Tislelizumab (oesophageal carcinoma, advanced, second line)

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

EXTRACT

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Patient and family involvement

No feedback was received in the framework of 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
ECOG PS	Eastern Cooperative Oncology Group Performance Status
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PD-1	programmed cell death protein 1
PD-L1	programmed cell death ligand 1
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book 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 tislelizumab. 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 20 December 2024.

Research question

The aim of this report is to assess the added benefit of tislelizumab as monotherapy in comparison with nivolumab as the appropriate comparator therapy (ACT) in adult patients with unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma after prior platinum-based chemotherapy.

The research question shown in Table 2 resulted from the ACT specified by the G-BA.

Table 2: Research question for the benefit assessment of tislelizumab

Therapeutic indication	**ACT[a]**
Adult patients with unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma after prior platinum-based chemotherapy[b]	Nivolumab
a. Presented is the ACT specified by the G-BA. b. The ACT was determined based on the study population of the BGB-A317-302 study. In accordance with the inclusion and exclusion criteria, the study only included patients who had not received prior therapy with a PD-1/PD-L1 antibody. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; PD-1: programmed cell death protein 1; PD-L1: programmed cell death ligand 1	

On 27 February 2024, the G-BA adjusted the ACT as shown in Table 2. In its dossier, however, the company referred to the ACT previously specified by the G-BA on 13 July 2023, defining 2 research questions based on the suitability of a systemic antineoplastic therapy option:

- Subpopulation A: Adult patients with unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma with progression during or after previous platinum-based chemotherapy, for whom systemic antineoplastic therapy is a suitable treatment option:
  - Treatment of physician's choice, selecting from docetaxel, nivolumab (only for patients who previously underwent fluoropyrimidine- and platinum-based combination chemotherapy) or paclitaxel

- Subpopulation B: Adult patients with unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma with progression during or after previous platinum-based chemotherapy, for whom further chemotherapy is not a suitable treatment option:
  - Best supportive care

The company claimed to be following the ACT selection for subpopulation A specified by the G-BA. In addition to the treatment options docetaxel and paclitaxel originally specified by the G-BA in the ACT, the company also listed irinotecan.

In the dossier, the company therefore deviated from the ACT currently specified by the G-BA by referring to the ACT previously determined by the G-BA, dated 13 July 2023. This benefit assessment was conducted in comparison with the current ACT specified by the G-BA on 27 February 2024, as shown in Table 2.

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 concurs with the company's inclusion criteria.

Results

A review of the completeness of the study pool identified no relevant studies for assessing the added benefit of tislelizumab in comparison with the ACT. This deviates from the company's view, which identified the RCT RATIONALE 302 from its information retrieval and used this study to assess the added benefit. The G-BA specified nivolumab as the ACT. In the RATIONALE 302 study, patients in the comparator arm were given a treatment of physician's choice, selecting from docetaxel, paclitaxel and irinotecan. The RATIONALE 302 study is therefore not suitable for the assessment of the added benefit of tislelizumab, as the ACT of the G-BA was not implemented in the study, i.e. no data are available for the comparison of tislelizumab with the comparator therapy specified by the G-BA.

Results on added benefit

Since no relevant study is available for the benefit assessment, there is no hint of an added benefit of tislelizumab 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 shows a summary of probability and extent of the added benefit of tislelizumab.

Table 3: Tislelizumab – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adult patients with unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma after prior platinum-based chemotherapy[b]	Nivolumab	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. The ACT was determined based on the study population of the BGB-A317-302 study. In accordance with the inclusion and exclusion criteria, the study only included patients who had not received prior therapy with a PD-1/PD-L1 antibody.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; PD-1: programmed cell death protein 1; PD-L1: programmed cell death ligand 1

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 tislelizumab as monotherapy in comparison with nivolumab as the ACT in adult patients with unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma after prior platinum-based chemotherapy.

The research question shown in Table 4 resulted from the ACT specified by the G-BA.

Table 4: Research question for the benefit assessment of tislelizumab

Therapeutic indication	**ACT[a]**
Adult patients with unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma after prior platinum-based chemotherapy[b]	Nivolumab
a. Presented is the ACT specified by the G-BA. b. The ACT was determined based on the study population of the BGB-A317-302 study. In accordance with the inclusion and exclusion criteria, the study only included patients who had not received prior therapy with a PD-1/PD-L1 antibody. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; PD-1: programmed cell death protein 1; PD-L1: programmed cell death ligand 1	

On 27 February 2024, the G-BA adjusted the ACT as shown in Table 4. In its dossier, however, the company referred to the ACT previously specified by the G-BA on 13 July 2023 [3], defining 2 research questions based on the suitability of a systemic antineoplastic therapy option:

- Subpopulation A: Adult patients with unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma with progression during or after previous platinum-based chemotherapy, for whom systemic antineoplastic therapy is a suitable treatment option:
  - Treatment of physician's choice, selecting from docetaxel, nivolumab (only for patients who previously underwent fluoropyrimidine- and platinum-based combination chemotherapy) or paclitaxel
- Subpopulation B: Adult patients with unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma with progression during or after previous platinum-based chemotherapy, for whom further chemotherapy is not a suitable treatment option:
  - Best supportive care

The company claimed to be following the ACT selection for subpopulation A specified by the G-BA. In addition to the treatment options docetaxel and paclitaxel originally specified by the G-BA in the ACT, the company also listed irinotecan.

In the dossier, the company therefore deviated from the ACT currently specified by the G-BA by referring to the ACT previously determined by the G-BA, dated 13 July 2023. This benefit assessment was conducted in comparison with the current ACT specified by the G-BA on 27 February 2024, as shown in Table 4.

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. This concurs 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 tislelizumab (status: 21 October 2024)
- Bibliographical literature search on tislelizumab (last search on 21 October 2024)
- Search of trial registries/trial results databases for studies on tislelizumab (last search on 21 October 2024)
- Search on the G-BA website for tislelizumab (last search on 21 October 2024)

To check the completeness of the study pool:

- Search of trial registries for studies on tislelizumab (last search on 15 January 2025); for search strategies, see I Appendix A of the full dossier assessment

A review of the completeness of the study pool – based on the current research question and the ACT as per the G-BA – identified no relevant studies for assessing the added benefit of tislelizumab in comparison with the ACT.

This deviates from the assessment of the company: The company's information retrieval identified the RCT RATIONALE 302 [4], which compared tislelizumab with a treatment of physician's choice selecting from docetaxel, paclitaxel or irinotecan, and which was used by the company to assess the added benefit for its subpopulation A. The RATIONALE 302 study is not suitable for the assessment of the added benefit of tislelizumab, however, as the ACT of the G-BA was not implemented in the study, i.e. no data are available for the comparison of tislelizumab with the comparator therapy specified by the G-BA. This is justified below.

In Module 4 A of the dossier, the company did not present any data for its subpopulation B. This is not commented on below and remains without consequence, as these patients are not included in the G-BA's research question.

Evidence provided by the company

RATIONALE 302 study

The RATIONALE 302 study is a completed, multicentre, open-label, phase 3 RCT, which compared tislelizumab with treatment of physician's choice, selecting from docetaxel, paclitaxel or irinotecan for the treatment of patients in the therapeutic indication to be assessed. The study included adult patients with unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma after previous first-line systemic treatment, which was defined as platinum-based chemotherapy as per protocol amendment 3. Patients had to have

an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1. According to the study eligibility criteria, patients who had received 2 or more lines of systemic treatment for advanced or metastatic, unresectable oesophageal squamous cell carcinoma were excluded. Prior therapy targeting PD-1 or PD-L1 also led to exclusion from the study.

A total of 512 patients were enrolled in the RATIONALE 302 study, including 498 (97.3%) who had been pretreated with platinum-based systemic therapy. Patients were randomized in a 1:1 ratio either to treatment with tislelizumab (N = 256) or to treatment of physician's choice, selecting from docetaxel, paclitaxel or irinotecan (N = 256). Randomization was stratified according to the characteristics of region (Asia [excluding Japan] versus Japan versus Europe/United States), ECOG PS (0 versus 1), and the chosen treatment of physician's choice (paclitaxel versus docetaxel versus irinotecan).

The primary outcome of the RATIONALE 302 study was overall survival. Patient-relevant secondary outcomes were outcomes on morbidity, health-related quality of life and adverse events.

No data on the comparison of tislelizumab with the comparator therapy specified by the G-BA

The G-BA specified nivolumab as the ACT. In the RATIONALE 302 study, patients in the comparator arm were given a treatment of physician's choice, selecting from docetaxel, paclitaxel and irinotecan. Thus, the ACT was not implemented in the RATIONALE 302 study, i.e. no data are available on the comparison of tislelizumab with the comparator therapy specified by the G-BA.

The RATIONALE 302 study is therefore not suitable for assessing the added benefit of tislelizumab in patients with unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma after prior platinum-based chemotherapy in comparison with the ACT specified by the G-BA.

I 4 Results on added benefit

No suitable data are available for the assessment of the added benefit of tislelizumab for the treatment of adult patients with unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma after prior platinum-based chemotherapy. There is no hint of an added benefit of tislelizumab in comparison with the ACT nivolumab.

I 5 Probability and extent of added benefit

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

Table 5: Tislelizumab – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adult patients with unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma after prior platinum-based chemotherapy[b]	Nivolumab	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. The ACT was determined based on the study population of the BGB-A317-302 study. In accordance with the inclusion and exclusion criteria, the study only included patients who had not received prior therapy with a PD-1/PD-L1 antibody.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; PD-1: programmed cell death protein 1; PD-L1: programmed cell death ligand 1

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

The G-BA decides on the added benefit.

I 6 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. 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/a24-130.html.