Nivolumab (colorectal cancer with dMMR or MSI-H, first line, combination with ipilimumab)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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[1] Translation of Sections I 1 to I 6 of the dossier assessment *Nivolumab (Kolorektalkarzinom mit dMMR oder MSI-H, Erstlinie, Kombination mit Ipilimumab) – Nutzenbewertung gemäß § 35a SGB V*. 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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Medical and scientific advice

No advisor on medical and scientific questions was involved in the present dossier assessment.

Patient and family involvement

No patients or families were involved in the present dossier assessment.

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Part I: Benefit assessment

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[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
dMMR	mismatch repair deficiency
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MSI-H	high microsatellite instability
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)

I 1 Executive summary of the benefit assessment

Background

The Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug nivolumab (in combination with ipilimumab) in accordance with §35a Social Code Book (SGB) V. 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 13 June 2025.

Research question

The aim of this report is to assess the added benefit of nivolumab in combination with ipilimumab (hereinafter referred to as nivolumab + ipilimumab) in comparison with the appropriate comparator therapy (ACT), pembrolizumab as monotherapy, in the first-line treatment of adult patients with unresectable or metastatic colorectal cancer with mismatch repair deficiency (dMMR) or high microsatellite instability (MSI-H).

The research question shown in Table 2 was defined in accordance with the ACT specified by the G-BA.

Table 2: Research question for the benefit assessment of nivolumab + ipilimumab

Therapeutic indication	**ACT**[a]
First-line treatment of adult patients with unresectable or metastatic colorectal cancer with dMMR or MSI-H[b]	pembrolizumab as monotherapy
a. Presented is the ACT specified by the G-BA. b. According to the G-BA, it is assumed for this therapeutic indication that treatment with curative intent or primary resection is not an option for patients with metastatic colorectal cancer. It is also assumed that antineoplastic therapy is indicated for patients in this therapeutic indication. ACT: appropriate comparator therapy; dMMR: mismatch repair deficiency; G-BA: Federal Joint Committee; MSI-H: high microsatellite instability	

The company followed the specification of the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) were used for the derivation of the added benefit.

Results

Concurring with the company, the review of the completeness of the study pool did not identify any relevant studies for the assessment of the added benefit of nivolumab + ipilimumab in comparison with the ACT.

Results on added benefit

No suitable data were available for the assessment of the added benefit of nivolumab + ipilimumab versus the ACT, pembrolizumab as monotherapy, in the first-line treatment of adult patients with unresectable or metastatic colorectal cancer with dMMR or MSI-H. There is no hint of an added benefit of nivolumab + ipilimumab 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 nivolumab + ipilimumab.

Table 3: Nivolumab + ipilimumab – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
First-line treatment of adult patients with unresectable or metastatic colorectal cancer with dMMR or MSI-H[b]	pembrolizumab as monotherapy	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, it is assumed for this therapeutic indication that treatment with curative intent or primary resection is not an option for patients with metastatic colorectal cancer. It is also assumed that antineoplastic therapy is indicated for patients in this therapeutic indication.

ACT: appropriate comparator therapy; dMMR: mismatch repair deficiency; G-BA: Federal Joint Committee; MSI-H: high microsatellite instability

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].

I 2 Research question

The aim of this report is to assess the added benefit of nivolumab in combination with ipilimumab (hereinafter referred to as nivolumab + ipilimumab) in comparison with the ACT, pembrolizumab as monotherapy, in the first-line treatment of adult patients with unresectable or metastatic colorectal cancer with dMMR or MSI-H.

The research question shown in Table 4 was defined in accordance with the ACT specified by the G-BA.

Table 4: Research question for the benefit assessment of nivolumab + ipilimumab

Therapeutic indication	**ACT**[a]
First-line treatment of adult patients with unresectable or metastatic colorectal cancer with dMMR or MSI-H[b]	pembrolizumab as monotherapy
a. Presented is the ACT specified by the G-BA. b. According to the G-BA, it is assumed for this therapeutic indication that treatment with curative intent or primary resection is not an option for patients with metastatic colorectal cancer. It is also assumed that antineoplastic therapy is indicated for patients in this therapeutic indication. ACT: appropriate comparator therapy; dMMR: mismatch repair deficiency; G-BA: Federal Joint Committee; MSI-H: high microsatellite instability	

The company followed the specification of the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs were used to derive the added benefit.

I 3 Information retrieval and study pool

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

Sources used by the company in the dossier:

- Study list on nivolumab + ipilimumab (status: 3 June 2025)
- Bibliographical literature search on nivolumab + ipilimumab (last search on 3 June 2025)
- Search of trial registries/trial results databases for studies on nivolumab + ipilimumab (last search on 3 June 2025)
- Search on the G-BA website for nivolumab + ipilimumab (last search on 3 June 2025)

To check the completeness of the study pool:

- Search of trial registries for studies on nivolumab + ipilimumab (last search on 30 June 2025); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, the review of the completeness of the study pool did not identify any studies for the direct comparison of nivolumab + ipilimumab with the ACT in the given therapeutic indication.

In Module 4 Z, the company presented the results of an interim analysis of the pivotal study CA209-8HW [3]. The company stated that it was using the results to present the medical benefit, but not to substantiate any added benefit of nivolumab + ipilimumab. The CA209-8HW study is an open-label, 3-arm RCT comparing nivolumab, nivolumab + ipilimumab, and chemotherapy of physician's choice. The study included adult patients with metastatic or recurrent unresectable colorectal cancer with dMMR or MSI-H. The company presented the results of the subpopulation of patients who received nivolumab + ipilimumab compared with chemotherapy of physician's choice, each as first-line treatment. The company excluded this study on the grounds that the comparator therapy used did not concur with the ACT specified by the G-BA, and did not use this study to derive the added benefit.

The company's approach was appropriate. Treatment in the comparator arm did not correspond to the ACT. This means that overall no suitable data were available for the comparison of nivolumab + ipilimumab with the G-BA's comparator therapy.

I 4 Results on added benefit

No suitable data were available for the assessment of the added benefit of nivolumab + ipilimumab versus the ACT, pembrolizumab as monotherapy, in the first-line treatment of adult patients with unresectable or metastatic colorectal cancer with dMMR or MSI-H. There is no hint of an added benefit of nivolumab + ipilimumab in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

The result of the assessment of the added benefit of nivolumab + ipilimumab in comparison with the ACT is summarized in Table 5.

Table 5: Nivolumab + ipilimumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
First-line treatment of adult patients with unresectable or metastatic colorectal cancer with dMMR or MSI-H[b]	pembrolizumab as monotherapy	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, it is assumed for this therapeutic indication that treatment with curative intent or primary resection is not an option for patients with metastatic colorectal cancer. It is also assumed that antineoplastic therapy is indicated for patients in this therapeutic indication.

ACT: appropriate comparator therapy; dMMR: mismatch repair deficiency; G-BA: Federal Joint Committee; MSI-H: high microsatellite instability

The assessment described above concurs with that by the company.

The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 7.0 [online]. 2023 [Accessed: 02.09.2024]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_version-7-0.pdf.

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The full report (German version) is published under https://www.iqwig.de/en/projects/a25-80.html.