IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A14-09

Addendum to Commission A13-37 (regorafenib)[1]

Addendum

Commission: A14-09
Version: 1.0
Status: 26 February 2014

[1] Translation of addendum A14-09 *Addendum zum Auftrag A13-37 (Regorafenib)* (Version 1.0; Status: 26 February 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.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Addendum to Commission A13-37 (regorafenib)

Commissioning agency:
Federal Joint Committee

Commission awarded on:
14 February 2014

Internal Commission No.:
A14-09

Address of publisher:
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Keywords: regorafenib, colorectal neoplasms, benefit assessment

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

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Abbreviation	Meaning
AE	adverse event
BSC	best supportive care
CTCAE	Common Terminology Criteria for Adverse Events
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30
EQ-5D	European Quality of Life Group Questionnaire 5D
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 14 February 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 A13-37 (benefit assessment of regorafenib [1]).

In the commenting procedure on the assessment of regorafenib, the pharmaceutical company (hereinafter abbreviated to "the company") submitted further data to the G-BA [2,3] that went beyond the information in the dossier [4]. These were data on the CORRECT study on the comparison of regorafenib + best supportive care (BSC) versus placebo + BSC. This study was already contained in the company's dossier and was included as relevant in the dossier assessment A13-37. However, the data presented in the dossier were not evaluable for the outcome on health-related quality of life because only analyses were available in which the proportion of patients who were not considered in the analysis were over 30% and missing values were not imputed. With the comments and after the oral hearing [2,3], the company subsequently submitted new analyses, which, from the company's point of view, allow to assess health-related quality of life.

For the assessment of side effects, adverse events (AEs), which were recorded using the Common Terminology Criteria for Adverse Events (CTCAE) of the grades 3, 4 and 5, were included as so-called "severe AEs" in the dossier assessment A13-37, among other factors. However, AEs of CTCAE grade 1 and 2 were not included in the assessment. The company did not consider this to be justified. Hence it claimed the inclusion of CTCAE grade 1 and 2 AEs into the benefit assessment.

After the oral hearing, the G-BA commissioned IQWiG to assess the analyses on health-related quality of life for the CORRECT study subsequently provided. Furthermore, the G-BA commissioned IQWiG to submit a comment on the objections put forward by the company on the exclusion of the results on CTCAE grade 1 and 2 AEs.

In the following Chapter 2, the additional analyses on health-related quality of life and the objections put forward by the company on the exclusion of the results on CTCAE grade 1 and 2 AEs are assessed according to the commission.

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 Health-related quality of life

In the framework of the benefit assessment A13-37 [1], results that were recorded using the functional scales of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) and using the European Quality of Life Group Questionnaire 5D (EQ-5D) were to be included for the assessment of health-related quality of life. The data presented in the dossier [4] were not evaluable for the benefit assessment. Only analyses were available in which the proportion of patients who were not considered in the analysis were over 30%, missing values were not imputed, and it remained unclear how many of the patients who were not considered had died before the end of treatment. The exact proportion of patients who had died before the end of treatment cannot be derived from the available Kaplan-Meier curve on overall survival (see benefit assessment A13-37). It can be determined, however, that it cannot have been so large as to explain the low response rate.

In Appendix 1 of its comment before the oral hearing [1], the company presented the "expected" and "actual" return of questionnaires per treatment cycle and at the end of treatment for both measurement instruments mentioned above. It could be seen at the end of treatment that the "actual" response rate was approximately 72 to 74%, depending on the measurement instrument (it was higher at the time point of the different treatment cycles). However, these rates did not relate to the total population, but to the population referred to as "expected population". According to the company, patients who had "dropped out of the study treatment" did not form part of the population referred to as "expected population". However, depending on the instrument, the response was only between 52 and 56% in the treatment groups in relation to the randomized patients.

In its comment after the oral hearing, the company subsequently submitted analyses based on living patients, but only on treatment cycle 2 (corresponding to approximately 4 weeks after the start of the study). The company justified this by claiming that only the number of the patients who died in cycle 1 was known. The company claimed that the response rates based on the patients that were still alive could no longer be analysed after that because patients who had dropped out of the study and then died could not be allocated to a date of visit and thus to a time point of filling in the measurement instruments for the recording of health-related quality of life. Even if this was the case, this does not justify the fact that the company did not present response rates at the end of treatment because date of death (if applicable) and date of the end of treatment were known for every patient. The isolated analyses at the start of cycle 2 could not be interpreted in a meaningful way because they only covered a very short treatment period.

Irrespective of this, the response rate provided by the company for cycle 2 showed that the very low response rate of the questionnaires can only be explained to a very small extent by

patients' death. The data on cycle 2 provided by the company showed that no questionnaire was received from 24.3%, but that only 1.7% of the patients (13 out of 760) had died.

Overall, the company provided no evaluable data for the outcome of health-related quality of life.

2.2 Adverse events of CTCAE grade 1 and 2

In its comment [2], the company claimed lesser harm from regorafenib than from BSC with considerable extent for CTCAE grade 1 AEs and with minor extent for CTCAE grade 2 AEs.

However, it did not present any valid analyses for this. The analyses presented by the company referred to the so-called "worst grade". This means, that only those patients were included in the analysis of a certain CTCAE grade who had not had a higher-grade AE. For the CTCAE grade 2 events, this means specifically that only 51% of the BSC group and 22% of the regorafenib group were included in the analysis because an AE of CTCAE grade 3, 4 or 5 was recorded for 49% of the patients under BSC and for 78% of the patients under regorafenib. This kind of analysis can obviously not be interpreted in a meaningful way.

It should be additionally noted that the problem that patients with higher grade AEs are not included in the analysis also exists for CTCAE grade 3 events. An analysis of CTCAE grade ≥ 3 AEs, which included all patients, confirmed the results of the analysis with CTCAE grade 3 AEs presented in the dossier assessment on regorafenib (A13-37) (see Table 1).

Table 1: Extent of added benefit at outcome level for AEs according to CTCAE: regorafenib + BSC vs. BSC

Outcome category **outcome**	**Regorafenib + BSC vs. BSC** **effect estimate [95% CI]** **p-value** **number of patients with event probability**[a]	**Derivation of extent**[b]
Severe AEs CTCAE grade ≥ 3	RR: 1.59 [1.39; 1.82] RR[c]: 0.63 [0.55; 0.72] p-value < 0.001 78.0% vs. 49.0% probability: "hint"	Outcome category "serious/severe AEs" CI_u < 0.75 greater harm, extent: "major"
a: Probability provided if statistically significant differences were present. b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u. c: Proportion of events BSC vs. regorafenib + BSC (reversed direction of effect to enable direct use of limits to derive the extent of added benefit). AE: adverse event; BSC: best supportive care; CI: confidence interval; CI_u: upper limit of CI; CTCAE: Common Terminology Criteria for Adverse Events; RR: relative risk; SAE: serious adverse event; vs.: versus		

2.3 Summary

In summary, neither the data on health-related quality of life subsequently submitted by the company nor the company's explanations on CTCAE grade 1 or 2 AEs change the result of the benefit assessment A13-37. Overall, there is therefore still a hint of a minor added benefit of regorafenib versus BSC [1].

3 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Regorafenib: Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A13-37 [online]. 19 December 2013 [accessed: 19 February 2014]. (IQWiG-Berichte; Volume 200). URL: https://www.iqwig.de/download/A13-37_Regorafenib_Nutzenbewertung-35a-SGB-V.pdf.

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4. Bayer Vital. Nutzenbewertungsverfahren zum Wirkstoff Regorafenib: Dossier [online]. [accessed: 19 February 2014]. URL: http://www.g-ba.de/informationen/nutzenbewertung/82.