Nivolumab (hepatocellular carcinoma, combination with ipilimumab)

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

EXTRACT

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

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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
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HCC	hepatocellular carcinoma
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
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) as first-line treatment of adult patients with unresectable or advanced hepatocellular carcinoma (HCC), in comparison with the appropriate comparator therapy (ACT).

The research questions presented in Table 2 were defined in accordance with the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of nivolumab + ipilimumab

Research question	Therapeutic indication[a]	ACT[b]
1	First-line treatment of adult patients with unresectable or advanced hepatocellular carcinoma ▪ with Child-Pugh A or no hepatic cirrhosis	▪ atezolizumab in combination with bevacizumab or ▪ durvalumab in combination with tremelimumab
2	First-line treatment of adult patients with unresectable or advanced hepatocellular carcinoma ▪ with Child-Pugh B	Best supportive care[c]

a. For the given therapeutic indication, it is assumed that curative treatment (for BLCL stage 0 and A), locoregional therapy in BLCL stage B, and transarterial (chemo)embolization (TACE or TAE) are (no longer) an option. It is also assumed that patients in BCLC stage D are ineligible for treatment with nivolumab in combination with ipilimumab.
b. Presented is the respective ACT specified by the G-BA.
c. Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

BCLC: Barcelona Clinic Liver Cancer; G-BA: Federal Joint Committee; TACE: transarterial chemoembolization; TAE: transarterial embolization

The company followed the specification of the ACT.

Since the company presented no data for either of the 2 research questions, both research questions are assessed below in joint sections of the report. 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 to derive the added benefit. This concurred with the company's inclusion criteria.

Results

Consistent with the findings of the company, a review of the completeness of the study pool did not identify any relevant RCTs for the direct comparison of nivolumab + ipilimumab with the ACT for either of the 2 research questions.

The company presented the study CA209-9DW in the dossier as the best available evidence, on the basis of which the marketing authorization of nivolumab for this therapeutic indication was granted. This study is an unblinded RCT comparing nivolumab + ipilimumab versus either sorafenib and lenvatinib, as selected by the investigator. Concurring with the assessment of the company, the study was unsuitable for the benefit assessment because the comparator therapy did not correspond to the ACT. This applies to both research questions. There were therefore no suitable data available for either research question.

Results on added benefit

Since no relevant study was available for the benefit assessment, there is no hint of an added benefit of nivolumab + ipilimumab in comparison with the ACT; an added benefit is therefore not proven. This applies to both research questions.

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.

[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: Nivolumab + ipilimumab – probability and extent of added benefit

Research question	**Therapeutic indication**[a]	**ACT**[b]	**Probability and extent of added benefit**
1	First-line treatment of adult patients with unresectable or advanced hepatocellular carcinoma ▪ with Child-Pugh A or no hepatic cirrhosis	▪ atezolizumab in combination with bevacizumab or ▪ durvalumab in combination with tremelimumab	Added benefit not proven
2	First-line treatment of adult patients with unresectable or advanced hepatocellular carcinoma ▪ with Child-Pugh B	Best supportive care[c]	Added benefit not proven

a. For the given therapeutic indication, it is assumed that curative treatment (for BLCL stage 0 and A), locoregional therapy in BLCL stage B, and transarterial (chemo)embolization (TACE or TAE) are (no longer) an option. It is also assumed that patients in BCLC stage D are ineligible for treatment with nivolumab in combination with ipilimumab.
b. Presented is the respective ACT specified by the G-BA.
c. Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

BCLC: Barcelona Clinic Liver Cancer; G-BA: Federal Joint Committee; TACE: transarterial chemoembolization; TAE: transarterial embolization

The G-BA decides on the added benefit.

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) as first-line treatment of adult patients with unresectable or advanced hepatocellular carcinoma (HCC), in comparison with the appropriate comparator therapy (ACT).

The research questions presented in Table 4 were defined in accordance with the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of nivolumab + ipilimumab

Research question	Therapeutic indication[a]	ACT[b]
1	First-line treatment of adult patients with unresectable or advanced hepatocellular carcinoma ▪ with Child-Pugh A or no hepatic cirrhosis	▪ atezolizumab in combination with bevacizumab or ▪ durvalumab in combination with tremelimumab
2	First-line treatment of adult patients with unresectable or advanced hepatocellular carcinoma ▪ with Child-Pugh B	Best supportive care[c]

a. For the given therapeutic indication, it is assumed that curative treatment (for BLCL stage 0 and A), locoregional therapy in BLCL stage B, and transarterial (chemo)embolization (TACE or TAE) are (no longer) an option. It is also assumed that patients in BCLC stage D are ineligible for treatment with nivolumab in combination with ipilimumab.
b. Presented is the respective ACT specified by the G-BA.
c. Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

BCLC: Barcelona Clinic Liver Cancer; G-BA: Federal Joint Committee; TACE: transarterial chemoembolization; TAE: transarterial embolization

The company followed the specification of the ACT.

Since the company presented no data for either of the 2 research questions, both research questions are assessed below in joint sections of the report. 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 to derive the added benefit. This concurred with the company's inclusion criteria.

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: 1 April 2025)
- Bibliographical literature search on nivolumab + ipilimumab (last search on 1 April 2025)
- Search of trial registries/trial results databases for studies on nivolumab + ipilimumab (last search on 24 March 2025)
- Search on the G-BA website for nivolumab + ipilimumab (last search on 1 April 2025)

To check the completeness of the study pool:

- Search of trial registries for studies on nivolumab + ipilimumab (last search on 1 July 2025); for search strategies, see I Appendix A of the full dossier assessment

Direct comparison

Concurring with the company's findings, the review of the completeness of the study pool did not identify any RCTs for a direct comparison of nivolumab + ipilimumab versus the ACT. This applies to both research questions.

Evidence presented by the company – CA2099DW study

Since the company did not identify any RCTs for the direct comparison of nivolumab + ipilimumab versus the respective ACT for either of the 2 research questions, it presented the study CA209-9DW [3] in the dossier as the best available evidence, on the basis of which the marketing authorization of nivolumab for this therapeutic indication was granted. The company itself stated that the study was not suitable for deriving an added benefit of nivolumab plus ipilimumab versus the respective ACT for either of the 2 research questions.

CA209-9DW is an unblinded RCT comparing nivolumab + ipilimumab versus either sorafenib and lenvatinib, as selected by the investigator. The study included adult patients with unresectable or advanced HCC and a Child-Pugh score of 5 or 6 who had not previously received systemic therapy for the HCC. A total of 668 patients were randomly allocated in a 1:1 ratio to the 2 study arms. Treatment with all drugs was in compliance with the summaries of product characteristics [4-6] and continued in both study arms until progression, withdrawal of consent or occurrence of unacceptable toxicity. Patients in the intervention arm could be treated for up to a maximum of 2 years. In both study arms, treatment beyond progression was possible if the patient continued to have a clinical benefit according to the investigator's assessment and tolerated the treatment. Overall survival was the primary

outcome of the study. In Module 4 Z B, the company presented study results from the 31 January 2024 data cut-off, which corresponded to the final analysis.

Concurring with the assessment of the company, the treatment in the comparator arm of CA209-9DW did not correspond to the ACT; hence no suitable data were available on the comparison of nivolumab + ipilimumab versus the comparator therapy specified by the G-BA. This applies to both research questions.

I 4 Results on added benefit

There were no suitable data for the assessment of the added benefit of nivolumab + ipilimumab as first-line treatment in adult patients with unresectable or advanced HCC in comparison with the ACT. This applies to both research questions. In either case, 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

Research question	Therapeutic indication[a]	ACT[b]	Probability and extent of added benefit
1	First-line treatment of adult patients with unresectable or advanced hepatocellular carcinoma ▪ with Child-Pugh A or no hepatic cirrhosis	▪ atezolizumab in combination with bevacizumab or ▪ durvalumab in combination with tremelimumab	Added benefit not proven
2	First-line treatment of adult patients with unresectable or advanced hepatocellular carcinoma ▪ with Child-Pugh B	Best supportive care[c]	Added benefit not proven

a. For the given therapeutic indication, it is assumed that curative treatment (for BLCL stage 0 and A), locoregional therapy in BLCL stage B, and transarterial (chemo)embolization (TACE or TAE) are (no longer) an option. It is also assumed that patients in BCLC stage D are ineligible for treatment with nivolumab in combination with ipilimumab.
b. Presented is the respective ACT specified by the G-BA.
c. Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

BCLC: Barcelona Clinic Liver Cancer; G-BA: Federal Joint Committee; TACE: transarterial chemoembolization; TAE: transarterial embolization

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.

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The full report (German version) is published under https://www.iqwig.de/en/projects/a25-79.html.