IQWiG Reports – Commission No. A22-75

Pembrolizumab (MSI-H or dMMR colorectal cancer) –

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

Extract

[1] Translation of Sections I 1 to I 5 of the dossier assessment *Pembrolizumab (Kolorektalkarzinom mit MSI-H oder dMMR) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 24 October 2022). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher
Institute for Quality and Efficiency in Health Care

Topic
Pembrolizumab (MSI-H or dMMR colorectal cancer) – Benefit assessment according to §35a Social Code Book V

Commissioning agency
Federal Joint Committee

Commission awarded on
25 July 2022

Internal Commission No.
A22-75

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

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

Medical and scientific advice

- Ingo Schmidt-Wolf, University Hospital Bonn, Germany

IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

IQWiG employees involved in the dossier assessment

- Sascha Abbas
- Nadia Abu Rajab
- Charlotte Guddat
- Lisa Junge
- Claudia Kapp
- Stefan Kobza
- Petra Kohlepp
- Volker Vervölgyi

Keywords: Pembrolizumab, Colorectal Neoplasms, Benefit Assessment

Part I: Benefit assessment

I Table of contents

Page

I List of tables[2]

Page

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
BSC	best supportive care
dMMR	mismatch repair deficient
EGFR	epidermal growth factor receptor
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MAIC	matching-adjusted indirect comparison
MSI-H	microsatellite instability high
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
VEGF	vascular endothelial growth factor

I 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 pembrolizumab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 25 July 2022.

Research question

The aim of the present report is to assess the added benefit of pembrolizumab in comparison with the appropriate comparator therapy (ACT) in adult patients with unresectable or metastatic microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer after previous fluoropyrimidine-based combination therapy.

The G-BA's specification of the ACT results in the research question presented in Table 2.

Table 2: Research question of the benefit assessment of pembrolizumab

Therapeutic indication	**ACT[a]**
Adults with unresectable or metastatic MSI-H or dMMR colorectal cancer; after previous fluoropyrimidine-based combination therapy[b]	Individualized treatment[c, d] depending on the type and number of prior therapies, RAS and BRAF mutation status, the location of the primary tumour, the patient's general condition, and the risk of toxicity induced by anti-VEGF and anti-VEGFR drugs, choosing from the following options: ▪ 5-fluorouracil + folinic acid + irinotecan (FOLFIRI) ± bevacizumab or aflibercept or ramucirumab ▪ 5-fluorouracil + folinic acid + irinotecan (FOLFIRI) ± cetuximab or panitumumab[d] ▪ 5-fluorouracil + folinic acid + oxaliplatin (FOLFOX) ± bevacizumab ▪ capecitabine + oxaliplatin (CAPOX) ± bevacizumab ▪ 5-fluorouracil + folinic acid ± bevacizumab ▪ capecitabine ± bevacizumab ▪ irinotecan monotherapy ▪ panitumumab monotherapy[d] ▪ cetuximab monotherapy[d] ▪ trifluridine/tipiracil ▪ irinotecan + cetuximab[d] ▪ encorafenib + cetuximab[e]

a. Presented is the ACT specified by the G-BA.
b. Treatment with curative intent is presumed not to be indicated, and primary or secondary resection is presumed to be impossible.
c. FOLFIRI-based therapy in the first line was to be followed by FOLFOX-based therapy in the second line, and FOLFOX-based therapy in the first line was to be followed by FOLFIRI-based therapy in the second line.
d. Only for patients with RAS wild type.
e. Only for patients with BRAF-V600E mutation.

ACT: appropriate comparator therapy; BRAF: rapidly accelerated fibrosarcoma – isoform B; CAPOX: capecitabine + oxaliplatin; dMMR: mismatch repair deficient; FOLFIRI: 5-fluorouracil + folinic acid + irinotecan; FOLFOX: 5-fluorouracil + folinic acid + oxaliplatin; G-BA: Federal Joint Committee; MSI-H: microsatellite instability high; RAS: rat sarcoma viral oncogene homologue; VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor

The company initially followed the ACT specified by the G-BA. For its information retrieval on other investigations, the company distinguished the 2 following research questions:

- patients after 1 previous systemic therapy (subpopulation A1 as per the company, subsequently referred to as research question A1) and
- patients after at least 2 previous systemic therapies (subpopulation A2 as per the company, subsequently referred to as research question A2)

For each of these research questions, the company chose certain treatment options identified by the G-BA in the context of individualized therapy:

- Company's research question A1: irinotecan-based or oxaliplatin-based treatment regimen ± anti-vascular endothelial growth factor (anti-VEGF) or anti-epidermal growth factor receptor (anti-EGFR) substances
- Company's research question A2: trifluridine/tipiracil

The company's approach of distinguishing 2 research questions and the associated restriction of the information retrieval to the treatment options selected by the company is not adequate. This assessment is performed on the basis of the research question specified by the G-BA in comparison with the associated ACT.

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

Results

Company's approach – incomplete information retrieval

Because the company found no randomized controlled trial (RCT) with a direct comparison, it conducted an information retrieval for other studies. For this purpose, the company performed a separate search in line with its research questions, looking for patients after 1 prior systemic therapy (company's research question A1) and for patients with at least 2 prior systemic therapies (company's research question A2). For its research question A1, the company searched only for studies with irinotecan-based or oxaliplatin-based treatment regimens ± anti-VEGF or anti-EGFR substances; for its research question A2, the company limited the search on the comparator side to studies with trifluridine/tipiracil. The company's information retrieval is therefore incomplete for the research question of the present benefit assessment.

For its research question A1, the company's approach leads to some treatment options being disregarded, particularly for patients in poor general health or patients who are not candidates for intensive therapy. For its research question A2, the company limited the ACT to trifluridine/tipiracil. The S3 guideline recommends trifluridine/tipiracil for patients who have undergone all available chemotherapies / antibody therapies or who are not candidates for said therapies. Presumably, a relevant percentage of third-line patients in the therapeutic indication have not yet exploited all available means of conventional therapy, and therefore, it is inadequate to limit the ACT in third-line therapy and thereafter to only trifluridine/tipiracil.

Data presented by the company – other reasons for the benefit assessment being unsuitable

Irrespective of the general unsuitability of the company's presented data, which neither address the benefit assessment's research question nor rest on a complete information retrieval, said data represent comparisons of individual arms from different studies. Due to the lack of randomization, these comparisons are subject to inherent uncertainty and do not constitute an adequate method for conducting an indirect comparison.

Regarding the company's research question A1, the identified effects potentially result solely from systematic bias due to confounders. For the company's research question A2, the approval-relevant and prognostic criterion MSI-H or dMMR was accounted for only on the intervention side, but not on the comparator side.

The data presented by the company are therefore generally unsuitable for drawing conclusions on the added benefit of pembrolizumab versus the ACT.

Results on added benefit

Because no usable data are available for the benefit assessment, there is no hint of an added benefit of pembrolizumab 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]

Table 3 presents a summary of the probability and extent of the added benefit of pembrolizumab.

[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].

Table 3: Pembrolizumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with unresectable or metastatic MSI-H or dMMR colorectal cancer; after previous fluoropyrimidine-based combination therapy[b]	Individualized treatment[c, d] depending on the type and number of prior therapies, RAS and BRAF mutation status, the location of the primary tumour, the patient's general condition, and the risk of toxicity induced by anti-VEGF and anti-VEGFR drugs, choosing from the following options: ▪ 5-fluorouracil + folinic acid + irinotecan (FOLFIRI) ± bevacizumab or aflibercept or ramucirumab ▪ 5-fluorouracil + folinic acid + irinotecan (FOLFIRI) ± cetuximab or panitumumab[d] ▪ 5-fluorouracil + folinic acid + oxaliplatin (FOLFOX) ± bevacizumab ▪ capecitabine + oxaliplatin (CAPOX) ± bevacizumab ▪ 5-fluorouracil + folinic acid ± bevacizumab ▪ capecitabine ± bevacizumab ▪ irinotecan monotherapy ▪ panitumumab monotherapy[d] ▪ cetuximab monotherapy[d] ▪ trifluridine/tipiracil ▪ irinotecan + cetuximab[d] ▪ encorafenib + cetuximab[e]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. Patients are presumed not to be medically indicated for treatment with curative intent, and primary or secondary resection is presumed to be impossible.
c. First-line FOLFIRI-based therapy was to be followed by second-line FOLFOX-based therapy, and first-line FOLFOX-based therapy was to be followed by second-line FOLFIRI-based therapy.
d. Only for patients with RAS wild type.
e. Only for patients with BRAF-V600E mutation.

ACT: appropriate comparator therapy; BRAF: rapidly accelerated fibrosarcoma – isoform B; CAPOX: capecitabine + oxaliplatin; dMMR: mismatch repair deficiency; FOLFIRI: 5-fluorouracil + folinic acid + irinotecan; FOLFOX: 5-fluorouracil + folinic acid + oxaliplatin; G-BA: Federal Joint Committee; MSI-H: microsatellite instability high; RAS: rat sarcoma viral oncogene homologue; VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor

The G-BA decides on the added benefit.

I 2 Research question

The aim of the present report is to assess the added benefit of pembrolizumab in comparison with the ACT in adult patients with unresectable or metastatic MSI-H or dMMR colorectal cancer after previous fluoropyrimidine-based combination therapy.

The research question presented in Table 4 is derived from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of pembrolizumab

Therapeutic indication	**ACT[a]**
Adults with unresectable or metastatic MSI-H or dMMR colorectal cancer; after previous fluoropyrimidine-based combination therapy[b]	Individualized treatment[c, d] depending on the type and number of prior therapies, RAS and BRAF mutation status, the location of the primary tumour, the patient's general condition, and the risk of toxicity induced by anti-VEGF and anti-VEGFR drugs, choosing from the following options: ▪ 5-fluorouracil + folinic acid + irinotecan (FOLFIRI) ± bevacizumab or aflibercept or ramucirumab ▪ 5-fluorouracil + folinic acid + irinotecan (FOLFIRI) ± cetuximab or panitumumab[d] ▪ 5-fluorouracil + folinic acid + oxaliplatin (FOLFOX) ± bevacizumab ▪ capecitabine + oxaliplatin (CAPOX) ± bevacizumab ▪ 5-fluorouracil + folinic acid ± bevacizumab ▪ capecitabine ± bevacizumab ▪ irinotecan monotherapy ▪ panitumumab monotherapy[d] ▪ cetuximab monotherapy[d] ▪ trifluridine/tipiracil ▪ irinotecan + cetuximab[d] ▪ encorafenib + cetuximab[e]

a. Presented is the ACT specified by the G-BA.
b. Patients are presumed not to be medically indicated for treatment with curative intent, and primary or secondary resection is presumed to be impossible.
c. First-line FOLFIRI-based therapy was to be followed by second-line FOLFOX-based therapy, and first-line FOLFOX-based therapy, by second-line FOLFIRI-based therapy.
d. Only for patients with RAS wild type.
e. Only for patients with BRAF-V600E mutation.

ACT: appropriate comparator therapy; BRAF: rapidly accelerated fibrosarcoma – isoform B; CAPOX: capecitabine + oxaliplatin; dMMR: mismatch repair deficient; FOLFIRI: 5-fluorouracil + folinic acid + irinotecan; FOLFOX: 5-fluorouracil + folinic acid + oxaliplatin; G-BA: Federal Joint Committee; MSI-H: microsatellite instability high; RAS: rat sarcoma viral oncogene homologue; VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor

The company initially followed the ACT specified by the G-BA. For its information retrieval on other investigations, the company distinguished the 2 following research questions:

- patients after 1 previous systemic therapy (subpopulation A1 as per the company, subsequently referred to as research question A1) and

- patients after at least 2 previous systemic therapies (subpopulation A2 as per the company, subsequently referred to as research question A2)

For each of these research questions, the company chose certain treatment options identified by the G-BA in the context of individualized therapy:

- company's research question A1: irinotecan-based or oxaliplatin-based treatment regimen ± anti-VEGF or anti-EGFR substances
- company's research question A2: trifluridine/tipiracil

The company's approach of distinguishing 2 research questions and the associated restriction of the information retrieval to the treatment options it selected is not adequate (see Section I 3). This assessment is performed on the basis of the research question specified by the G-BA in comparison with the associated ACT.

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

I 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 pembrolizumab (status: 1 June 2022)
- bibliographical literature search on pembrolizumab (last search on 2 May 2022)
- search in trial registries / trial results databases for studies on pembrolizumab (last search on 2 May 2022)
- search on the G-BA website for pembrolizumab (last search on 17 May 2022)
- bibliographical literature search on the ACT (last search on 2 May 2022)
- search in trial registries / trial results databases for studies on the ACT (last search on 3 May 2022)
- search on the G-BA website for the ACT (last search on 17 May 2022)

To check the completeness of the study pool:

- search in trial registries for studies on pembrolizumab (last search on 18 August 2022); for search strategies, see I Appendix A of the full dossier assessment

The check of completeness of the study pool identified no RCTs for a direct or adjusted indirect comparison via a common comparator versus the ACT specified by the G-BA.

Company's approach – incomplete information retrieval

Not having identified any RCTs for a direct comparison, the company conducted an information retrieval for further studies. The company conducted a separate search in accordance with its research questions (see Section I 2) for patients who had undergone 1 previous systemic therapy (company's research question A1) and for patients with at least 2 previous systemic therapies (company's research question A2). For its research question A1, the company searched only for studies with irinotecan-based or oxaliplatin-based treatment regimens ± anti-VEGF or anti-EGFR substances; for its research question A2, the company limited the search on the comparator side to studies with trifluridine/tipiracil.

The company's approach is not appropriate because as a result, only 6 of the 12 options listed by the G-BA are taken into account for the company's research question A1 and only 1 of 12 for its research question A2. A complete search of the available evidence on the ACT, including all options identified by the G-BA for individualized therapy (see Table 4) for all patients in the present therapeutic indication, is missing. The company's information retrieval is therefore incomplete for the research question of the present benefit assessment.

For its research question A1, the company limited the ACT to the treatment regimens it viewed as common in patients with prior therapy (irinotecan or oxaliplatin-based treatment regimens ± anti-VEGF or anti-EGFR substances) [3,4]. Regarding its research question A1, this approach leads to the disregard of treatment options, particularly those for patients in poor general health or who are not candidates for intensive therapy. According to the S3 guideline on colorectal cancer, for instance, they include anti-EGFR monotherapies [3] such as panitumumab or cetuximab, which also represent ACT options specified by the G-BA (see Table 4). For its research question A2, the company limited the ACT to trifluridine/tipiracil. According to the Summary of Product Characteristics (SPC), trifluridine/tipiracil is used in patients who have already been treated with available therapies or who are not candidates for these therapies [5]. The S3 guideline recommends trifluridine/tipiracil for patients who have undergone all available chemotherapies/antibody therapies or who are not candidates for them [3]. Presumably, a relevant percentage of third-line patients in the therapeutic indication have not yet exploited all available means of conventional therapy, and therefore, it is inadequate to limit the ACT to only trifluridine/tipiracil in third-line therapy and thereafter.

A check for completeness of the study pool on the ACT side was foregone because the data presented by the company fail to address the benefit assessment's research question (see Section I 2). The data are unsuitable for drawing conclusions on the added benefit of pembrolizumab in comparison with the ACT because they neither address the research question of the benefit assessment nor are based on a complete information retrieval.

Further defects of the information retrieval

The company reports that in its study selection, it disregarded MSI-H/dMMR status if no suitable study was found when it took into account said MSI-H/dMMR status. Disregarding MSI-H/dMMR status in the study selection is not appropriate because this benefit assessment's research question addresses the added benefit of pembrolizumab versus the ACT in patients with dMMR or MSI-H colorectal cancer. Conversely, patients whose tumours exhibit neither MSI-H nor dMMR are excluded from the research question. As a consequence of this approach, the company includes on the comparator side studies disregarding MSI-H/dMMR status to answer its research question A2 (see section below).

Furthermore, the company reports that where several studies of different evidence levels were found to be relevant, it took into account only the studies of the highest evidence level. When comparing individual arms from different studies, this approach is inadequate. For instance, in the comparison of individual arms, single-arm studies are potentially of equal relevance as individual arms from RCTs.

Irrespective of their general unsuitability, the data presented by the company for the benefit assessment are unsuitable for other reasons as well. The rationale is provided below.

Data presented by the company

Company's research question A1: comparison of individual arms from the KEYNOTE-164 study and the retrospective Tougeron 2020 study

For its research question A1 (patients after 1 previous systemic therapy), the company has submitted a comparison between individual arms treated with pembrolizumab (KEYNOTE-164 study [6-9]) versus chemotherapy (Tougeron 2020 publication [10]), exclusively for the outcome of overall survival. Alongside results from the comparison of individual arms from different studies, the company presented noncomparative results of the KEYNOTE-164 study.

The KEYNOTE-164 study is a single-arm, 2-cohort study on pembrolizumab conducted in patients with locally advanced unresectable or metastatic MSI-H or dMMR colorectal cancer. At enrolment, patients had to have been previously treated with standard treatment regimens. For Cohort A, these included patients with prior fluoropyrimidine, oxaliplatin, and irinotecan treatment; for Cohort B, patients had prior treatment with at least 1 systemic standard therapy (fluoropyrimidine + oxaliplatin or irinotecan ± monoclonal anti-VEGF/EGFR antibodies).

A total of 124 patients were included. For comparing individual arms, the company used a subpopulation of 30 patients with 1 prior therapy. Pembrolizumab is dosed in accordance with the SPC [11]. Multiple study reports are available for interim analyses. For its research questions A1 and A2, the company used the data cut-off for the final analysis, 19 February 2021. For this data cut-off, which was also the basis for the marketing authorization [12], results are available in a shortened study report.

The Tougeron 2020 study is a retrospective investigation of adult patients with metastatic MSI-H or dMMR colorectal cancer. The analysis includes patients who received a corresponding diagnosis in the period from 2007 through 2017. For the comparison of individual arms, the company used patients with second-line chemotherapy ± targeted therapy (N = 136). As second-line chemotherapy, these patients received irinotecan (n = 89; 65%), oxaliplatin (n = 33; 24%), and other therapies (n = 8; 6%); no information is available for 6 patients. Furthermore, 103 patients (76%) received targeted therapy (anti-VEGF, anti-EGFR, or regorafenib). No information is available on the dosage of the medication [10].

Irrespective of the general unsuitability of the presented data, which neither address the benefit assessment's research question nor rest on a complete information retrieval, the comparisons between individual arms from different studies represent comparisons without common comparator. Due to the absence of randomization, these comparisons are subject to inherent uncertainty and fail to represent an adequate method for an indirect comparison [1]. Furthermore, in the present scenario of a comparison of individual arms from different studies, the identified effects for overall survival may potentially result solely from systematic bias due to confounders. In addition, no results on side effects are available, rendering a weighing of benefits versus harm impossible.

Company's research question A2: comparison of individual arms from the KEYNOTE-164 study and the RECOURSE and TERRA studies

For its research question A2 (patients after at least 2 prior systemic therapies), the company presented a comparison between individual arms from different studies, receiving pembrolizumab (KEYNOTE-164 study) versus trifluridine/tipiracil (RECOURSE study [13-16] and TERRA study [15-17]) regarding the patient-relevant outcomes of overall survival, serious adverse events, and severe adverse events. On the intervention side, the company used the KEYNOTE-164 study's subpopulation of patients with at least 2 prior systemic therapies (94 patients). On the comparator side, the company found no studies when taking into account MSI-H/dMMR status and therefore searched for studies irrespective of MSI-H/dMMR status. The company thus identified the RECOURSE and TERRA RCTs and used each of these studies' trifluridine/tipiracil arm for a comparison of individual arms.

The RECOURSE and TERRA studies are double-blind RCTs comparing trifluridine/tipiracil + best supportive care (BSC) versus placebo + BSC. Benefit assessment A20-35 on trifluridine/tipiracil in patients with metastatic colorectal cancer who have been previously treated describes these studies in detail [15]. Both studies included adult patients with metastatic colorectal cancer with at least 2 prior standard treatment regiments for the metastatic stage. Neither study provided any information on MSI-H or dMMR status. Given that only about 6.3% to 9.7% of metastatic colorectal cancer cases involve MSI-H/dMMR tumours (see Sections II.1.3.1 and II.1.3.2 of the full dossier assessment), it is safe to assume that a similarly low percentage of RECOURSE and TERRA participants' tumours exhibited this characteristic. A total of 800 patients in the RECOURSE study and 406 patients in the TERRA study were randomly allocated in a 2:1 ratio to treatment with trifluridine/tipiracil + BSC (534 RECOURSE participants and 271 TERRA participants) or placebo + BSC (266 RECOURSE participants and 135 TERRA participants). For the comparison between individual arms, the company used all patients of the RECOURSE study's trifluridine/tipiracil arm (N = 534) and, from the TERRA study's trifluridine/tipiracil arm, the subpopulation pretreated in line with the European marketing authorization according to the company's trifluridine/tipiracil assessment procedure (N = 61) [15,16]. In both studies, trifluridine/tipiracil was dosed in compliance with the SPC [5].

The company has submitted an unadjusted comparison and a matching-adjusted indirect comparison (MAIC) analysis, each without common comparator. In addition, the company has submitted noncomparative results of the KEYNOTE-164 study.

The MAIC analyses presented by the company without a common comparator are generally not an adequate option for confounder adjustment [1]. Furthermore, in the case of non-randomized comparisons without a common comparator, meaningful approaches towards confounder adjustment are usually only those that – unlike the MAIC analysis – involve the use of individual patient data [18]. The MAIC analysis takes confounding into account on the basis of aggregate data.

Irrespective of the general unsuitability of the presented data, which neither address the benefit assessment's research question nor rest on a complete information retrieval, the presented comparison of individual arms takes into account the approval-relevant and – according to the S3 guideline – prognostic criterion of MSI-H or dMMR [3] only on the intervention side, but not on the comparator side. Hence, the comparator side fails to reflect the population of the research question.

Irrespective of this defect, the study pool presented by the company without regard of MSI-H/dMMR status is incomplete because, for instance, the TALLISUR study was disregarded on the comparator side [15,16,19]. The TALLISUR study is a nonrandomized comparative study of trifluridine/tipiracil + BSC versus BSC in adult patients with metastatic colorectal cancer who had received prior treatment with available therapies or who are not candidates for available therapies. The study was designed and conducted due to the time limit imposed by the G-BA in the trifluridine/tipiracil benefit assessment in the therapeutic indication of metastatic colorectal cancer.

Summary

The data presented by the company are unsuitable for drawing any conclusions on the added benefit of pembrolizumab versus the ACT. Firstly, the data do not address the research question of the benefit assessment, and secondly, the company's information retrieval is incomplete with respect to the present benefit assessment's research question. Irrespective of these defects, the effects found in the company's comparisons of individual arms from different studies are potentially due solely to systematic bias from confounders; for the company's research question A2, the approval-relevant and prognostic criterion of MSI-H or dMMR was taken into account only on the intervention side, but not on the comparator side.

I 4 Results on added benefit

The company has presented no suitable data to assess the added benefit of pembrolizumab in comparison with the ACT in adult patients with unresectable or metastatic MSI-H or dMMR colorectal cancer following prior fluoropyrimidine-based combination therapy. This results in no hint of an added benefit of pembrolizumab in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

Table 5 summarizes the result of the assessment of added benefit of pembrolizumab in comparison with the ACT.

Table 5: Pembrolizumab – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adults with unresectable or metastatic MSI-H or dMMR colorectal cancer; after previous fluoropyrimidine-based combination therapy[b]	Individualized treatment[c, d] depending on the type and number of prior therapies, RAS and BRAF mutation status, the location of the primary tumour, the patient's general condition, and the risk of toxicity induced by anti-VEGF and anti-VEGFR drugs, choosing from the following options: ▪ 5-fluorouracil + folinic acid + irinotecan (FOLFIRI) ± bevacizumab or aflibercept or ramucirumab ▪ 5-fluorouracil + folinic acid + irinotecan (FOLFIRI) ± cetuximab or panitumumab[d] ▪ 5-fluorouracil + folinic acid + oxaliplatin (FOLFOX) ± bevacizumab ▪ capecitabine + oxaliplatin (CAPOX) ± bevacizumab ▪ 5-fluorouracil + folinic acid ± bevacizumab ▪ capecitabine ± bevacizumab ▪ irinotecan monotherapy ▪ panitumumab monotherapy[d] ▪ cetuximab monotherapy[d] ▪ trifluridine/tipiracil ▪ irinotecan + cetuximab[d] ▪ encorafenib + cetuximab[e]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. Patients are presumed not to be medically indicated for treatment with curative intent, and primary or secondary resection is presumed to be impossible.
c. First-line FOLFIRI-based therapy was to be followed by second-line FOLFOX-based therapy, and first-line FOLFOX-based therapy was to be followed by second-line FOLFIRI-based therapy.
d. Only for patients with RAS wild type.
e. Only for patients with BRAF-V600E mutation.

ACT: appropriate comparator therapy; BRAF: rapidly accelerated fibrosarcoma – isoform B; CAPOX: capecitabine + oxaliplatin; dMMR: mismatch repair deficiency; FOLFIRI: 5-fluorouracil + folinic acid + irinotecan; FOLFOX: 5-fluorouracil + folinic acid + oxaliplatin; G-BA: Federal Joint Committee; MSI-H: microsatellite instability high; RAS: rat sarcoma viral oncogene homologue; VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor

This assessment departs from the company's, which derived a hint of non-quantifiable added benefit on the basis of comparisons of individual arms from different studies separately for patients with 1 or at least 2 prior systematic therapies.

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.

1. Institute for Quality and Efficiency in Health Care. General Methods; Version 6.1 [online]. 2022 [Accessed: 17.08.2022]. URL: https://www.iqwig.de/methoden/general-methods_version-6-1.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://dx.doi.org/10.1002/bimj.201300274.

3. Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF. S3-Leitlinie Kolorektales Karzinom; Langversion 2.1 [online]. 2019 [Accessed: 20.09.2022]. URL: https://www.awmf.org/uploads/tx_szleitlinien/021-007OLl_S3_Kolorektales-Karzinom-KRK_2019-01.pdf.

4. Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie. Kolonkarzinom; Leitlinie; Empfehlungen der Fachgesellschaft zur Diagnostik und Therapie hämatologischer und onkologischer Erkrankungen [online]. 2022 [Accessed: 20.09.2022]. URL: https://www.onkopedia.com/de/onkopedia/guidelines/kolonkarzinom/@@pdf-latest?filename=kolonkarzinom.pdf.

5. Servier Deutschland. Lonsurf [online]. 2020 [Accessed: 13.09.2022]. URL: https://www.fachinfo.de.

6. Merck Sharp & Dohme. A Phase II Study of Pembrolizumab (MK-3475) as Monotherapy in Subjects with Previously Treated Locally Advanced Unresectable or Metastatic (Stage IV) Mismatched Repair Deficient or Microsatellite Instability-High Colorectal Carcinoma (KEYNOTE-164) [online]. [Accessed: 29.08.2022]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-001852-32.

7. Merck Sharp & Dohme. Study of Pembrolizumab (MK-3475) as Monotherapy in Participants With Previously-Treated Locally Advanced Unresectable or Metastatic Colorectal Cancer (MK-3475-164/KEYNOTE-164) [online]. 2022 [Accessed: 29.08.2022]. URL: https://ClinicalTrials.gov/show/NCT02460198

8. Le DT, Kim TW, Van Cutsem E et al. Phase II Open-Label Study of Pembrolizumab in Treatment-Refractory, Microsatellite Instability-High/Mismatch Repair-Deficient Metastatic Colorectal Cancer: KEYNOTE-164. J Clin Oncol 2020; 38(1): 11-19. https://dx.doi.org/10.1200/JCO.19.02107.

9. Merck Sharp & Dohme. Phase II Study of Pembrolizumab (MK-3475) as Monotherapy in Subjects with Previously Treated Locally Advanced Unresectable or Metastatic (Stage IV) Mismatched Repair Deficient or Microsatellite Instability-High Colorectal Carcinoma; study KEYNOTE-164; clinical study report - synopsis [unpublished]. 2021.

10. Tougeron D, Sueur B, Zaanan A et al. Prognosis and chemosensitivity of deficient MMR phenotype in patients with metastatic colorectal cancer: An AGEO retrospective multicenter study. Int J Cancer 2020; 147(1): 285-296. https://dx.doi.org/10.1002/ijc.32879.

11. MSD. KEYTRUDA 25 mg/ml Konzentrat zur Herstellung einer Infusionslösung [online]. 2022 [Accessed: 09.09.2022]. URL: https://www.fachinfo.de.

12. European Medicines Agency. Keytruda; Assessment report [online]. 2022 [Accessed: 13.09.2022]. URL: https://www.ema.europa.eu/documents/variation-report/keytruda-h-c-003820-ii-0109-epar-assessment-report-variation_en.pdf.

13. Taiho Oncology. Study of TAS-102 in Patients With Metastatic Colorectal Cancer Refractory to Standard Chemotherapies (RECOURSE) [online]. 2020 [Accessed: 02.05.2022]. URL: https://clinicaltrials.gov/ct2/show/NCT01607957.

14. Taiho Oncology. Randomized, Double-blind, Phase 3 Study of TAS-102 Plus Best Supportive Care (BSC) Versus Placebo Plus BSC in Patients with Metastatic Colorectal Cancer Refractory to Standard Chemotherapies [online]. [Accessed: 02.05.2022]. URL: https://www.clinicaltrialsregister.eu/ctr-search/trial/2012-000109-66/GB.

15. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Trifluridin/Tipiracil (Kolorektalkarzinom); Nutzenbewertung gemäß § 35a SGB V (Ablauf Befristung); Dossierbewertung [online]. 2020 [Accessed: 06.07.2020]. URL: http://www.iqwig.de/download/A20-35_Trifluridin-Tipiracil_Nutzenbewertung-35a-SGB-V_V1-0.pdf.

16. Servier Deutschland. Trifluridin/Tipiracil (Lonsurf): Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 2020 [Accessed: 20.07.2020]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/541/#dossier.

17. Taiho Pharmaceutical. Study of Trifluridine/Tipiracil (TAS-102) in Patients With Metastatic Colorectal Cancer in Asia (TERRA) [online]. 2020 [Accessed: 02.05.2022]. URL: https://clinicaltrials.gov/ct2/show/NCT01955837.

18. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Konzepte zur Generierung versorgungsnaher Daten und deren Auswertung zum Zwecke der Nutzenbewertung von Arzneimitteln nach § 35a SGB V; Rapid Report [online]. 2020 [Accessed: 02.06.2020]. URL: https://www.iqwig.de/download/A19-43_Versorgungsnahe-Daten-zum-Zwecke-der-Nutzenbewertung_Rapid-Report_V1-1.pdf.

19. Weiss L, Karthaus M, Riera-Knorrenschild J et al. Efficacy, safety and quality-of-life data from patients with pre-treated metastatic colorectal cancer receiving trifluridine/tipiracil: results of the TALLISUR trial. ESMO Open 2022; 7(1): 100391. https://dx.doi.org/10.1016/j.esmoop.2022.100391.

The full report (German version) is published under https://www.iqwig.de/en/projects/a22-75.html.