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Second Addendum to Commission A13-44 (ipilimumab, new therapeutic indication)[1]

Addendum

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[1] Translation of addendum A14-15 *2. Addendum zum Auftrag A13-44 (Ipilimumab, neues Anwendungsgebiet*) (Version 1.0; Status: 16 May 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.

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

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Abbreviation	Meaning
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)

1 Background

On 7 May 2014 the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct a supplementary assessment for Commission A13-44 (benefit assessment of ipilimumab, new therapeutic indication) [1] and for Commission A14-11 (*Addendum to Commission A13-44 [ipilimumab, new therapeutic indication]*) [2].

In the commenting procedure on the assessment of ipilimumab, on 7 April 2014, the pharmaceutical company (hereinafter abbreviated to "the company") submitted further data to the G-BA [3] that went beyond the information in the dossier [4]. On the one hand, these were corrected and updated analyses on the (unadjusted indirect) comparison of ipilimumab versus the comparator therapy dacarbazine in patients with advanced (unresectable or metastatic) melanoma who have not received prior therapy to treat advanced melanoma, which was already presented in the dossier. These analyses were additionally supplemented by sensitivity and subgroup analyses. As the uncertainty of results was too great, this comparison was assessed as unsuitable to be able to derive conclusions on the added benefit of ipilimumab [1]. On the other hand, with its comment the company submitted new analyses, which, from the company's point of view, are suitable to resolve the points of criticism mentioned in the dossier assessment. Furthermore, the company submitted in its comment a correction and update of the indirect comparison versus vemurafenib in BRAF V600 mutation-positive patients presented in the dossier. This comparison was also considered unsuitable to be able to derive conclusions on the added benefit of ipilimumab [2]. In the dossier, the company claimed no added benefit of ipilimumab versus vemurafenib. From the company's point of view, the conclusions drawn in the dossier are not changed by the updated analyses.

The G-BA now commissioned IQWiG to assess these analyses subsequently submitted.

In the following Chapter 2, the analyses subsequently submitted on the comparison of ipilimumab versus dacarbazine (Section 2.1) and on the comparison of ipilimumab versus vemurafenib (Section 2.2) are assessed according to the commission. The overall conclusion on the added benefit of ipilimumab under consideration of the analyses subsequently submitted is then described (Section 2.3).

The responsibility for the present assessment and its result lies solely with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

2.1 Assessment of the data on the comparison of ipilimumab versus dacarbazine subsequently submitted by the company

With its comment, the company subsequently submitted updated and corrected analyses on the comparison of ipilimumab versus dacarbazine already presented in the dossier. The basic methods of the comparison were unchanged compared with the dossier. This was an unadjusted indirect comparison based on individual patient data from different studies on ipilimumab and an individual study on dacarbazine. A detailed description of this comparison can be found in the benefit assessment of ipilimumab (new therapeutic indication, A13-44 [4]).

As already described in detail in the dossier assessment A13-44, the uncertainty of the comparison presented by the company was too great already because of the underlying methods (unadjusted indirect comparison) and therefore unsuitable to be able to derive conclusions on the added benefit of ipilimumab versus dacarbazine [1]. An added benefit can only be derived from this kind of comparison in case of very large effects for which it can be excluded that they are caused by systematic bias alone [5,6]. The company did not justify this sufficiently in its dossier or in its comment.

In addition to this general uncertainty, there were further flaws in the comparison presented by the company in the dossier, which further increased the uncertainty. For example, the results were relevantly biased in favour of ipilimumab because of the selective exclusion of patients from the analysis. Overall, the treatment effect on overall survival presented by the company was therefore not interpretable. This also applied to the results on further outcomes presented by the company (health-related quality of life, adverse events).

On the one hand, the company submitted corrected analyses in its comment because, according to the company's statements, the analyses presented in the dossier were based on an "erroneously incomplete data set" [3]. Only those patients were included in the original analysis for whom data on all confounders considered were available (see dossier assessment A13-44 [1]). On the ipilimumab side of the comparison a total of approximately 40% of the patients were not considered because of this. With the correction, data on all confounders considered were now available for some of these patients, so that these could be included in the analysis. On the other hand, the analyses were updated with data from a new data cut-off of the retrospective observational studies CA184332 and CA184338. The company additionally presented different sensitivity analyses with its comment.

The analyses subsequently submitted with the comment exclusively address the additional flaws mentioned above. In contrast, the underlying methods of the comparison (unadjusted indirect comparison based on individual patient data), which were the main reason for the uncertainty, were unchanged. The data subsequently submitted could not resolve the basic uncertainty of the analysis presented by the company.

Moreover, they were also insufficient to completely resolve the uncertainty resulting from the additional flaws. For example, also in the analyses subsequently submitted, for overall survival a large proportion of patients were still not considered on the ipilimumab side of the indirect comparison despite the update described above, whereas almost all the patients were included in the analysis on the dacarbazine side. The difference is not as clear as it was in the analyses presented in the dossier, but still only 335 out of 423 patients (79.2%) were included in the analysis on the ipilimumab side, whereas these were 250 out of 252 (99.2%) patients on the dacarbazine side. Hence the difference between the 2 sides of the indirect comparison was approximately 20 percentage points. Such a difference often leads to the results being not interpretable – even in randomized controlled trials. To investigate the influence of these missing values, the company presented sensitivity analyses, in which these values were imputed. However, the company did not describe the approach used, which is therefore not sufficiently comprehensible. According to the company, it is a prerequisite for the imputation that the imputed values are missing at random, i.e. independent form the actual observation and therefore independent from the patients' prognoses (missing [completely] at random). It is questionable, however, that this assumption, which, moreover, cannot be verified [7], is fulfilled in the available data. The company also provided no reasons. None of the analyses subsequently submitted or updated showed an effect that was so large that it could not be caused by bias alone.

The company provided an analysis, which it called "sensitivity analysis based on the Korn model", as additional sensitivity analysis in its comment. In the work by Korn et al. 2008, a prognostic model for survival time functions for patients with metastatic melanoma was developed [8]. The model and the company's approach were described in the comment [3]. The analysis presented by the company on the basis of the prognostic model developed by Korn et al. 2008, is generally unsuitable for the assessment of the added benefit, however. The company's approach corresponds to the one of an unadjusted indirect comparison, i.e. the comparison of non-randomized treatment arms from different studies. Moreover, the company provided no inferential statistical results for its comparison (hazard ratio, confidence intervals or p-values) so that the effect size cannot be estimated.

Conclusion

Overall it is to be concluded that the apparent bias in favour of ipilimumab due to the selective exclusion of patients, which was determined in the dossier assessment A13-44, is no longer present to the same degree in the analyses subsequently submitted. However, it can also not be excluded even under consideration of these analyses. What is more important, however, is that the documents subsequently submitted did not address the uncertainty resulting from the underlying methods. The comparison presented by the company is therefore still unsuitable to prove an added benefit of ipilimumab versus dacarbazine.

Overall, the data subsequently submitted by the company did not change the result of the benefit assessment A13-44. Overall, an added benefit of ipilimumab versus dacarbazine in

patients with advanced (unresectable or metastatic) melanoma who have not received prior therapy to treat advanced melanoma is not proven.

2.2 Assessment of the data on the comparison of ipilimumab versus vemurafenib submitted by the company

For the comparison of ipilimumab versus vemurafenib, the company presented an indirect comparison using the common comparator dacarbazine in the dossier. Whereas it included a direct comparative study (BRIM-3 study) for the comparison of vemurafenib versus dacarbazine, it used the comparison of ipilimumab and dacarbazine described above (Section 2.2), which was also indirect but unadjusted, as the best possible evidence from the company's point of view for the ipilimumab side of the indirect comparison. As justified in detail in addendum A14-11, this indirect comparison of ipilimumab versus vemurafenib is unsuitable to derive conclusions on the added benefit [2].

As the analyses presented in the comment were only an update of the patient data included in the ipilimumab side of the indirect comparison, but the underlying methods of the indirect comparison were the same, the points of criticism named in addendum A14-11 are still valid [2]. Hence the results presented by the company on the outcomes "mortality" and "adverse events" from the indirect comparison cannot be interpreted overall and are therefore unsuitable to derive conclusions on the added benefit of ipilimumab compared with vemurafenib.

Overall, an added benefit of ipilimumab versus vemurafenib in (BRAF V600 mutation-positive) patients with advanced (unresectable or metastatic) melanoma who have not received prior therapy to treat advanced melanoma is not proven.

2.3 Extent and probability of added benefit

Overall, the data subsequently submitted by the company neither change the result of the benefit assessment A13-44 on the comparison of ipilimumab versus dacarbazine [1] nor the result of the addendum A14-11 on the comparison of ipilimumab versus vemurafenib [2]. The result of the assessment of the added benefit of ipilimumab is shown in Table 1.

Table 1: Ipilimumab – extent and probability of added benefit

Therapeutic indication	Comparator therapy	Extent and probability of added benefit
Adult patients with advanced (unresectable or metastatic) melanoma who have not received prior therapy to treat advanced melanoma	Dacarbazine	Added benefit not proven
Adult (BRAF V600 mutation-positive) patients with advanced (unresectable or metastatic) melanoma who have not received prior therapy to treat advanced melanoma	Vemurafenib	Added benefit not proven

The G-BA decides on the added benefit.

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