IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Pertuzumab – Addendum to Commission A15-34[1]

Addendum

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[1] Translation of addendum A16-01 *Pertuzumab – Addendum zum Auftrag A15-34* (Version 1.0; Status: 29 January 2016). 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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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)
ITT	intention to treat
pCR	pathological complete response
SGB	Sozialgesetzbuch (Social Code Book)
tpCR	total pathological complete response

1 Background

On 14 January 2016, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A15-34 (Pertuzumab – Benefit assessment according to §35a Social Code Book [SGB] V [1]).

In its written comments [2], the pharmaceutical company (hereinafter referred to as "the company") sent supplementary information, which went beyond the information provided in the dossier [3], to prove the added benefit. These particular referred to data on the outcome "pathological complete response (pCR)". The G-BA's commission comprised the assessment of the analyses submitted by the company on the "transferability of the effect shown in the pCR rate to the absence of recurrence in the patients" (outcome for the recording of the overall treatment success after 5 years).

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 of the analysis of the transferability of the effect shown in the pCR rate to the absence of recurrence in the patients

In its comment, the company defined a new outcome it denominated "overall treatment success" for the analysis of the transferability of the effect shown in the pCR rate to the absence of recurrence in patients. According to the company, this meant the rate of patients who 1) have achieved total pCR (tpCR) at the end of the neoadjuvant phase and who 2) develop no recurrence in the post neoadjuvant phase or follow-up phase.

The company conducted its analysis in 3 steps. First, it named the proportion of patients (referring to the ITT population) who achieved a tpCR in the neoadjuvant phase (42/107 [39.3%] in the pertuzumab arm, 23/107 [21.5%]) in the comparator arm. In the second and third step, it then described for how many patients with tpCR, recurrence was documented in the adjuvant treatment phase (0 in the pertuzumab arm, 1 in the comparator arm) and in the follow-up phase (6 in the pertuzumab arm, 3 in the comparator arm). The company then calculated the corresponding rates of recurrence-free patients after tpCR (patients with overall treatment success) on the basis of the total intention to treat (ITT) population (overall treatment success in the pertuzumab arm: 36/107 [33.6%], in the comparator arm: 19/107 [17.8%]) and not on the basis of the 42 patients in the pertuzumab arm and of the 23 patients in the comparator arm who achieved tpCR. The company concluded that the difference between the study arms translated proportionally from the tpCR to the absence of recurrence.

This analysis appeared not to be meaningful for various reasons. The relevant event for the patients is the occurrence of recurrence, which shows that the attempt to cure the disease by a curative treatment approach has not been successful. It is not important whether the recurrence has been preceded by a pCR or not; the consideration of the pCR as treatment success (as component of an overall treatment success) is therefore not relevant. Furthermore, the company did not consider in its analysis recurrences in patients who had achieved no pCR, and therefore considered only a part of the relevant events.

Results on recurrences in the group of patients with and without pCR were not available in the study documents. However, the following Table shows an analysis of disease-free survival in the total population and for patients with and without pCR.

Table 1: Disease-free survival – RCT, direct comparison: pertuzumab + trastuzumab + docetaxel vs. trastuzumab + docetaxel

Study **Outcome category** **Outcome**	**Pertuzumab + trastuzumab + docetaxel**		**Trastuzumab + docetaxel**		**Pertuzumab + trastuzumab + docetaxel vs. trastuzumab + docetaxel**
	N	**Median survival time in months [95% CI]** **Patients with event n (%)**	**N**	**Median survival time in months [95% CI]** **Patients with event n (%)**	**RR [95% CI]; p-value**
NeoSphere **(data cut-off 20 October 2014)**					
Disease-free survival					
All patients	101[a]	67.2 [67.2; 72.2] 15 (14.9)[b]	103[a]	NA 18 (17.5)	0.60 [0.28; 1.27]; 0.185
Patients with pCR	42[c]	72.2 [ND] 6 (14.3)	23[c]	NA 4 (17.4)	0.62 [0.15; 2.50]
Patients without pCR	59[d]	67.2 [ND] 9 (15.3)	80[d]	NA 14 (17.5)	0.52 [0.19; 1.43]

a: Number of patients who had surgery.
b: The analysis of disease-free survival, besides recurrence, also included 2 deaths (in the pertuzumab + trastuzumab + docetaxel arm). One further patient with disease progression was not included in disease-free survival, but presumably in the recurrence rate.
c: Number of patients (with surgery) for whom pCR was documented.
d: Number of patients (with surgery) for whom no pCR was documented.

CI: confidence interval; HR: hazard ratio; N: number of analysed patients; n: number of patients with event; NA: not achieved; ND: no data; pCR: pathological complete response; RCT: randomized controlled trial; RR: relative risk; vs.: versus

The analyses showed no statistically significant differences for disease-free survival in the total population or in patients with or without pCR. Moreover, the rates of patients with event in the treatment arms did not differ to a relevant degree between the subgroups of patients with and without pCR.

3 References

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2. Roche Pharma AG. Stellungnahme zum IQWiG-Bericht Nr. 343: Pertuzumab; Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A15-34. 2015: [Soon available under https://www.g-ba.de/informationen/nutzenbewertung/188/#tab/beschluesse in the document "Zusammenfassende Dokumentation"].

3. Roche Pharma AG. Pertuzumab (Perjeta): Dossier zur Nutzenbewertung gemäß § 35a SGB V; Modul 4 A; Neoadjuvante Therapie des primären Brustkrebses; medizinischer Nutzen und medizinischer Zusatznutzen, Patientengruppen mit therapeutisch bedeutsamen Zusatznutzen [online]. 18 August 2015 [accessed: 26 January 2016]. URL: https://www.g-ba.de/downloads/92-975-941/2015-08-18_Modul4A_Pertuzumab.pdf