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

Addendum

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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]:

- Susanne Haag
- Wiebke Sieben
- Volker Vervölgyi
- Beate Wieseler

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

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

1 Background

On 11 March 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]).

The company presented an indirect comparison of ipilimumab versus vemurafenib in its dossier from 29 November 2013 [2]. This comparison was not considered in the dossier assessment because, at the time point of the dossier assessment, vemurafenib was not the appropriate comparator therapy (ACT). The G-BA now commissioned IQWiG to assess the indirect comparison of ipilimumab versus vemurafenib, particularly also considering separately the patient group with BRAF V600 mutation-positive melanoma.

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 Selection of analyses for the benefit assessment

The assessment was conducted based on the indirect comparison of ipilimumab and vemurafenib presented by the company in its dossier from 29 November 2013 [2].

2.2 Information retrieval

The study pool for the assessment was compiled on the basis of these sources by the company in the dossier:

- study list on ipilimumab (studies completed up to 11 November 2013)
- bibliographical literature search on ipilimumab (last search on 7 November 2013)
- search in trial registries for studies on ipilimumab (last search on 13 November 2013)
- bibliographical literature search on vemurafenib (last search on 7 November 2013)
- search in trial registries for studies on vemurafenib (last search on 13 November 2013)

For the indirect comparison, the company conducted the searches in bibliographical databases and trial registries required in accordance with the dossier templates. As already described in the benefit assessment of ipilimumab, the information retrieval of the company was unsuitable to ensure the completeness of the study pool [1].

However, no check of the completeness of the study pool presented by the company was performed because no further relevant studies were identified in a comparison with the dossiers and the dossier assessments on ipilimumab [1,2] and vemurafenib [3,4].

The studies identified from the steps of information retrieval mentioned were unsuitable for the derivation of conclusions on the added benefit of ipilimumab in comparison with vemurafenib in adult BRAF V600 mutation-positive patients with advanced melanoma who have not received prior therapy to treat advanced melanoma. This is justified in the following Section.

2.3 Assessment of the data presented by the company

As no study was available for a direct comparison of ipilimumab with vemurafenib, the company searched for studies that would allow an indirect comparison. The company chose dacarbazine as common comparator because, according to the company, active-controlled studies on vemurafenib are only available in comparison with this drug.

On the vemurafenib side, the company identified one study in its information retrieval, which, from the company's point of view, was relevant for an indirect comparison. This was the BRIM-3 study, a randomized, active-controlled, open-label phase 3 study comparing vemurafenib with dacarbazine. Non-pretreated patients with unresectable stage IIIc or IV

malignant melanoma and proven BRAF V600 mutation were enrolled in this study. The study treatments vemurafenib and dacarbazine were administered according to a therapeutic regimen described in the respective Summary of Product Characteristics (SPC) [5,6]. Detailed characteristics of the study and the patient population included are presented in the benefit assessment of vemurafenib [7].

On the ipilimumab side, no studies were available that would allow a direct or an adjusted indirect comparison of ipilimumab and dacarbazine. As the best possible evidence from the company's point of view, the company therefore used another indirect comparison of ipilimumab and dacarbazine on the ipilimumab side of the indirect comparison on vemurafenib. It used an unadjusted indirect comparison based on individual patient data from different studies on ipilimumab and an individual study on dacarbazine. This was the same comparison as the one the company presented to prove the added benefit of ipilimumab versus the ACT dacarbazine. A detailed description of this comparison can be found in the benefit assessment of ipilimumab (new therapeutic indication, A13-44 [1]).

Overall, the company considered the indirect comparison of ipilimumab and vemurafenib as suitable to derive conclusions on added benefit. Due to the lack of statistical significance with regard to outcomes, it did not consider there to be proof of an added benefit or greater or lesser harm from ipilimumab versus vemurafenib.

The data availability presented by the company for the indirect comparison of ipilimumab and vemurafenib is presented in Figure 1.

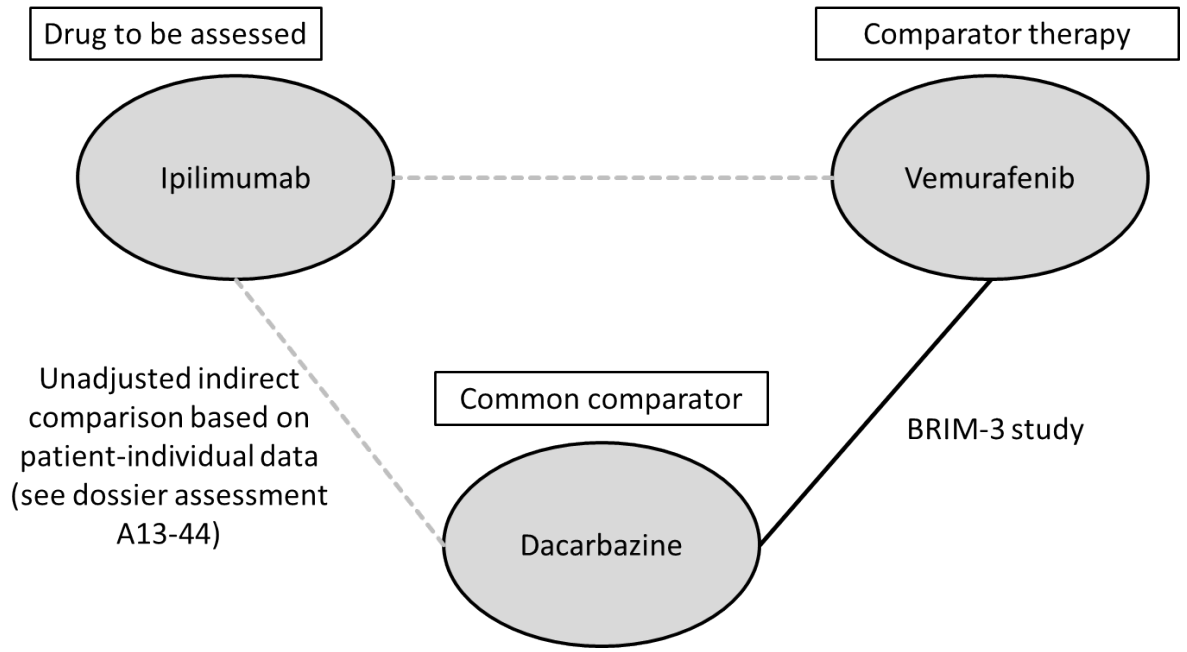

Figure 1: Data availability presented by the company for the indirect comparison of ipilimumab versus vemurafenib in BRAF V600 mutation-positive patients

As explained in benefit assessment A13-44, the evidence included on the ipilimumab side of the indirect comparison (ipilimumab versus dacarbazine) is unsuitable to derive conclusions on the added benefit of ipilimumab versus dacarbazine. The uncertainty of the analysis presented (unadjusted indirect comparison) is too great. Moreover, the effect on overall survival described by the company as "dramatic" was relevantly biased in favour of ipilimumab because of the selective exclusion of patients from the analysis. The observed effect was therefore not sufficiently large to be able to exclude that it was only caused by systematic bias. The certainty of results was further reduced by the lack of consideration of further known confounders in the conduct of the propensity score 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 (e.g. adverse events).

The company described the data availability outlined in Figure 1 as adjusted indirect comparison in the methods section of the dossier. This assessment was not followed. In an adjusted indirect comparison, an effect from a direct comparative study (ipilimumab versus dacarbazine) must be included also on the ipilimumab side. However, this was not the case for the comparison of ipilimumab with the common comparator dacarbazine. As this was not a direct comparison and because of the lack of interpretability of the observed treatment effect (e.g. due to the selective exclusion of patients) described above, this effect estimate can also not be used in a subsequent indirect comparison of ipilimumab and vemurafenib. The certainty of results, which was too low anyway for conclusions on added benefit, is further decreased by considering these data in a subsequent indirect comparison. 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. This applies both to the total population of the patients included in the comparison and to the patient group with BRAF V600 mutation-positive melanoma.

Moreover it should be noted that the company's designation of the indirect comparison is misleading. It included the comparison of ipilimumab with dacarbazine as direct comparison in the indirect comparison of ipilimumab with vemurafenib. In Module 4, Section 4.3.2.1.3.1 (particularly Figure 14), it even suggested that 3 direct comparative studies on the comparison of ipilimumab with dacarbazine were included in the indirect comparison for the outcome "mortality". For the reasons stated above however, the unadjusted indirect comparison of ipilimumab with dacarbazine presented by the company cannot be equated with a direct comparison at all.

As, for the reasons given, the indirect comparison of ipilimumab with vemurafenib presented by the company is not suited to derive conclusions on the added benefit, additional aspects are not discussed further which would have been necessary for assessing the suitability of the indirect comparison (suitability of the statistical methods, structural quality [e.g. similarity of

the studies], risk of bias of the data included and suitability for a conclusion for patients with BRAF V600 mutation).

2.4 Extent and probability of added benefit

The result of the assessment of the added benefit of ipilimumab in comparison with vemurafenib in (BRAF V600 mutation-positive) patients with advanced melanoma is shown in Table 1.

Table 1: Ipilimumab in BRAF V600 mutation-positive patients – extent and probability of added benefit

Therapeutic indication	Comparator therapy	Extent and probability of added benefit
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

From the data presented by the company, no proof of added benefit of ipilimumab versus vemurafenib for the treatment of adult (BRAF 600 mutation-positive) patients with advanced (unresectable or metastatic) melanoma who have not received prior therapy to treat advanced melanoma can be derived.

The G-BA decides on the added benefit.

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