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Neratinib (breast cancer) –

Addendum to Commission A19-98[1]

Addendum

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Address of publisher
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

IQWiG employees involved in the addendum

- Cornelia Rüdig
- Sascha Abbas
- Katharina Biester
- Matthias Maiworm

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List of abbreviations

Abbreviation	Meaning
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HER2	human epidermal growth factor receptor 2
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LOCF	last observation carried forward
NRI	non-responder imputation
OC	observed cases
RR	relative risk

1 Background

On 6 April 2020, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A19-98 (Neratinib – Benefit assessment according to §35a Social Code Book V) [1].

In its dossier [2], the pharmaceutical company (hereinafter referred to as "the company") presented results of the ExteNET study, which compared treatment with neratinib versus placebo in patients with early-stage human epidermal growth factor receptor 2 (HER2)-overexpressed/amplified breast cancer. For the outcome "recurrence" for the subpopulation of the ExteNET study relevant for the benefit assessment (hormone-receptor-positive patients who completed trastuzumab therapy less than 1 year ago), the proportion of patients with recurrence was considered in the dossier assessment on neratinib (A19-98) and the relative risk (RR) was used. There was a high risk of bias for the results from this analysis, as the proportion of imputed values was unclear. Due to this unknown proportion of imputed values, the robustness of the estimated effect cannot be checked with sensitivity analyses.

With its comments [3], the company presented the following data with regard to the relevant subpopulation of the ExteNET study: information on patients for whom missing values were imputed, and sensitivity analyses.

The G-BA commissioned IQWiG with the assessment of the sensitivity analyses on the outcome "recurrence" for the relevant subpopulation (hormone-receptor-positive patients who completed trastuzumab therapy less than 1 year ago) presented by the company in the comments.

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

2 Assessment

2.1 Analyses on the outcome "recurrence"

For the calculation of the RR in the outcome "recurrence" considered in the dossier assessment on Commission A19-98, patients were included in the analysis with their last known status before study discontinuation (last observation carried forward [LOCF]). For patients in whom no event had occurred at the end of their observation period, it is assumed that no event would have occurred up to the time point of the analysis (non-responder imputation [NRI]). As described in the dossier assessment, it is a general problem of imputation methods that the increase in sample size tends to increase the precision of the resulting effect estimations, although uncertainty is rather increased by the imputation of missing values. This increased uncertainty can be taken into account by the estimation of the missing values using Higgins' modified estimation of variance [4]. In the company's dossier, however, no information was available for the relevant subpopulation on the proportion of patients who had discontinued the study and for whom no recurrence had been documented up to that time point. For the Institute's calculation of the RR in the dossier assessment, the information provided by the company on the proportion of patients with recurrence was used, although it was unclear how many patients were imputed with LOCF/NRI in the calculation. Sensitivity analyses using a modified estimation of variance according to Higgins were not possible. A high risk of bias for the results on the outcome "recurrence" was therefore assumed.

Sensitivity analyses presented by the company

With its comments, the company presented information on the proportion of patients with missing values for the relevant subpopulation of the study. According to this information, 128 (19.1%) of the patients treated with neratinib, and 85 (12.8%) of the patients treated with placebo had discontinued the study until the first data cut-off (7 July 2014) without having been diagnosed with recurrence until study discontinuation. For these patients, the missing values were imputed as "no recurrence" (LOCF/NRI). This analysis was used in the dossier assessment and is referred to as "primary analysis" below.

With its comments, the company presented several analyses using a modified estimation of variance according to Higgins [4] for the outcome "recurrence" for the results at the first data cut-off (7 July 2014) to check the robustness of the effects in the outcome "recurrence".

The company investigated the following imputation strategies:

- Primary analysis: imputation of missing values in both treatment arms as "no event".
- Sensitivity analysis 1: imputation of missing values in both treatment arms according to the risk of recurrence in the control group.
- Sensitivity analysis 2: imputation of missing values in the neratinib arm according to the risk of recurrence in the control group. In the control group, patients who had

discontinued the study without documented recurrence up to that time point were assumed not to have had a recurrence at the time of the data cut-off.

- Sensitivity analysis 3: imputation of missing values in both treatment arms according to the double risk of recurrence in the control group.

The imputation strategies defined by the company are principally adequate to check the robustness of the result for the outcome "recurrence". Each of the sensitivity analyses mentioned above concurs with conservative approaches to account for missing values. Of these 3 analyses, sensitivity analysis 2 makes the most unfavourable assumptions for neratinib.

For the sensitivity analyses, the company determined the risk of the control group of being diagnosed with recurrence based on the analysis of the outcome "recurrence", in which missing values had been imputed using LOCF/NRI. In this analysis, the risk in the control group was 9.0%. However, the problem with this approach is that in this analysis used by the company, missing values had already been replaced with the value "no recurrence". Thus, the risk of recurrence may have been underestimated.

Institute's calculation

Due to the possible underestimation of the risk of recurrence in the company's approach (see above), the risk of recurrence for the present addendum was recalculated based on the fully observed patients (observed cases [OC] analysis). In the control group, 579 patients were fully observed. Recurrence was documented in 60 of these patients (10.4%). Based on this OC analysis, the risk of recurrence in the control group was determined to be 10.4% at the first data cut-off.

The analyses were recalculated for the relevant subpopulation using the imputation strategies defined by the company with the risk of 10.4% (single risk) and 20.7% (double risk) and are presented in Table 1 below. The analyses presented by the company can be found in Table 9 of the comments.

Table 1: Results on recurrences for hormone-receptor-positive patients who completed trastuzumab therapy less than 1 year ago – RCT, direct comparison: neratinib vs. placebo

Study Outcome category Outcome Imputation strategy	Neratinib N	Neratinib Patients with event n (%)	Placebo N	Placebo Patients with event n (%)	Neratinib vs. placebo RR [95% CI]; p-value[a]
ExteNET					
Morbidity					
Recurrence[b]					
LOCF/NRI[c]	670	26 (3.9)	664	60 (9.0)	0.43 [0.26; 0.70]; < 0.001
Sensitivity analyses:					
Sensitivity analysis 1 – imputation according to the risk of the control group[d]	670	– (5.9)	664	– (10.4)	0.57 [0.37; 0.86]; 0.007
Sensitivity analysis 2 – imputation in the neratinib arm according to the risk of the control group[e]	670	– (5.9)	664	– (9.0)	0.65 [0.42; 0.99]; 0.046
Sensitivity analysis 3 – imputation according to the double risk of the control group[f]	670	– (7.8)	664	– (11.7)	0.67 [0.47; 0.97]; 0.032

a. Institute's calculation, asymptotic: estimation of variance according to the dataset resizing approach (approach W3 in [4]).
b. Composite outcome consisting of the following components: distant metastases, invasive contralateral breast cancer, invasive ipsilateral breast cancer, local/regional invasive recurrence, ductal carcinoma in situ, or death from any cause, whichever occurred first.
c. Primary analysis in the company's comments. In both treatment groups, the missing values of the patients who discontinued the study and for whom no recurrence was documented until study discontinuation are rated as "no event".
d. In both treatment groups, missing values are imputed according to the observed risk in the control group (10.4%).
e. Missing values in the neratinib arm are imputed according to the observed risk in the control group (10.4%). In the control group, missing values are set to "no event".
f. In both treatment groups, missing values are imputed according to the double observed risk in the control group (20.7%).

CI: confidence interval; LOCF: last observation carried forward; n: number of patients with (at least one) event; N: number of analysed patients; NRI: non-responder imputation; RCT: randomized controlled trial; RR: relative risk; vs.: versus

2.2 Results

Morbidity

Recurrence

Based on the analysis using LOCF/NRI-imputed values, a statistically significant difference in favour of neratinib in comparison with placebo between the treatment groups was shown for

the composite outcome "recurrence". Due to the large proportion of imputed values (neratinib arm: 19.1%, control arm: 12.8%), this result had a high risk of bias, however.

The sensitivity analyses conducted with calculations by the Institute in each case also showed a statistically significant difference in favour of neratinib versus placebo. Thus, a robust effect in favour of neratinib was assumed for the outcome "recurrence". Despite the high risk of bias, a high certainty of the effect was therefore assumed. The size of the effect remained unclear, however.

Overall, an indication of an added benefit of neratinib in comparison with watchful waiting was derived for the outcome "recurrence" for the relevant subpopulation.

2.3 Extent and probability of added benefit

Table 2 shows the probability and the extent of added benefit for the outcome "recurrence" under consideration of the data subsequently submitted.

Table 2: Extent of added benefit at outcome level: neratinib vs. placebo

Outcome category **Outcome** **Imputation strategy**	**Neratinib vs. placebo** **Proportion of events** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Morbidity		
Recurrence		Outcome category: serious/severe symptoms/late complications added benefit, extent: "non-quantifiable"[c]
LOCF/NRI	3.9% vs. 9.0% RR: 0.43 [0.26; 0.70]; p < 0.001	
Sensitivity analysis 1 – imputation according to the risk of the control group	RR: 0.57 [0.37; 0.86]; p = 0.007	
Sensitivity analysis 2 – imputation in the neratinib arm according to the risk of the control group	RR: 0.65 [0.42; 0.99]; p = 0.046	
Sensitivity analysis 3 – imputation according to the double risk of the control group	RR: 0.67 [0.47; 0.97]; p = 0.032	
	probability: "indication"	

a. Probability provided if a statistically significant and relevant effect is present.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. Due to the consistent advantage of neratinib, an indication of an added benefit is derived in the overall consideration. Due to the deviations in the extent of the results of individual analyses, the extent of the added benefit in the overall consideration is non-quantifiable, at least minor.

CI: confidence interval; CI_u: upper limit of confidence interval; LOCF: last observation carried forward; NRI: non-responder imputation; RR: relative risk; vs.: versus

2.4 Overall conclusion on added benefit

Table 3 summarizes the results considered in the overall conclusion on extent of added benefit.

Table 3: Positive and negative effects from the assessment of neratinib in comparison with watchful waiting

Positive effects	**Negative effects**
Serious/severe symptoms/ late complications ▪ **Recurrence: indication of an added benefit – extent: "non-quantifiable"**	Serious/severe side effects ▪ SAEs: hint of greater harm – extent: "minor" ▪ Severe AEs (CTCAE grade ≥ 3): indication of greater harm – extent: "major" ▪ Specific AEs (CTCAE grade ≥ 3): ▫ gastrointestinal disorders (SOC)[a]: indication of greater harm – extent: "major" ▫ fatigue (PT), metabolism and nutrition disorders (SOC), nervous system disorders (SOC), investigations (SOC): hint of greater harm – extent: "considerable"
–	Non-serious/non-severe side effects ▪ Discontinuation due to AEs; hint of greater harm – extent: "considerable" ▪ Specific AEs: ▫ muscle spasms (PT): indication of greater harm – extent: "considerable" ▫ skin and subcutaneous tissue disorders (SOC): hint of greater harm – extent: "considerable"

a. Including: diarrhoea (PT).

The results presented in **bold** result from the analyses subsequently submitted by the company with its written comments.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; PT: Preferred Term; SAE: serious adverse event; SOC: System Organ Class

With the data subsequently submitted with the comments, there was a positive effect of neratinib consisting of an indication of a non-quantifiable added benefit in the outcome "recurrence". As already described in dossier assessment A19-98, this advantage was accompanied by important disadvantages in side effects during the treatment phase. The decisive aspect for the negative effects was the indication of harm of major extent in the outcome category of serious/severe side effects in the outcome "gastrointestinal disorders".

In summary, there is a hint of a minor added benefit of neratinib versus the ACT watchful waiting for patients with early-stage hormone-receptor-positive HER2-overexpressed/ amplified breast cancer and who completed trastuzumab therapy less than 1 year ago.

2.5 Summary

The data subsequently submitted by the company in the commenting procedure have changed the conclusion on the added benefit of neratinib from dossier assessment A19-98.

The following Table 4 shows the result of the benefit assessment of neratinib under consideration of dossier assessment A19-98 and the present addendum.

Table 4: Neratinib – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**[b]
Extended adjuvant treatment of adult patients with early-stage hormone-receptor-positive HER2-overexpressed/amplified breast cancer and who completed adjuvant trastuzumab-based therapy less than 1 year ago	Watchful waiting	**Hint of minor added benefit**[c]

a. Presentation of the respective ACT specified by the G-BA.
b. Changes in comparison with dossier assessment A19-98 are printed in **bold**.
c. Only women were included in the ExteNET study. It remains unclear whether the observed effects can be transferred to men.

G-BA: Federal Joint Committee

The assessment described above deviates from that of the company, which overall derived an indication of considerable added benefit.

The G-BA decides on the added benefit.

3 References

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4. Higgins JPT, White IR, Wood AM. Imputation methods for missing outcome data in meta-analysis of clinical trials. Clin Trials 2008; 5(3): 225-239.