

IQWiG Reports – Commission No. A15-43

Regorafenib – Benefit assessment according to §35a Social Code Book V¹

Extract

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³ Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSC	best supportive care
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EGFR	epidermal growth factor receptor
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer - Core 30
EQ-5D	European Quality of Life-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
KRAS	Kirsten rat sarcoma viral oncogene homologue
MCRC	metastatic colorectal cancer
PFS	progression-free survival
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
VAS	visual analogue scale
VEGF	vascular endothelial growth factor

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug regorafenib. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as “the company”). The dossier was sent to IQWiG on 1 October 2015.

The company submitted a first dossier of the drug to be evaluated on 1 October 2013 for the early benefit assessment. In this procedure, by decision of 20 March 2014, the G-BA limited its decision until 1 October 2015.

Research question

The aim of this report was to assess the added benefit of regorafenib compared with best supportive care (BSC) as appropriate comparator therapy (ACT) in adult patients with metastatic colorectal cancer (MCRC) who have been previously treated with, or are not considered candidates for, available therapies (therapies included: fluoropyrimidine-based chemotherapy, anti-vascular endothelial growth factor (VEGF) therapy, and, anti-epidermal growth factor receptor (EGFR) therapy).

The G-BA specified BSC as ACT. BSC means the best possible supportive therapy, optimized for the individual patient, for alleviation of symptoms and improvement in the quality of life. The company used the ACT specified by the G-BA.

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier. Only direct comparative randomized controlled trials (RCTs) were included in the analysis.

Results

Study pool

Data suitable for the benefit assessment were available for the included studies CONCUR and CORRECT. Results from the CORRECT study were already contained in the dossier from 1 October 2013 for the first benefit assessment of regorafenib (dossier assessment A13-37), which the company supplemented with new analyses on symptoms, health-related quality of life and adverse events (AEs) in its dossier from 1 October 2015.

Study characteristics

See dossier assessment A13-37 for a description of the study and intervention characteristics of the already known CORRECT study.

The CONCUR study was a randomized, double-blind, placebo-controlled phase 3 study. The study was only conducted in Asia. Adult patients with MCRC (stage IV) whose disease had progressed during or within 3 months following the last administration of an approved standard treatment were enrolled. Standard treatments had to include fluoropyrimidine, oxaliplatin and irinotecan.

Anti-VEGF and anti-EGFR pretreatment, which is specified in the approval of regorafenib, was not mandatory for study inclusion. Anti-EGFR treatment only concerns patients with Kirsten rat sarcoma viral oncogene homologue (KRAS) wild type (negative KRAS mutation status), however. The relevant subpopulation therefore included patients pretreated with fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab and, in case of KRAS wild type, cetuximab or panitumumab (= anti-EGFR treatment). The subpopulation comprised 50 patients in the intervention arm and 25 patients in the control arm.

All patients received supportive concomitant treatment (BSC) in addition to regorafenib (160 mg once daily) or placebo. Other investigational or approved anti-tumour drug treatments were excluded from BSC. Treatment was continued until disease progression, death or discontinuation of the study medication by patient or physician.

The patients had to have a baseline Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1. As in the CORRECT study, patients with ECOG PS of 2 or higher were not included.

There was no information on the median treatment duration for the relevant subpopulation. The primary outcome was overall survival. Patient-relevant outcomes on morbidity, health-related quality of life and AEs were additionally recorded.

From the total population, 31% of the patients in the regorafenib + BSC arm and 43% of the patients in the placebo + BSC arm received further systemic anti-tumour treatments in the follow-up phase, after completion of the study medication. No such data were available for the relevant subpopulation.

Risk of bias

The risk of bias at study level was classed as low for both studies. For the CONCUR study, the risk of bias was rated as low for the outcomes “overall survival”, “serious adverse events (SAEs)” and “discontinuation due to AEs”, and as high for the outcome “health status (European Quality of Life-5 Dimensions visual analogue scale [EQ-5D VAS]). The risk of bias was also rated as high for the respective specific AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade 3) “exanthema” and “hand-foot syndrome”.

The risk of bias for the CORRECT study was rated as high for all newly submitted data on the outcome “health status” and as low for all further relevant outcomes with new analyses with usable data.

Overall assessment of the certainty of conclusions

The reduced informative value of the results of the CORRECT study, which was already described in dossier assessment A13-37, also applies to the CONCUR study for the same reasons. The main reason for the uncertainty was that it remained unclear also for the CONCUR study whether the anti-tumour treatments excluded from the BSC would have relieved symptoms and thus could have been part of the BSC. In addition, the study only included patients with an ECOG PS of 0 or 1. Overall, no more than hints of an added benefit can therefore be derived.

Results*Mortality*

Whereas based on the median a numerical difference to the disadvantage of regorafenib was shown for the outcome “overall survival” in the CONCUR study, based on the hazard ratio a numerical difference in favour of regorafenib was shown in this study. The meta-analysis of the studies CONCUR and CORRECT showed a statistically significant result, which deviated only marginally from the result of the CORRECT study alone. Overall, there was a hint of an added benefit of regorafenib + BSC compared with placebo + BSC for the outcome “overall survival”.

Morbidity

The company presented no usable data for the outcome “symptoms” (measured with the symptom scales of the European Organisation for Research and Treatment of Cancer - Core 30 [EORTC QLQ-C30]). The company’s approach did not comply with the specifications provided in the manual of the questionnaire, whereas the company had implemented the specifications of the manual in the original dossier. There was no hint of an added benefit of regorafenib + BSC in comparison with placebo + BSC for this outcome; an added benefit is therefore not proven.

The meta-analysis of the results on the outcome “health status” (measured with the EQ-5D VAS) showed no statistically significant difference between the treatment groups. This resulted in no hint of an added benefit of regorafenib + BSC in comparison with placebo + BSC for this outcome; an added benefit is therefore not proven.

Health-related quality of life

The company presented no usable data for the outcome “health-related quality of life” (measured with the functional scales and the global health status of the EORTC QLQ-C30) in its dossier. Again, the company’s approach did not comply with the specifications provided in the manual of the questionnaire, whereas the company had implemented the specifications of the manual in the original dossier. This resulted in no hint of an added benefit of regorafenib + BSC in comparison with placebo + BSC for this outcome; an added benefit is therefore not proven.

Adverse events

The meta-analysis of the results on the outcome “SAEs” and on the outcome “discontinuation due to AEs” in each case showed no statistically significant difference between the treatment groups. Hence for these outcomes there was no hint of greater or lesser harm from regorafenib + BSC in comparison with placebo + BSC; greater or lesser harm is therefore not proven.

The results of the CONCUR study were not usable for the individual events “diarrhoea” and “fatigue” (in each case severe AEs CTCAE grade 3). Hence only the data of the CORRECT study were usable for the overall rate of severe AEs CTCAE grade ≥ 3 . There was a hint of greater harm of regorafenib + BSC in comparison with placebo + BSC for the outcome “severe AEs”. A statistically significant difference to the disadvantage of regorafenib + BSC in comparison with placebo + BSC was shown for the individual events “exanthema” and “hand-foot syndrome” (in each case severe AEs CTCAE grade 3) on the basis of the corresponding meta-analyses, and for the individual events “diarrhoea” and “fatigue” on the basis of the CORRECT study. This resulted in a hint of greater harm of regorafenib + BSC compared with placebo + BSC for these outcomes.

Extent and probability of added benefit, patient groups with therapeutically important added benefit⁴

The data presented by the company resulted in no qualitative change of the available data in comparison with the first assessment of regorafenib (see dossier assessment A13-37). Hence the assessment of the added benefit has not changed either. The assessment was:

On the basis of the results presented, the extent and probability of the added benefit of the drug regorafenib compared with the ACT in the therapeutic indication “metastatic colorectal cancer” is assessed as follows:

In the overall assessment, there are positive and negative effects of equal certainty of results (hint).

On the positive side, there is an added benefit in the category “mortality” with the extent “considerable”. On the negative side, there is greater harm up to the extent “major” in the category “severe/serious AEs” (severe AEs CTCAE grade ≥ 3 , including CTCAE grade 3 diarrhoea, exanthema and hand-foot syndrome with the extent “major” as well as fatigue with

⁴ On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, no added benefit, or less benefit). For further details see [1,2].

the extent “considerable”). Even though the extent is “major” for severe/serious AEs, this does not completely outweigh the mortality advantage of regorafenib.

Overall, there is a hint of a minor added benefit of regorafenib versus the ACT BSC for patients with MCRC.

Table 2 presents a summary of the extent and probability of the added benefit of regorafenib.

Table 2: Regorafenib – extent and probability of added benefit

Therapeutic indication	ACT ^a	Extent and probability of added benefit
Treatment of adult patients with MCRC who have been previously treated with, or are not considered candidates for, available therapies. These include fluoropyrimidine-based chemotherapy, an anti-VEGF therapy, and an anti-EGFR therapy.	BSC	Hint of minor added benefit
a: Presentation of the appropriate comparator therapy specified by the G-BA. ACT: appropriate comparator therapy; BSC: best supportive care; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; MCRC: metastatic colorectal cancer; VEGF: vascular endothelial growth factor		

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

Supplementary information on the implementation of the conditions of the limitation

In the present dossier, the company did not fulfil the conditions of the limitation formulated in the first decision on regorafenib. For disease-specific morbidity (symptoms) and health-related quality of life, the company presented inadequate analyses disregarding the manual of the questionnaire used (EORTC QLQ-C30), although it had considered the requirements of the manual for the analyses in the first dossier. In addition, it presented no studies including patients with ECOG PS 2 or higher.

2.2 Research question

The aim of this report was to assess the added benefit of regorafenib compared with BSC as ACT in adult patients with MCRC who have been previously treated with, or are not considered candidates for, available therapies. These include fluoropyrimidine-based chemotherapy, an anti-VEGF therapy, and an anti-EGFR therapy.

The G-BA specified BSC as ACT. BSC means the best possible supportive therapy, optimized for the individual patient, for alleviation of symptoms and improvement in the quality of life.

The company used the ACT specified by the G-BA.

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier. Only direct comparative RCTs were included in the analysis.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on regorafenib (status: 5 August 2015)
- bibliographical literature search on regorafenib (last search on 5 August 2015)
- search in trial registries for studies on regorafenib (last search on 5 August 2015)

To check the completeness of the study pool:

- search in trial registries for studies on regorafenib (last search on 16 October 2015)

No additional relevant study was identified from the check.

2.3.1 Studies included

The studies CONCUR and CORRECT listed in the following table were included in the benefit assessment.

Table 3: Study pool – RCT, direct comparison: regorafenib + BSC vs. placebo + BSC

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study ^a (yes/no)	Third-party study (yes/no)
CONCUR	Yes	Yes	No
CORRECT	Yes	Yes	No
a: Study for which the company was sponsor, or in which the company was otherwise financially involved. BSC: best supportive care; RCT: randomized controlled trial; vs.: versus			

The CORRECT study was already presented in the dossier from 1 October 2013 for the first benefit assessment of regorafenib in the therapeutic indication “MCRC” (see dossier assessment A13-37 [3]). In the new dossier, the company presented new analyses on symptoms, health-related quality of life and AEs for the CORRECT study.

In addition to the CORRECT study, the company presented the CONCUR study in the present benefit assessment.

Section 2.6 contains a reference list for the studies included.

2.3.2 Study characteristics

Table 4 and Table 5 describe the studies used for the benefit assessment.

Table 4: Characteristics of the studies included – RCT, direct comparison: regorafenib + BSC vs. placebo + BSC

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes ^a
CONCUR	RCT, double-blind, placebo-controlled, parallel	Adult patients with MCRC (adenocarcinoma, stage 4) and ECOG PS \leq 1 with disease progression during treatment with approved standard treatments ^b	Regorafenib + BSC (N = 136) ^c placebo + BSC (N = 68) ^c Relevant subpopulation thereof ^d : regorafenib + BSC (n = 50) placebo + BSC (n = 25)	Treatment duration: until disease progression, death or discontinuation of study medication by the patient or the investigator (median treatment duration for the relevant subpopulation: no data)	25 centres in Asia (China, Hong Kong, South Korea, Taiwan, Vietnam) 4/2012 until 5/2014 Data cut-off for the planned formal analysis of overall survival after 154 deaths: 29 November 2013	Primary: overall survival Secondary: morbidity, health-related quality of life, adverse events
CORRECT	RCT, double-blind, placebo-controlled, parallel	Adult patients with MCRC (adenocarcinoma, stage 4) and ECOG PS \leq 1 with disease progression during treatment with approved standard treatments ^e	Regorafenib + BSC (N = 505) placebo + BSC (N = 255)	Treatment duration: until disease progression, death, discontinuation of study medication by the patient or investigator (median treatment duration under regorafenib + BSC: 7.4 weeks; placebo + BSC: 7.0 weeks)	105 centres in Asia, Australia, North America, Eastern Europe and Western Europe 4/2010 until 1/2014 First data cut-off after 175 deaths for futility analysis ^f Second data cut-off July 2011 (408 deaths), futility analysis, efficacy and safety analysis Third data cut-off November 2011, as part of the approval process, analysis on OS before start of crossover	Primary: overall survival Secondary: morbidity, health-related quality of life, adverse events

(continued)

Table 4: Characteristics of the studies included – RCT, direct comparison: regorafenib + BSC vs. placebo + BSC (continued)

a: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on the relevant available outcomes for this benefit assessment.

b: Standard treatments included fluoropyrimidine, oxaliplatin and irinotecan. Pretreatment with bevacizumab and – in case of KRAS wild type – cetuximab or panitumumab was not mandatory.

c: The total population is not relevant for the assessment and, unless stated otherwise, is not shown in the following tables.

d: Patients who have received pretreatment with bevacizumab and – in case of KRAS wild type – cetuximab or panitumumab besides fluoropyrimidine, oxaliplatin and irinotecan (subpopulation with approval-compliant treatment).

e: Standard treatments included fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab and – if KRAS wild type – cetuximab or panitumumab.

f: Called “check for futility” by the company; a futility analysis serves to check whether statistically significant effects regarding the objectives of the study are unlikely in order to possibly decide to discontinue the study prematurely.

BSC: best supportive care; ECOG PS: Eastern Cooperative Oncology Group Performance Status; KRAS: Kirsten rat sarcoma viral oncogene homologue; MCRC: metastatic colorectal cancer; N: number of randomized patients; n: relevant subpopulation; OS: overall survival; RCT: randomized controlled trial; vs.: versus

Table 5: Characteristics of the interventions – RCT, direct comparison: regorafenib + BSC vs. placebo + BSC

Study	Intervention	Comparison	Pretreatment
CONCUR	<ul style="list-style-type: none"> Regorafenib 160 mg (4 tablets of 40 mg) once daily for 3 weeks followed by one week off treatment BSC 	<ul style="list-style-type: none"> Placebo 4 tablets once daily for 3 weeks followed by one week off treatment BSC 	Fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab and – in case of KRAS wild type – cetuximab or panitumumab
CORRECT	<ul style="list-style-type: none"> Regorafenib 160 mg (4 tablets of 40 mg) once daily for 3 weeks followed by one week off treatment BSC 	<ul style="list-style-type: none"> Placebo 4 tablets once daily for 3 weeks followed by one week off treatment BSC 	Fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab and – in case of KRAS wild type – cetuximab or panitumumab
Definition BSC: <ul style="list-style-type: none"> any concomitant medications or treatments: antibiotics, analgesics, radiotherapy for pain control (limited to bone metastases), corticosteroids, transfusions, psychotherapy, growth factors, palliative surgery, or any other symptomatic therapy necessary to provide BSC excluded: other investigational or approved anti-tumour drug treatments such as cytostatics, signal transduction inhibitors, immunotherapy, hormonal therapy and other tyrosine-kinase inhibitors 			
BSC: best supportive care; KRAS: Kirsten rat sarcoma viral oncogene homologue; RCT: randomized controlled trial; vs.: versus			

See dossier assessment A13-37 for a description of the study and intervention characteristics of the already known CORRECT study.

The CONCUR study was a randomized, double-blind, placebo-controlled phase 3 study. The study was only conducted in Asia. Adult patients with MCRC (stage IV) whose disease had progressed during or within 3 months following the last administration of an approved standard treatment were enrolled. Standard treatments had to include fluoropyrimidine, oxaliplatin and irinotecan. Patients pretreated with oxaliplatin in an adjuvant setting should have progressed during or within 6 months of completion of an oxaliplatin-based treatment. Patients who had progressed more than 6 months of completion of oxaliplatin-based adjuvant treatment were to be retreated with oxaliplatin-based treatment to be eligible for enrolment in the study. Patients who had discontinued standard treatment due to unacceptable toxicity precluding retreatment with the same agent prior to progression of disease were also allowed into the study. Anti-VEGF and anti-EGFR pretreatment, which is specified in the approval of regorafenib [4], was not mandatory for study inclusion. Anti-EGFR treatment only concerns patients with KRAS wild type (negative KRAS mutation status), however. The relevant subpopulation therefore included patients pretreated with fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab and, in case of KRAS wild type, cetuximab or panitumumab (= anti-EGFR treatment).

The patients had to have a baseline Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1. As in the CORRECT study, patients with ECOG PS of 2 or higher were not included.

A total of 204 patients were randomly assigned in a ratio of 2:1, either to treatment with regorafenib + BSC (136 patients) or to treatment with placebo + BSC (68 patients). The relevant subpopulation comprised 50 patients in the regorafenib + BSC arm and 25 patients in the placebo + BSC arm. Patients were stratified by type of metastasis (metastases in one organ or metastases in several organs) and by the time since diagnosis of the metastatic disease (≥ 18 months or < 18 months).

In the CONCUR study, the drug regorafenib was administered according to its approval (160 mg [4 tablets of 40 mg] once daily). Patients in the placebo + BSC arm received 4 tablets of identical appearance once daily. Regorafenib and placebo were each taken over a time period of 3 weeks, followed by one week off therapy to make up one cycle. All patients additionally received supportive concomitant treatment (BSC). Other investigational or approved anti-tumour drug treatments were excluded from BSC. Treatment was continued until disease progression, death or discontinuation of the study medication by patient or physician.

The primary outcome was overall survival. Patient-relevant outcomes on morbidity, health-related quality of life and AEs were additionally recorded.

From the total population, 31% of the patients in the regorafenib + BSC arm and 43% of the patients in the placebo + BSC arm received further systemic anti-tumour treatments in the follow-up phase of the CONCUR study, after completion of the study medication (see Appendix B of the full dossier assessment). No such data were available for the relevant subpopulation. As in the CORRECT study, anti-tumour treatments that might have relieved symptoms and thus could have been part of the BSC were therefore excluded.

Table 6 shows the planned duration of follow-up of the patients for the individual outcomes.

Table 6: Planned duration of follow up – RCT, direct comparison: regorafenib + BSC vs. placebo + BSC

Study	Planned follow-up
Outcome category	
Outcome	
CONCUR	
Mortality	
Overall survival	Until death
Morbidity	
EORTC QLQ-C30 (symptoms)	Until the end of study treatment
EQ-5D VAS	Until the end of study treatment
Health-related quality of life	
EORTC QLQ-C30 (functions)	Until the end of study treatment
Adverse events	
All AE outcomes	Until 30 days after the last study treatment
CORRECT	
Mortality	
Overall survival	Until death
Morbidity	
EORTC QLQ-C30 (symptoms)	Until the end of study treatment
EQ-5D VAS	Until the end of study treatment
Health-related quality of life	
EORTC QLQ-C30 (functions)	Until the end of study treatment
Adverse events	
All AE outcomes	Until 30 days after the last study treatment
AE: adverse event; BSC: best supportive care; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; QLQ-C30: Quality of Life Questionnaire Core-30; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus	

The planned follow-up of the patients for the outcome “overall survival” was conducted until death in both studies. The final analysis of overall survival for the CONCUR study was planned after 154 deaths; the corresponding data cut-off was performed on 29 November 2013. It was planned for the other outcomes included to observe the patients until the end of the study treatment – except AEs, for which the patients were observed up to 30 days after the last study treatment.

Table 7 and Table 8 show the characteristics of the patients in the studies included.

Table 7: Characteristics of the study populations (demography) – RCT, direct comparison: regorafenib + BSC vs. placebo + BSC

Study Group	N	Age [years] mean (SD)	Sex [F/M] %	Region North America, Western Europe, Israel, Australia/Asia/South America, Turkey, Eastern Europe %	Ethnicity Caucasian/Black, African American/Asian/American Indian, Native Alaskan/not reported/multiple %	Treatment discontinuation n (%)	Study discontinuation n (%)
CONCUR							
Regorafenib + BSC	50	57 (ND)	38/62	0/100/0	0/0/100/0/0/0	ND	ND
Placebo + BSC	25	54 (ND)	56/44	0/100/0	0/0/100/0/0/0	ND	ND
CORRECT							
Regorafenib + BSC	505	61 (10)	38/62	83.2/13.7/3.2 ^a	77.6/1.2/15.0/0.2/5.7/0.2	448 ^{b, c} (88.7)	ND
Placebo + BSC	255	60 (10)	40/60	83.1/13.7/3.1 ^a	78.8/3.1/13.7/0.4/3.9/0	244 ^{b, d} (95.7)	ND
<p>a: No patients were randomized in the centres in South America and Turkey.</p> <p>b: Out of this, 336 (75.0%) of the patients in the regorafenib + BSC arm and 205 (84.0%) of the patients in the placebo + BSC arm discontinued the study due to disease progression (Institute's calculation; the number of events is the sum of the patients in whom the reason for treatment discontinuation was "disease progression", "disease progression – radiological progression" or "disease progression – clinical progression").</p> <p>c: Including 7 (1.4%) deaths.</p> <p>d: Including 4 (1.6%) deaths.</p> <p>BSC: best supportive care; F: female; M: male; N: number of randomized (or included) patients; n: number of patients with event; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus</p>							

Table 8: Characteristics of the study populations (disease characteristics) – RCT, direct comparison: regorafenib + BSC vs. placebo + BSC

Study Group	N	Time between first diagnosis of the metastatic disease and randomization [weeks] mean (SD)	ECOG PS 0/1 n (%)	Location of primary tumour colon/rectum/colon and rectum/ not provided n (%)	KRAS mutation yes/no/unknown n (%)
CONCUR					
Regorafenib + BSC	50	101.7 [26.6; 250.9] ^a	15 (30.0)/35 (70.0)	27 (54)/22 (44)/1 (2)/0 (0)	19 (38.0)/18 (36.0)/13 (26.0)
Placebo + BSC	25	101.6 [13.0; 211.0] ^a	7 (28.0)/18 (72.0)	15 (60)/9 (36)/1 (4)/0 (0)	7 (28.0)/10 (40.0)/8 (32.0)
CORRECT					
Regorafenib + BSC	505	151.7 (93.7)	265 (52.5)/240 (47.5)	323 (64.0)/151 (29.9)/30 (5.9)/1 (0.2)	273 (54.1)/205 (40.6)/27 (5.3)
Placebo + BSC	255	150.3 (89.2)	146 (57.3)/109 (42.7)	172 (67.5)/69 (27.1)/14 (5.5)/0 (0)	157 (61.6)/94 (36.9)/4 (1.6)
a: Values as mean [min; max]. BSC: best supportive care; ECOG PS: Eastern Cooperative Oncology Group Performance Status; KRAS: Kirsten rat sarcoma viral oncogene homologue; max: maximum; min: minimum; N: number of randomized (or included) patients; n: number of patients with event; RCT: randomized controlled trial; SD: standard deviation; vs.: versus					

The characteristics between the treatment arms of the CONCUR study in the relevant subpopulation were balanced. The mean age of the patients was 54 (regorafenib + BSC arm) and 57 years (placebo + BSC arm); the patients were therefore younger on average than in the CORRECT study, which had included already comparatively young patients. The study was only conducted in Asia. No information was available on observation period and on treatment and study discontinuations for the relevant subpopulation of the CONCUR study.

The metastatic disease had been diagnosed for about 2 years on average, and was localized in the colon in more than half of the patients. At baseline, 70% (regorafenib + BSC arm) and 72% (placebo + BSC arm) of the patients had an ECOG PS of 1; the KRAS mutation status was unknown in 26% and 32% of the patients.

Although according to the approval, treatment with regorafenib, in principle, is an option for all tumour types of colorectal cancer, the CONCUR study only included patients with adenocarcinoma. With more than 95%, this tumour type constitutes the majority of colorectal cancers [5,6].

Table 9 shows the risk of bias at study level.

Table 9: Risk of bias at study level – RCT, direct comparison: regorafenib + BSC vs. placebo + BSC

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
CONCUR	Yes	Yes	Yes	Yes	Yes	Yes	Low
CORRECT	Yes	Yes	Yes	Yes	Yes	Yes	Low
BSC: best supportive care; RCT: randomized controlled trial; vs.: versus							

The risk of bias at study level was classed as low for both studies. This concurs with the company's assessment.

Overall assessment of the certainty of conclusions

The reduced informative value of the results of the CORRECT study, which was already described in dossier assessment A13-37, also applies to the CONCUR study for the same reasons (see Section 2.7.2.4.1 of the full dossier assessment). The main reason for the uncertainty was that it remained unclear also for the CONCUR study whether the anti-tumour treatments excluded from the BSC would have relieved symptoms and thus could have been part of the BSC. In addition, the study only included patients with an ECOG PS of 0 or 1.

Overall, no more than hints of an added benefit can therefore be derived. This deviates from the company's assessment, which derived proof.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.2.4.3 of the full dossier assessment):

- Mortality
 - overall survival
- Morbidity
 - symptoms, measured with the symptom scales of the EORTC QLQ-C30
 - health status, measured with the EQ-5D VAS
- Health-related quality of life
 - measured with the functional scales and the global health status of the EORTC QLQ-C30
- Adverse events
 - SAEs
 - discontinuation due to AEs
 - severe AEs (CTCAE grade ≥ 3)
 - if applicable, further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 A) (see Section 2.7.2.4.3 of the full dossier assessment). Besides the surrogate outcome “progression-free survival (PFS)”, the company included the dimensions of the EQ-5D also for health-related quality of life and also considered further operationalizations for severe AEs, instead of only CTCAE grade ≥ 3 . The company did not explicitly include specific AEs in its benefit assessment. Furthermore, the company allocated the EQ-5D VAS to health-related quality of life.

The data presented by the company based on EORTC QLQ-C30 scales were not usable for the outcomes “symptoms” and “health-related quality of life”. In contrast to the approach in its original dossier, the company had not used analyses that comply with the specifications in the manual.

Table 10 shows for which outcomes data were available in the included studies.

Table 10: Matrix of outcomes – RCT, direct comparison: regorafenib + BSC vs. placebo + BSC

Study	Outcomes										
	Overall survival	Symptoms (EORTC QLQ-C30) ^a	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30) ^b	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)	Diarrhoea (NCI CTCAE term, grade 3)	Fatigue (NCI CTCAE term, grade 3)	Exanthema (NCI CTCAE term, grade 3)	Hand-foot syndrome (NCI CTCAE term, grade 3)
CONCUR	Yes	No ^c	Yes	No ^c	Yes	Yes	Yes	Yes	Yes	Yes	Yes
CORRECT	Yes	No ^c	Yes	No ^c	Yes	Yes	Yes	Yes	Yes	Yes	Yes
<p>a: Measured with the symptom scales of the EORTC QLQ-C30 questionnaire version 3.0.</p> <p>b: Measured with the functional scales of the EORTC QLQ-C30 questionnaire version 3.0.</p> <p>c: No usable data available; for reasons, see Section 2.7.2.4.3 of the full dossier assessment.</p> <p>AE: adverse event; BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; NCI: National Cancer Institute; QLQ-C30: Quality of Life Questionnaire Core-30; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus</p>											

2.4.2 Risk of bias

Table 11 shows the risk of bias for the relevant outcomes.

Table 11: Risk of bias at study and outcome level – RCT, direct comparison: regorafenib + BSC vs. placebo + BSC

Study	Study level	Outcomes										
		Overall survival	Symptoms (EORTC QLQ-C30) ^a	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30) ^b	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)	Diarrhoea (CTCAE grade 3)	Fatigue (CTCAE grade 3)	Exanthema (CTCAE grade 3)	Hand-foot syndrome (CTCAE grade 3)
CONCUR	L	L	- ^c	H ^d	- ^c	L	L	- ^e	- ^e	- ^e	H ^f	H ^f
CORRECT	L	L	- ^c	H ^g	- ^c	L	L	L	L	L	L	L

a: Measured with the symptom scales of the EORTC QLQ-C30 questionnaire version 3.0.
b: Measured with the functional scales of the EORTC QLQ-C30 questionnaire version 3.0.
c: No usable data available.
d: Due to the unclear proportion of missing values at the study visits after the start of the study in the relevant subpopulation; at the end of treatment, the data for 25% of the randomized patients were missing in the total population.
e: Due to the heterogeneity, results on these outcomes were only used from the CORRECT study; see Section 2.4.3.
f: Due to unknown treatment durations and therefore observation periods; the median treatment duration in the regorafenib + BSC arm (10.6 weeks) was 1.5 times as long as in the placebo + BSC arm (only 7 weeks) in the total population.
g: Due to the large proportion of missing values (48% of the randomized patients at the end of treatment).
AE: adverse event; BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; H: high; L: low; QLQ-C30: Quality of Life Questionnaire Core-30; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

For the CONCUR study, the risk of bias was rated as low for the outcomes “overall survival”, “SAEs” and “discontinuation due to AEs”, and as high for the outcome “health status (EQ-5D VAS)”. This concurs with the company’s assessments. The risk of bias was also rated as high for the respective specific AEs (CTCAE grade 3) “exanthema” and “hand-foot syndrome”. These assessments deviate from those of the company, which did not use the specific AEs for the benefit assessment.

The risk of bias for the CORRECT study was rated as high for all newly submitted data on the outcome “health status” and as low for all further relevant outcomes with new analyses with usable data. This concurs with the company’s assessments.

Since no usable data were available for the outcomes “symptoms” and “health-related quality of life” overall, and, for the CONCUR study, for the outcomes “severe AEs CTCAE grade ≥ 3” and for the specific AEs “diarrhoea” and “fatigue”, the outcome-specific risk of bias was not assessed. This deviates from the company, which found a high risk of bias for the data it

had included on symptoms and health-related quality of life and a low risk of bias for severe AEs CTCAE grade ≥ 3 .

Reasons for the assessment of the risk of bias can be found in Section 2.7.2.4.2 of the full dossier assessment.

2.4.3 Results

Table 12 to Table 15 summarize the results on the comparison of regorafenib + BSC with placebo + BSC in MCRC patients. Where necessary, the data from the company's dossier were supplemented by the Institute's calculations.

Table 12 shows the results on overall survival. The corresponding Kaplan-Meier curves can be found in Appendix A of the full dossier assessment. The results on continuous outcomes are presented in Table 13; Table 14 and Table 15 contain results on AEs.

Table 12: Results (time to event: mortality) – RCT, direct comparison: regorafenib + BSC vs. placebo + BSC

Outcome category Outcome	Regorafenib + BSC		Placebo + BSC		Regorafenib + BSC vs. placebo + BSC	
	N	Median survival time in days [95% CI] Patients with event n (%)	N	Median survival time in days [95% CI] Patients with event n (%)	HR [95% CI]	p-value
Mortality						
Overall survival						
CONCUR	50	183 [151; 403] 36 (72)	25	203 [105; 266] 22 (88)	0.68 [0.40; 1.18] ^a	0.186 ^b
CORRECT						
21 Jul 2011	505	196 [178; 222] 275 (54.5)	255	151 [134; 177] 157 (61.6)	0.77 [0.64; 0.94] ^c	0.011 ^d
13 Nov 2011	505	194 [177; 214] 369 (73.1)	255	152 [134; 178] 197 (77.3)	0.79 [0.66; 0.94] ^c	0.008 ^d
Total ^e					0.78 [0.66; 0.92]	0.003
a: Adjusted for presence of organs with metastases (solitary/multiple) and time since diagnosis of the metastatic disease (≥ 18 months, < 18 months).						
b: Log-rank test.						
c: Adjusted for pretreatment with anti-VEGF drugs (yes/no), time since diagnosis of the metastatic disease (≥ 18 months, < 18 months) and geographical region (1 = North America, Western Europe, Israel, Australia; 2 = Asia; 3 = South America, Turkey, Eastern Europe).						
d: Institute's calculation; Wald test.						
e: Meta-analysis of the results of the CONCUR study and of the data cut-off from 13 November 2011 of the CORRECT study.						
BSC: best supportive care; CI: confidence interval; HR: hazard ratio; N: number of analysed patients; n: number of patients with event; RCT: randomized controlled trial; VEGF: vascular endothelial growth factor; vs.: versus						

Table 13: Results (continuous outcomes) – RCT, direct comparison: regorafenib + BSC vs. placebo + BSC

Outcome category	Regorafenib + BSC			Placebo + BSC			Regorafenib + BSC vs. placebo + BSC
Outcome	N ^a	Baseline values mean (SD)	Change at end of study LS mean ^b (SD)	N ^a	Baseline values mean (SD)	Change at end of study LS mean ^b (SD)	LS MD [95% CI]; p-value Hedges' g [95% CI]
Morbidity							
Symptoms (EORTC QLQ-C30)	No usable data ^c						
Health status (EQ-5D VAS)							
CONCUR	50	71.5 (17.4)	-2.52 (ND)	25	70.0 (18.5)	-4.38 (ND)	1.87 [-4.17; 7.90]; 0.543
CORRECT	472	67.3 (47.2)	-4.94 (ND)	235	65.8 (20.5)	-2.19 (ND)	0.14 [-0.34; 0.62]
Total							-2.75 [-5.61; 0.11]; 0.060
							-0.06 [-0.21; 0.10]
							ND
							-0.04 [-0.19; 0.11]; p-value: 0,62 ^d
Health-related quality of life							
Health-related quality of life (EORTC QLQ-C30)	No usable data ^c						
a: Number of patients with a value at baseline and at least one later time point.							
b: MMRM analysis.							
c: Due to inadequate analysis of the EORTC QLQ-C30 questionnaire.							
d: Overall effect, CI and p-value calculated from meta-analysis.							
BSC: best supportive care; CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life Questionnaire-5 Dimensions; LS: least square; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; ND: no data; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale; vs.: versus							

Table 14: Results (time to event: AEs) – RCT, direct comparison: regorafenib + BSC vs. placebo + BSC

Outcome category Outcome Study	Regorafenib + BSC		Placebo + BSC		Regorafenib + BSC vs. placebo + BSC	
	N	Median time in days [95% CI] Patients with event n (%)	N	Median time in days [95% CI] Patients with event n (%)	HR [95% CI]	p-value
Adverse events						
SAEs						
CONCUR	50	429 [120; NA] 17 (34)	25	NA [37; NA] 7 (28)	1.06 [0.43; 2.60]	0.903 ^{a, b}
CORRECT	500	139 [127; 169] 219 (43.8)	253	109 [90; NA] 100 (39.5)	0.91 [0.72; 1.16]	0.465 ^{a, b}
Total					0.92 [0.73; 1.17] ^c	0.50 ^{b, c}
<p>a: Log-rank test.</p> <p>b: Analysis based on the rates showed no qualitative difference; relative risk, CI and p-value (CMH test): study CONCUR: 1.21 [0.58; 2.54]; 0.602; study CORRECT: 1.11 [0.92; 1.33]; 0.263; total: 1.11 [0.93; 1.33]; 0.231 (Institute's calculation from meta-analysis).</p> <p>c: Calculated from meta-analysis.</p> <p>AE: adverse event; BSC: best supportive care; CI: confidence interval; CMH: Cochran-Mantel-Haenszel; HR: hazard ratio; N: number of analysed patients; n: number of patients with (at least one) event; NA: not achieved; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus</p>						

Table 15: Results (dichotomous outcomes), patients with event – RCT, direct comparison: regorafenib + BSC vs. placebo + BSC

Outcome category	Regorafenib + BSC		Placebo + BSC		Regorafenib + BSC vs. placebo + BSC
Outcome	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Study					
Adverse events					
AEs (supplementary information)					
CONCUR	50	50 (100)	25	22 (88)	–
CORRECT	500	498 (99.6)	253	245 (96.8)	–
Discontinuation due to AEs					
CONCUR	50	5 ^a (10 ^b)	25	0 (0)	5.61 [0.32; 97.56]; 0.114 ^c
CORRECT	500	88 (17.6)	253	32 (12.7)	1.39 [0.96; 2.03]; 0.081 ^d
Total					1.42 [0.98; 2.07]; 0.06 ^e
Severe AEs CTCAE grade ≥ 3					
CONCUR				No usable data ^f	
CORRECT	500	390 (78.0)	253	124 (49.0)	1.59 [1.39; 1.82]; < 0.001 ^g
Diarrhoea CTCAE grade 3					
CONCUR				No usable data ^f	
CORRECT	500	41 (8.2)	253	5 (2.0)	4.15 [1.66; 10.37]; < 0.001 ^g
Fatigue CTCAE grade 3					
CONCUR				No usable data ^f	
CORRECT	500	75 (15.0)	253	21 (8.3)	1.81 [1.14; 2.86]; 0.009 ^g
Exanthema CTCAE grade 3					
CONCUR	50	3 (6)	25	0 (0)	3.57 [0.19; 66.52]; 0.256 ^g
CORRECT	500	29 (5.8)	253	1 (0.4)	14.67 [2.01; 107.10]; < 0.001 ^g
Total					9.39 [1.81; 48.60]; 0.008 ^h
Hand-foot syndrome CTCAE grade 3					
CONCUR	50	7 (14)	25	0 (0)	7.65 [0.45; 128.74]; 0.053 ^g
CORRECT	500	83 (16.6)	253	1 (0.4)	42.00 [5.88; 299.93]; < 0.001 ^g
Total					23.91 [4.64; 123.15]; < 0.001 ^h
<p>a: Discrepant information in the dossier; in a different section, 7 patients with event and the corresponding calculations on RR, CI and p-value (CMH test) are provided: 7.65 [0.45; 128.74]; 0.051. The Institute's calculation of the corresponding meta-analysis showed no qualitative difference: 1.82 [0.53; 6.28]; 0.341.</p> <p>b: Institute's calculation.</p> <p>c: Institute's calculation, unconditional exact test (CSZ method according to [7]).</p> <p>d: CMH test.</p> <p>e: Calculated from meta-analysis.</p> <p>f: Due to the heterogeneity, results on these outcomes were only used from the CORRECT study; see Section 2.4.3.</p> <p>g: Institute's calculation of RR, CI (with missing events in one treatment arm with continuity correction of 0.5 in both treatment arms) and p-value (unconditional exact test, CSZ method according to [7]).</p> <p>h: Institute's calculation from meta-analysis.</p> <p>AE: adverse event; BSC: best supportive care; CI: confidence interval; CMH: Cochran-Mantel-Haenszel; CSZ: convexity, symmetry, z score; CTCAE: Common Terminology Criteria for Adverse Events; N: number of analysed patients; n: number of patients with (at least one) event; RCT: randomized controlled trial; RR: relative risk; vs.: versus</p>					

Mortality

Overall survival

Whereas based on the median a numerical difference to the disadvantage of regorafenib was shown for the outcome “overall survival” in the CONCUR study, based on the hazard ratio a numerical difference in favour of regorafenib was shown in this study. The meta-analysis of the studies CONCUR and CORRECT showed a statistically significant result, which deviated only marginally from the result of the CORRECT study alone. Overall, there was a hint of an added benefit of regorafenib + BSC compared with placebo + BSC for the outcome “overall survival”. This deviates from the company’s assessment, which claimed proof of an added benefit.

Morbidity

Symptoms

The company presented no usable data for the outcome “symptoms” (recorded with the symptom scales of the EORTC QLQ-C30). There was no hint of an added benefit of regorafenib + BSC in comparison with placebo + BSC for this outcome; an added benefit is therefore not proven. This deviates from the company, which included data on symptoms in its assessment, but did not derive an added benefit based on these data.

Health status

The meta-analysis of the results on the outcome “health status” (measured with the EQ-5D VAS) showed no statistically significant difference between the treatment groups. This resulted in no hint of an added benefit of regorafenib + BSC in comparison with placebo + BSC for this outcome; an added benefit is therefore not proven. This concurs with the assessment of the company, which allocated this outcome to health-related quality of life, however.

Health-related quality of life

The company presented no usable data for the outcome “health-related quality of life” (measured with the functional scales and the global health status of the EORTC QLQ-C30) in its dossier. This resulted in no hint of an added benefit of regorafenib + BSC in comparison with placebo + BSC for this outcome; an added benefit is therefore not proven. This deviates from the company, which included data on health-related quality of life in its assessment, but did not derive an added benefit based on these data.

Adverse events

Serious adverse events and discontinuation due to adverse events

The meta-analysis of the results on the outcome “SAEs” and on the outcome “discontinuation due to AEs” in each case showed no statistically significant difference between the treatment groups. Hence for these outcomes there was no hint of greater or lesser harm from

regorafenib + BSC in comparison with placebo + BSC; greater or lesser harm is therefore not proven. This concurs with the company's assessment.

Specific AEs CTCAE grade ≥ 3 and specific AEs (diarrhoea, fatigue, exanthema, hand-foot syndrome [each CTCAE grade 3])

Data for the outcome “severe AEs CTCAE grade ≥ 3 ” were available both from the CORRECT study and from the CONCUR study.

The CORRECT study produced a statistically significant result to the disadvantage of regorafenib + BSC in comparison with placebo + BSC for the outcome “severe AEs CTCAE grade ≥ 3 ”. As described in dossier assessment A13-37, this difference was largely due to the patient-relevant severe individual AEs “diarrhoea”, “fatigue”, “exanthema” and “hand-foot syndrome”. In contrast, no diarrhoea or fatigue events classified as severe occurred under regorafenib + BSC in the CONCUR study (see Appendix A of the full dossier assessment). Correspondingly, the results of both studies for diarrhoea and fatigue were heterogeneous; in each case, the heterogeneity test provided a p-value below 0.2 (see Appendix A of the full dossier assessment). Pooling both studies was therefore not meaningful for the events “diarrhoea” and “fatigue”. The results of the CORRECT study, which, in contrast to the CONCUR study, was partly conducted in Europe, were used for the present benefit assessment.

Since the results on the events “diarrhoea” and “fatigue” were included to a relevant degree in the overall rate of severe AEs CTCAE grade ≥ 3 , only the result of the CORRECT study was therefore considered for this outcome. Since only the data from the CORRECT study were used both for the overall rate of severe AEs and for the individual events “diarrhoea” and “fatigue”, the analyses using the relative risk (RR) that had already been used in the first assessment were used for the present benefit assessment.

Overall, there was a hint of greater harm of regorafenib + BSC in comparison with placebo + BSC for the outcome “severe AEs CTCAE grade ≥ 3 ”. This deviates from the company's assessment, which derived proof of greater harm based on the meta-analysis of the results of both studies.

A statistically significant difference to the disadvantage of regorafenib + BSC in comparison with placebo + BSC was shown for the specific AEs “exanthema” and “hand-foot syndrome” on the basis of the corresponding meta-analyses, and for the individual events “diarrhoea” and “fatigue” (in each case CTCAE grade 3) on the basis of the CORRECT study. This resulted in a hint of greater harm of regorafenib + BSC compared with placebo + BSC for these outcomes. The assessments on the 4 specific AEs “diarrhoea”, “fatigue”, “exanthema” and “hand-foot syndrome” (in each case CTCAE grade 3) deviate from the company's approach, which did not use these outcomes for its benefit assessment.

2.4.4 Subgroups and other effect modifiers

No subgroup analyses on the CONCUR study were used (see Section 2.7.2.4.3 of the full dossier assessment). Subgroup results on the CORRECT study are presented in dossier assessment A13-37 [3]. These had no consequence for the overall conclusion on the added benefit.

2.5 Extent and probability of added benefit

The derivation of extent and probability of added benefit is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.5.1 Assessment of added benefit at outcome level

Based on the data presented in Section 2.4, there is a hint of an added benefit of regorafenib for the outcome “overall survival”. A hint of greater harm of regorafenib was shown for the outcome “AEs CTCAE grade ≥ 3 ” and the included outcomes “diarrhoea”, “fatigue”, “exanthema” and “hand-foot syndrome” (in each case CTCAE grade 3). The company presented non usable data for the outcomes “symptoms” and “health-related quality of life”, although this would have been possible for the company.

The extent of the respective added benefit at outcome level was estimated from these results (see Table 16).

Table 16: Extent of added benefit at outcome level: regorafenib + BSC vs. placebo + BSC

Outcome category Outcome	Regorafenib + BSC vs. placebo + BSC Median time to event or proportion of patients with event or mean change Effect estimate [95% CI] p-value Probability^a	Derivation of extent^b
Mortality		
Overall survival	Median: 183 to 194 vs. 152 to 203 days ^c HR: 0.78 [0.66; 0.92] p = 0.003 probability: “hint”	Outcome category: mortality $0.85 \leq CI_u < 0.95$ added benefit, extent “considerable”
Morbidity		
Symptoms (symptom scales of the EORTC QLQ- C30)	No usable data	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)	LS mean: -4.94 to -2.52 vs. -4.38 to -2.19 ^c Hedges' g: -0.04 [-0.19; 0.11] p = 0.62	Lesser benefit/added benefit not proven
Health-related quality of life		
Functional scales and global health status of the EORTC QLQ-C30	No usable data	Lesser benefit/added benefit not proven
Adverse events		
SAEs	Median: 139 to 429 ^c vs. 109 days and NA ^d HR: 0.92 [0.73; 1.17]; p = 0.50	Greater/lesser harm not proven
Discontinuation due to AEs	Proportion: 10% to 17.6% vs. 0% to 12.7% ^c RR: 1.42 [0.98; 2.07]; p = 0.06	Greater/lesser harm not proven

(continued)

Table 16: Extent of added benefit at outcome level: regorafenib + BSC vs. placebo + BSC (continued)

Outcome category Outcome	Regorafenib + BSC vs. placebo + BSC Median time to event or proportion of patients with event or mean change Effect estimate [95% CI] p-value Probability ^a	Derivation of extent ^b
Severe AEs CTCAE grade $\geq 3^c$	Proportion: 78.0% vs. 49.0% RR: 1.59 [1.39; 1.82] RR ^f : 0.63 [0.55; 0.72] p < 0.001 probability: “hint”	Outcome category: serious/severe adverse events CI _u < 0.75, risk $\geq 5\%$ greater harm, extent: “major”
Diarrhoea CTCAE grade 3^c	Proportion: 8.2% vs. 2.0% RR: 4.15 [1.66; 10.37] RR ^f : 0.24 [0.10; 0.60] p < 0.001 probability: “hint”	Outcome category: serious/severe adverse events CI _u < 0.75, risk $\geq 5\%$ greater harm, extent: “major”
Fatigue CTCAE grade 3^c	Proportion: 15.0% vs. 8.3% RR: 1.81 [1.14; 2.86] RR ^f : 0.55 [0.35; 0.88] p-value = 0.009 probability: “hint”	Outcome category: serious/severe adverse events 0.75 \leq CI _u < 0.90 greater harm, extent: “considerable”
Exanthema CTCAE grade 3	Proportion: 5.8% to 6% vs. 0% to 0.4% ^c RR: 9.39 [1.81; 48.60] RR ^f : 0.11 [0.02; 0.55] p = 0.008 probability: “hint”	Outcome category: serious/severe adverse events CI _u < 0.75, risk $\geq 5\%$ greater harm, extent: “major”
Hand-foot syndrome CTCAE grade 3	Proportion: 14% to 16.6% vs. 0% to 0.4% ^c RR: 23.91 [4.64; 123.15] RR ^f : 0.04 [0.01; 0.22] p < 0.001 probability: “hint”	Outcome category: serious/severe adverse events CI _u < 0.75, risk $\geq 5\%$ greater harm, extent: “major”
<p>a: Probability provided if statistically significant differences are present.</p> <p>b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.</p> <p>c: Minimum and maximum time to event or proportions of patients with event or mean changes per treatment arm in the studies included.</p> <p>d: The median time to event was not achieved in the CONCUR study.</p> <p>e: Data of the CONCUR study were not used for the derivation of the added benefit.</p> <p>f: Institute’s calculation: reversed direction of effect to enable use of limits to derive the extent of the added benefit.</p> <p>AE: adverse event; BSC: best supportive care; CI: confidence interval; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; LS: least square; NA: not achieved; QLQ-C30: Quality of Life Questionnaire Core-30; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus</p>		

2.5.2 Overall conclusion on added benefit

Table 17 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 17: Positive and negative effects from the assessment of regorafenib + BSC compared with placebo + BSC

Positive effects	Negative effects
<ul style="list-style-type: none"> Hint of an added benefit - extent: “considerable” (mortality: overall survival) 	<ul style="list-style-type: none"> Hint of greater harm – extent: “major” (severe/serious AEs: severe AEs CTCAE grade ≥ 3; including diarrhoea, exanthema, hand-foot syndrome, in each case CTCAE grade 3 – extent: “major”, fatigue CTCAE grade 3 – extent: “considerable”)
AE: adverse event; BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events	

The data presented by the company resulted in no qualitative change of the available data in comparison with the first assessment of regorafenib (see dossier assessment A13-37). Hence the assessment of the added benefit has not changed either. The assessment was:

In the overall assessment, there are positive and negative effects of equal certainty of results (hint).

On the positive side, there is an added benefit in the category “mortality” with the extent “considerable”. On the negative side, there is greater harm up to the extent “major” in the category “severe/serious AEs” (severe AEs CTCAE grade ≥ 3 , including CTCAE grade 3 diarrhoea, exanthema and hand-foot syndrome with the extent “major” as well as fatigue with the extent “considerable”). Even though the extent is “major” for severe/serious AEs, this does not completely outweigh the mortality advantage of regorafenib.

Overall, there is a hint of a minor added benefit of regorafenib versus the ACT BSC for patients with MCRC.

The result of the assessment of the added benefit of regorafenib in comparison with the ACT is summarized in Table 18.

Table 18: Regorafenib: extent and probability of added benefit

Therapeutic indication	ACT ^a	Extent and probability of added benefit
Treatment of adult patients with MCRC who have been previously treated with, or are not considered candidates for, available therapies. These include fluoropyrimidine-based chemotherapy, an anti-VEGF therapy, and an anti-EGFR therapy.	BSC	Hint of minor added benefit
a: Presentation of the appropriate comparator therapy specified by the G-BA. ACT: appropriate comparator therapy; BSC: best supportive care; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; MCRC: metastatic colorectal cancer; VEGF: vascular endothelial growth factor		

This deviates from the company's approach, which derived proof of a considerable added benefit.

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

Supplementary information on the implementation of the conditions of the limitation

The G-BA's justification on the first assessment of regorafenib included the following statement [8]:

“For the new benefit assessment after expiry of the resolution, data must be presented that have been recorded in a clinical study using patient-relevant outcomes on mortality, morbidity, health-related quality of life and on adverse events and that, regarding the evidence for the added benefit of regorafenib provided so far, also allow conclusions on disease-specific morbidity and quality of life besides mortality and adverse events. The study population must sufficiently concur with the actual health care setting in Germany, which particularly requires inclusion of patients with a baseline ECOG Performance Status of 2 or higher.”

The company did not adhere to these requirements in the present dossier. For disease-specific morbidity (symptoms) and health-related quality of life, the company presented inadequate analyses disregarding the manual of the questionnaire used (EORTC QLQ-C30), although it had considered the requirements of the manual for the analyses in the first dossier. In addition, it presented no studies including patients with ECOG PS 2 or higher.

2.6 List of included studies

CONCUR

Bayer. Asian subjects with metastatic colorectal cancer treated with regorafenib or placebo after failure of standard therapy (CONCUR): full text view [online]. In: ClinicalTrials.gov. 28 May 2015 [accessed: 10 July 2015]. URL: <https://clinicaltrials.gov/ct2/show/NCT01584830>.

Bayer HealthCare. IND 75,642 / BAY 73-4506 / regorafenib: pre-sNDA meeting information package [unpublished]. 2014.

Bayer HealthCare. A randomized, double-blind, placebo-controlled phase III study of regorafenib plus best supportive care (BSC) versus placebo plus BSC in Asian subjects with metastatic colorectal cancer (CRC) who have progressed after standard therapy (CONCUR): study 15808; integrated clinical study protocol; version 2.0 [unpublished]. 2012.

Bayer HealthCare. A randomized, double-blind, placebo-controlled phase III study of regorafenib plus best supportive care (BSC) versus placebo plus BSC in Asian subjects with metastatic colorectal cancer (CRC) who have progressed after standard therapy (CONCUR): study 15808; clinical study report [unpublished]. 2014.

Bayer HealthCare. A randomized, double-blind, placebo-controlled phase III study of regorafenib plus best supportive care (BSC) versus placebo plus BSC in Asian subjects with metastatic colorectal cancer (CRC) who have progressed after standard therapy (CONCUR): study 15808; statistical analysis plan [unpublished]. 2014. (Band Protocol No.: BAY No. 73-4506/15808).

Schwenke Consulting: Strategies and Solutions in Statistics. Regorafenib (Stivarga): Analysen zu Modul 4A [unpublished]. 2015.

CORRECT

Bayer. Patients with metastatic colorectal cancer treated with regorafenib or placebo after failure of standard therapy: full text view [online]. In: ClinicalTrials.gov. 28 May 2015 [accessed: 8 December 2015]. URL: <https://clinicaltrials.gov/ct2/show/NCT01103323>.

Bayer. Patients with metastatic colorectal cancer treated with regorafenib or placebo after failure of standard therapy: study results [online]. In: ClinicalTrials.gov. 28 May 2015 [accessed: 8 December 2015]. URL: <https://clinicaltrials.gov/ct2/show/results/NCT01103323>.

Bayer HealthCare. A randomized, double-blind, placebo-controlled phase III study of regorafenib plus BSC versus placebo plus BSC in patients with metastatic colorectal cancer (CRC) who have progressed after standard therapy. Patients with metastatic colorectal cancer treated with regorafenib or placebo after failure of standard therapy (CORRECT): study 14387; statistical analysis plan; supplement 01/TLF; specification document [unpublished]. 2012.

Bayer HealthCare. A randomized, double-blind, placebo-controlled phase III study of regorafenib plus BSC versus placebo plus BSC in patients with metastatic colorectal cancer (CRC) who have progressed after standard therapy: study 14387; clinical study report [unpublished]. 2012.

Bayer HealthCare. A randomized, double-blind, placebo-controlled phase III study of regorafenib plus BSC versus placebo plus BSC in patients with metastatic colorectal cancer (CRC) who have progressed after standard therapy: study 14387; statistical analysis plan; amendment 01 [unpublished]. 2011.

Bayer HealthCare. A randomized, double-blind, placebo-controlled phase III study of regorafenib plus BSC versus placebo plus BSC in patients with metastatic colorectal cancer (CRC) who have progressed after standard therapy; study 14387; integrated clinical study protocol; version 4.0 [unpublished]. 2011.

Bayer HealthCare. Study 14387: clinical study report; 14.2 descriptive OS update based on 13Nov2011 data cutoff [unpublished]. 2012.

Bayer HealthCare. Study 14387: clinical study report; 16.1.9.2 ad-hoc Germany reimbursement statistical analysis [unpublished]. 2011.

Bayer HealthCare. Study 14387: clinical study report; 16.1.9.2 Germany reimbursement statistical analysis 2 [unpublished]. 2011.

Bayer HealthCare. Study 14387: clinical study report; 16.1.9.2 Germany reimbursement statistical analysis 3 [unpublished]. 2011.

Bayer HealthCare. Study 14387: clinical study report; 16.1.9.2 OS update2 based on 13Nov2011 data cutoff [unpublished]. 2011.

Bayer HealthCare. Study 14387: odds ratios for safety endpoints [unpublished]. 2011.

Schwenke Consulting: Strategies and Solutions in Statistics. Regorafenib (Stivarga): Analysen zu Modul 4A [unpublished]. 2015.

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Please see full dossier assessment for full reference list.

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The full report (German version) is published under <https://www.iqwig.de/de/projekte-ergebnisse/projekte/arzneimittelbewertung/a15-43-regorafenib-nutzenbewertung-gemaess-35a-sgb-v.7046.html>.