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Addendum to Commission A13-10 (pertuzumab)[1]

Addendum

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

Table of contents

List of tables

Page

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
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 6 August 2013 the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct a supplementary assessment for Commission A13-10 (benefit assessment of pertuzumab [1]).

In the commenting procedure on the assessment of pertuzumab, on 18 July 2013, the pharmaceutical company (hereinafter abbreviated to "the company") submitted further data to the G-BA that went beyond the information in the dossier [2,3]. These refer to data on the CLEOPATRA study (comparison of pertuzumab/trastuzumab/docetaxel versus trastuzumab/ docetaxel). The study was already contained in the company's dossier and was included as relevant by IQWiG in Assessment A13-10. The data presented were not evaluable for the outcomes on adverse events (AEs). With the comments, the company subsequently submitted new analyses, which, from the company's point of view, allow to assess the AEs.

The G-BA commissioned IQWiG with the assessment of the analyses subsequently submitted for the CLEOPATRA study in the commenting procedure. The results on AEs were to be assessed under consideration of the data presented in the dossier and in the company's comment. In addition, the question was to be addressed to what extent consequences result from this supplementary assessment for the reliability of the conclusions for the overall result of the benefit assessment.

In the following Chapter 2 the additional results for the CLEOPATRA study are assessed according to the commission. The extent and probability of added benefit of pertuzumab are then described under consideration of the analyses subsequently submitted.

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

2.1 Additional analyses provided by the company

An assessment of the AEs from the CLEOPATRA study was not possible in the dossier assessment on pertuzumab [1]. Treatment durations with the study medication (and hence also the observation durations) differed considerably in the 2 treatment arms (median treatment duration with the study medication 18.5 months in the pertuzumab arm, and 12.4 months in the comparator arm). The data presented by the company on the basis of the naive proportions (proportion of patients with at least one event) did therefore not constitute an adequate analysis [4]. Moreover, the dossier contained no analyses of AEs in the 2 subgroups of patients with visceral and non-visceral metastases. It was therefore not possible to draw conclusions on harm in these subgroups, which differed in benefit.

In its comment on the dossier assessment [2,3], the company presented analyses on AEs in the subgroups of patients with visceral and non-visceral metastases. These analyses included, on the one hand, relative risks based on the raw event rates in the treatment groups and, on the other hand, time-adjusted analyses.

2.2 Assessment of the data presented

As explained in the dossier assessment [1], relative risks based on naive proportions are not an adequate analysis in the case of treatment durations that deviate considerably in the treatment arms (here: median treatment duration with the study medication: 18.5 months in the pertuzumab arm, 12.4 months in the comparator arm). The relative risks on AEs in the subgroups of patients with visceral and non-visceral metastases presented by the company were therefore not evaluable.

Effect measures that are estimated using adequate methods for survival times are a suitable approach for the analysis of event data with variable observation durations. These were not presented by the company.

Instead, the company presented data (for the total population and for the subgroups according to the status of metastases) on the total number of events per time unit for both treatment groups including the corresponding confidence intervals. No further explanations were provided why the company chose confidence intervals at a level of 80% and 90% instead of the commonly used 95%. Effect estimates for the comparison of the treatment groups were not provided. These kinds of methods of analysis are subject to strong prerequisites, which, in practice, can usually only be regarded as at least approximately fulfilled in rare events and short observation durations [1]. These prerequisites do not apply to the outcomes considered in the assessment of pertuzumab.

Due to the large uncertainties described, the data on AE presented by the company are unsuitable for a valid quantitative estimation of the treatment effect.

2.3 Extent and probability of added benefit – summary

As described in Section 2.2, the analyses on AEs subsequently submitted with the company's comment still do not allow to draw a valid quantitative conclusion on the harm of pertuzumab. Due to the still insufficient analysis of the outcomes regarding harm, the increased uncertainty in the assessment remains. The probability of the added benefit in the subgroup of patients with visceral metastases is therefore still downgraded from "indication" to "hint". The extent of added benefit is still assessed as "major".

An unchanged overview of the assessment of pertuzumab/trastuzumab/docetaxel in comparison with the ACT for the 2 subpopulations is given below (see Table 1).

Table 1: Pertuzumab: extent and probability of added benefit – summary

Therapeutic indication	**ACT**	**Extent and probability of added benefit**
Subpopulation 1: Treatment of HER2-positive metastatic breast cancer		
with visceral metastases	Trastuzumab + taxane (docetaxel)	Hint of a major added benefit
with non-visceral metastases	Trastuzumab + taxane (docetaxel)	Added benefit not proven
Subpopulation 2: Treatment of HER2-positive locally recurrent unresectable breast cancer	Radiotherapy	Added benefit not proven

The overall assessment deviates considerably from that of the company. The company claimed proof of a major added benefit for both subpopulations.

3 References

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2. Roche Pharma. Zusätzliche Analysen zur CLEOPATRA-Studie (WO20698-TOC4129g): Sicherheitsauswertung für die Subgruppe Art der Erkrankung (viszeral; nicht-viszeral) [unpublished]. 2013.

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