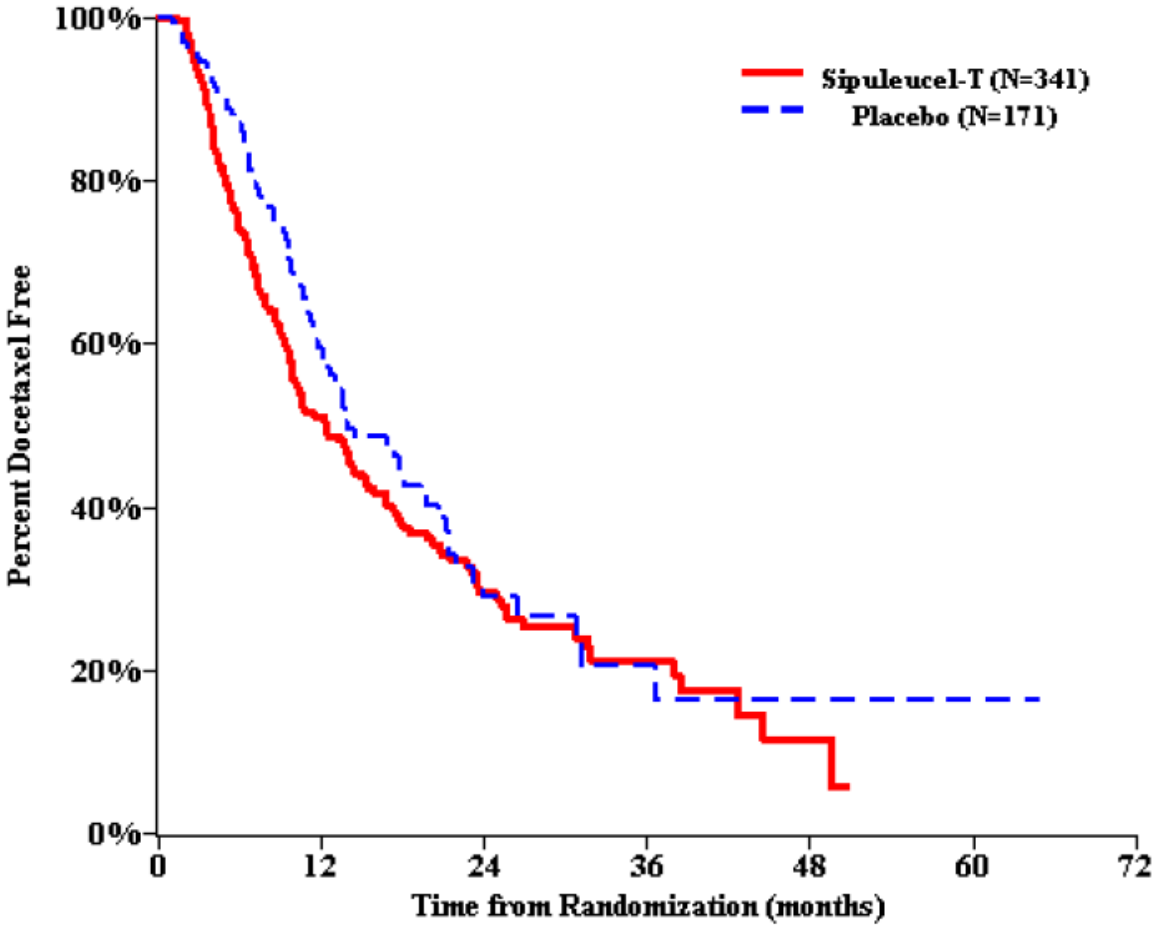

Figure 1: Analysis of the time to the first use of docetaxel – RCT, direct comparison: sipuleucel-T + ADT vs. sham treatment + ADT (IMPACT study)

Sensitivity analyses on the influence of the time point of docetaxel administration on overall survival (censoring and or time-dependent adjustment in the administration of docetaxel)

In its comment, the company presented different sensitivity analyses, in which the influence of docetaxel administration in the course of the study on overall survival was to be investigated. The following Table 2 presents the primary analysis on overall survival as well as sensitivity analyses in which patients were censored at the first administration of docetaxel (sensitivity analysis 1) or in which the administration of docetaxel was considered as time-dependent covariable in the Cox regression model (sensitivity analysis 2). These analyses were only individually available for the IMPACT study, and additionally as cross-study analyses for all 3 studies (so-called “integrated studies”) and hence as meta-analysis of the individual patient data.

Table 2: Sensitivity analyses on the influence of the time point of docetaxel administration on overall survival – RCT, direct comparison: sipuleucel-T + ADT vs. sham treatment + ADT

Outcome Study/studies	Sipuleucel-T vs. placebo HR [95% CI]	 p-value
Overall survival		
Primary analysis[c]		
IMPACT	0.78 [0.61; 0.98]	0.032
Total[a,b]	0.74 [0.61; 0.88]	< 0.001
Sensitivity analysis 1[d]		
IMPACT	0.65 [0.47; 0.90]	0.009
Total[a,b]	0.71 [0.56; 0.91]	0.006
Sensitivity analysis 2[e]		
IMPACT	0.78 [0.62; 0.98]	0.034
Total[a,b]	0.74 [0.61; 0.88]	< 0.001

a: Meta-analysis on the basis of individual patient data of the 3 studies IMPACT, D9901 and D9902A.
b: Stratified analysis by study.
c: Cox regression model, adjusted for the logarithms of the values of PSA and LDH to baseline.
d: Cox regression model, adjusted for the logarithms of the values of PSA and LDH to baseline. Patients were censored at the time point of the first docetaxel administration.
e: Cox regression model, adjusted for the logarithms of PSA and LDH as well as docetaxel administration (time-dependent covariable).
ADT: androgen deprivation therapy; CI: confidence interval; HR: hazard ratio; LDH: lactate dehydrogenase; N: number of analysed patients: PSA: prostate-specific antigen; RCT: randomized controlled trial; vs.: versus

The effect estimates of the sensitivity analyses largely concur with the ones of the primary analysis; the results were also consistent with regard to statistical significance.

The company additionally presented Kaplan-Meier curves on overall survival, once with and once without censoring of the patients at the start of docetaxel treatment (IMPACT study: Figure 2, joint consideration of all 3 studies: Figure 3). Both figures show that the respective courses of the curves with or without censoring are largely very similar in both treatment groups.

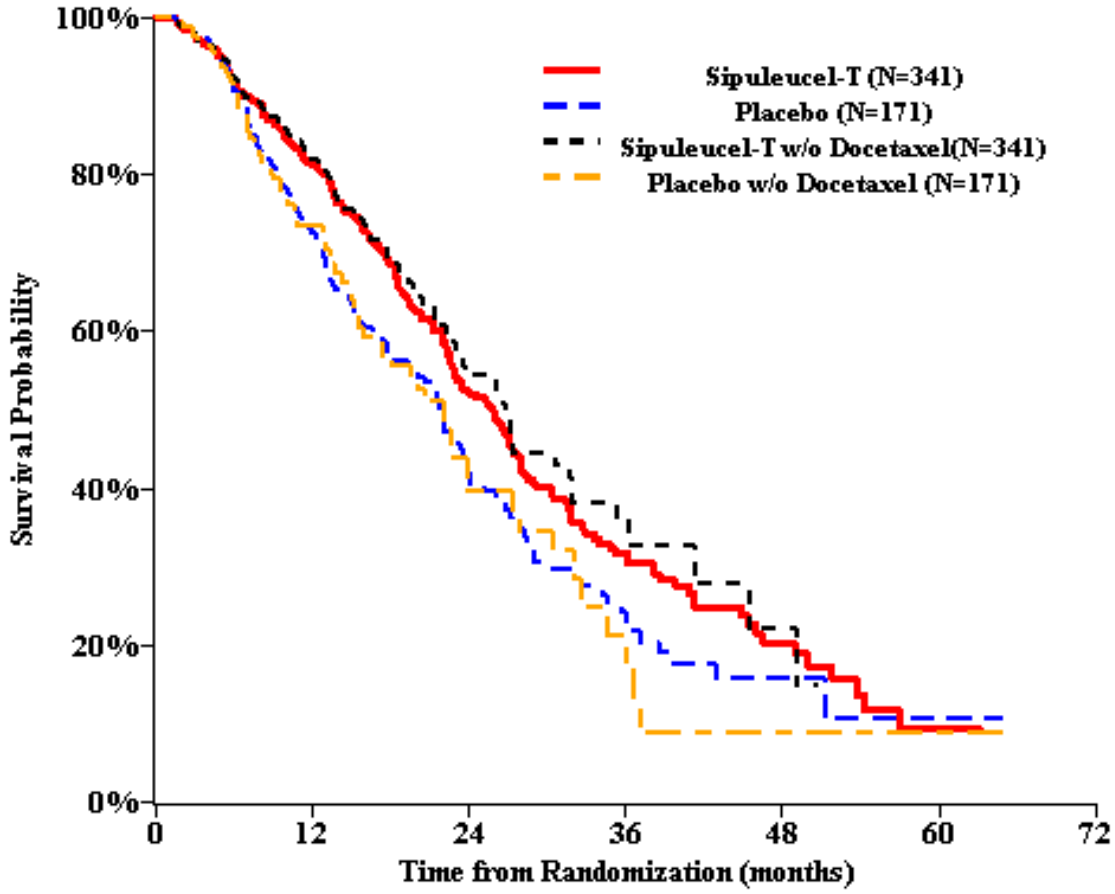

Figure 2: Kaplan-Meier curves on overall survival with and without censoring at the start of docetaxel treatment – RCT, direct comparison: sipuleucel-T + ADT vs. sham treatment + ADT (IMPACT study)

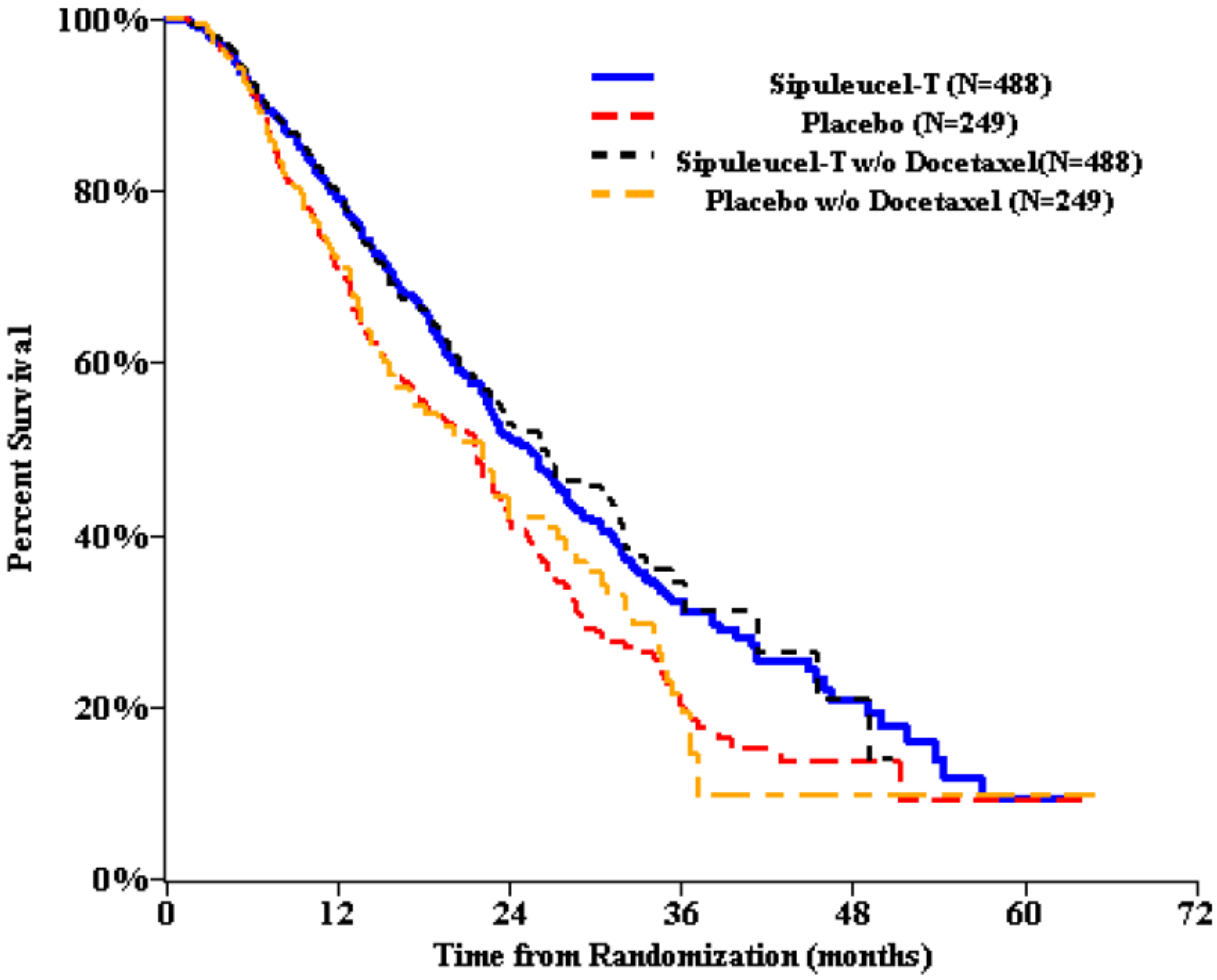

Figure 3: Kaplan-Meier curves on overall survival with and without censoring at the start of docetaxel treatment – RCT, direct comparison: sipuleucel-T + ADT vs. sham treatment + ADT (pool of all 3 studies)

Further information and sensitivity analyses were additionally available for the IMPACT study: In the analysis with docetaxel as time-dependent covariable (sensitivity analysis 2 in Table 2), the provided effect estimate based on docetaxel was HR = 0.88 (95% CI: [0.69; 1.12], p = 0.30). In a multifactorial model that included not only docetaxel but also an interaction of sipuleucel-T and docetaxel, the effect estimates remained largely unchanged (sipuleucel-T: HR = 0.67 [0.49; 0.92], docetaxel: HR = 0.71 [0.48; 1.05]); the interaction itself was not statistically significant (p = 0.171). In another model in which docetaxel was considered time-dependent as the only explaining variable, i.e. which did not contain a treatment effect from sipuleucel-T, the corresponding effect estimate for docetaxel was not statistically significant (HR = 0.88 [0.69; 1.12]; p = 0.286).

Sensitivity analyses on overall survival under the assumption of a positive effect of docetaxel

In its comment, the company presented analyses on overall survival in which a fixed assumed reduction of the hazard rate was conducted for patients from the time point of the first docetaxel administration (so-called "penalized Cox regression"). As in the sensitivity analyses described above, this model also considered the docetaxel administration as time-dependent covariable, but in contrast to those sensitivity analyses, this was done with a fixed effect [5]. The company showed results for different assumptions on the size of this effect (see Table 3), but only for the IMPACT study.

Table 3: Sensitivity analyses on the influence of an assumed docetaxel effect on overall survival – RCT, direct comparison: sipuleucel-T + ADT vs. sham treatment + ADT (IMPACT study)

Assumption docetaxel effect (HR)	Sipuleucel-T vs. sham treatment	
	HR[a] [95% CI]	p-value[a]
0.1	0.83 [0.67; 1.04]	0.112
0.2	0.82 [0.65; 1.02]	0.076
0.3	0.80 [0.64; 1.01]	0.057
0.4	0.80 [0.64; 0.995]	0.045
0.5	0.79 [0.63; 0.99]	0.038
0.6	0.78 [0.63; 0.98]	0.032
0.7	0.78 [0.62; 0.97]	0.028
0.8	0.77 [0.62; 0.97]	0.025
0.9	0.77 [0.62; 0.96]	0.022
1	0.77 [0.61; 0.96]	0.020

a: Cox regression model, adjusted for logarithms of PSA and LDH after baseline and as fixed assumed time-dependent effect from docetaxel (according to the assumption) from the start of the treatment with this drug.
ADT: androgen deprivation therapy; CI: confidence interval; HR: hazard ratio; LDH: lactate dehydrogenase; N: number of analysed patients: PSA: prostate-specific antigen; RCT: randomized controlled trial; vs.: versus

These analyses showed that the treatment effect of sipuleucel-T changes towards the direction of the null effect with increasing docetaxel effect (i.e. lower HR). However, it is no longer statistically significant only when a very large effect with a hazard ratio below 0.4 is assumed for docetaxel.

Sensitivity analyses on overall survival with separate analysis of patients with and without subsequent docetaxel treatment

In its comment, the company refers to the statistical evaluation report of sipuleucel-T by the US regulatory authority Food and Drug Administration (FDA) [6]. This report discusses another sensitivity analysis of the IMPACT study, in which overall survival is compared separately for the groups of patients with and without docetaxel treatment between sipuleucel-

T and sham treatment. The corresponding Kaplan-Meier curves for these patient groups are shown in Figure 4.

Figure 4 Survival Analysis by Docetaxel Subgroup

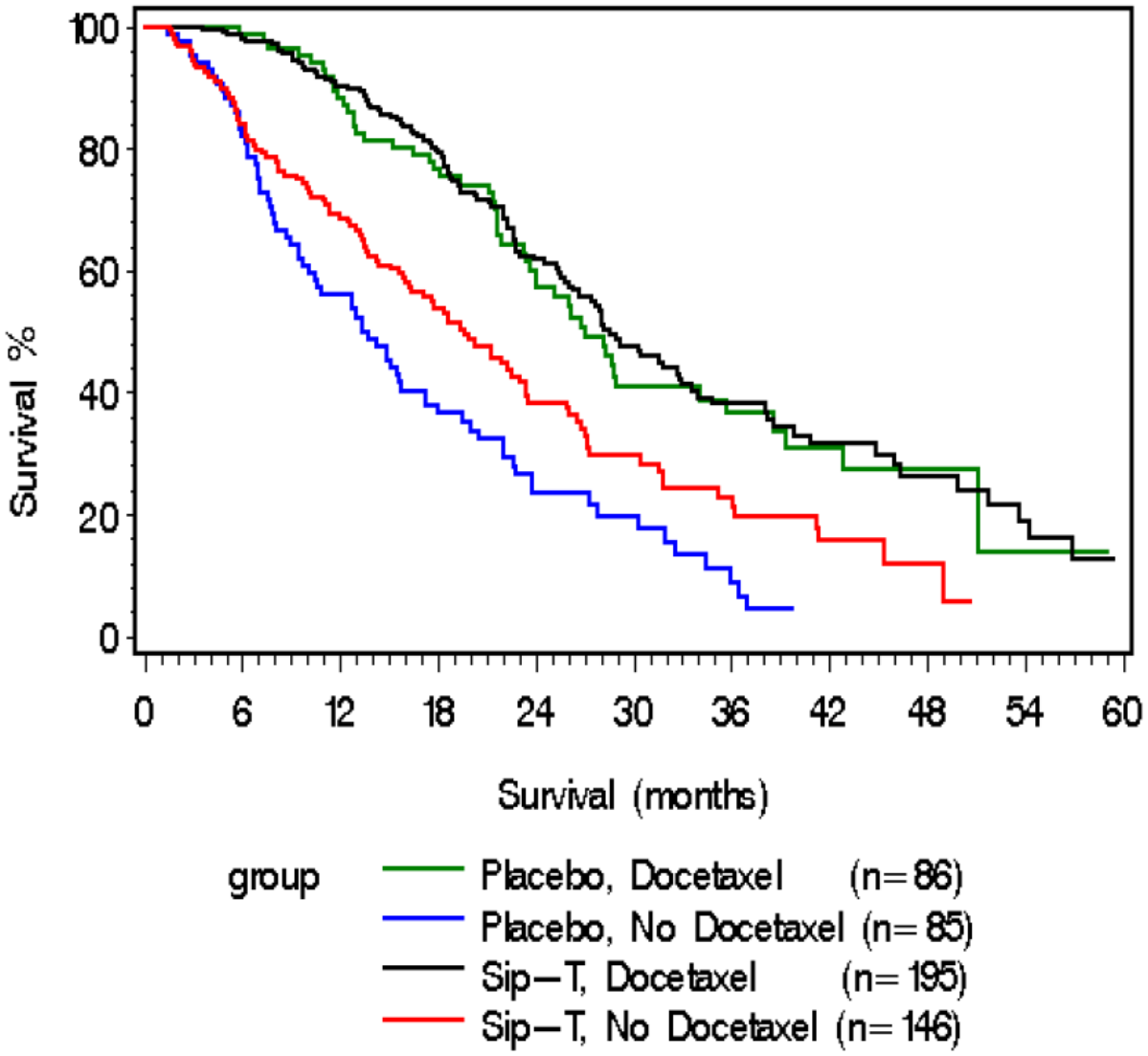

Figure 4: Kaplan-Meier curves on overall survival by treatment arm and docetaxel administration – RCT, direct comparison: sipuleucel-T + ADT vs. sham treatment + ADT (IMPACT study) [6]

There were no important differences in survival time curves between the treatment groups for the subset of patients who received docetaxel during the course of the study. In contrast, there was a marked difference in patients who received no docetaxel with patients under sham treatment dying earlier than the ones with sipuleucel-T treatment. This difference is also shown by a statistically significant hazard ratio (HR = 0.68 [0.50; 0.92], p = 0.012); this did not apply to the group with docetaxel treatment (HR = 0.94 [0.67; 1.31], p = 0.694). It is to be

noted, however, that – as described by the FDA [6] – these were not randomized comparisons because it can be assumed that docetaxel was not administered at random.

2.3 Summarizing assessment of the information on docetaxel administration and overall survival

The analyses of the studies D9901 and D9902A on the outcome "overall survival" could not be assessed in the original benefit assessment because no information on the difference in the time of docetaxel administration was available for the respective treatment groups. In the IMPACT study, docetaxel administration was conducted earlier in the sipuleucel-T study arm than in the sham treatment arm. It could therefore be assumed that a similar difference also occurred in the 2 other studies of similar design. The additional analyses (Table 1) show a different picture for the 2 studies D9901 and D9902A. In the D9901 study, patients in the control group received docetaxel earlier and more frequently, which suggests that these patients even had an advantage regarding docetaxel administration. In contrast, no final conclusions could be drawn on the data of the D9902A study. Regarding the median time to the first administration of docetaxel, there was an advantage for patients in the sham treatment arm, which was not confirmed by the corresponding HR, however. There was no Kaplan-Meier curve, which would have been helpful for the assessment of the data. No final conclusion could be drawn regarding the proportion of patients who received treatment with docetaxel in the course of the study either. With 33.8% in the sipuleucel-T compared with 30.3% in the sham treatment arm, there was only a marginal difference to the disadvantage of the control group. However, the corresponding information on potential docetaxel administration was lacking for some of the patients in the sipuleucel-T arm (12.3%) so that the difference regarding docetaxel administration might have been markedly higher. In summary, at least in the D9901 study, the disadvantage regarding time point and frequency suggested by the IMPACT study was not confirmed. Overall, considering the 3 studies it cannot be excluded with certainty that there was a systematic bias regarding overall survival to the advantage of patients in the sipuleucel-T arm due to the first administration of docetaxel.

The sensitivity analyses, in which (1) patients were censored at the first administration of docetaxel, and (2) docetaxel administration was imputed as time-dependent covariable in the Cox regression model (see Table 2) both showed similar results in comparison with the originally planned primary analysis with regard to the treatment effect. The results did not suggest that the administration of docetaxel had an influence on the effect of the sipuleucel-T treatment, but such an influence can also not be excluded with certainty. The decision of first docetaxel administration is made by the physician for an individual patient based on the state of the patient and is therefore not made at random. This results in an informative censoring of the patients or a time point of treatment switching influenced by further unknown factors, which may cause important bias in the effect estimates of randomized treatment and subsequent treatment (see e.g. [7,8]). This uncertainty in the assessment of the results correspondingly also applies for the further sensitivity analyses of the company, in which,

besides the administration of docetaxel, an interaction of sipuleucel-T and docetaxel or docetaxel alone were considered as time-dependent factors in the model. Moreover, the sensitivity analyses could only address some of the uncertainties. If docetaxel was withheld from some of the patients because of the potential treatment switching in the studies, this was not considered by the sensitivity analyses. Due to the study design and the respective model assumptions, the sensitivity analyses presented were therefore unsuitable to assess without doubt the influence of docetaxel or the treatment effect from sipuleucel-T.

In association with these analyses, the company presented the Kaplan-Meier curves for the survival time of all patients, contrasting the courses without censoring at the time point of the first docetaxel administration with the ones with censoring (Figure 2 and Figure 3). For the IMPACT study (Figure 2), the courses in the respective treatment groups were almost identical up to the time point of the median survival time and largely comparable also in the further course. The curves were also largely comparable for the joint consideration of all studies (Figure 3). In principle, this picture is conceivable under the assumption that sipuleucel-T has no effect on overall survival because it is to be noted that the censoring at the start of the docetaxel administration did not happen at random. It is conceivable that mainly patients with poor prognosis received docetaxel in the studies and that these would have benefitted from docetaxel. Hence this sensitivity analysis alone is also insufficient to clear the existing uncertainty.

In contrast to the sensitivity analyses assessed above, in which a potential effect from the administration of docetaxel was estimated, the company investigated in further sensitivity analyses (see Table 3) for the IMPACT study which influence different effects of docetaxel that are assumed to be known and fixed with survival advantage have on the effect estimate of the treatment effect from sipuleucel-T. The HRs 0.1 (= very large survival advantage of docetaxel) up to 1 (= no effect of docetaxel) were considered as examples. The results showed that even under the assumption of a large docetaxel effect of HR = 0.4, the treatment effect of sipuleucel-T was still statistically significant. The assumption of an even larger effect of docetaxel would be necessary to no longer be able to detect a treatment effect from sipuleucel-T. Since such a large effect from docetaxel cannot be assumed [3,4], these analyses suggest that the treatment effect observed in the IMPACT study in fact cannot be explained by the administration of docetaxel (alone). However, the models used also contained time-dependent covariables, which is why the results may be biased for the reasons stated above. Moreover, the company did not present a corresponding analysis including all 3 studies.

The sensitivity analysis presented to the FDA (see Figure 4) showed the Kaplan-Meier curves for overall survival with the respective treatment groups separately for the patient groups with and without docetaxel administration. In patients who received docetaxel in the course of the study, there were no important differences in the course of the curve between the treatment groups, but markedly different courses for patients without docetaxel administration. Furthermore, for patients without docetaxel administration, the curves were consistently below the ones of the other patients, thus indicating a considerably increased risk of dying.

However, since the docetaxel administration was not conducted at random, the difference cannot be causally attributed to this. Under the hypothesis that there is no sipuleucel-T effect, the observed difference of the Kaplan-Meier curves of patients without docetaxel administration could only be explained by another factor, possibly prognostic factors, which are also associated with the administration of docetaxel at the same time.

Overall, the sensitivity analyses described above show a consistent picture in comparison with the primary analysis. In the overall consideration of the analyses, particularly due to the analysis under the assumption of a fixed effect of docetaxel, it was therefore not assumed that the effect observed in the studies can be explained by different administration of docetaxel alone. Hence it can also not be assumed that there is no effect on overall survival from sipuleucel-T in comparison with sham treatment. Nevertheless, the scenarios of sensitivity analyses presented by the company are still subject to uncertainty, and plausible scenarios are conceivable for some of these analyses, which could be explained under assumption of the null hypothesis. As described above, these analyses cannot address all uncertainties because of allowed treatment switching of the control to the experimental intervention resulting from the design of the studies. The statistical models used in the sensitivity analyses are based on probably unfulfilled assumptions, and hence there is still a high risk of bias. For the D9901 study, the available information showed no advantage of the sipuleucel-T treatment arms from concomitant docetaxel treatment. In the D9902A study, there was uncertainty in the interpretation of the results because of missing data on the docetaxel administration in some patients. Moreover, some sensitivity analyses were missing, particularly those for the assumption of fixed docetaxel effects and those on potential differences in the courses in patients with and without docetaxel administration. Furthermore, also under the assumption that sipuleucel-T has a treatment effect on overall survival, it cannot be excluded that the patients in the control groups of the 3 studies were put at a disadvantage because they received a modified form of sipuleucel-T after treatment switching. Overall it is to be noted that the uncertainties could have been avoided if the design of the studies had not allowed switching from the control to the (modified) experimental intervention.

Because of the high risk of bias in the 3 studies, in summary, there is an indication of an added benefit of sipuleucel-T in comparison with watchful waiting regarding overall survival.

2.4 Derivation of the added benefit

As justified in Section 2.3, there is an indication of an added benefit of sipuleucel-T in comparison with watchful waiting for overall survival. Since an influence from concomitant treatments for the effect estimates of all studies cannot be excluded with certainty, no final assessment of the extent of the effect can be conducted, which is therefore non-quantifiable. The analyses discussed in the present addendum therefore change the conclusion of dossier assessment A14-38.

Hereinafter, based on the data presented in Section 2.4 of dossier assessment A14-38 and under consideration of the assessment on the results on overall survival changed in the present addendum, the derivation of the extent and probability of the added benefit is presented.

Table 4 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 4: Positive and negative effects from the assessment of sipuleucel-T compared with watchful waiting

Positive effects	**Negative effects**
Indication of a non-quantifiable added benefit (mortality: overall survival)	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 positive and negative effects of sipuleucel-T remain at outcome level on the basis of the available results.

The positive effect consists of an indication of a non-quantifiable added benefit in overall survival. The negative effects consist in each case 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).

The events underlying the negative effects were overall of minor severity and in their vast majority only occurred immediately after the administration of sipuleucel-T. In the overall assessment of benefits and harms, they did not result in downgrading of the positive effect in overall survival of sipuleucel-T.

Overall, there is therefore an indication of a non-quantifiable added benefit of sipuleucel-T versus the ACT, watchful waiting while maintaining ongoing conventional androgen deprivation therapy (ADT) for patients with asymptomatic or minimally symptomatic metastatic (non-visceral) castrate-resistant prostate cancer in whom chemotherapy is not yet clinically indicated.

The result of the assessment of the added benefit of sipuleucel-T in comparison with the ACT is summarized in Table 5.

Table 5: 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	Indication of a non-quantifiable added benefit
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.

3 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Sipuleucel-T: Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A14-38 [online]. 23 December 2014 [accessed: 8 January 2015]. (IQWiG-Berichte; volume 269). URL: https://www.iqwig.de/download/A14-38_Sipuleucel-T_Nutzenbewertung-35a-SGB-V.pdf.

2. Dendreon. Stellungnahme zum IQWiG-Bericht Nr. 269: Sipuleucel-T; Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A14-38. [Soon available under: https://www.g-ba.de/informationen/nutzenbewertung/143/#tab/beschluesse in the document "Zusammenfassende Dokumentation"].

3. Berthold DR, Pond GR, Soban F, De Wit R, Eisenberger M, Tannock IF. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: updated survival in the TAX 327 study. J Clin Oncol 2008; 26(2): 242-245.

4. Kawalec P, Paszulewicz A, Holko P, Pilc A. Sipuleucel-T immunotherapy for castration-resistant prostate cancer: a systematic review and meta-analysis. Arch Med Sci 2012; 8(5): 767-775.

5. Simes J, Voysey M, O'Connell R, Glasziou P, Best JD, Scott R et al. A novel method to adjust efficacy estimates for uptake of other active treatments in long-term clinical trials. PLoS One 2010; 5(1): e8580.

6. Food and Drug Administration. Provenge (sipuleucel-T, APC8015): statistical review and evaluation [online]. [Accessed: 25 February 2015]. URL: http://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM214543.pdf.

7. Latimer NR, Abrams KR, Lambert PC, Crowther MJ, Wailoo AJ, Morden JP et al. Adjusting survival time estimates to account for treatment switching in randomized controlled trials: an economic evaluation context; methods, limitations, and recommendations. Med Decis Making 2014; 34(3): 387-402.

8. Watkins C, Huang X, Latimer N, Tang Y, Wright EJ. Adjusting overall survival for treatment switches: commonly used methods and practical application. Pharm Stat 2013; 12(6): 348-357.