Tislelizumab
(oesophageal carcinoma, advanced, first line)

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

EXTRACT

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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.

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Part I: Benefit assessment

I Table of contents

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
5-FU	5-fluorouracil
ACT	appropriate comparator therapy
CPS	combined positive score
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PD-L1	programmed cell death ligand 1
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
TAP	Tumour Area Positivity

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 (in combination with platinum-based chemotherapy). 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, in combination with platinum-based chemotherapy, in comparison with the appropriate comparator therapy (ACT) for the first-line treatment of adult patients with unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma whose tumours express programmed cell death ligand 1 (PD-L1) with a Tumour Area Positivity (TAP) score ≥ 5%.

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

Table 2: Research questions for the benefit assessment of tislelizumab in combination with platinum-based chemotherapy

Research question	**Therapeutic indication**[a]	**ACT**[b, c]
First-line treatment of adults with unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma that is not treatable with curative intent, whose tumours express PD-L1 with a TAP score ≥ 5%, and		
1	with tumour cell PD-L1 expression ≥ 1% or a CPS ≥ 10	▪ nivolumab in combination with fluoropyrimidine- and platinum-based chemotherapy (tumour cell PD-L1 expression ≥ 1%) or ▪ nivolumab in combination with ipilimumab (tumour cell PD-L1 expression ≥ 1%) or ▪ pembrolizumab in combination with fluoropyrimidine- and platinum-based chemotherapy (CPS ≥ 10)
2	no tumour cell PD-L1 expression ≥ 1% and no CPS ≥ 10	Cisplatin in combination with 5-fluorouracil[d]

a. According to the G-BA, the treatment decision in this therapeutic indication depends, among other things, on the PD-L1 expression of the tumours. PD-L1 expression is determined using various methods, including tumour cell PD-L1 expression, CPS or TAP score. In the therapeutic indication in question, tislelizumab is approved for patients with a TAP score ≥ 5%. The breakdown of the research question as per the G-BA – in accordance with the approval characteristics of the eligible drugs at the time of determination of the ACT – is based on tumour cell PD-L1 expression or CPS.
b. Presented is the respective ACT specified by the G-BA.
c. In accordance with the G-BA, it is assumed that curative treatment with definitive radiochemotherapy is not an option for patients with unresectable cancer.
d. In accordance with the G-BA, it is assumed that the patients are candidates for cisplatin-containing chemotherapy.

ACT: appropriate comparator therapy; CPS: combined positive score; G-BA: Federal Joint Committee; PD-L1: programmed cell death ligand 1; TAP: Tumour Area Positivity

The company initially claimed to be following the ACT specified by the G-BA. However, the populations in the company's research questions deviate from the G-BA's specifications. It allocated

- patients with a PD-L1 expression of ≥ 10% (TAP score ≥ 10%) to research question 1, and
- patients with a PD-L1 expression of ≥ 5% to < 10% (TAP score ≥ 5% to < 10%) to research question 2.

The company only used the TAP score to determine PD-L1 expression. It did not take tumour cell PD-L1 expression and combined positive score (CPS) into account. In addition, it specified threshold values for the TAP score that deviate from the G-BA specifications (research question 1: TAP score ≥ 10%, research question 2: TAP score ≥ 5% to < 10%). The company did

not justify its approach. It is only stated in Module 3 E of its dossier that the TAP score has a high degree of consistency with the CPS [1,2]. There is no explanation in the company's dossier regarding the fact that patients with a TAP score ≥ 5% to < 10% do not have a CPS ≥ 10. The company did not provide any information on the degree of consistency between TAP score and tumour cell PD-L1 expression. The approach of the company is not appropriate.

This benefit assessment was conducted based on the research questions and in comparison with the ACT specified by the G-BA.

Results

A review of the completeness of the study pool identified no relevant studies on the comparison of tislelizumab in combination with platinum-based chemotherapy versus the ACT for either research question.

For research question 1 (patients with a TAP score ≥ 5% and a tumour cell PD-L1 expression ≥ 1% or a CPS ≥ 10), this is in line with the company, which also found no relevant studies.

For research question 2 (patients with a TAP score ≥ 5%, no tumour cell PD-L1 expression ≥ 1% and no CPS ≥ 10), the company included the RATIONALE 306 [3] study in its study pool. It presented the results of what it considered to be a relevant subpopulation and used these results for the assessment. The data presented by the company are unsuitable for drawing conclusions on the added benefit of tislelizumab in combination with platinum-based chemotherapy in comparison with the ACT. This is justified below.

RATIONALE 306 study

The RATIONALE 306 study is a double-blind, multicentre and completed randomized controlled trial (RCT), which included patients with unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma with PD-L1-expressing tumours (TAP score ≥ 5%) under first-line treatment. The study compared tislelizumab versus placebo, each in combination with platinum-based chemotherapy. The following treatment options were available for chemotherapy: platinum (cisplatin or oxaliplatin) + 5-fluorouracil (5-FU), platinum (cisplatin or oxaliplatin) + capecitabine, or platinum (cisplatin or oxaliplatin) + paclitaxel. The chemotherapy was assigned by the physician prior to randomization. A total of 326 patients were randomized to the intervention arm and 323 to the comparator arm of the study. The study's primary outcome was overall survival.

The subpopulation presented by the company is unsuitable for the benefit assessment

The company presented results of a subpopulation of those patients who were treated with tislelizumab or placebo, each in combination with cisplatin + 5-FU, and who had a TAP score of ≥ 5% to < 10%. This subpopulation comprised 13 patients in the intervention arm and 17 in the comparator arm.

The approach of the company is not appropriate. Firstly, the restriction of the subpopulation to a TAP score of ≥ 5% to < 10% does not comply with the G-BA specification (TAP score ≥ 5%, no tumour cell PD-L1 expression ≥ 1% and no CPS ≥ 10). Secondly, in the RATIONALE 306 study, PD-L1 expression was only determined with the TAP score, and not with both the CPS and tumour cell PD-L1 expression. The company provided no evidence that the subpopulation it presented was without both tumour cell PD-L1 expression ≥ 1% and CPS ≥ 10, which would have allowed it to be assigned to research question 2.

Therefore, the RATIONALE 306 subpopulation presented by the company cannot be used for the benefit assessment of tislelizumab in combination with platinum-based chemotherapy.

Results on added benefit

Since no suitable data are available for the benefit assessment, there is no hint of an added benefit of tislelizumab in combination with platinum-based chemotherapy 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 tislelizumab in combination with platinum-based chemotherapy.

[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 [4,5].

Table 3: Tislelizumab in combination with platinum-based chemotherapy – probability and extent of added benefit

Research question	**Therapeutic indication**[a]	**ACT**[b, c]	**Probability and extent of added benefit**
First-line treatment of adults with unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma that is not treatable with curative intent, whose tumours express PD-L1 with a TAP score ≥ 5%, and			
1	with tumour cell PD-L1 expression ≥ 1% or a CPS ≥ 10	▪ nivolumab in combination with fluoropyrimidine- and platinum-based chemotherapy (tumour cell PD-L1 expression ≥ 1%) or ▪ nivolumab in combination with ipilimumab (tumour cell PD-L1 expression ≥ 1%) or ▪ pembrolizumab in combination with fluoropyrimidine- and platinum-based chemotherapy (CPS ≥ 10)	Added benefit not proven
2	no tumour cell PD-L1 expression ≥ 1% and no CPS ≥ 10	Cisplatin in combination with 5-fluorouracil[d]	Added benefit not proven

a. According to the G-BA, the treatment decision in this therapeutic indication depends, among other things, on the PD-L1 expression of the tumours. PD-L1 expression is determined using various methods, including tumour cell PD-L1 expression, CPS or TAP score. In the therapeutic indication in question, tislelizumab is approved for a TAP score ≥ 5%. The given differentiation of the research question according to the G-BA – in accordance with the approval characteristics of the eligible drugs at the time of determination of the ACT – is based on tumour cell PD-L1 expression or CPS.
b. Presented is the respective ACT specified by the G-BA.
c. In accordance with the G-BA, it is assumed that curative treatment with definitive radiochemotherapy is not an option for patients with unresectable cancer.
d. In accordance with the G-BA, it is assumed that the patients are candidates for cisplatin-containing chemotherapy.

ACT: appropriate comparator therapy; CPS: combined positive score; G-BA: Federal Joint Committee; PD-L1: programmed cell death ligand 1; TAP: Tumour Area Positivity

The G-BA decides on the added benefit.

I 2 Research question

The aim of this report is to assess the added benefit of tislelizumab, in combination with platinum-based chemotherapy, in comparison with the ACT for the first-line treatment of adult patients with unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma whose tumours express PD-L1 with a TAP score ≥ 5%.

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

Table 4: Research questions for the benefit assessment of tislelizumab in combination with platinum-based chemotherapy

Research question	Therapeutic indication[a]	ACT[b, c]
First-line treatment of adults with unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma that is not treatable with curative intent, whose tumours express PD-L1 with a TAP score ≥ 5%, and		
1	with tumour cell PD-L1 expression ≥ 1% or a CPS ≥ 10	▪ nivolumab in combination with fluoropyrimidine- and platinum-based chemotherapy (tumour cell PD-L1 expression ≥ 1%) or ▪ nivolumab in combination with ipilimumab (tumour cell PD-L1 expression ≥ 1%) or ▪ pembrolizumab in combination with fluoropyrimidine- and platinum-based chemotherapy (CPS ≥ 10)
2	no tumour cell PD-L1 expression ≥ 1% and no CPS ≥ 10	Cisplatin in combination with 5-fluorouracil[d]

a. According to the G-BA, the treatment decision in this therapeutic indication depends, among other things, on the PD-L1 expression of the tumours. PD-L1 expression is determined using various methods, including tumour cell PD-L1 expression, CPS or TAP score. In the therapeutic indication in question, tislelizumab is approved for patients with a TAP score ≥ 5%. The breakdown of the research question as per the G-BA – in accordance with the approval characteristics of the eligible drugs at the time of determination of the ACT – is based on tumour cell PD-L1 expression or CPS.
b. Presented is the respective ACT specified by the G-BA.
c. In accordance with the G-BA, it is assumed that curative treatment with definitive radiochemotherapy is not an option for patients with unresectable cancer.
d. In accordance with the G-BA, it is assumed that the patients are candidates for cisplatin-containing chemotherapy.

ACT: appropriate comparator therapy; CPS: combined positive score; G-BA: Federal Joint Committee; PD-L1: programmed cell death ligand 1; TAP: Tumour Area Positivity

The company initially claimed to be following the ACT specified by the G-BA. However, the populations in the company's research questions deviate from the G-BA's specifications. It allocated

- patients with a PD-L1 expression of ≥ 10% (TAP score of ≥ 10%) to research question 1, and
- patients with a PD-L1 expression of ≥ 5% to < 10% (TAP score of ≥ 5% to < 10%) to research question 2.

The company only used the TAP score to determine PD-L1 expression. It did not take tumour cell PD-L1 expression and CPS into account. In addition, it specified threshold values for the TAP score that deviate from the G-BA specifications (research question 1: TAP score ≥ 10%, research question 2: TAP score ≥ 5% to < 10%). The company did not justify its approach. It is only stated in Module 3 E of its dossier that the TAP score has a high degree of consistency with the CPS [1,2]. There is no explanation in the company's dossier regarding the fact that patients with a TAP score ≥ 5% to < 10% do not have a CPS ≥ 10. The company did not provide any information on the degree of consistency between TAP score and tumour cell PD-L1 expression.

The approach of the company is not appropriate. The treatment decision in this therapeutic indication depends on the PD-L1 expression. This can be determined using various methods, including tumour cell PD-L1 expression, CPS or TAP score. The approval of each of the various immune checkpoint inhibitors in this therapeutic indication is linked to one of these methods with a specific threshold value: tislelizumab to the TAP score of ≥ 5%, pembrolizumab to the CPS of ≥ 10, and nivolumab to the tumour cell PD-L1 expression of ≥ 1%. These different approvals are reflected in the research questions and the ACT of the G-BA.

This benefit assessment was conducted based on the research questions and in comparison with the ACT specified by the G-BA.

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 of 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 identified no relevant studies on the comparison of tislelizumab in combination with platinum-based chemotherapy versus the ACT for either of the research questions.

For research question 1 (patients with a TAP score ≥ 5% and a tumour cell PD-L1 expression ≥ 1% or a CPS ≥ 10), this is in line with the company, which also found no relevant studies.

For research question 2 (patients with a TAP score ≥ 5%, no tumour cell PD-L1 expression ≥ 1% and no CPS ≥ 10), the company included the RATIONALE 306 [3] study in its study pool. It presented the results of what it considered to be a relevant subpopulation and used these results for the assessment. The data presented by the company are unsuitable for drawing conclusions on the added benefit of tislelizumab in combination with platinum-based chemotherapy in comparison with the ACT. This is justified below.

RATIONALE 306 study

The RATIONALE 306 study is a double-blind, multicentre and completed RCT, which included patients with unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma with PD-L1-expressing tumours (TAP score ≥ 5%) under first-line treatment. The study compared tislelizumab versus placebo, each in combination with platinum-based chemotherapy. The following treatment options were available for chemotherapy: platinum (cisplatin or oxaliplatin) + 5-FU, platinum (cisplatin or oxaliplatin) + capecitabine, or platinum (cisplatin or oxaliplatin) + paclitaxel. The chemotherapy was assigned by the physician prior to randomization. A total of 326 patients were randomized to the intervention arm and 323 to the comparator arm of the study. The study's primary outcome was overall survival.

The subpopulation presented by the company is unsuitable for the benefit assessment

The company presented results of a subpopulation of those patients who were treated with tislelizumab or placebo, each in combination with cisplatin + 5-FU, and who had a TAP score of ≥ 5% to < 10%. This subpopulation comprised 13 patients in the intervention arm and 17 in the comparator arm. According to the information provided by the company in Module 4 E, randomization in the RATIONALE 306 study was broken by the selection of the subpopulation. The company did not justify this assessment.

The approach of the company is not appropriate. Firstly, the restriction of the subpopulation to a TAP score of ≥ 5% to < 10% does not comply with the G-BA specification (TAP score ≥ 5%, no tumour cell PD-L1 expression ≥ 1% and no CPS ≥ 10). Secondly, in the RATIONALE 306 study, PD-L1 expression was only determined with the TAP score, and not with both the CPS and tumour cell PD-L1 expression. The company provided no evidence that the subpopulation it presented was without both tumour cell PD-L1 expression ≥ 1% and CPS ≥ 10, which would have allowed it to be assigned to research question 2.

Therefore, the RATIONALE 306 subpopulation presented by the company cannot be used for the benefit assessment of tislelizumab in combination with platinum-based chemotherapy.

I 4 Results on added benefit

No suitable data are available for the assessment of the added benefit of tislelizumab in adults with unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma that is not treatable with curative intent, whose tumours express PD-L1 with a TAP score ≥ 5%. There is no hint of an added benefit of tislelizumab in combination with platinum-based chemotherapy in comparison with the ACT for either of the research questions of the G-BA; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

Table 5 presents a summary of the probability and extent of the added benefit of tislelizumab in combination with platinum-based chemotherapy.

Table 5: Tislelizumab in combination with platinum-based chemotherapy – probability and extent of added benefit

Research question	Therapeutic indication[a]	ACT[b, c]	Probability and extent of added benefit
First-line treatment of adults with unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma that is not treatable with curative intent, whose tumours express PD-L1 with a TAP score ≥ 5%, and			
1	with tumour cell PD-L1 expression ≥ 1% or a CPS ≥ 10	▪ nivolumab in combination with fluoropyrimidine- and platinum-based chemotherapy (tumour cell PD-L1 expression ≥ 1%) or ▪ nivolumab in combination with ipilimumab (tumour cell PD-L1 expression ≥ 1%) or ▪ pembrolizumab in combination with fluoropyrimidine- and platinum-based chemotherapy (CPS ≥ 10)	Added benefit not proven
2	no tumour cell PD-L1 expression ≥ 1% and no CPS ≥ 10	Cisplatin in combination with 5-fluorouracil[d]	Added benefit not proven

a. According to the G-BA, the treatment decision in this therapeutic indication depends, among other things, on the PD-L1 expression of the tumours. PD-L1 expression is determined using various methods, including tumour cell PD-L1 expression, CPS or TAP score. In the therapeutic indication in question, tislelizumab is approved for a TAP score ≥ 5%. The given differentiation of the research question according to the G-BA – in accordance with the approval characteristics of the eligible drugs at the time of determination of the ACT – is based on tumour cell PD-L1 expression or CPS.
b. Presented is the respective ACT specified by the G-BA.
c. In accordance with the G-BA, it is assumed that curative treatment with definitive radiochemotherapy is not an option for patients with unresectable cancer.
d. In accordance with the G-BA, it is assumed that the patients are candidates for cisplatin-containing chemotherapy.

ACT: appropriate comparator therapy; CPS: combined positive score; G-BA: Federal Joint Committee; PD-L1: programmed cell death ligand 1; TAP: Tumour Area Positivity

The assessment described above differs from that of the company, which derived a hint of a non-quantifiable added benefit for patients with unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma in first-line treatment, with PD-L1 expression of ≥ 5% to < 10%.

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. Liu C, Fang F, Kong Y et al. Tumor Area Positivity (TAP) score of programmed death-ligand 1 (PD-L1): a novel visual estimation method for combined tumor cell and immune cell scoring. Diagn Pathol 2023; 18(1): 48. https://doi.org/10.1186/s13000-023-01318-8.

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The full report (German version) is published under https://www.iqwig.de/en/projects/a24-129.html.