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Encorafenib (colorectal cancer) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment Encorafenib *(*Kolorektalkarzinom*)* – *Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 September 2020). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
BRAF	rapidly accelerated fibrosarcoma - isoform B
CRC	Colorectal Cancer
EGFR	epidermal growth factor receptor
ESMO	European Society for Medical Oncology
FOLFIRI	folinic acid + 5-fluorouracil + irinotecan
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
NRAS	neuroblastoma rat sarcoma viral oncogene homologue
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
TKK	Tumorregister Kolorektales Karzinom (German Colorectal Carcinoma Cancer Registry)

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 encorafenib. 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 30 June 2020.

Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented in Module 5 of the company's dossier.

Research question

The aim of the present report is the assessment of the added benefit of encorafenib in combination with cetuximab (encorafenib + cetuximab) in comparison with individual treatment as appropriate comparator therapy (ACT) in adult patients with metastatic colorectal cancer (MCRC) with rapidly accelerated fibrosarcoma - isoform B (BRAF) V600E mutation, who have received prior systemic therapy.

The research question for the benefit assessment presented in Table 2 resulted from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of encorafenib + cetuximab

Therapeutic indication	**ACT[b]**
Adult patients with MCRC with BRAF V600E mutation, who have received prior systemic therapy	Individual treatment choosing from ▪ 5-fluorouracil + folinic acid + oxaliplatin ± bevacizumab ▪ capecitabin + oxaliplatin ± bevacizumab ▪ 5-fluorouracil + folinic acid + irinotecan ± aflibercept or ramucirumab or bevacizumab ▪ irinotecan ▪ trifluridine/tipiracil ▪ 5-fluorouracil ± bevacizumab ▪ capecitabin ± bevacizumab under consideration of the general condition and the type and number of prior therapies
a. It is assumed that the present therapeutic indication comprised no treatment-naive patients and that there was no indication for treatment with curative intent or for primary or secondary resectability. b. Presentation of the ACT specified by the G-BA. The company chose irinotecan + cetuximab or FOLFIRI + cetuximab as comparator therapy, which does not correspond to any of the options specified by the G-BA. ACT: appropriate comparator therapy; BRAF: rapidly accelerated fibrosarcoma – isoform B; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; G-BA: Federal Joint Committee; MCRC: metastatic colorectal cancer	

The assessment was conducted versus the ACT by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Deviation of the company from the ACT

The company deviates from the ACT by extending 2 options of the ACT as follows:

- "folinic acid + 5-fluorouracil + irinotecan (FOLFIRI) ± aflibercept or ramucirumab or bevacizumab"
  - extended by "or cetuximab or panitumumab"
- "irinotecan"
  - Extension by "± cetuximab"

The company conducted the benefit assessment of encorafenib + cetuximab versus cetuximab + FOLFIRI or cetuximab + irinotecan as comparator therapy.

The deviation from the ACT is not appropriate. Making reference to several guidelines, the company stated that the exclusion of epidermal growth factor receptor (EGFR) inhibitors from the ACT should be viewed critically, since the guidelines do not explicitly exclude their use in the therapeutic indication. However, this does not mean that the guidelines consider the use of EGFR inhibitors as relevant treatment option in the therapeutic indication, as implied by the company. Most of the guidelines cited by the company question the efficacy of anti-EGFR treatment in patients with BRAF V600 mutant tumour or recommend it only in case of Kirsten rat sarcoma viral oncogene homologue (KRAS), neuroblastoma rat sarcoma viral oncogene homologue (NRAS), or BRAF wild type tumour. The S3 guideline relevant in Germany does not comment on this, but considers the administration of anti-EGFR agents in the presence of a BRAF mutation as subject of a controversial debate.

The argumentation of the company, according to which EGFR inhibitors should be part of the ACT in the therapeutic indication, is not substantive. Therefore, the company's extension of the ACT is considered not appropriate. The present assessment was made in comparison with the ACT specified by the G-BA.

The study BEACON CRC presented by the company is unsuitable for the assessment

The company presented the 3-arm open-label, randomized approval study BEACON CRC on the comparison of encorafenib + cetuximab and encorafenib + binimetinib + cetuximab in the intervention arms versus cetuximab + irinotecan or cetuximab + FOLFIRI in the control arm. The study is unsuitable to derive an added benefit of encorafenib versus the ACT, because in its control arm, cetuximab was administered in combination with irinotecan or FOLFIRI and the ACT was thus not implemented. There are no data demonstrating that the results of the BEACON CRC study are not relevantly biased in favour of encorafenib + cetuximab by the addition of cetuximab in the control arm.

Results

Data for the assessment of the added benefit of encorafenib + cetuximab in comparison with the ACT in patients with pretreated MCRC with BRAF V600E mutation are not available. Hence, there was no hint of an added benefit of encorafenib + cetuximab in comparison with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Data for the assessment of the added benefit of encorafenib + cetuximab in comparison with the ACT in patients with pretreated MCRC with BRAF V600E mutation are not available. Hence, an added benefit of encorafenib + cetuximab versus the ACT is not proven.

Table 3 shows a summary of probability and extent of the added benefit of encorafenib.

Table 3: Encorafenib + cetuximab – probability and extent of added benefit

Subindication[a]	**ACT**[b]	**Probability and extent of added benefit**
Adult patients with MCRC with BRAF V600E mutation, who have received prior systemic therapy	Individual treatment choosing from ▪ 5-fluorouracil + folinic acid + oxaliplatin ± bevacizumab ▪ capecitabin + oxaliplatin ± bevacizumab ▪ 5-fluorouracil + folinic acid + irinotecan ± aflibercept or ramucirumab or bevacizumab ▪ irinotecan ▪ trifluridine/tipiracil ▪ 5-fluorouracil ± bevacizumab ▪ capecitabin ± bevacizumab under consideration of the general condition and the type and number of prior therapies	Added benefit not proven

a. It is assumed that the present therapeutic indication comprised no treatment-naive patients and that there was no indication for treatment with curative intent or for primary or secondary resectability.
b. Presentation of the ACT specified by the G-BA. The company chose irinotecan + cetuximab or FOLFIRI + cetuximab as comparator therapy, which does not correspond to any of the options specified by the G-BA.

ACT: appropriate comparator therapy; BRAF: rapidly accelerated fibrosarcoma – isoform B; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; G-BA: Federal Joint Committee; MCRC: metastatic colorectal cancer

The G-BA decides on the added benefit.

[3] 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, added benefit not proven, or less benefit). For further details see [1,2].

2.2 Research question

The aim of the present report is the assessment of the added benefit of encorafenib in combination with cetuximab (encorafenib + cetuximab) in comparison with individual treatment as ACT in adult patients with MCRC with BRAF V600E mutation, who have received prior systemic therapy.

For the benefit assessment, the research question presented in Table 4 resulted from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of encorafenib + cetuximab

Subindication[a]	**ACT**[b]
Adult patients with MCRC with BRAF V600E mutation, who have received prior systemic therapy	Individual treatment choosing from ▪ 5-fluorouracil + folinic acid + oxaliplatin ± bevacizumab ▪ capecitabin + oxaliplatin ± bevacizumab ▪ 5-fluorouracil + folinic acid + irinotecan ± aflibercept or ramucirumab or bevacizumab ▪ irinotecan ▪ trifluridine/tipiracil ▪ 5-fluorouracil ± bevacizumab ▪ capecitabin ± bevacizumab under consideration of the general condition and the type and number of prior therapies
a. It is assumed that the present therapeutic indication comprised no treatment-naive patients and that there was no indication for treatment with curative intent or for primary or secondary resectability. b. Presentation of the ACT specified by the G-BA. The company chose irinotecan + cetuximab or FOLFIRI + cetuximab as comparator therapy, which does not correspond to any of the options specified by the G-BA. ACT: appropriate comparator therapy; BRAF: rapidly accelerated fibrosarcoma – isoform B; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; G-BA: Federal Joint Committee; MCRC: metastatic colorectal cancer	

The assessment was conducted versus the ACT by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Deviation of the company from the ACT

The company also cited individual therapy as ACT, but deviated from the G-BA's specification by extending 2 of the above options as follows:

- "FOLFIRI ± aflibercept or ramucirumab or bevacizumab"
  - extended by "or cetuximab or panitumumab"
- "irinotecan"
  - Extension by "± cetuximab"

The company conducted the benefit assessment of encorafenib + cetuximab versus cetuximab + FOLFIRI or cetuximab + irinotecan as comparator therapy.

The deviation from the ACT is not appropriate. The argumentation of the company and the reason why this deviation is not appropriate is explained below.

Making reference to several guidelines [3-7], the company stated that the exclusion of EGFR inhibitors from the ACT should be viewed critically, since on the one hand the guidelines contain only limited evidence of anti-EGFR treatment in patients with BRAF V600E mutant tumours from the 2nd line of treatment, and on the other hand, the guidelines do not explicitly exclude their application. The company's opinion that the guidelines do not explicitly exclude anti-EGFR treatment in patients in the therapeutic indication is generally accepted. However, this does not mean that the guidelines consider the use of EGFR inhibitors as relevant treatment option in the therapeutic indication, as implied by the company. Rather, the Australian guideline for the prevention, early detection and management of colorectal cancer (CRC) [5], for instance, questions the efficacy of anti-EGFR treatment in patients with BRAF V600E mutant tumours. This view is also reflected in the 2016 guideline of the European Society for Medical Oncology (ESMO) [8], which thus deviates from the older version of 2014 cited by the company [6]. The panitumumab and cetuximab toxicity management guidelines [9] as part of the Canadian guideline [10] (the company cited the older version [3]) recommend anti-EGFR treatment only in case of a KRAS, NRAS, or BRAF wild-type tumour.

The S3 guideline relevant in Germany [7] does not comment on this, but considers the administration of anti-EGFR agents in the presence of a BRAF mutation as subject of a controversial debate.

Moreover, making reference to the unpublished sources on the German Colorectal Carcinoma Cancer Registry (Tumorregister Kolorektales Karzinom [TKK]) [11] and the epidemiology project MORSE-CRC [12], the company wanted to show that the anti-EGFR treatments were effective and were frequently used in the therapeutic indication. Therefore, they belonged to the generally accepted state of medical knowledge and should be part of the ACT. However, these two sources do not allow such a conclusion, as they only contain data on very few patients in the therapeutic indication, of whom only a small proportion received anti-EGFR treatment. Moreover, the company also intended to confirm the routine use of anti-EGFR therapies in the therapeutic indication based on the follow-up therapies in the approval study BEACON CRC. These data also do not show that treatment with anti-EGFR therapies belongs to the generally accepted state of medical knowledge in the therapeutic indication. The proportion of patients with anti-EGFR follow-up therapy (see Table 15 of the full dossier assessment) cannot be used for this purpose, as cetuximab was already applied as a study medication in the study. The data cited by the company therefore reflect the renewed administration of cetuximab after treatment discontinuation or the continuation of cetuximab despite the occurrence of a reason to discontinue the study medication (e.g. progression or toxicity). However, according to guidelines [13,14], systemic treatment shall be switched to another drug after the occurrence of a reason for discontinuation. Thus, the data referenced by the company do not represent the guideline-compliant use of cetuximab in healthcare.

Conclusion

The argumentation of the company, according to which EGFR inhibitors should be part of the ACT in the therapeutic indication, is not substantive. Therefore, the company's extension of the ACT is considered not appropriate. The present assessment was made in comparison with the ACT specified by the G-BA.

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 encorafenib (status: 15 April 2020)
- bibliographical literature search on encorafenib (last search on 15 April 2020)
- search in trial registries/trial results databases for studies on encorafenib (last search on 16 April 2020)
- search on the G-BA website for encorafenib (last search on 15 April 2020)
- bibliographical literature search on the ACT (last search on 5 May 2020)
- search in trial registries/trial results databases for the ACT (last search on 5 May 2020)
- search on the GBA website for the ACT (last search on 5 May 2020)

To check the completeness of the study pool:

- search in trial registries for studies on encorafenib (last search on 10 July 2020)

No relevant study was identified from the check.

The study listed in the following table was included by the company. Moreover, the company conducted a search for studies for an adjusted indirect comparison versus the treatment options defined by the G-BA (Table 4). The company identified no such randomized controlled trials.

Table 5: Study pool of the company – RCT, direct comparison: encorafenib + cetuximab vs. cetuximab + IRI or cetuximab + FOLFIRI

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
ARRAY-818-302 (BEACON CRC[c])	Yes	No[d]	Yes[d]	No[e]	Yes, [15-19]	Yes, [20,21]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. In the following tables, the study is referred to with this abbreviated form.
d. The sponsor of the BEACON CRC study is the company Array BioPharma Inc. (Boulder, USA). Pierre Fabre and Array BioPharma Inc. have signed an exclusive license agreement for the development and commercialization of Braftovi and Mektovi in Europe and other regions.
e. Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented in Module 5 of the company's dossier.

CSR: clinical study report; G-BA: Federal Joint Committee; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; IRI: irinotecan; RCT: randomized controlled trial; vs.: versus

The approval study BEACON CRC presented by the company is a 3-arm, open-label randomized controlled trial (RCT) comparing encorafenib + cetuximab and encorafenib + binimetinib + cetuximab in the intervention arms with cetuximab + irinotecan or cetuximab + FOLFIRI in the control arm. Which of the two options was to be administered in the case of allocation to the control arm was determined by the investigator prior to randomization. As of the two interventions only encorafenib + cetuximab is approved, the arm on encorafenib + binimetinib + cetuximab is not further described.

The BEACON CRC study included adult patients with MCRC and BRAF V600E mutant tumour who had tumour progression after 1 or 2 therapy regimens in the metastatic stage. A total of 220 patients were assigned to the intervention arm with encorafenib + cetuximab and 221 patients were assigned to the control arm.

The BEACON study is unsuitable to derive an added benefit of encorafenib + cetuximab, because in its control arm, cetuximab was administered in combination with irinotecan or FOLFIRI and the ACT was thus not implemented. There are no data demonstrating that the results of the BEACON CRC study are not relevantly biased in favour of encorafenib + cetuximab by the addition of cetuximab in the control arm.

The BEACON CRC study is presented in Appendix A of the full dossier assessment for informative reasons. However, conclusions on the added benefit of encorafenib + cetuximab versus the ACT cannot be derived on the basis of the BEACON CRC study.

2.4 Results on added benefit

Data for the assessment of the added benefit of encorafenib + cetuximab in comparison with the ACT in patients with pretreated MCRC with BRAF V600E mutation are not available. Hence, there was no hint of an added benefit of encorafenib + cetuximab in comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

Data for the assessment of the added benefit of encorafenib + cetuximab in comparison with the ACT in patients with pretreated MCRC with BRAF V600E mutation are not available. Hence, an added benefit of encorafenib + cetuximab versus the ACT is not proven.

The result of the assessment of the added benefit of encorafenib + cetuximab in comparison with the ACT is summarized in Table 6.

Table 6: Encorafenib + cetuximab – probability and extent of added benefit

Subindication[a]	**ACT**[b]	**Probability and extent of added benefit**
Adult patients with MCRC with BRAF V600E mutation, who have received prior systemic therapy	Individual treatment choosing from ▪ 5-fluorouracil + folinic acid + oxaliplatin ± bevacizumab ▪ capecitabin + oxaliplatin ± bevacizumab ▪ 5-fluorouracil + folinic acid + irinotecan ± aflibercept or ramucirumab or bevacizumab ▪ irinotecan ▪ trifluridine/tipiracil ▪ 5-fluorouracil ± bevacizumab ▪ capecitabin ± bevacizumab under consideration of the general condition and the type and number of prior therapies	Added benefit not proven

a. It is assumed that the present therapeutic indication comprised no treatment-naive patients and that there was no indication for treatment with curative intent or for primary or secondary resectability.
b. Presentation of the ACT specified by the G-BA. The company chose irinotecan + cetuximab or FOLFIRI + cetuximab as comparator therapy, which does not correspond to any of the options specified by the G-BA.

ACT: appropriate comparator therapy; BRAF: rapidly accelerated fibrosarcoma – isoform B; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; G-BA: Federal Joint Committee; MCRC: metastatic colorectal cancer

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

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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