# Tislelizumab (gastric or gastroesophageal junction adenocarcinoma, HER2-negative)

## 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 *Tislelizumab (Adenokarzinom des Magens oder des gastroösophagealen Übergangs, HER2-negativ) – 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**

- Jörg Trojan

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

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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 |
| CPS | combined positive score |
| ECOG PS | Eastern Cooperative Oncology Group Performance Status |
| G-BA | Gemeinsamer Bundesausschuss (Federal Joint Committee) |
| HER2 | human epidermal growth factor receptor 2 |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care) |
| PD-L1 | programmed 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. 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- and fluoropyrimidine-based chemotherapy (hereinafter referred to as tislelizumab + chemotherapy), in comparison with the appropriate comparator therapy (ACT) for the first-line treatment of adults with human epidermal growth factor receptor 2 (HER2)-negative locally advanced unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumours express programmed death ligand 1 (PD-L1) with a Tumour Area Positivity (TAP) score ≥ 5%.

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

Table 2: Research questions for the benefit assessment of tislelizumab + chemotherapy

| Research question | Therapeutic indication | ACT[a, b] |
|---|---|---|
| Adults with HER2-negative locally advanced unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma and tumour PD-L1 expression with a TAP (Tumour Area Positivity) score ≥ 5%, and | | |
| 1 | tumour PD-L1 expression ≥ 1 (combined positive score; CPS)[c] for first-line treatment | ▪ nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy (only for tumours with PD-L1 expression [CPS] ≥ 5)<br>or<br>▪ pembrolizumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy (only for tumours with PD-L1 expression [CPS] ≥ 1) |
| 2 | tumour PD-L1 expression < 1 (combined positive score; CPS)[c] for first-line treatment | ▪ cisplatin + capecitabine<br>or<br>▪ oxaliplatin + capecitabine<br>or<br>▪ cisplatin + S-1 (tegafur/gimeracil/oteracil)<br>or<br>▪ cisplatin + 5-fluorouracil (only for patients with oesophageal adenocarcinoma)<br>or<br>▪ cisplatin + 5-fluorouracil + folinic acid (only for patients with oesophageal adenocarcinoma)<br>or<br>▪ epirubicin + cisplatin + capecitabine<br>or<br>▪ epirubicin + cisplatin + 5-fluorouracil<br>or<br>▪ epirubicin + oxaliplatin + capecitabine<br>or<br>▪ docetaxel + cisplatin + 5-fluorouracil<br>or<br>▪ 5-fluorouracil + oxaliplatin + epirubicin (only for patients with oesophageal adenocarcinoma) |

a. Presented are the respective ACTs specified by the G-BA.
b. It is assumed that curative treatment with definitive radiochemotherapy is not an option for patients with unresectable cancer.
c. The treatment decision in this therapeutic indication depends, among other things, on the PD-L1 expression of the tumours. In the therapeutic indication in question, tislelizumab is approved for TAP ≥ 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 the CPS, however. According to the G-BA, the company was required to explain in the dossier compiled for the benefit assessment to what extent patients whose tumours express PD-L1 with a TAP score ≥ 5% are to be assigned to research question 1 (CPS ≥ 1) or research question 2 (CPS < 1).

ACT: appropriate comparator therapy; CPS: combined positive score; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; PD-L1: programmed death ligand 1; TAP: Tumour Area Positivity

Shortly before the dossier was received on 10 December 2024, the G-BA adjusted the ACT as shown in Table 2. Based on this adjustment, the population was divided according to tumour PD-L1 expression, resulting in chemotherapy alone being an ACT option only for patients with a tumour PD-L1 expression of < 1 (combined positive score [CPS]). For patients with a tumour PD-L1 expression of ≥ 1 (CPS), however, the resulting ACT is immunochemotherapy. According to the G-BA, the company was required to explain to what extent the tumour PD-L1 expression, in accordance with the approved therapeutic indication of tislelizumab (TAP ≥ 5%), is to be assigned to research question 1 (CPS ≥ 1) or research question 2 (CPS < 1).

The company deviated from the G-BA's specification of the ACT. It did not refer to the current ACT of 10 December 2024, but to the ACT from the consultation of 11 April 2024, in which the population was not divided according to tumour PD-L1 expression. According to the company, it was following this ACT and selected oxaliplatin + capecitabine (independent of tumour PD-L1 expression according to CPS) from the options. Accordingly, the company did not present any data divided by research question and also did not explain to what extent a tumour PD-L1 expression of TAP ≥ 5% is to be assigned to research question 1 (CPS ≥ 1) or 2 (CPS < 1) of this benefit assessment. The present benefit assessment was conducted 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. Randomized controlled trials (RCTs) were used to derive the added benefit.

**Results**

As described above, the company did not refer to the current ACT of the G-BA, but to the ACT from the consultation of 11 April 2024, in which the population was not divided according to tumour PD-L1 expression. Accordingly, the company did not present any data divided by research question. From its information retrieval, the company identified the RCT RATIONALE 305 and used the study's subpopulation of patients with tumour PD-L1 expression with a TAP score of ≥ 5% for its assessment. The presented data were unsuitable for the present benefit assessment, however. The RATIONALE 305 study is described below and reasons for the unsuitability of the data presented by the company in the dossier are provided for research questions 1 and 2 of this assessment in turn.

***Evidence presented by the company – RATIONALE 305 study***

The RATIONALE 305 study is a completed, double-blind, randomized phase III study comparing tislelizumab versus placebo – each in combination with platinum- and fluoropyrimidine-based chemotherapy – as first-line treatment in adult patients with locally advanced unresectable or metastatic HER2-negative gastric or gastroesophageal junction adenocarcinoma. The chemotherapy options were oxaliplatin + capecitabine, or cisplatin + 5-fluorouracil.

A total of 997 patients were included in the study and randomly allocated in a 1:1 ratio either to treatment with tislelizumab + chemotherapy (N = 501) or to placebo + chemotherapy (N = 496). In accordance with the approval of tislelizumab, the company used the subpopulation of patients with a tumour PD-L1 expression of TAP ≥ 5% (N = 274 versus N = 272) for the benefit assessment.

***Research question 1: No data on the comparison of tislelizumab with the comparator therapy specified by the G-BA***

The ACT specified by the G-BA for adults under first-line treatment of HER2-negative locally advanced unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma and tumour PD-L1 expression of ≥ 1% (CPS) (research question 1) was chemoimmunotherapy (nivolumab or pembrolizumab, each in combination with fluoropyrimidine- and platinum-based combination chemotherapy), based on the extent of the tumour PD-L1 expression.

In the RATIONALE 305 study presented, however, all patients in the comparator arm received platinum- and fluoropyrimidine-based chemotherapy of investigator's choice, i.e. oxaliplatin + capecitabine, or cisplatin + 5-fluorouracil. This does not correspond to any of the treatment options named by the G-BA for patients with tumour PD-L1 expression ≥ 1 (CPS). Thus, the ACT of research question 1 was not implemented in the RATIONALE 305 study, i.e. no data are available on the comparison of tislelizumab with the comparator therapy specified by the G-BA.

***Research question 2: no data on patients with tumour PD-L1 expression < 1 (CPS)***

Research question 2 of this benefit assessment includes patients with a PD-L1-positive tumour with a TAP score of ≥ 5% in line with the approval of tislelizumab, which at the same time is characterized as PD-L1-negative with a CPS of < 1. Only for these patients does chemotherapy alone represent the ACT.

In the RATIONALE 305 study presented by the company, all patients in the comparator arm received chemotherapy alone (oxaliplatin + capecitabine, or cisplatin + 5-fluorouracil). However, post-hoc analyses of the patient-specific TAP and CPS scores are available for the patients from the RATIONALE 305 study, which show a high level of agreement between the TAP and CPS scores (95% agreement between TAP ≥ 1% and CPS ≥ 1). Based on the available information, it would not be possible to assign more than individual patients of the subpopulation presented by the company (PD-L1-positive with TAP ≥ 5%) to research question 2 (PD-L1-negative with CPS < 1) of the present benefit assessment. Instead, the vast majority of patients in the subpopulation presented by the company (with a tumour PD-L1 expression of TAP ≥ 5%) are not included in research question 2.

In addition, the constellation of PD-L1 positivity using the TAP score with concurrent PD-L1 negativity using the CPS score would also contradict the design objective of the TAP score, as

the TAP score was developed as a variant of the CPS score that is easier to analyse. Such a constellation is therefore more of a theoretical consideration that can only exist in individual cases.

Overall, the data presented by the company are therefore unsuitable for assessing the added benefit of tislelizumab + chemotherapy in comparison with the ACT specified by the G-BA for research question 2 of this benefit assessment.

**Results on added benefit**

Since no suitable data are available for the benefit assessment, there is no hint of an added benefit of tislelizumab + 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 shows a summary of probability and extent of the added benefit of tislelizumab + 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 [1,2].

Table 3: Tislelizumab + chemotherapy – probability and extent of added benefit (multipage table)

| Research question | Therapeutic indication | ACT[a, b] | Probability and extent of added benefit |
|---|---|---|---|
| Adults with HER2-negative locally advanced unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma and tumour PD-L1 expression with a TAP (Tumour Area Positivity) score ≥ 5%, and | | | |
| 1 | tumour PD-L1 expression ≥ 1 (combined positive score; CPS)[c] for first-line treatment | ▪ nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy (only for tumours with PD-L1 expression [CPS] ≥ 5)<br>or<br>▪ pembrolizumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy (only for tumours with PD-L1 expression [CPS] ≥ 1) | Added benefit not proven |
| 2 | tumour PD-L1 expression < 1 (combined positive score; CPS)[c] for first-line treatment | ▪ cisplatin + capecitabine<br>or<br>▪ oxaliplatin + capecitabine<br>or<br>▪ cisplatin + S-1 (tegafur/gimeracil/oteracil)<br>or<br>▪ cisplatin + 5-fluorouracil (only for patients with oesophageal adenocarcinoma)<br>or<br>▪ cisplatin + 5-fluorouracil + folinic acid (only for patients with oesophageal adenocarcinoma)<br>or<br>▪ epirubicin + cisplatin + capecitabine<br>or<br>▪ epirubicin + cisplatin + 5-fluorouracil<br>or<br>▪ epirubicin + oxaliplatin + capecitabine<br>or<br>▪ docetaxel + cisplatin + 5-fluorouracil<br>or<br>▪ 5-fluorouracil + oxaliplatin + epirubicin (only for patients with oesophageal adenocarcinoma) | Added benefit not proven |

Table 3: Tislelizumab + chemotherapy – probability and extent of added benefit (multipage table)

| Research question | Therapeutic indication | ACT[a, b] | Probability and extent of added benefit |
|---|---|---|---|
| a. Presented are the respective ACTs specified by the G-BA.<br>b. It is assumed that curative treatment with definitive radiochemotherapy is not an option for patients with unresectable cancer.<br>c. The treatment decision in this therapeutic indication depends, among other things, on the PD-L1 expression of the tumours. In the therapeutic indication in question, tislelizumab is approved for TAP ≥ 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 the CPS, however. According to the G-BA, the company was required to explain in the dossier compiled for the benefit assessment to what extent patients whose tumours express PD-L1 with a TAP score ≥ 5% are to be assigned to research question 1 (CPS ≥ 1) or research question 2 (CPS < 1).<br>ACT: appropriate comparator therapy; CPS: combined positive score; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; PD-L1: programmed death ligand 1; TAP: Tumour Area Positivity | | | |

## I 2 Research question

The aim of this report is to assess the added benefit of tislelizumab, in combination with platinum- and fluoropyrimidine-based chemotherapy (hereinafter referred to as tislelizumab + chemotherapy), in comparison with the ACT for the first-line treatment of adults with HER2-negative locally advanced unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumours express PD-L1 with a TAP score ≥ 5%.

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

Table 4: Research questions for the benefit assessment of tislelizumab + chemotherapy (multipage table)

| Research question | Therapeutic indication | ACT[a, b] |
|---|---|---|
| Adults with HER2-negative locally advanced unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma and tumour PD-L1 expression with a TAP (Tumour Area Positivity) score ≥ 5%, and | | |
| 1 | tumour PD-L1 expression ≥ 1 (combined positive score; CPS)[c] for first-line treatment | ▪ nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy (only for tumours with PD-L1 expression [CPS] ≥ 5)<br>or<br>▪ pembrolizumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy (only for tumours with PD-L1 expression [CPS] ≥ 1) |
| 2 | tumour PD-L1 expression < 1 (combined positive score; CPS)[c] for first-line treatment | ▪ cisplatin + capecitabine<br>or<br>▪ oxaliplatin + capecitabine<br>or<br>▪ cisplatin + S-1 (tegafur/gimeracil/oteracil)<br>or<br>▪ cisplatin + 5-fluorouracil (only for patients with oesophageal adenocarcinoma)<br>or<br>▪ cisplatin + 5-fluorouracil + folinic acid (only for patients with oesophageal adenocarcinoma)<br>or<br>▪ epirubicin + cisplatin + capecitabine<br>or<br>▪ epirubicin + cisplatin + 5-fluorouracil<br>or<br>▪ epirubicin + oxaliplatin + capecitabine<br>or<br>▪ docetaxel + cisplatin + 5-fluorouracil<br>or<br>▪ 5-fluorouracil + oxaliplatin + epirubicin (only for patients with oesophageal adenocarcinoma) |

a. Presented are the respective ACTs specified by the G-BA.
b. It is assumed that curative treatment with definitive radiochemotherapy is not an option for patients with unresectable cancer.
c. The treatment decision in this therapeutic indication depends, among other things, on the PD-L1 expression of the tumours. In the therapeutic indication in question, tislelizumab is approved for TAP ≥ 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 the CPS, however. According to the G-BA, the company was required to explain in the dossier compiled for the benefit assessment to what extent patients whose tumours express PD-L1 with a TAP score ≥ 5% are to be assigned to research question 1 (CPS ≥ 1) or research question 2 (CPS < 1).

ACT: appropriate comparator therapy; CPS: combined positive score; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; PD-L1: programmed death ligand 1; TAP: Tumour Area Positivity

Shortly before the dossier was received on 10 December 2024, the G-BA adjusted the ACT as shown in Table 4 [3]. Based on this adjustment, the population was divided according to tumour PD-L1 expression, resulting in chemotherapy alone being an ACT option only for patients with a tumour PD-L1 expression of < 1 (CPS). For patients with a tumour PD-L1 expression of ≥ 1 CPS, however, the resulting ACT is immunochemotherapy. According to the G-BA, the company was required to explain to what extent the tumour PD-L1 expression, in accordance with the approved therapeutic indication of tislelizumab (TAP ≥ 5%), is to be assigned to research question 1 (CPS ≥ 1) or research question 2 (CPS < 1).

The company deviated from the G-BA's specification of the ACT. It did not refer to the current ACT of 10 December 2024, but to the ACT from the consultation of 11 April 2024, in which the population was not divided according to tumour PD-L1 expression. According to the company, it was following this ACT and selected oxaliplatin + capecitabine (independent of tumour PD-L1 expression according to CPS) from the options. Accordingly, the company did not present any data divided by research question and also did not explain to what extent a tumour PD-L1 expression of TAP ≥ 5% is to be assigned to research question 1 (CPS ≥ 1) or 2 (CPS < 1) of this benefit assessment. The present benefit assessment was conducted 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 Research question 1: tumour PD-L1 expression ≥ 1 (CPS)

### I 3.1 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 did not identify any relevant studies on the comparison of tislelizumab + chemotherapy versus the ACT specified by the G-BA for research question 1 of this benefit assessment.

The company did not refer to the current ACT of the G-BA, but to the ACT from the consultation of 11 April 2024, in which the population was not divided according to tumour PD-L1 expression (see Chapter I 2). Accordingly, the company did not present any data divided by research question. From its information retrieval, the company identified the RCT RATIONALE 305 [4] and used the study's subpopulation of patients with tumour PD-L1 expression with a TAP score of ≥ 5% for its assessment. The data presented are unsuitable for research question 1 of the present benefit assessment. The RATIONALE 305 study is described below and reasons for the unsuitability of the data presented by the company in the dossier are provided.

**Evidence presented by the company – RATIONALE 305 study**

The RATIONALE 305 study is a completed, double-blind, randomized phase III study comparing tislelizumab versus placebo – each in combination with platinum- and fluoropyrimidine-based chemotherapy – as first-line treatment in adult patients with locally advanced unresectable or metastatic HER2-negative gastric or gastroesophageal junction adenocarcinoma. The chemotherapy options were oxaliplatin + capecitabine, or cisplatin + 5-fluorouracil. The chemotherapy regimen was chosen by the investigators before randomization.

At study inclusion, patients had to have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≤ 1 and were not allowed to have received previous systemic therapy for locally advanced unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma. Central assessment of the PD-L1 expression of the tumour tissue was required for study inclusion. However, patients were included in the study regardless of their PD-L1 expression. PD-L1 expression was determined using the VENTANA PD-L1 (SP263) assay.

A total of 997 patients were included in the study and randomly allocated in a 1:1 ratio either to treatment with tislelizumab + chemotherapy (N = 501) or to placebo + chemotherapy (N = 496). In accordance with the approval of tislelizumab, the company used the subpopulation of patients with a tumour PD-L1 expression of TAP ≥ 5% (N = 274 versus N = 272) for the benefit assessment.

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

The ACT specified by the G-BA for adults under first-line treatment of HER2-negative locally advanced unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma and tumour PD-L1 expression of ≥ 1% CPS (research question 1) was chemoimmunotherapy (nivolumab or pembrolizumab, each in combination with fluoropyrimidine- and platinum-based combination chemotherapy), based on the extent of the tumour PD-L1 expression.

In the RATIONALE 305 study presented, however, all patients in the comparator arm received platinum- and fluoropyrimidine-based chemotherapy of investigator's choice, i.e. oxaliplatin + capecitabine, or cisplatin + 5-fluorouracil. This does not correspond to any of the ACT options named by the G-BA for patients with tumour PD-L1 expression ≥ 1 (CPS). Thus, the ACT of research question 1 was not implemented in the RATIONALE 305 study, i.e. no data are available on the comparison of tislelizumab with the comparator therapy specified by the G-BA.

### I 3.2 Results on added benefit

No suitable data in comparison with the ACT are available for the assessment of the added benefit of tislelizumab + chemotherapy for the first-line treatment of adults with HER2-negative locally advanced unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma and tumour PD-L1 expression with a TAP score ≥ 5% and CPS ≥ 1. There is no hint of an added benefit of tislelizumab + chemotherapy in comparison with the ACT; an added benefit is therefore not proven.

### I 3.3 Probability and extent of added benefit

No suitable data are available for the assessment of the added benefit of tislelizumab + chemotherapy in comparison with the ACT for the first-line treatment of adults with HER2-

negative locally advanced unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma and tumour PD-L1 expression with a TAP score ≥ 5% and CPS ≥ 1; an added benefit is therefore not proven.

This differs from the assessment of the company, which did not present data separately by research question and derived an indication of a major added benefit of tislelizumab in comparison with chemotherapy for patients with tumour PD-L1 expression with a TAP score of ≥ 5%.

## I 4 Research question 2: tumour PD-L1 expression < 1 (CPS)

### I 4.1 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 did not identify any relevant studies on the comparison of tislelizumab + chemotherapy versus the ACT specified by the G-BA for research question 2 of this benefit assessment.

The company did not refer to the current ACT of the G-BA, but to the ACT from the consultation of 11 April 2024, in which the population was not divided according to tumour PD-L1 expression (see Chapter I 2). Accordingly, the company did not present any data divided by research question. From its information retrieval, the company identified the RCT RATIONALE 305 [4] and used the study's subpopulation of patients with tumour PD-L1 expression with a TAP score of ≥ 5% for its assessment. The data presented are unsuitable for research question 2 of the present benefit assessment. This is justified below.

**Evidence presented by the company – RATIONALE 305 study**

For a description of the RATIONALE 305 study, see Section I 3.1.

**No data on patients with tumour PD-L1 expression < 1 (CPS)**

Research question 2 of this benefit assessment includes patients with a PD-L1-positive tumour with a TAP score of ≥ 5% in line with the approval of tislelizumab, which at the same time is characterized as PD-L1-negative with a CPS of < 1. Only for these patients does chemotherapy alone represent the ACT.

In the RATIONALE 305 study presented by the company, all patients in the comparator arm received chemotherapy alone (oxaliplatin + capecitabine, or cisplatin + 5-fluorouracil). However, post-hoc analyses of the patient-specific TAP and CPS scores are available for the

patients from the RATIONALE 305 study, which show a high level of agreement between the TAP and CPS scores (95% agreement between TAP ≥ 1% and CPS ≥ 1) [5]. Based on the available information, it would not be possible to assign more than individual patients of the subpopulation presented by the company (PD-L1-positive with TAP ≥ 5%) to research question 2 (PD-L1-negative with CPS < 1) of the present benefit assessment. Instead, the vast majority of patients in the subpopulation presented by the company (with a tumour PD-L1 expression of TAP ≥ 5%) are not included in research question 2.

In addition, the constellation of PD-L1 positivity using the TAP score with concurrent PD-L1 negativity using the CPS score would also contradict the design objective of the TAP score, as the TAP score was developed as a variant of the CPS score that is easier to analyse [6]. Such a constellation is therefore more of a theoretical consideration that can only exist in individual cases.

Overall, the data presented by the company are therefore unsuitable for assessing the added benefit of tislelizumab + chemotherapy in comparison with the ACT specified by the G-BA for research question 2 of this benefit assessment.

### I 4.2 Results on added benefit

No suitable data in comparison with the ACT are available for the assessment of the added benefit of tislelizumab + chemotherapy for the first-line treatment of adults with HER2-negative locally advanced unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma and tumour PD-L1 expression with a TAP score ≥ 5% and concurrent CPS < 1. There is no hint of an added benefit of tislelizumab + chemotherapy in comparison with the ACT; an added benefit is therefore not proven.

### I 4.3 Probability and extent of added benefit

No suitable data are available for the assessment of the added benefit of tislelizumab + chemotherapy in comparison with the ACT for the first-line treatment of adults with HER2-negative locally advanced unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma and tumour PD-L1 expression with a TAP score ≥ 5% and concurrent CPS < 1; an added benefit is therefore not proven.

This differs from the assessment of the company, which did not present data separately by research question and derived an indication of a major added benefit of tislelizumab in comparison with chemotherapy for patients with tumour PD-L1 expression with a TAP score of ≥ 5%.

## I 5 Probability and extent of added benefit – summary

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

Table 5: Tislelizumab + chemotherapy – probability and extent of added benefit (multipage table)

| Research question | Therapeutic indication | ACT[a, b] | Probability and extent of added benefit |
|---|---|---|---|
| Adults with HER2-negative locally advanced unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma and tumour PD-L1 expression with a TAP (Tumour Area Positivity) score ≥ 5%, and | | | |
| 1 | tumour PD-L1 expression ≥ 1 (combined positive score; CPS)[c] for first-line treatment | ▪ nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy (only for tumours with PD-L1 expression [CPS] ≥ 5)<br>or<br>▪ pembrolizumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy (only for tumours with PD-L1 expression [CPS] ≥ 1) | Added benefit not proven |
| 2 | tumour PD-L1 expression < 1 (combined positive score; CPS)[c] for first-line treatment | ▪ cisplatin + capecitabine<br>or<br>▪ oxaliplatin + capecitabine<br>or<br>▪ cisplatin + S-1 (tegafur/gimeracil/oteracil)<br>or<br>▪ cisplatin + 5-fluorouracil (only for patients with oesophageal adenocarcinoma)<br>or<br>▪ cisplatin + 5-fluorouracil + folinic acid (only for patients with oesophageal adenocarcinoma)<br>or<br>▪ epirubicin + cisplatin + capecitabine<br>or<br>▪ epirubicin + cisplatin + 5-fluorouracil<br>or<br>▪ epirubicin + oxaliplatin + capecitabine<br>or<br>▪ docetaxel + cisplatin + 5-fluorouracil<br>or<br>▪ 5-fluorouracil + oxaliplatin + epirubicin (only for patients with oesophageal adenocarcinoma) | Added benefit not proven |

Table 5: Tislelizumab + chemotherapy – probability and extent of added benefit (multipage table)

| Research question | Therapeutic indication | ACT[a, b] | Probability and extent of added benefit |
|---|---|---|---|
| a. Presented are the respective ACTs specified by the G-BA.<br>b. It is assumed that curative treatment with definitive radiochemotherapy is not an option for patients with unresectable cancer.<br>c. The treatment decision in this therapeutic indication depends, among other things, on the PD-L1 expression of the tumours. In the therapeutic indication in question, tislelizumab is approved for TAP ≥ 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 the CPS, however. According to the G-BA, the company was required to explain in the dossier compiled for the benefit assessment to what extent patients whose tumours express PD-L1 with a TAP score ≥ 5% are to be assigned to research question 1 (CPS ≥ 1) or research question 2 (CPS < 1).<br>ACT: appropriate comparator therapy; CPS: combined positive score; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; PD-L1: programmed death ligand 1; TAP: Tumour Area Positivity | | | |

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/a24-131.html.*