IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Regorafenib – Benefit assessment according to §35a Social Code Book V[1]

Extract

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSC	best supportive care
CORRECT	colorectal cancer treated with regorafenib or placebo after failure of standard therapy
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EGFR	epidermal growth factor
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-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
ORR	objective response rate
PFS	progression-free survival
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
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 2013.

Research question

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

The G-BA specified BSC as ACT. The company concurred with this specification in the dossier.

The assessment was based on patient-relevant outcomes. One direct comparative randomized controlled trial (RCT) was included in the assessment.

Results

One direct comparative study (CORRECT) was available for the present research question. This is a multinational, randomized, parallel, placebo-controlled, double-blind phase 3 study comparing regorafenib + BSC with placebo + BSC. BSC comprised any drug or non-drug treatment to alleviate symptoms and improve quality of life. Other investigational or approved anti-tumour treatments were excluded.

760 adult patients with histologically or cytologically confirmed metastatic adenocarcinoma (stage 4) of the colon or rectum were enrolled in the study. Patients were required to have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1 at the start of the study.

Three data cut-offs were performed during the study. The first data cut-off was planned after 175 deaths and served as a futility analysis[4]. The second data cut-off was planned after 408 deaths. A futility analysis was performed again, and efficacy and safety were analysed. This

[4] The company called this a "check for futility". 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.

data cut-off was done on 21 July 2011 and was based on 432 deceased patients. Because the results on overall survival were in favour of regorafenib + BSC (meeting the primary outcome), the study was discontinued, and patients who had not yet progressed were offered to cross over to regorafenib treatment. The third data cut-off, which had not been planned a priori, was conducted on 13 November 2011, immediately before the start of the crossover. This data cut-off was agreed upon with the regulatory authorities and served as additional analysis of overall survival. It was based on 566 deceased patients. A final analysis was originally planned after 582 deaths.

The median treatment duration was 7.3 weeks in the regorafenib arm, and 7.0 weeks in the placebo arm. No data were available for the observation duration.

Overall survival was recorded as patient-relevant primary outcome. Further patient-relevant outcomes were morbidity (symptoms), health-related quality of life and adverse events (AEs).

After the end of the study treatment, between 25 and 30% of the patients received further systemic anti-tumour treatments in the follow-up phase. There were no important differences between the treatment arms.

The risk of bias at study level was rated as low. The risk of bias for the outcome “overall survival” and for the outcomes regarding harm was also rated as low. There were no evaluable data for the outcomes “morbidity” and “health-related quality of life”. Therefore no outcome-specific assessment of the risk of bias was conducted for these outcomes.

For the CORRECT study, several reasons led to an uncertainty, which weakened the informative value of the results. The main reason for this uncertainty was that it remained unclear 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. According to the approval, patients with a higher ECOG PS are not excluded from treatment. Patients with an ECOG PS > 1 are not uncommon in every-day clinical health care, however. Overall, the reliability of the conclusions is reduced so that not more than “hints” can be derived from the CORRECT study.

Mortality

In the data cut-offs on 21 July 2011 and 13 November 2011, treatment with regorafenib + BSC resulted in a statistically significant prolongation of overall survival in comparison with placebo + BSC. There is therefore a hint of an added benefit of regorafenib + BSC compared with the ACT BSC.

For the outcome “overall survival”, there was an indication of an effect modification for the characteristic “primary site of disease (colon/rectum)” at the data cut-off on 21 July 2011. There was no effect modification on the later data cut-off date (13 November 2011) anymore.

Overall, these results were not considered further in the benefit assessment because of the inconsistent picture they provide.

Morbidity

The symptoms were recorded using the symptom scales of the disease-specific instrument European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30). The data presented in the dossier were not evaluable, however, because, at the end of the treatment, data were only available for a small part of the patients (fewer than 70% of the randomized patients). For the most part, the low response rate cannot be explained by the death of the patients. An added benefit of regorafenib + BSC in comparison with the ACT BSC for morbidity is therefore not proven.

Health-related quality of life

Health-related quality of life was recorded using the functional scales of the disease-specific instrument EORTC QLQ-C30 and using the European Quality of Life-5 Dimensions (EQ-5D). The data presented in the dossier were not evaluable, however, because, at the end of the treatment, data were only available for a small part of the patients (fewer than 70% of the randomized patients). For the most part, the low response rate here can also not be explained by the death of the patients. An added benefit of regorafenib + BSC in comparison with the ACT BSC for health-related quality of life is therefore not proven.

Adverse events

Serious adverse events and treatment discontinuations due to adverse events

The overall rates of serious adverse events (SAEs) and treatment discontinuations due to AEs were not statistically significantly different between regorafenib + BSC and placebo + BSC. Lesser or greater harm from regorafenib + BSC than from BSC is not proven for these outcomes.

Severe adverse events (CTCAE grade 3, 4 and 5)

Severe AEs of Common Terminology Criteria for Adverse Events (CTCAE) grade 4 and 5 were not statistically significantly different between the treatment arms. In contrast, severe AEs of CTCAE grade 3 were more common in patients treated with regorafenib + BSC than in patients treated with placebo + BSC. The difference between the treatment groups was statistically significant. The biggest differences between the treatment groups (≥ 5%) occurred in the following individual events: hypertension, fatigue, diarrhoea, hand-foot syndrome and exanthema. At least fatigue, diarrhoea, hand-foot syndrome and exanthema are to be categorized as severe AEs because of the respective definition of the severity grade 3 according to the CTCAE. Hence the difference between the treatment groups in AEs of CTCAE grade 3 is largely caused by patient-relevant individual severe AEs. Overall, there is a hint of greater harm from regorafenib + BSC compared with the ACT BSC for this outcome.

For the outcome "severe AEs of CTCAE grade 3" there was an indication of an effect modification for the characteristic "age" (< 65 years/≥ 65 years) and for the characteristic "ethnicity" (white/Asian). However, the statistically significant effects were not opposite in the subgroups and in each case had the same extent ("major") as in the total population. These results were therefore not considered further in the benefit assessment.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[5]

On the basis of the results presented, the extent and probability of the added benefit of the drug regorafenib compared with the ACT BSC 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 with the extent "major" in the category "severe AEs" (severe AEs of CTCAE grade 3). Even though the extent is "major" for severe AEs, this does not completely outweigh the mortality advantage of regorafenib.

Overall, there is a hint of a minor added benefit of regorafenib + BSC versus the ACT.

The result of the assessment of the added benefit of regorafenib in comparison with the ACT is summarized in Table 2.

Table 2: Regorafenib: extent and probability of added benefit

Therapeutic indication	ACT	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 a minor added benefit
ACT: appropriate comparator therapy; BSC: best supportive care; EGFR: endothelial growth factor receptor; MCRC: metastatic colorectal cancer; VEGF: vascular endothelial growth factor		

[5] 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), see [1]. 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), see [2].

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

2.2 Research question

The aim of this report is 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. This means the best possible supportive therapy, optimized for the individual patient, for alleviation of symptoms and improvement in the quality of life.

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

The assessment was conducted based on patient-relevant outcomes and on RCTs.

Further information about the research question can be found in Module 3, Section 3.1, and Module 4, Section 4.2.1 of the dossier, and in Sections 2.7.1 and 2.7.2.1 of the full dossier assessment.

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 (studies completed up to 26 August 2013)
- bibliographical literature search on regorafenib (last search on 14 October 2013)
- search in trial registries for studies on regorafenib (last search on 13 August 2013)

The Institute's own search to check the completeness of the study pool:

- bibliographical literature search on regorafenib (last search on 18 October 2013)
- search in trial registries for studies on regorafenib (last search on 18 October 2013)

This check produced no deviations from the study pool presented in the dossier.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier, and in Sections 2.7.2.1 and 2.7.2.3 of the full dossier assessment.

2.3.1 Studies included

The study listed in Table 3 was 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)
CORRECT	Yes	Yes	No
a: Study for which the company was sponsor, or in which the company was otherwise financially involved.			

Section 2.6 contains a reference list for the study included.

Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4, Sections 4.3.1.1 and 4.3.2.1.1 of the dossier and in Sections 2.7.2.3.1 and 2.7.2.3.2 of the full dossier assessment.

2.3.2 Study characteristics

Table 4 and Table 5 show the characteristics of the CORRECT study and of the interventions investigated in this study.

Table 4: Characteristics of the study 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]
CORRECT	RCT, double-blind, placebo-controlled, parallel, multicentre	Adult patients with MCRC (adenocarcinoma, stage 4) with progression during treatment with approved standard treatments[b]	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: 7.3 weeks; placebo + BSC: 7.0 weeks) Observation period: monthly follow-up after cessation of study treatment until death (mean/average observation duration: ND)	105 centres in Asia, Australia, North America, Eastern Europe and Western Europe Study start 4/2010 – ongoing First data cut-off after 175 deaths for futility analysis[c] Second data cut-off 7/2011 (408 deaths), futility analysis, efficacy and safety analysis Third data cut-off 11/2011, as part of the approval process, analysis on OS before start of crossover	Primary: OS Secondary: morbidity (symptoms), health-related quality of life, AEs

a: Primary outcomes contain information without consideration of its relevance for the present benefit assessment. Secondary outcomes contain exclusively information on relevant available outcomes for the present benefit assessment.
b: Standard treatments included fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab and – if KRAS wild type – cetuximab or panitumumab.
c: The company called this a "check for futility". 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.

AE: adverse event; BSC: best supportive care; KRAS: Kirsten rat sarcoma viral oncogene homologue; MCRC: metastatic colorectal cancer: N: number of randomized patients; ND: no data; 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
CORRECT	▪ Regorafenib 160 mg (4 x 40 mg tablets) once daily for 3 weeks followed by 1 week off treatment ▪ BSC	▪ Placebo 4 tablets once daily for 3 weeks followed by 1 week off treatment ▪ BSC
	BSC included 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. Other investigational or approved anti-tumour drug treatments such as cytostatics, signal transduction inhibitors, immunotherapy, hormonal therapy and other tyrosine-kinase inhibitors were excluded.	
BSC: best supportive care; RCT: randomized controlled trial; vs.: versus		

The CORRECT study (colorectal cancer treated with regorafenib or placebo after failure of standard therapy) included by the company is a multinational, randomized, parallel, double-blind phase 3 approval study of regorafenib. Regorafenib + BSC was compared with placebo + BSC. Adult patients with histologically or cytologically confirmed metastatic adenocarcinoma (stage 4) of the colon or rectum were enrolled. These patients were required to have disease progression during or within 3 months after the last standard treatment (see Table 4 for information on standard treatment). Patients who had progressed during or within 6 months after oxaliplatin-based treatment were to be retreated with oxaliplatin-based treatment to be eligible for enrolment. Patients were required to have an ECOG PS of 0 or 1 at the start of the study. Their life expectancy was to be at least 3 months.

A total of 760 patients were randomly assigned in a ratio of 2:1, either to a treatment with regorafenib + BSC (505 patients) or to a treatment with placebo + BSC (255 patients). The patients were stratified by previous anti-VEGF treatment, time from diagnosis of metastatic disease and geographic region.

Three data cut-offs were performed during the study. The first data cut-off was planned after 175 deaths and served as a futility analysis[6]. The second data cut-off was planned after 408 deaths. A futility analysis was performed again, and efficacy and safety were analysed. This data cut-off was done on 21 July 2011 and was based on 432 deceased patients. Because the results on overall survival were in favour of regorafenib + BSC (meeting the primary outcome), the study was discontinued, and patients who had not yet progressed were offered to cross over to regorafenib treatment. The third data cut-off, which had not been planned a priori, was conducted on 13 November 2011, immediately before the start of the crossover.

[6] The company called this a "check for futility". 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.

This data cut-off was agreed upon with the regulatory authorities and served as additional analysis of overall survival. It was based on 566 deceased patients. A final analysis was originally planned after 582 deaths.

The drug regorafenib was administered according to its approval (160 mg regorafenib [4 x 40 mg tablets] once daily). Patients in the placebo arms took 4 matching tablets a day. Regorafenib and placebo were each taken for 3 weeks, followed by 1 week off therapy to make up 1 cycle. The patients additionally received BSC to alleviate symptoms and improve quality of life. BSC comprised any drug or non-drug treatment. Other investigational or approved anti-tumour treatments were excluded.

Treatment with regorafenib or placebo was continued until the occurrence of either disease progression, death or the doctor's and patient's decision.

Overall survival was recorded as patient-relevant primary outcome. Further patient-relevant outcomes were morbidity (symptoms), health-related quality of life and AEs.

The median treatment duration was 7.3 weeks in the regorafenib arm, and 7.0 weeks in the placebo arm. AEs were recorded up to 30 days after the last administration of study medication. Overall survival was recorded monthly. No data were available for the observation duration.

After the end of the study treatment, between 25 and 30% of the patients received further systemic anti-tumour treatments in the follow-up phase. There were no important differences between the treatment arms (see Table 22 in Appendix A of the full dossier assessment). Because of the palliative goal of the BSC treatment, it remained unclear whether the anti-tumour treatments excluded from the BSC (see above) might have relieved symptoms and thus could have been part of the BSC.

Table 6 shows the characteristics of the patients in the study included.

Table 6: Characteristics of the study populations – RCT, direct comparison: regorafenib + BSC vs. placebo + BSC

Study Characteristics Category	**Regorafenib + BSC N = 505**	**Placebo + BSC N = 255**
CORRECT		
Age [years]: mean (SD)	61 (10)	60 (10)
Sex: [f/m] %	38/62	40/60
Region, n (%)		
North America, Western Europe, Israel, Australia	420 (83.2)	212 (83.1)
Asia	69 (13.7)	35 (13.7)
South America[a], Turkey[a], Eastern Europe	16 (3.2)	8 (3.1)
Ethnicity, n (%)		
White	392 (77.6)	201 (78.8)
Black	6 (1.2)	8 (3.1)
Asian	76 (15.0)	35 (13.7)
Native Americans or Native Alaskans	1 (0.2)	1 (0.4)
Not specified	29 (5.7)	10 (3.9)
Multiple	1 (0.2)	0 (0)
Disease duration: time from first diagnosis of metastatic disease to randomization [weeks], mean (SD)	151.7 (93.7)	150.3 (89.2)
ECOG PS, n (%)		
0	265 (52.5)	146 (57.3)
1	240 (47.5)	109 (42.7)
Primary site of disease, n (%)		
Colon	323 (64.0)	172 (67.5)
Rectum	151 (29.9)	69 (27.1)
Colon and rectum	30 (5.9)	14 (5.5)
Not specified	1 (0.2)	0 (0)
KRAS mutation, n (%)		
No	205 (40.6)	94 (36.9)
Yes	273 (54.1)	157 (61.6)
Unknown	27 (5.3)	4 (1.6)
Treatment discontinuations[b], n (%)	448[c] (88.7)	244 (95.7)

a: No patients were randomized in the centres in South America and Turkey.
b: Out of this, 336 (75.0%) of the patients in the regorafenib arm and 205 (84.0%) of the patients in the placebo 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".
c: The number of patients originates from the study documents. There is a discrepancy to the information in Module 4 of the dossier, where 488 patients are cited.

BSC: best supportive care; ECOG PS: Eastern Cooperative Oncology Group Performance Status; f: female; KRAS: Kirsten rat sarcoma viral oncogene homologue; m: male; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The characteristics were balanced between the study arms. The mean age of patients was about 60 years and the metastatic disease had been diagnosed for about 3 years on average. About 40% of patients were women. The majority of the patients came from Western countries and were therefore white. Approximately 55% of the patients had an ECOG PS of 0, the remaining 45% had an ECOG PS of 1. In about 2 thirds of the patients, the primary tumour was located in the colon. A little more than half of the patients had a mutation of the Kirsten rat sarcoma viral oncogene homologue (KRAS) gene.

The overall rate of patients who discontinued treatment permanently was about 89% in the regorafenib arm and about 96% in the placebo arm. These numbers also include patients who discontinued treatment due to disease progression (75% in the regorafenib arm and 84% in the placebo arm).

Although according to the approval, treatment with regorafenib, in principle, also is an option for patients with other tumour types of colorectal cancer (such as neuroendocrine tumours or sarcomas), the CORRECT study only included patients with adenocarcinomas. With more than 95%, this tumour type constitutes the vast majority of colorectal cancers.

Table 7 shows the risk of bias at study level.

Table 7: 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			
CORRECT	Yes	Yes	Yes	Yes	Yes	Yes	Low

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

Overall assessment of the reliability of the conclusions

For the CORRECT study, several reasons led to an uncertainty, which weakened the informative value of the results (see Section 2.7.2.4.1 of the full dossier assessment). The main reason for this uncertainty was that it remained unclear 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, the reliability of the conclusions is reduced so that not more than "hints" can be

derived from the CORRECT study. This deviates from the company's assessment, which derived proof from the study.

Further information on study design, study populations and the risk of bias at study level can be found in Module 4, Sections 4.3.1.2.1, 4.3.1.2.2 and 4.3.2.1.2, and in Appendix 4-G of the dossier, and in Sections 2.7.2.4.1 and 2.7.2.4.2 of the full dossier assessment.

2.4 Results on added benefit

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

- mortality (overall survival)
- adverse events
  - SAEs
  - treatment discontinuation due to AEs
  - severe AEs (CTCAE grade 3, 4 and 5)

Morbidity (measured using the symptom scales of the disease-specific instrument EORTC QLQ-C30) and health-related quality of life (measured using the functional scales of the disease-specific instrument EORTC QLQ-C30 and using the EQ-5D) were to be investigated and included in the present benefit assessment. However, no interpretable data were available.

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in Module 4 (see Section 2.7.2.4.3 of the full dossier assessment). These outcomes included progression-free survival (PFS) as combined outcome for mortality/morbidity, as well as objective response rate (ORR), disease control rate (DCR) and duration of tumour stabilization as morbidity outcomes. Moreover, in contrast to the company, non-severe AEs (CTCAE grade 1 and 2) and AEs that led to dose modifications were not included in the present benefit assessment. For the assessment of morbidity, the EORTC QLQ-C30 symptom scales were considered relevant; for the assessment of health-related quality of life, the EQ-5D was also considered relevant.

Table 8 shows for which outcomes data were available in the study included. Table 9 shows the risk of bias for these outcomes.

Table 8: Matrix of outcomes – RCT, direct comparison: regorafenib + BSC vs. placebo + BSC

Study	Outcomes							
	All-cause mortality	Morbidity[a]	Health-related quality of life[b]	SAEs	Discontinuation due to AEs	Severe AEs CTCAE grade 3	Severe AEs CTCAE grade 4	Severe AEs (CTCAE grade 5)
CORRECT	Yes	No[c]	No[c]	Yes	Yes	Yes	Yes	Yes

a: Measured with the symptom scales of the disease-specific instrument EORTC QLQ-C30.
b: Measured with the functional scales of EORTC QLQ-C30 and with EQ-5D.
c: No evaluable data available. Only analysis without imputation of missing values available, the proportion of patients not considered in the analysis was > 30%.

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-Core 30; EQ-5D: European Quality of Life-5 Dimensions; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

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

Study		Outcomes							
	Study level	All-cause mortality	Morbidity[a]	Health-related quality of life[b]	SAEs	Discontinuation due to AEs	Severe AEs CTCAE grade 3	Severe AEs CTCAE grade 4	Severe AEs (CTCAE grade 5)
CORRECT	L	L	-[c]	-[c]	L	L	L	L	L

a: Measured with the symptom scales of the disease-specific instrument EORTC QLQ-C30.
b: Measured with the functional scales of EORTC QLQ-C30 and with EQ-5D.
c: No evaluable data available. Only analysis without imputation of missing values available, the proportion of patients not considered in the analysis was > 30%.

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-Core 30; EQ-5D: European Quality of Life-5 Dimensions; L: low; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

The risk of bias for the outcome "overall survival" was rated as low. The risk of bias was also rated as low for the outcomes on AEs. This concurs with the company's assessments.

The dossier contained no evaluable data on the outcomes "morbidity" and "health-related quality of life". Therefore no outcome-specific assessment of the risk of bias was conducted.

Further information on the choice of outcomes and risk of bias at outcome level can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3 and 4.3.2.1.3 of the dossier, and in Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment.

Table 10 shows the results on overall survival. Figure 1 and Figure 2 show the Kaplan-Meier curves for overall survival at the data cut-off on 21 July 2011 and at the data cut-off on 13 November 2011.

The company used a 1-tailed log-rank test with the probability level of 0.025 for the comparison between the treatments for results of overall survival. Since, in the context of this assessment, a 2-tailed research question was posed, a 2-tailed test with the probability level of 0.05 was used (see Section 2.7.2.4.3 of the full dossier assessment).

Table 10: Results on overall survival, morbidity and health-related quality of life – RCT, direct comparison: regorafenib + BSC vs. placebo + BSC

Study **Outcome**	**Regorafenib + BSC**		**Placebo + BSC**		**Regorafenib + BSC vs. placebo + BSC**	
Data cut-off	**N**	**Median survival time in days [95% CI]**	**N**	**Median survival time in days [95% CI]**	**HR[a] [95% CI]**	**p-value[b]**
CORRECT						
Overall survival						
Data cut-off 21 July 2011	505	196 [178; 222]	255	151 [134; 177]	0.77 [0.64; 0.94]	0.011
Data cut-off 13 November 2011	505	194 [177; 214]	255	152 [134; 178]	0.79 [0.66; 0.94]	0.008
Morbidity		No evaluable data[c]				
Health-related quality of life		No evaluable data[c]				

a: adjusted according to prior anti-VEGF therapies, time since diagnosis of the metastatic disease and geographic region.
b: Institute's calculation; Wald test.
c: No evaluable data available. Only analysis without imputation of missing values available, the proportion of patients not considered in the analysis was > 30%.

BSC: best supportive care; CI: confidence interval; HR: Hazard Ratio; N: number of analysed patients; RCT: randomized controlled trial; VEGF: vascular endothelial growth factor; vs.: versus

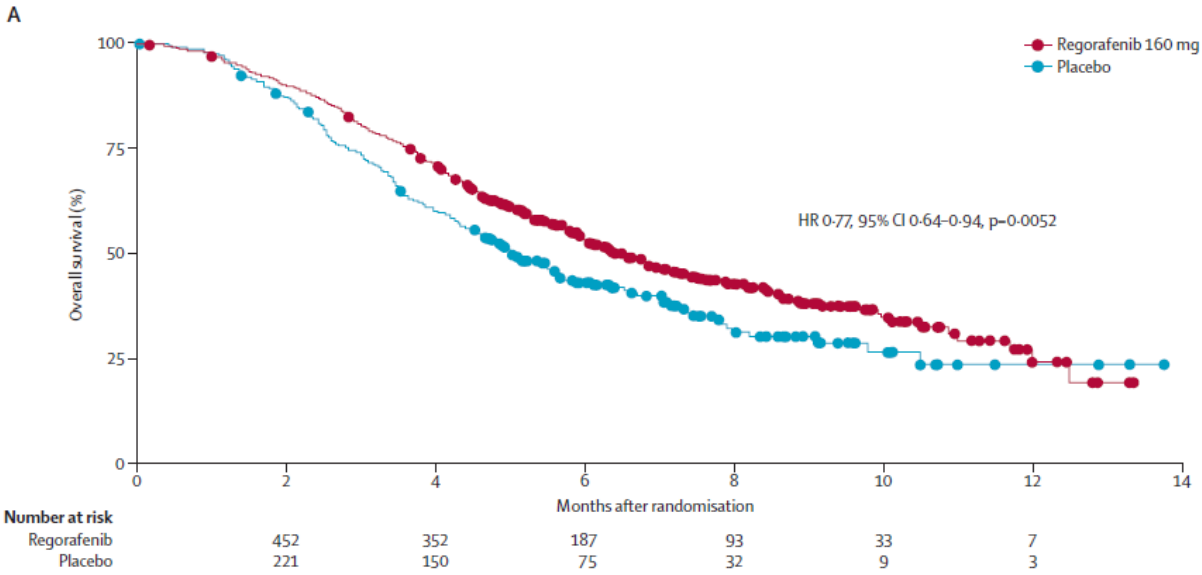

Figure 1: Kaplan-Meier curve for overall survival (data cut-off 21 July 2011) – RCT, direct comparison: regorafenib + BSC versus placebo + BSC

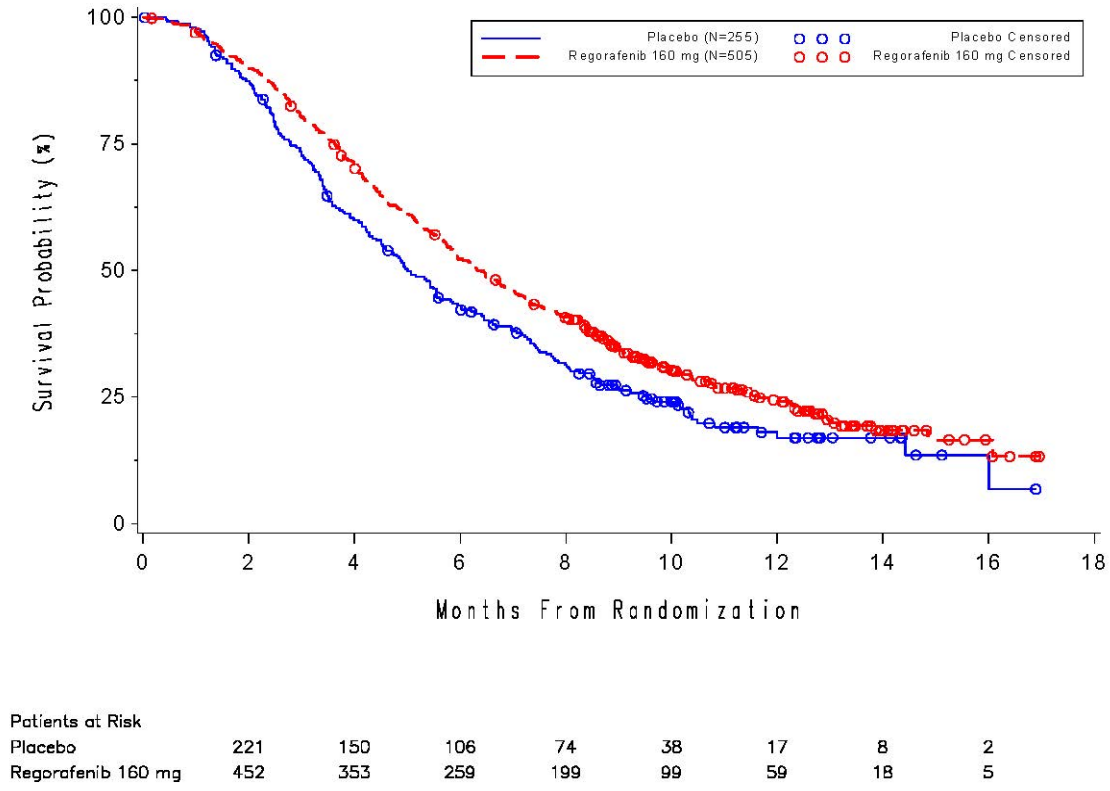

Figure 2: Kaplan-Meier curve for overall survival (data cut-off 13 November 2011) – RCT, direct comparison: regorafenib + BSC versus placebo + BSC

Table 11 summarizes the results on AEs. Table 12 contains additional information on the most common severe AEs of CTCAE grade 3 that occurred in at least 2% of the patients in one treatment arm. The data from the company's dossier were supplemented, where necessary, by the Institute's own calculations.

Table 11: Results on AEs – RCT, direct comparison: regorafenib + BSC vs. placebo + BSC

Study **Outcome category** **Outcome** *Data cut-off 21 July 2011*	**Regorafenib + BSC**		**Placebo + BSC**		**Regorafenib + BSC vs. placebo + BSC**
	N	**Patients with events n (%)**	**N**	**Patients with events n (%)**	**RR [95% CI]; p-value[a]**
CORRECT					
Adverse events					
Total	500	498 (100)	253	245 (97)	
Serious adverse events					
Total	500	219 (43.8)	253	100 (39.5)	1.11 [0.92; 1.33]; 0.269
Treatment discontinuations due to adverse events					
Total	500	88 (17.6)	253	32 (12.6)	1.39 [0.96; 2.03]; 0.081
Severe adverse events					
CTCAE grade 3					
Total	500	280 (56.0)	253	67 (26.5)	2.11 [1.70; 2.63]; < 0.001
CTCAE grade 4					
Total	500	43 (8.6)	253	20 (7.9)	1.09 [0.65; 1.81]; 0.766
CTCAE grade 5					
Total	500	67 (13.4)	253	37 (14.6)	0.92 [0.63; 1.33]; 0.661

a: Institute's calculation, unconditional exact test (CSZ method according to [3]).

BSC: best supportive care; CI: confidence interval; CSZ: convexity, symmetry, z score; CTCAE: Common Terminology Criteria for Adverse Events; N: number of analysed patients; n: number of patients with event; RCT: randomized controlled trial; vs.: versus

Table 12: Results on AEs – AEs of CTCAE grade 3 that occurred in ≥ 2% of patients in one treatment arm – RCT, direct comparison: regorafenib + BSC vs. placebo + BSC

Category **NCI CTCAE term** *Data cut-off* *21 July 2011*	**Regorafenib + BSC (N = 500)** **Patients with events n (%)**	**Placebo + BSC (N = 253)** **Patients with events n (%)**
Total	280 (56.0)	67 (26.5)
Blood/bone marrow	49 (9.8)	8 (3.2)
Haemoglobin	27 (5.4)	8 (3.2)
Platelets	17 (3.4)	1 (0.4)
Cardiac general	40 (8.0)	3 (1.2)
Hypertension	38 (7.6)	2 (0.8)
Constitutional symptoms	87 (17.4)	27 (10.7)
Fatigue	75 (15.0)	21 (8.3)
Constitutional symptoms – other (specify)	11 (2.2)	10 (4.0)
Gastrointestinal	101 (20.2)	30 (11.9)
Anorexia	23 (4.6)	11 (4.3)
Dehydration	10 (2.0)	6 (2.4)
Diarrhoea	41 (8.2)	5 (2.0)
Mucositis (functional/symptomatic), oral cavity	16 (3.2)	0 (0)
Obstruction, GI, small bowel NOS	3 (0.6)	5 (2.0)
Hepatobiliary/pancreas	12 (2.4)	4 (1.6)
Infections	32 (6.4)	13 (5.1)
Musculoskeletal/soft tissues	8 (1.6)	5 (2.0)
Metabolism/laboratory	100 (20.0)	22 (8.7)
Alkaline phosphatase	11 (2.2)	4 (1.6)
Aspartate aminotransferase (AST)	12 (2.4)	3 (1.2)
Bilirubin (hyperbilirubinaemia)	34 (6.8)	11 (4.3)
Lipase	15 (3.0)	1 (0.4)
Hypokalaemia	13 (2.6)	1 (0.4)
Hyponatraemia	18 (3.6)	4 (1.6)
Hypophosphataemia	23 (4.6)	1 (0.4)
Neurology	19 (3.8)	10 (4.0)
Pain	49 (9.8)	17 (6.7)
Pain, abdomen NOS	24 (4.8)	5 (2.0)
Pulmonary/upper respiratory	11 (2.2)	12 (4.7)
Dyspnoea (shortage of breath)	7 (1.4)	8 (3.2)
Renal/genitourinay	12 (2.4)	9 (3.6)
Dermatology/skin	112 (22.4)	2 (0.8)
Hand-foot skin reaction	83 (16.6)	1 (0.4)
Rash/desquamation	29 (5.8)	1 (0.4)

(continued)

Table 12: Results on AEs – AEs of CTCAE grade 3 that occurred in ≥ 2% of patients in one treatment arm – RCT, direct comparison: regorafenib + BSC vs. placebo + BSC (continued)

AE: adverse event; BSC: best supportive care; N: number of analysed patients; n: number of patients with event; NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; RCT: randomized controlled trial; vs.: versus

Mortality

In both data cut-offs (21 July 2011 and 13 November 2011), treatment with regorafenib + BSC resulted in a statistically significant prolongation of overall survival in comparison with placebo + BSC. There is therefore a hint of an added benefit of regorafenib + BSC compared with the ACT BSC. This deviates from the company's assessment, which claimed proof of an added benefit.

Morbidity

The company did not present any evaluable data on symptoms in its dossier (see Section 2.7.2.4.3). An added benefit of regorafenib + BSC in comparison with BSC is not proven for morbidity (symptoms). This deviates from the company, which derived proof of an added benefit on the basis of the outcomes "PFS" and "ORR" (+ associated outcomes of tumour control).

Health-related quality of life

The company did not present any evaluable data on health-related quality of life in its dossier (see Section 2.7.2.4.3). An added benefit of regorafenib + BSC in comparison with BSC is not proven for health-related quality of life. This deviates from the company, which included data on health-related quality of life in its assessment, but did not derive proof of an added benefit based on these data.

Adverse events

Serious adverse events and treatment discontinuations due to adverse events

The overall rates of SAEs and of treatment discontinuations due to AEs were not statistically significantly different between regorafenib + BSC and placebo + BSC. Lesser or greater harm from regorafenib + BSC than from BSC is not proven for these outcomes. This concurs with the company's assessment.

Severe adverse events (CTCAE grade 3, 4 and 5)

Severe AEs of CTCAE grade 4 and 5 were not statistically significantly different between the treatment arms. In contrast, severe AEs of CTCAE grade 3 were more common in patients treated with regorafenib + BSC than in patients treated with placebo + BSC. The difference between the treatment groups was statistically significant. The biggest differences between the treatment groups (≥ 5%) occurred in the following individual events: hypertension, fatigue, diarrhoea, hand-foot syndrome and exanthema (see Table 12). At least fatigue,

diarrhoea, hand-foot syndrome and exanthema are to be categorized as severe AEs because of the respective definition of the severity grade 3 according to the CTCAE (see Table 21 in Appendix A of the full dossier assessment). Hence the difference between the treatment groups in AEs of CTCAE grade 3 is largely caused by patient-relevant individual severe AEs. Overall, there is a hint of greater harm from regorafenib + BSC compared with the ACT BSC for this outcome. This deviates from the company's assessment, which derived proof of greater harm from regorafenib + BSC.

Subgroup analyses

With respect to the outcomes "overall survival" and to the outcomes regarding harm "SAEs" and "treatment discontinuations due to AEs", subgroup analyses were available on the following characteristics:

- age (< 65 years/≥ 65 years)
- sex (male/female)
- ethnicity (white/Asian)
- ECOG PS (0/1)
- region (region 1 [North America, Western Europe, Israel, Australia]/region 2 [Asia])
- time since diagnosis of the metastatic disease (< 18 months/≥ 18 months)
- number of lines of treatment since diagnosis of the metastatic disease (≤ 3/> 3)
- historical KRAS mutation status (yes/no)
- primary site of disease (colon/rectum)

The dossier contained no subgroup analyses for the outcomes regarding harm "severe AEs of CTCAE grade 3, 4 and 5", but the Institute could conduct its own calculations for the characteristics "age", "sex", "ethnicity" and "ECOG PS".

There were 3 relevant results from the subgroup analyses, which concerned the outcomes "overall survival" and "severe AEs of grade 3".

Overall survival

The results of the subgroup analyses for overall survival according to the characteristic "primary site of disease" are presented in Table 13.

Table 13: Subgroups: overall survival according to the characteristic "primary site of disease" – RCT, direct comparison: regorafenib + BSC vs. placebo + BSC

Study Data cut-off	Regorafenib + BSC		Placebo + BSC		Regorafenib + BSC vs. placebo + BSC	
Characteristic Subgroup	N	Median survival time in days [95% CI]	N	Median survival time in days [95% CI]	HR [95% CI]	p-value
CORRECT						
Data cut-off 21 July 2011						
Primary site of disease						
Colon	323	184 [ND]	172	140 [ND]	0.70 [0.56; 0.89]	0.003[a]
Rectum	151	246 [ND]	69	237 [ND]	0.95 [0.63; 1.44]	0.818[a]
					Interaction:	0.180[b]
Data cut-off 13 November 2011						
Primary site of disease						
Colon	323	181 [ND]	172	140 [ND]	0.75 [0.61; 0.93]	0.007[a]
Rectum	151	211 [ND]	69	218 [ND]	0.97 [0.69; 1.38]	0.877[a]
					Interaction:	0.201

a: Institute's calculation; Wald test.
b: Despite the presentation of results for the 3 subgroups "colon", "rectum" and "colon and rectum" in Module 4, the p-value presented as the corresponding value referred to an interaction test, which was only conducted for the subgroups "colon" and "rectum".
BSC: best supportive care; CI: confidence interval; HR: hazard ratio; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; vs.: versus

For the outcome "overall survival", analysis of the 2 subgroups "colon" and "rectum" were available for the characteristic "primary site of disease" for the data cut-offs 21 July 2011 and 13 November 2011. On the earlier data cut-off date, there was an indication of an effect modification for these subgroups (interaction test: $P = 0.180$). There was no effect modification on the later data cut-off date anymore (see Table 13). Overall, these results were not considered further in the benefit assessment because of the inconsistent picture they provide.

Severe adverse events of CTCAE grade 3

The results of the subgroup analyses for the outcome "severe AEs of CTCAE grade 3" according to the characteristics "age" and "ethnicity" are presented in Table 14.

Table 14: Subgroups: severe AEs of CTCAE grade 3 according to the characteristics "age" and "ethnicity" – RCT, direct comparison: regorafenib + BSC vs. placebo + BSC

Study Characteristic / Subgroup	Regorafenib + BSC		Placebo + BSC		Regorafenib + BSC vs. placebo + BSC	
	N	Patients with events n (%)	N	Patients with events n (%)	RR [95% CI][a]	p-value
CORRECT						
Age						
< 65 years	307	170 (55.4)	164	48 (29.3)	1.89 [1.46; 2.45]	< 0.001[b]
≥ 65 years	193	110 (57.0)	89	19 (21.3)	2.67 [1.76; 4.05]	< 0.001[b]
					Interaction:	0.169[c]
Ethnicity						
White	389	206 (53.0)	200	53 (26.5)	2.00 [1.56; 2.56]	< 0.001[b]
Asian	74	54 (73.0)	34	7 (20.6)	3.54 [1.81; 6.96]	< 0.001[b]
					Interaction:	0.118[c]

a: Institute's calculation; effect estimate and CI (asymptotic).
b: Institute's calculation, unconditional exact test (CSZ method according to [3]).
c: Institute's calculation, Cochran's Q test.
BSC: best supportive care; CI: confidence interval; CSZ: convexity, symmetry, z score; CTCAE: Common Terminology Criteria for Adverse Events; N: number of analysed patients; n: number of patients with event; RCT: randomized controlled trial; RR: relative risk; vs.: versus

The subgroup analyses on the outcome "severe AEs of CTCAE grade 3" showed a statistically significantly higher risk of a severe AE of CTCAE grade 3 under regorafenib + BSC than under placebo + BSC for both age strata (< 65 year/≥ 65 years). The effect to the disadvantage of regorafenib + BSC was greater in patients ≥ 65 years than in patients < 65 years. For the ethnicities "white" and "Asian", there was also a statistically significantly higher risk of a severe AE of CTCAE grade 3 under regorafenib + BSC than under placebo + BSC. The effect to the disadvantage of regorafenib + BSC was greater in Asians than in whites. Because the statistically significant effects were not opposite in the subgroups and in each case had the same extent as in the total population ("major", see information on the assessment of extent in Section 2.5.1), the results were not considered further in the benefit assessment.

Further information on the choice of outcomes, on risk of bias at outcome level, and on outcome results can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3 and 4.3.2.1.3 of the dossier and in Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment.

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

The data presented in Section 2.4 resulted in a hint of an added benefit of regorafenib + BSC versus the ACT BSC for the outcome “overall survival”. In contrast, there was a hint of greater harm from regorafenib + BSC regarding the outcomes “severe AEs of grade 3”. The extent of the respective added benefit at outcome level was estimated from these results (see Table 15).

Table 15: Extent of added benefit at outcome level: regorafenib + BSC vs. BSC

Outcome category **Outcome**	**Regorafenib + BSC vs. BSC** **effect estimates [95% CI]** **p-value** **time to event or** **proportion of patients with event** **probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival		
Data cut-off 21 July 2011	HR: 0.77 [0.64; 0.94] p-value = 0.011 median: 196 vs. 151 days probability: "hint"	Outcome category: survival time $0.85 < CI_u < 0.95$ added benefit, extent: "considerable"
Data cut-off 13 November 2011	HR: 0.79 [0.66; 0.94] p-value = 0.008 median: 194 vs. 152 days probability: "hint"	Outcome category: survival time $0.85 < CI_u < 0.95$ added benefit, extent: "considerable"
Morbidity		
	No evaluable data	
Health-related quality of life		
	No evaluable data	
Adverse events		
SAEs	RR: 1.11 [0.92; 1.33] p-value = 0.269 43.8% vs. 39.5%	Lesser/greater harm not proven
Treatment discontinuations due to AEs	RR: 1.39 [0.96; 2.03] p-value = 0.081 17.6% vs. 12.6%	Lesser/greater harm not proven
Severe AEs CTCAE grade 3	RR: 2.11 [1.70; 2.63] RR[c]: 0.47 [0.38; 0.59] p-value = < 0.001 56.0% vs. 26.5% probability: "hint"	Outcome category "serious/severe AEs" $CI_u < 0.75$ greater harm, extent: "major"
Severe AEs CTCAE grade 4	RR: 1.09 [0.65; 1.81] p-value = 0.766 8.6% vs. 7.9%	Lesser/greater harm not proven
Severe AEs (CTCAE grade 5)	RR: 0.92 [0.63; 1.33] p-value = 0.661 13.4% vs. 14.6%	Lesser/greater harm not proven

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 confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; RR: relative risk; SAE: serious adverse event; vs.: versus

2.5.2 Overall conclusion on added benefit

Table 16 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 16: Positive and negative effects from the assessment of regorafenib + BSC compared with BSC

Positive effects	Negative effects
Hint of an added benefit – extent: "considerable" (mortality: overall survival)	Hint of greater harm – extent: "major" (severe AEs: AEs of CTCAE grade 3)
AE: adverse event; BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events	

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 with the extent "major" in the category "severe AEs" (severe AEs of CTCAE grade 3). Even though the extent is "major" for severe AEs, this does not completely outweigh the mortality advantage of regorafenib.

Overall, there is a hint of a minor added benefit of regorafenib + BSC versus the ACT.

The result of the assessment of the added benefit of regorafenib in comparison with the ACT is summarized in Table 17.

Table 17: Regorafenib: extent and probability of added benefit

Therapeutic indication	ACT	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 a minor added benefit
ACT: appropriate comparator therapy; BSC: best supportive care; EGFR: endothelial growth factor receptor; MCRC: metastatic colorectal cancer; VEGF: vascular endothelial growth factor		

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

Further information about the extent and probability of the added benefit can be found in Module 4, Section 4.4 of the dossier, and in Section 2.7.2.8 of the full dossier assessment.

2.6 List of included studies

Bayer. Patients with metastatic colorectal cancer treated with regorafenib or placebo after failure of standard therapy: full text view [online]. In: Clinicaltrials.gov. 30 October 2013 [accessed: 27 November 2013]. URL: http://www.clinicaltrials.gov/ct2/show/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: study 14387; integrated clinical study protocol [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 A53306; clinical study report [unpublished]. 2012.

Bayer Healthcare. Studie 14387 CORRECT: ad-hoc Germany reimbursement statistical analysis [unpublished]. 2012.

Bayer Healthcare. Studie 14387 CORRECT: descriptive OS update based on 13Nov2011 data cutoff [unpublished]. 2012.

Bayer Healthcare. Studie 14387 CORRECT: Germany reimbursement statistical analysis 2 [unpublished]. 2013.

Bayer Healthcare. Studie 14387 CORRECT: Germany reimbursement statistical analysis 3 [unpublished]. 2013.

Bayer Healthcare. Studie 14387 CORRECT: OS update2 based on 13NOV2011 data cutoff [unpublished]. 2012.

Bayer Healthcare. Studie 14387 CORRECT: post hoc Analyse zu relativen Risiken und Odds Ratios von Verträglichkeitsparametern [unpublished]. 2013.

Grothey A, Van Cutsem E, Sobrero A, Siena S, Falcone A, Ychou M et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 2013; 381(9863): 303-312.

References for English extract

Please see full dossier assessment for full reference list.

1. Institute for Quality and Efficiency in Health Care. General methods: version 4.0 [online]. 23 September 2011 [accessed: 5 May 2012]. URL: https://www.iqwig.de/download/General_Methods_4-0.pdf.

2. Institute for Quality and Efficiency in Health Care. Ticagrelor: benefit assessment according to §35a Social Code Book V; extract; commission no. A11-02 [online]. 29 September 2011 [accessed: 5 May 2012]. URL: https://www.iqwig.de/download/A11-02_Extract_of_dossier_assessment_Ticagrelor.pdf.

3. Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Comput Stat Data Anal 1994; 17(5): 555-574.

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