

Tislelizumab (nasopharyngeal carcinoma)

Benefit assessment according to §35a SGB V¹

A decorative horizontal bar composed of 18 squares of varying shades of blue and grey. The word 'EXTRACT' is centered in white text on a dark blue rectangular background that spans most of the width of the bar.

EXTRACT

Project: A25-119

Version: 1.0

Status: 22 Dec 2025

DOI: 10.60584/A25-119_en

¹ Translation of Sections I 1 to I 6 of the dossier assessment *Tislelizumab (Nasopharynxkarzinom)* – *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.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Tislelizumab (nasopharyngeal carcinoma) – Benefit assessment according to §35a SGB V

Commissioning agency

Federal Joint Committee

Commission awarded on

18 September 2025

Internal Project No.

A25-119

DOI-URL

https://doi.org/10.60584/A25-119_en

Address of publisher

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Siegburger Str. 237
50679 Köln
Germany

Phone: +49 221 35685-0

Fax: +49 221 35685-1

E-mail: berichte@iqwig.de

Internet: www.iqwig.de

Recommended citation

Institute for Quality and Efficiency in Health Care. Tislelizumab (nasopharyngeal carcinoma); Benefit assessment according to §35a SGB V; Extract [online]. 2025 [Accessed: DD.MM.YYYY]. URL: https://doi.org/10.60584/A25-119_en.

Keywords

Tislelizumab, Gemcitabine, Cisplatin, Nasopharyngeal Carcinoma, Benefit Assessment, NCT03924986

Medical and scientific advice

- Jochem Potenberg, Waldkrankenhaus Protestant Hospital, Berlin, Germany

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 within the framework of this dossier assessment.

IQWiG employees involved in the dossier assessment

- Silva Wolters
- Tobias Effertz
- Anna-Lena Firle
- Katharina Hirsch
- Thomas Jakubeit
- Michaela Florina Kerekes
- Stefan Kobza
- Ana Liberman
- Volker Vervölgyi

Part I: Benefit assessment

I Table of contents

	Page
I List of tables	I.3
I List of abbreviations.....	I.5
I 1 Executive summary of the benefit assessment	I.0
I 2 Research question.....	I.8
I 3 Information retrieval and study pool.....	I.9
I 3.1 Studies included	I.9
I 3.2 Study characteristics	I.10
I 4 Results on added benefit.....	I.27
I 4.1 Outcomes included	I.27
I 4.2 Risk of bias	I.30
I 4.3 Results.....	I.32
I 4.4 Subgroups and other effect modifiers	I.39
I 5 Probability and extent of added benefit	I.45
I 5.1 Assessment of added benefit at outcome level.....	I.45
I 5.2 Overall conclusion on added benefit	I.50
I 6 References for English extract	I.53

I List of tables²

	Page
Table 2: Research question for the benefit assessment of tislelizumab + gemcitabine + cisplatin.....	I.0
Table 3: Tislelizumab + gemcitabine + cisplatin – probability and extent of added benefit ...	I.7
Table 4: Research question for the benefit assessment of tislelizumab + gemcitabine + cisplatin.....	I.8
Table 5: Study pool – RCT, direct comparison: tislelizumab + gemcitabine + cisplatin vs. gemcitabine + cisplatin	I.9
Table 6: Characteristics of the study included – RCT, direct comparison: tislelizumab + gemcitabine + cisplatin vs. placebo + gemcitabine + cisplatin.....	I.10
Table 7: Characteristics of the intervention – RCT, direct comparison: tislelizumab + gemcitabine + cisplatin vs. placebo + gemcitabine + cisplatin.....	I.12
Table 8: Planned duration of follow-up – RCT, direct comparison: tislelizumab + gemcitabine + cisplatin vs. placebo + gemcitabine + cisplatin.....	I.15
Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: tislelizumab + gemcitabine + cisplatin vs. placebo + gemcitabine + cisplatin	I.16
Table 10: Information on the course of the study – RCT, direct comparison: tislelizumab + gemcitabine + cisplatin vs. placebo + gemcitabine + cisplatin.....	I.20
Table 11: Information on subsequent antineoplastic therapies – RCT, direct comparison: tislelizumab + gemcitabine + cisplatin vs. placebo + gemcitabine + cisplatin.....	I.21
Table 12: Information on subsequent antineoplastic therapies of patients from the comparator arm who switched treatment – RCT.....	I.23
Table 13: Risk of bias across outcomes (study level) – RCT, direct comparison: tislelizumab + gemcitabine + cisplatin vs. placebo + gemcitabine + cisplatin.....	I.25
Table 14: Matrix of outcomes – RCT, direct comparison: tislelizumab + gemcitabine + cisplatin vs. placebo + gemcitabine + cisplatin.....	I.28
Table 15: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: tislelizumab + gemcitabine + cisplatin vs. placebo + gemcitabine + cisplatin.....	I.31
Table 16: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: tislelizumab + gemcitabine + cisplatin vs. placebo + gemcitabine + cisplatin.....	I.33

² Table numbers start with “2” as numbering follows that of the full dossier assessment.

Table 17: Subgroups (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: tislelizumab + gemcitabine + cisplatin vs. placebo + gemcitabine + cisplatin	I.41
Table 18: Extent of the added benefit at outcome level: tislelizumab + gemcitabine + cisplatin vs. gemcitabine + cisplatin	I.46
Table 19: Positive and negative effects from the assessment of tislelizumab + gemcitabine + cisplatin in comparison with gemcitabine + cisplatin.....	I.51
Table 20: Tislelizumab + gemcitabine + cisplatin – probability and extent of added benefit.....	I.52

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
EBV	Epstein-Barr virus
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC	European Organisation for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
EURACAN	European Reference Network for Rare Adult Solid Tumours
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
IRC	independent review committee
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effects model with repeated measures
NPC	nasopharyngeal carcinoma
PFS	progression-free survival
QLQ-C30	Quality of Life Questionnaire-Core 30
QLQ-H&N35	Quality of Life Questionnaire-Head and Neck Cancer 35
RANK-L	receptor activator of NF- κ B ligand
RCT	randomized controlled trial
RECIST v1.1	Response Evaluation Criteria in Solid Tumours Version 1.1
RPFST	rank preserving structural failure time
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SmPC	summary of product characteristics

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 gemcitabine and cisplatin). 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 18 September 2025.

Research question

The aim of this report is to assess the added benefit of tislelizumab, in combination with gemcitabine and cisplatin (hereinafter referred to as ‘tislelizumab + gemcitabine + cisplatin’), compared with gemcitabine and cisplatin (hereinafter referred to as ‘gemcitabine + cisplatin’) as the appropriate comparator therapy (ACT) for the first-line treatment of adult patients with recurrent, not amenable to curative surgery or radiotherapy, or metastatic nasopharyngeal carcinoma (NPC).

The research question shown in Table 2 was defined in accordance with the ACT specified by the Federal Joint Committee (G-BA).

Table 2: Research question for the benefit assessment of tislelizumab + gemcitabine + cisplatin

Therapeutic indication	ACT ^a
Adult patients with recurrent, not amenable to curative surgery or radiotherapy, or metastatic nasopharyngeal carcinoma (NPC) in first-line treatment	cisplatin in combination with gemcitabine ^{b, c}
a. Presented is the ACT specified by the G-BA. b. Gemcitabine does not have a marketing authorization for this therapeutic indication. According to the G-BA, in accordance with the generally recognized state of medical knowledge, it must be established in the overall assessment that the off-label use of cisplatin in combination with gemcitabine is generally preferable to the medicinal products previously approved in the therapeutic indication. c. According to the G-BA, based on the available evidence, the administration of consolidating locoregional radiotherapy is recommended, particularly depending on the response to systemic therapy. Radiotherapy should be made available to eligible patients as part of a clinical study. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company followed the G-BA’s 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 to derive the added benefit. This concurred with the company’s inclusion criteria.

Study pool and study design

The RATIONALE 309 study is used for the benefit assessment. The study is a completed, double-blind, multicentre RCT comparing tislelizumab + gemcitabine + cisplatin versus placebo + gemcitabine + cisplatin. It exclusively included Asian adult patients aged up to 75 years with recurrent, not amenable to curative surgery or radiotherapy, or metastatic NPC, and who had not previously received any systemic therapy for the treatment of recurrent or metastatic NPC.

A total of 263 patients were included and randomly allocated in a 1:1 ratio either to treatment with tislelizumab + gemcitabine + cisplatin (N = 131) or to placebo + gemcitabine + cisplatin (N = 132). Randomization was stratified by sex (female versus male) and the presence of liver metastases (yes versus no).

Treatment with tislelizumab in the intervention arm was carried out in compliance with the SmPC. In both study arms, the chemotherapy regimen consisted of gemcitabine + cisplatin. Neither drug has marketing authorization for this therapeutic indication; consequently, the SmPCs do not provide any direct recommendations regarding the dosage or duration of treatment. There are no German guidelines for the treatment of NPC. International guidelines recommend chemotherapy with gemcitabine and cisplatin for this therapeutic indication. The dosage and treatment regimen for gemcitabine + cisplatin in the RATIONALE 309 pivotal study were in line with those in the studies referred to in the guidelines. The chemotherapy regimen was administered over 4 to 6 cycles. Treatment with the study medication was to continue in both arms until the occurrence of unacceptable toxicity, disease progression, loss of clinical benefit, withdrawal of consent, study termination, start of a new anticancer therapy or death.

Patients in the comparator arm had the option of receiving tislelizumab monotherapy (treatment switching) following confirmation of radiographic disease progression per RECIST v1.1 by an independent review committee (IRC).

The study's primary outcome was progression-free survival (PFS). Patient-relevant secondary outcomes were outcomes in the categories of mortality, morbidity, health-related quality of life and side effects.

Limitations of the RATIONALE 309 study

Treatment switching

As described above, patients in the comparator arm had the option of receiving tislelizumab monotherapy (treatment switching) following confirmation of radiographic disease progression (RECIST v1.1) if certain conditions were met. Tislelizumab as monotherapy is not an authorized treatment for NPC in Germany. The treatment switching was taken into account in the assessment of the risk of bias at outcome level.

Restriction of supportive concomitant therapies

Consolidation and palliative radiation

The clinical practice guideline issued by the European Society for Medical Oncology (ESMO) and the European Reference Network for Rare Adult Solid Tumours (EURACAN) for diagnosis and treatment of NPC recommends the addition of locoregional radiotherapy in patients with newly diagnosed metastatic NPC, to consolidate the therapeutic effect of systemic therapy and prolong survival. In addition to radiation of locoregional lesions, palliative radiation of other organs, such as the bones, the lungs or the brain, may also be necessary for symptom control. In the RATIONALE 309 study, palliative radiation therapy for pain control or prophylaxis of bone fractures was permitted only for non-target lesions. No further information was available on the approach used in the study in cases where the guidelines recommended consolidation, locoregional or palliative radiation for target lesions, or on the number of patients for whom this was the case. Restrictions of consolidation and palliative radiation may affect the patient-reported outcomes on morbidity and health-related quality of life, and potentially overall survival.

Availability of bisphosphonates and RANK-L inhibitors

The S3 guideline on supportive therapy for oncological patients recommends treatment with bisphosphonates or the receptor activator of NF- κ B ligand (RANK-L) inhibitor denosumab to prevent complications associated with bone metastases, taking into account the specific entity in question. According to the study design, concomitant treatment with bisphosphonates and RANK-L inhibitors for the treatment of bone metastases was permitted, if initiated prior to enrolment and at a stable dose. Overall, it was unclear why some of the patients with bone metastases did not receive bisphosphonates or RANK-L inhibitors prior to enrolment – and therefore not during the course of the study either – and how many patients developed a need for such concomitant treatment during the course of the study.

Summary of uncertainties arising from restrictions of supportive concomitant therapies

The uncertainties described above may influence various outcome categories and were taken into account when assessing the certainty of conclusions of the results.

Data cuts

Results on 2 data cuts were available. For this benefit assessment, the results on the final data cut from 8 December 2023 were used, which had been planned after 181 progression events and was conducted after 201 progression events.

Subsequent therapies

In RATIONALE 309, subsequent antineoplastic therapies were permitted without restrictions in both study arms. When considering the 69 patients who received tislelizumab monotherapy following radiographic disease progression, it was apparent that more patients in the

comparator arm received subsequent systemic therapy than in the intervention arm. It was assumed that most patients with disease progression received subsequent therapy. Apart from tislelizumab, chemotherapy and immunotherapy were the most commonly used subsequent systemic therapies in both study arms. The proportion of patients receiving subsequent systemic therapy following tislelizumab monotherapy given as part of treatment switch, as well as the distribution of the drug classes administered, were comparable to those in the intervention and comparator arms. According to international guidelines, there is no standard treatment for second- and third-line therapy in the given therapeutic indication. Treatment options listed include immunotherapy and chemotherapy, as well as radiotherapy or surgical resection for the treatment of metastases. In the absence of specific recommendations in the guidelines, it was overall not assumed that patients in RATIONALE 309 were deprived of effective subsequent therapies to any relevant extent.

Risk of bias

The risk of bias across outcomes for RATIONALE 309 was rated as low.

The results on overall survival showed a high risk of bias because a high proportion of patients (52%) switched from the comparator arm to tislelizumab monotherapy. The risk of bias in the results relating to symptoms, health-related quality of life and side effects, excluding the outcome discontinuation due to AEs, was assessed as high due to incomplete observations for potentially informative reasons. Although the risk of bias for the outcome discontinuation due to AEs was low, the certainty of results for this outcome was limited.

Summary assessment of the certainty of conclusions

Independent of the high risk of bias for all outcomes except discontinuation due to AEs, there were relevant uncertainties regarding the restrictions around supportive concomitant therapies. Consequently, the certainty of conclusions for all outcomes was limited. Thus, at most hints, e.g. of an added benefit, can be derived for all outcomes on the basis of the effects shown in the RATIONALE 309 study.

Results

Mortality

Overall survival

No statistically significant difference between treatment groups was found for the outcome overall survival. There is no hint of an added benefit of tislelizumab + gemcitabine + cisplatin in comparison with the ACT; an added benefit is therefore not proven.

Morbidity

Symptoms (recorded using the EORTC QLQ-C30 and QLQ-H&N35)

Nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, pain, dysphagia, senses problems, problems with teeth, problems with mouth opening, dry mouth, coughing and feeding tube

No statistically significant difference between the treatment groups was found for the outcomes of nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation and diarrhoea (recorded using the EORTC QLQ-C30), as well as pain, dysphagia, senses problems, problems with teeth, problems with mouth opening, coughing and feeding tube (recorded using the EORTC QLQ-H&N35). There is no hint of an added benefit of tislelizumab + gemcitabine + cisplatin in comparison with the ACT for any of the outcomes; an added benefit is therefore not proven for these outcomes.

Fatigue

For the outcome fatigue of the EORTC QLQ-C30, no statistically significant difference between the treatment arms was found when considering the total population. However, there is an effect modification by the characteristic of age. There is a hint of lesser benefit of tislelizumab + gemcitabine + cisplatin in comparison with the ACT for patients ≥ 65 years of age. For patients < 65 years of age, there is no hint of an added benefit or of lesser benefit of tislelizumab + gemcitabine + cisplatin in comparison with the ACT. An added benefit for patients < 65 years of age is therefore not proven.

Speech problems

For the outcome 'speech problems' of the EORTC QLQ-H&N35, no statistically significant difference between the treatment arms was found when considering the total population. There was an effect modification by the characteristic 'presence of liver metastases', however. There is a hint of an added benefit of tislelizumab + gemcitabine + cisplatin in comparison with the ACT for patients with liver metastases. For patients without liver metastases, there is no hint of an added benefit or of lesser benefit of tislelizumab + gemcitabine + cisplatin in comparison with the ACT. An added benefit for patients without liver metastases is therefore not proven.

Feeling ill

For the outcome 'feeling ill' of the EORTC QLQ-H&N35, a statistically significant difference between the treatment arms was found when considering the total population, which was no more than marginal, however. There was an effect modification by the characteristic 'presence of liver metastases'. There is a hint of lesser benefit of tislelizumab + gemcitabine + cisplatin in comparison with the ACT for patients without liver metastases. For patients with liver metastases, there is no hint of an added benefit or of lesser benefit of tislelizumab +

gemcitabine + cisplatin in comparison with the ACT. An added benefit for patients with liver metastases is therefore not proven.

Health-related quality of life

No statistically significant difference was found between the treatment arms for any of the following outcomes: general health status, physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning (assessed using the EORTC QLQ-C30), trouble with social eating, trouble with social contact and less sexuality (assessed using the EORTC QLQ-H&N35). In each case, there is no hint of an added benefit of tislelizumab + gemcitabine + cisplatin in comparison with the ACT; an added benefit is therefore not proven.

Side effects

SAEs, severe AEs, and discontinuation due to AEs

There was no statistically significant difference between the treatment arms for any of the outcomes of SAEs, severe AEs or discontinuation due to AEs. There is no hint of greater or lesser harm of tislelizumab + gemcitabine + cisplatin in comparison with the ACT for any of the outcomes; greater or lesser harm is therefore not proven for these outcomes.

Immune-mediated SAEs

No statistically significant difference between the treatment arms was shown for the outcome of immune-mediated SAEs. There is no hint of greater or lesser harm of tislelizumab + gemcitabine + cisplatin in comparison with the ACT; an added benefit is therefore not proven.

Immune-mediated severe AEs

A statistically significant difference to the disadvantage of tislelizumab + gemcitabine + cisplatin compared with placebo + gemcitabine + cisplatin was shown for the outcome of immune-mediated severe AEs. There is therefore a hint of greater harm of tislelizumab + gemcitabine + cisplatin in comparison with the ACT.

Fever (AE)

A statistically significant difference to the disadvantage of tislelizumab + gemcitabine + cisplatin compared with placebo + gemcitabine + cisplatin was shown for the outcome fever. There was an effect modification for the characteristic 'presence of liver metastases'. There is a hint of greater harm of tislelizumab + gemcitabine + cisplatin in comparison with the ACT for patients without liver metastases. There is no hint of greater or lesser harm of tislelizumab + gemcitabine + cisplatin in comparison with the ACT for patients with liver metastases; greater or lesser harm is therefore not proven for this group.

Probability and extent of added benefit, patient groups with therapeutically important added benefit³

On the basis of the results presented, the probability and extent of the added benefit of the drug tislelizumab, in combination with gemcitabine and cisplatin, in comparison with the ACT are assessed as follows:

Overall, there are both positive and negative effects of tislelizumab + gemcitabine + cisplatin in comparison with gemcitabine + cisplatin. For the overall population, there is a negative effect in the category of severe/serious side effects: For immune-mediated severe AEs, there is a hint of greater harm of minor extent of tislelizumab + gemcitabine + cisplatin compared with gemcitabine + cisplatin; however, only a few events occurred.

For various subgroups, there are negative effects and one positive effect for outcomes in the categories of non-severe / non-serious symptoms / late complications and side effects. The effects are particularly evident here depending on the presence of liver metastases. For patients without liver metastases, there are hints of a lesser benefit of considerable extent in feeling ill and fever. For patients with liver metastases, there is, in contrast, a hint of an added benefit of considerable extent in speech problems. Furthermore, there is a disadvantage of considerable extent of tislelizumab + gemcitabine + cisplatin compared with gemcitabine + cisplatin in fatigue for patients ≥ 65 years. For no patient group are there any effects sufficient for the derivation of an added benefit or lesser benefit.

In summary, an added benefit of tislelizumab + gemcitabine + cisplatin versus the ACT, gemcitabine + cisplatin, is not proven for the first-line treatment of patients with recurrent, not amenable to curative surgery or radiotherapy, or metastatic NPC.

Table 3 shows a summary of the probability and extent of the added benefit of tislelizumab + gemcitabine + cisplatin.

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 + gemcitabine + cisplatin – probability and extent of added benefit

Therapeutic indication	ACT ^a	Probability and extent of added benefit
Adult patients with recurrent, not amenable to curative surgery or radiotherapy, or metastatic nasopharyngeal carcinoma (NPC) in first-line treatment	cisplatin in combination with gemcitabine ^{b, c}	Added benefit not proven ^d
a. Presented is the ACT specified by the G-BA. b. Gemcitabine does not have a marketing authorization for this therapeutic indication. According to the G-BA, in accordance with the generally recognized state of medical knowledge, it must be established in the overall assessment that the off-label use of cisplatin in combination with gemcitabine is generally preferable to the medicinal products previously approved in the therapeutic indication. c. According to the G-BA, based on the available evidence, the administration of consolidating locoregional radiotherapy is recommended, particularly depending on the response to systemic therapy. Radiotherapy should be made available to eligible patients as part of a clinical study. d. The RATIONALE 309 study included only patients with an ECOG-PS of 0 or 1. It remains unclear whether the observed effects are transferable to patients with an ECOG PS ≥ 2. ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee		

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. 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 gemcitabine and cisplatin (hereinafter referred to as ‘tislelizumab + gemcitabine + cisplatin’), compared with gemcitabine and cisplatin (hereinafter referred to as ‘gemcitabine + cisplatin’) as the appropriate comparator therapy (ACT) for the first-line treatment of adult patients with recurrent, not amenable to curative surgery or radiotherapy, or metastatic nasopharyngeal carcinoma (NPC).

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 tislelizumab + gemcitabine + cisplatin

Therapeutic indication	ACT ^a
Adult patients with recurrent, not amenable to curative surgery or radiotherapy, or metastatic nasopharyngeal carcinoma (NPC) in first-line treatment	cisplatin in combination with gemcitabine ^{b, c}
a. Presented is the ACT specified by the G-BA. b. Gemcitabine does not have a marketing authorization for this therapeutic indication. According to the G-BA, in accordance with the generally recognized state of medical knowledge, it must be established in the overall assessment that the off-label use of cisplatin in combination with gemcitabine is generally preferable to the medicinal products previously approved in the therapeutic indication. c. According to the G-BA, based on the available evidence, the administration of consolidating locoregional radiotherapy is recommended, particularly depending on the response to systemic therapy. Radiotherapy should be made available to eligible patients as part of a clinical study. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company followed the G-BA’s 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 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 tislelizumab in combination with gemcitabine and cisplatin (status: 20 August 2025)
- Bibliographical literature search on tislelizumab in combination with gemcitabine and cisplatin (last search on 20 August 2025)
- Search of trial registries / trial results databases for studies on tislelizumab in combination with gemcitabine and cisplatin (last search on 12 August 2025)
- Search on the G-BA website for tislelizumab in combination with gemcitabine and cisplatin (last search on 11 August 2025)

To check the completeness of the study pool:

- Search of trial registries for studies on tislelizumab (last search on 9 October 2025); for search strategies, see I Appendix A of the full dossier assessment

The search did not identify any additional relevant studies.

I 3.1 Studies included

The study presented in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: tislelizumab + gemcitabine + cisplatin vs. gemcitabine + cisplatin

Study	Study category			Available sources		
	Study for the marketing authorization of the drug to be assessed (yes/no)	Sponsored study ^a (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries ^b (yes/no [citation])	Publication and other sources ^c (yes/no [citation])
BGB-A317-309 (RATIONALE 309 ^d)	Yes	Yes	No	Yes [3]	Yes [4]	Yes [5,6]
a. Study sponsored by the company. b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries. c. Other sources: documents from the search on the G-BA website and other publicly available sources. d. In the following tables, the study is referred to by this acronym. CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial						

I 3.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: tislelizumab + gemcitabine + cisplatin vs. placebo + gemcitabine + cisplatin (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes ^a
RATIONALE 309	RCT, double-blind, parallel	Adult patients up to 75 years of age, with ▪ recurrent, not amenable to curative surgery or radiotherapy, or metastatic NPC ▪ no previous systemic therapy of recurrent or metastatic NPC ▪ ECOG PS ≤ 1	tislelizumab + gemcitabine + cisplatin (N = 131) placebo + gemcitabine + cisplatin (N = 132)	Screening: 28 days Treatment: ▪ gemcitabine + cisplatin for 4–6 cycles of 3 weeks each, or until unacceptable toxicity or disease progression^b ▪ tislelizumab/placebo monotherapy until unacceptable toxicity, disease progression^b, loss of clinical benefit, withdrawal of consent, study termination, start of a new anticancer therapy or death Observation^c: outcome-specific, at most until death, lost to follow-up, withdrawal of consent, or study termination	37 centres in China, Taiwan and Thailand 4/2019–12/2023 Data cuts: 26 March 2021 (primary analysis^d) 8 December 2023 (final analysis^e)	Primary: progression-free survival Secondary: overall survival, morbidity, health-related quality of life, AEs

Table 6: Characteristics of the study included – RCT, direct comparison: tislelizumab + gemcitabine + cisplatin vs. placebo + gemcitabine + cisplatin (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes ^a
a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment. b. In the event of disease progression per RECIST v1.1 during chemotherapy, as determined by the investigator, treatment could be continued until confirmation by the IRC (at least 28 days later or at the next tumour assessment), provided the patient was stable. In the event of disease progression per RECIST v1.1 confirmed by the IRC at any timepoint, treatment with tislelizumab monotherapy could be continued in the intervention arm, provided that specified criteria were met and at the discretion of the investigator. Patients in the comparator arm also had the option to receive tislelizumab monotherapy, provided that specified criteria were met and at the discretion of the investigator and the sponsor. Once disease progression was determined by the IRC, blinding was lifted. c. Outcome-specific information is provided in Table 8. d. Planned after the occurrence of 127 progression events and conducted after the occurrence of 152 progression events. e. Planned after the occurrence of 181 progression events and conducted after the occurrence of 201 progression events. AE: adverse event; ECOG PS: Eastern Cooperative Oncology Group Performance Status; IRC: Independent Review Committee; N: number of randomized patients; NPC: nasopharyngeal carcinoma; RCT: randomized controlled trial; RECIST v1.1: Response Evaluation Criteria in Solid Tumours version 1.1						

Table 7: Characteristics of the intervention – RCT, direct comparison: tislelizumab + gemcitabine + cisplatin vs. placebo + gemcitabine + cisplatin (multipage table)

Study	Intervention	Comparison
RATIONALE 309	<u>4–6 cycles^a of 3 weeks each</u> tislelizumab 200 mg, IV, on Day 1 of a cycle + chemotherapy: ▫ gemcitabine 1000 mg/m² BSA, IV, on Days 1+8 of a cycle ▫ cisplatin 80 mg/m² BSA, IV, on Day 1 of a cycle <u>followed by</u> tislelizumab 200 mg, IV, on Day 1 of a 3-week cycle Dose modification: ▪ tislelizumab/placebo: no dose reduction permitted; treatment interruptions due to toxicity were possible^b ▪ gemcitabine/cisplatin: per drug, a maximum of 2 dose reductions of 25% each were permitted; once a dose reduction had been made, a subsequent increase was not permitted; dose interruptions due to toxicity/AEs ≤ 21 days; if one component of the chemotherapy was interrupted, the other component also had to be suspended; tislelizumab/placebo treatment could be continued; in case of discontinuation of tislelizumab/placebo due to toxicity, the chemotherapy could be continued Allowed prior treatment ▪ Any prior neoadjuvant or adjuvant chemotherapy, radiotherapy or chemoradiotherapy with curative intent in patients with non-metastatic disease must have been completed ≥ 6 months before ▪ Neoadjuvant chemotherapy regimen for < 4 cycles Disallowed prior treatment ▪ Any systemic anticancer therapy, including hormonal therapy, ≤ 28 days prior to study start^c and prior therapies targeting PD-1 or PD-L1 ▪ Any immunotherapy (including but not limited to interferons, interleukin-2, tumour necrosis factor interleukin and thymoxin) or any investigational therapies ≤ 14 days or 5 half-lives (whichever is longer) before randomization	<u>4–6 cycles^a of 3 weeks each</u> placebo IV on Day 1 of a cycle + chemotherapy: ▫ gemcitabine 1000 mg/m² BSA, IV, on Days 1+8 of a cycle ▫ cisplatin 80 mg/m² BSA, IV, on Day 1 of a cycle <u>followed by</u> placebo IV on Day 1 of a 3-week cycle

Table 7: Characteristics of the intervention – RCT, direct comparison: tislelizumab + gemcitabine + cisplatin vs. placebo + gemcitabine + cisplatin (multipage table)

Study	Intervention	Comparison
	Allowed concomitant treatment ▪ Systemic corticosteroids for the control of immune-mediated AEs^d ▪ Bisphosphonates and RANK-L inhibitors for the treatment of bone metastases, as well as bisphosphonates for the treatment of non-malignant indications, if initiated prior to enrolment and at a stable dose ▪ Whole-brain radiation therapy and stereotactic radiosurgery for CNS metastases ▪ Palliative radiation or other focally ablative therapy for non-target sites or bone metastases ▪ Immunosuppressants only for the management of treatment-related AEs ▪ Chemotherapy premedication according to the local standard of care (including antiemetics, IV hydration and dexamethasone) Disallowed concomitant treatment ▪ Antineoplastic therapy ▪ Herbal remedies with immune-stimulating properties or that can potentially interfere with liver or other major organ functions	
a. The number of cycles was at the discretion of the investigator. b. If the interruption lasted > 12 weeks, the treatment had to be discontinued. If the delay was > 10 days, the dose should be skipped. If infusion-related or immune-mediated AEs occurred, specifically defined dose modifications were to be made. c. Except for patients with palliative radiotherapy for bone metastases or soft tissue lesions if completed > 7 days prior to baseline imaging. d. Had to be tapered gradually to non-immunosuppressive doses (≤ 10 mg/day of prednisone or equivalent) before the next tislelizumab/placebo administration. AE: adverse event; BSA: body surface area; CNS: central nervous system, CTCAE: Common Terminology Criteria for Adverse Events; RANK-L: receptor activator of NF-κB ligand; RCT: randomized controlled trial		

Study design

The RATIONALE 309 study is a completed, double-blind, multicentre RCT comparing tislelizumab + gemcitabine + cisplatin versus placebo + gemcitabine + cisplatin. The study exclusively included Asian adult patients aged up to 75 years with recurrent, not amenable to curative surgery or radiotherapy, or metastatic NPC, and who had not previously received any systemic therapy for the treatment of recurrent or metastatic NPC. Furthermore, patients had to be in good general condition according to an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1.

A total of 263 patients were included and randomly allocated in a 1:1 ratio either to treatment with tislelizumab + gemcitabine + cisplatin (N = 131) or to placebo + gemcitabine + cisplatin (N = 132). Randomization was stratified by sex (female versus male) and the presence of liver metastases (yes versus no).

Treatment with tislelizumab in the intervention arm was carried out in compliance with the summary of product characteristics (SmPC) [7]. In both study arms, the chemotherapy regimen consisted of gemcitabine + cisplatin. Neither drug has marketing authorization for this therapeutic indication; consequently, the SmPCs do not provide any direct recommendations regarding the dosage or duration of treatment [8,9]. There are no German guidelines for the treatment of NPC. International guidelines recommend chemotherapy with gemcitabine and cisplatin for this therapeutic indication. The dosage and treatment regimen for gemcitabine + cisplatin in the RATIONALE 309 pivotal study were in line with those in the studies referred to in the guidelines [10-15]. The chemotherapy regimen was administered over 4 to 6 cycles. Treatment with the study medication was to continue in both arms until the occurrence of unacceptable toxicity, disease progression, loss of clinical benefit, withdrawal of consent, study termination, start of a new anticancer therapy or death. Contrary to the SmPC recommendations, treatment with tislelizumab could be continued beyond radiographically confirmed disease progression (as per the Response Evaluation Criteria in Solid Tumours Version 1.1 [RECIST v1.1]) provided that the patient showed a benefit from treatment as assessed by the investigator, and had no symptoms or signs indicating unequivocal progression of disease, no tumour progression at critical anatomical sites, and no decline in ECOG PS that could be attributed to disease progression. The study documents did not provide a clear definition to distinguish between unequivocal progression of disease and radiographic progression. In total, 10% of patients in the intervention arm continued the treatment accordingly.

Patients in the comparator arm had the option of receiving tislelizumab monotherapy (treatment switching) following confirmation of radiographic disease progression per RECIST v1.1 by an independent review committee (IRC). For a treatment switch to be possible, patients had to have an ECOG PS score of ≤ 1 , and no rapid progression of disease and no progressive tumour at critical anatomical sites that could not be managed by protocol-compliant concomitant medical interventions. Where possible, treatment was to be initiated within 42 days after the disease progression was determined.

The study's primary outcome was progression-free survival (PFS). Patient-relevant secondary outcomes were outcomes in the categories of mortality, morbidity, health-related quality of life and side effects.

Data cuts

The RATIONALE 309 study is complete and 2 data cuts were available:

- 1st data cut (26 March 2021): interim analysis, planned after 127, conducted after 152 progression events

- 2nd data cut (8 December 2023): final analysis, planned after 181, conducted after 201 progression events

The company presented results on both data cuts. The final data cut of 8 December 2023 was relevant to this benefit assessment.

Planned duration of follow-up

Table 8 shows the planned duration of patient follow-up for the individual outcomes.

Table 8: Planned duration of follow-up – RCT, direct comparison: tislelizumab + gemcitabine + cisplatin vs. placebo + gemcitabine + cisplatin

Study Outcome category Outcome	Planned follow-up
RATIONALE 309	
Mortality Overall survival	Until death, lost to follow-up, withdrawal of consent, or end of study ^a
Morbidity Symptoms (EORTC QLQ-C30 and EORTC QLQ-H&N35)	Until the end of treatment with the study medication
Health-related quality of life (EORTC QLQ-C30 and EORTC QLQ-H&N35)	Until the end of treatment with the study medication
Side effects AEs / SAEs / CTCAE grade ≤ 3 AEs	Up to 30 days after the last dose of the study medication or start of a new anticancer therapy (whichever was first)
Immune-mediated AEs	Up to 90 days after the last dose of the study medication
a. Recordings following disease progression and a potential treatment switch were carried out unblinded. AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-H&N35: Quality of Life Questionnaire-Head and Neck Cancer 35; RCT: randomized controlled trial; SAE: serious adverse event	

The observation periods for the outcomes of morbidity, health-related quality of life and side effects were systematically shortened because they were only recorded for the time period of treatment with the study medication (plus up to 30/90 days for side effects). However, to draw a reliable conclusion on the total study period or the time to patient death, it would also be necessary to record these outcomes for the total period, as was done for survival.

Patient characteristics

Table 9 shows the patient characteristics of the included study.

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: tislelizumab + gemcitabine + cisplatin vs. placebo + gemcitabine + cisplatin (multipage table)

Study Characteristic Category	tislelizumab + gemcitabine + cisplatin N = 131	placebo + gemcitabine + cisplatin N = 132
RATIONALE 309		
Age [years], mean (SD)	49 (11)	50 (11)
Age group, n (%)		
< 65 years	121 (92)	120 (91)
≥ 65 years	10 (8)	12 (9)
Sex [F/M], %	21/79	22/78
Region, n (%)		
China	122 (93)	126 (96)
Thailand	5 (4)	1 (1)
Taiwan	4 (3)	5 (4)
ECOG PS, n (%)		
0	51 (39)	46 (35)
1	80 (61)	86 (65)
Smoking status, n (%)		
Never	74 (57)	66 (50)
Current	6 (5)	6 (5)
Former	51 (39)	60 (46)
Histology, n (%)		
Undifferentiated, non-keratinizing	98 (75)	96 (73)
Differentiated, non- keratinizing	18 (14)	21 (16)
Keratinizing squamous cell carcinoma	8 (6)	10 (8)
Unclassified	7 (5)	5 (4)
Disease stage at baseline, n (%)		
Locally recurrent	5 (4)	7 (5)
Metastatic	126 (96)	125 (95)
Primary	46 (35)	40 (30)
Recurrent	80 (61)	85 (64)
EBV DNA level, n (%)		
< 500 IU/mL	26 (20)	37 (28)
≥ 500 IU/mL	105 (80)	95 (72)
Patients with any prior anticancer drug therapy, n (%) ^a	83 (63)	88 (67)
Adjuvant ^b	28 (34)	24 (27)
Neoadjuvant ^b	62 (75)	65 (74)
Concurrent with radiotherapy ^b	65 (78)	76 (86)

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: tislelizumab + gemcitabine + cisplatin vs. placebo + gemcitabine + cisplatin (multipage table)

Study Characteristic Category	tislelizumab + gemcitabine + cisplatin N = 131	placebo + gemcitabine + cisplatin N = 132
Other	6 (7)	4 (5)
Patients with prior surgery, n (%)	6 (5)	4 (3)
Patients with prior radiotherapy, n (%)	84 (64)	91 (69)
Location of metastases, n (%)		
Bone	58 (44)	63 (48)
Liver	56 (43)	56 (42)
Lung	61 (47)	63 (48)
Brain	3 (2)	2 (2)
Lymph nodes	88 (67)	73 (55)
Other	18 (14)	18 (14)
Treatment discontinuation, n (%) ^c	131 (100)	132 (100)
Disease progression	74 (57)	91 (69)
Withdrawal of consent	26 (20)	23 (17)
AE	12 (9)	5 (4)
Decision of the investigator	5 (4)	11 (8)
Study discontinuation, n (%) ^d	80 (61)	91 (69)
Withdrawal of consent	15 (12)	20 (15)
Lost to follow-up	7 (5)	5 (4)
a. Although patient recruitment was completed by the first data cut-off, there is a discrepancy between the data for the first and second data cuts. Data from the first data cut: any prior anticancer drug therapy: adjuvant 36 (43%) vs. 32 (36%), neoadjuvant 55 (66%) vs. 59 (67%), concurrent with radiotherapy 61 (74%) vs. 67 (76%), other 6 (7%) vs. 4 (5%). b. The percentages are based on the number of patients with any prior anticancer drug therapy. c. Presented are the most common reasons for treatment discontinuation (≥ 5% of patients in one study arm). d. Presented are the most common reasons for study discontinuation (≥ 5% of patients in one study arm). The data additionally include patients who died during the course of the study (intervention arm: 57 [44%] vs. control arm: 66 [50%]). In addition, 51 (39%) vs. 41 (31%) of the patients completed the study as planned. AE: adverse event; EBV: Epstein-Barr virus; ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; IU: international units; M: male; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation		

The patient characteristics at the start of treatment were largely comparable in both study arms. The patients' mean age was about 50 years, and most patients were male. Only 8% versus 9% of the patients were 65 years or older. Furthermore, the proportion of patients with locally recurrent disease was low (around 5%).

All patients discontinued treatment. The most common reason in both study arms was disease progression (57% versus 69%). Furthermore, a high proportion of patients in both study arms – 20% versus 17% – discontinued treatment by withdrawing their consent. 61% of patients in the intervention arm and 69% of those in the comparator arm discontinued the study.

Limitations of the RATIONALE 309 study

Determination of disease progression

According to the study documents, disease progression was assessed based on the RECIST v1.1 by both the investigator and the IRC. The decisive factor for the discontinuation of the study treatment and the option to switch to tislelizumab monotherapy for patients in the comparator arm was the determination of disease progression by the IRC. This was generally considered appropriate. However, the study documents did not contain any information as to whether the IRC's assessment took place in parallel with that of the investigator, or how much time elapsed between imaging and the IRC's assessment. The timing of the IRC's assessment may have had implications for the treatment of patients (Table 6). Overall, it was assumed that this aspect had no relevant impact on the study results.

Treatment switching

As described above, patients in the comparator arm had the option of receiving tislelizumab monotherapy (treatment switching) following confirmation of radiographic disease progression (RECIST v1.1) if certain conditions were met. Tislelizumab as monotherapy is not an authorized treatment for NPC in Germany. The treatment switching was taken into account in the assessment of the risk of bias at outcome level (see Section I 4.2).

Restrictions of supportive concomitant therapies

Consolidation and palliative radiation

The clinical practice guideline issued by the European Society for Medical Oncology (ESMO) and the European Reference Network for Rare Adult Solid Tumours (EURACAN) for diagnosis and treatment of NPC recommends the addition of locoregional radiotherapy in patients with newly diagnosed metastatic NPC, to consolidate the therapeutic effect of systemic therapy and prolong survival [12]. In addition to radiation of locoregional lesions, palliative radiation of other organs, such as the bones [16], the lungs or the brain, may also be necessary for symptom control. In the RATIONALE 309 study, palliative radiation therapy for pain control or prophylaxis of bone fractures was permitted only for non-target lesions. According to the data provided in Module 4 B, the target lesions were located in the nasopharynx in 29% and 21% of patients, respectively. In a large proportion of the patients, the target lesions were located in organs other than the nasopharynx, such as the lungs (33% and 36% respectively). No further information was available on the approach used in the study in cases where the guidelines recommended consolidation, locoregional or palliative radiation for target lesions,

or on the number of patients for whom this was the case. Restrictions of consolidation and palliative radiation may affect various patient-relevant outcomes, including overall survival.

Availability of bisphosphonates and RANK-L inhibitors

The S3 guideline on supportive therapy for oncological patients recommends treatment with bisphosphonates or the receptor activator of NF- κ B ligand (RANK-L) inhibitor denosumab to prevent complications associated with bone metastases, taking into account the specific entity in question [16]. It is also described that treatment with bisphosphonates / RANK-L inhibitors can be provided in parallel with radiotherapy. According to the study design, concomitant treatment with bisphosphonates and RANK-L inhibitors for the treatment of bone metastases was permitted, if initiated prior to enrolment and at a stable dose. At baseline, 46% of the patients included in the study had bone metastases, and 27% were given bisphosphonates as concomitant treatment during the course of the study. Overall, it was unclear why some of the patients with bone metastases did not receive bisphosphonates or RANK-L inhibitors prior to enrolment – and therefore not during the course of the study either – and how many patients developed a need for such concomitant treatment during the course of the study.

Summary of uncertainties arising from restrictions of supportive concomitant therapies

The uncertainties described above may influence various outcome categories and were taken into account when assessing the certainty of conclusions of the results (see Section I 4.2).

Information on the course of the study

Table 10 shows patients' median and mean treatment durations and the median and mean observation periods for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: tislelizumab + gemcitabine + cisplatin vs. placebo + gemcitabine + cisplatin

Study Duration of the study phase Outcome category/outcome	tislelizumab + gemcitabine + cisplatin	placebo + gemcitabine + cisplatin
RATIONALE 309	N ^a = 131	N ^a = 132
Treatment duration [months] ^b		
Median [Q1; Q3]	10.5 [5.8; 20.9]	7.8 [4.6; 10.1]
Mean (SD)	15.5 (13.9)	9.1 (7.9)
Observation period [months]		
Overall survival ^c		
Median [95% CI]	41.4 [40.1; 42.2]	40.8 [39.8; 41.7]
Symptoms, health-related quality of life (EORTC QLQ-C30, EORTC QLQ-H&N35) ^d		
Median [min; max]	10.6 [0.0; 52.4]	7.9 [0.0; 45.9]
Mean (SD)	15.5 (13.7)	9.2 (7.8)
Side effects ^e		
Median [min; max]	10.9 [0.3; 52.4]	8.1 [0.1; 46.9]
Mean (SD)	15.9 (13.7)	9.4 (7.9)
Immune-mediated side effects ^f		
Median [min; max]	12.9 [0.3; 52.4]	9.9 [0.1; 48.9]
Mean (SD)	17.4 (13.4)	11.1 (8.1)
a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant. b. The conversion from weeks to months was carried out by IQWiG (weeks x 7 x 12 / 365.25). c. The observation period was calculated using the reverse Kaplan-Meier method. Deceased patients are censored at the time of death, whereas non-deceased patients are counted as event at the time of the end of observation. d. The time from randomization to the last valid assessment of the patient-reported outcome. For patients without baseline or post-baseline recordings, the time of randomization is considered to be the last recording. Observations made after the treatment switching were not taken into account. e. The period from the date of the first dose to the earliest of the following dates: the date of death, the date of study discontinuation, the data cut-off date, the last date of study treatment + 30 days, or the date a new anticancer therapy was started. Observations made after the treatment switching were not taken into account. f. The period from the date of the first dose to the earliest of the following dates: the date of death, the date of study discontinuation, the data cut-off date or the last date of study treatment + 90 days. CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; max: maximum; min: minimum; N: number of analysed patients; Q1: first quartile; Q3: third quartile; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-H&N35: Quality of Life Questionnaire-Head and Neck Cancer 35; RCT: randomized controlled trial; SD: standard deviation		

Whilst the median observation periods for overall survival were comparable between the 2 study arms, the median and mean treatment durations, as well as the mean and median observation periods for the other outcomes, were all longer in the intervention arm than in

the comparator arm. Thus, the median observation period for the patient-reported outcomes in the comparator arm was approximately 75% of that in the intervention arm. Furthermore, the observation periods in both arms for the outcomes in the categories of morbidity, health-related quality of life and side effects – which were linked to the end of treatment (plus 30 days or 90 days, respectively, for side effects) – were shorter than the observation period for overall survival.

Table 11 shows the subsequent therapies patients received after discontinuing the study medication. Table 12 shows the subsequent therapies received by patients in the comparator arm who, following radiographic disease progression, initially received tislelizumab monotherapy as part of a treatment switch.

Table 11: Information on subsequent antineoplastic therapies – RCT, direct comparison: tislelizumab + gemcitabine + cisplatin vs. placebo + gemcitabine + cisplatin (multipage table)

Study Type of therapy Drug class Drug	Patients with subsequent therapy n (%) ^a	
	tislelizumab + gemcitabine + cisplatin	placebo + gemcitabine + cisplatin
	N = 131	N = 132
RATIONALE 309		
any subsequent systemic therapy	78 (59.5)	32 (24.2)
Chemotherapy ^b	62 (79.5)	26 (81.3)
capecitabine	26 (33.3)	8 (25.0)
nab-paclitaxel	25 (32.1)	9 (28.1)
cisplatin	16 (20.5)	8 (25.0)
carboplatin	12 (15.4)	5 (15.6)
docetaxel	9 (11.5)	1 (3.1)
nedaplatin	7 (9.0)	6 (18.8)
paclitaxel	7 (9.0)	6 (18.8)
gemcitabine	4 (5.1)	3 (9.4)
gimeracil / oteracil potassium / tegafur	4 (5.1)	3 (9.4)
fluorouracil	2 (2.6)	2 (6.3)
lobaplatin	2 (2.6)	0 (0)
gemcitabine hydrochloride	1 (1.3)	2 (6.3)
raltitrexed	1 (1.3)	1 (3.1)
epirubicin	0 (0)	2 (6.3)
vinorelbine	0 (0)	2 (6.3)

Table 11: Information on subsequent antineoplastic therapies – RCT, direct comparison: tislelizumab + gemcitabine + cisplatin vs. placebo + gemcitabine + cisplatin (multipage table)

Study Type of therapy Drug class Drug	Patients with subsequent therapy n (%) ^a	
	tislelizumab + gemcitabine + cisplatin	placebo + gemcitabine + cisplatin
	N = 131	N = 132
Immunotherapy ^b	31 (39.7)	18 (56.3)
toripalimab	9 (11.5)	5 (15.6)
Shr 1701	6 (7.7)	2 (6.3)
camrelizumab	5 (6.4)	2 (6.3)
tislelizumab	4 (5.1)	5 (15.6) ^c
pembrolizumab	3 (3.8)	0 (0)
QI 1706	3 (3.8)	0 (0)
sintilimab	2 (2.6)	3 (9.4)
nivolumab	1 (1.3)	2 (6.3)
Targeted therapy ^b	28 (35.9)	13 (40.6)
catequentinib hydrochloride	7 (9.0)	3 (9.4)
nimotuzumab	7 (9.0)	6 (18.8)
catequentinib	4 (5.1)	0 (0)
rivoceranib mesylate	3 (3.8)	0 (0)
bevacizumab	2 (2.6)	1 (3.1)
famitinib	2 (2.6)	0 (0)
lucitanib	2 (2.6)	0 (0)
cetuximab	1 (1.3)	2 (6.3)
denosumab	1 (1.3)	2 (6.3)
niraparib tosylate monohydrate	0 (0)	2 (6.3)
Chinese herb medicine ^b	7 (9.0)	5 (15.6)
Unspecified herbal and traditional medicine	5 (6.4)	2 (6.3)
<i>Brucea javanica</i> oil; glycerol; lecithin	1 (1.3)	1 (3.1)
cinobufagin	1 (1.3)	1 (3.1)
lentinan	1 (1.3)	1 (3.1)
<i>Astragalus mongholicus</i> root; oxymatrine; <i>Panax ginseng</i> dry extract	0 (0)	2 (6.3)
<i>Smilax spp.</i> tuber, <i>Sophora flavescens</i> root	0 (0)	2 (6.3)
Antibody-drug conjugate ^b	5 (6.4)	0 (0)
Mrg 003	3 (3.8)	0 (0)
BI B01d1	2 (2.6)	0 (0)
Other ^b	1 (1.3)	2 (6.3)

Table 11: Information on subsequent antineoplastic therapies – RCT, direct comparison: tislelizumab + gemcitabine + cisplatin vs. placebo + gemcitabine + cisplatin (multipage table)

Study Type of therapy Drug class Drug	Patients with subsequent therapy n (%) ^a	
	tislelizumab + gemcitabine + cisplatin	placebo + gemcitabine + cisplatin
	N = 131	N = 132
Any subsequent non-systemic therapy	32 (24.4)	18 (13.6)
Surgery ^d	5 (15.6)	1 (5.6)
Radiotherapy ^d	29 (90.6)	18 (100.0)
a. Subsequent therapies used by ≥ 2 patients. Each patient was counted only once in each category. It is unclear to which lines of treatment the information provided by the company refers, and whether / in what combinations the listed drugs were administered. b. Percentages for the drug classes and the drugs listed below: Institute's calculation, based on the number of patients with any subsequent systemic therapy. c. 69 patients in the comparator arm received tislelizumab as part of the treatment switch and were excluded from the presentation of subsequent therapies by the company. d. Percentages are calculated by the Institute, based on the number of patients with any non-systemic subsequent therapy. n: number of patients with subsequent therapy; N: number of analysed patients; nab: albumin-bound nanoparticles; RCT: randomized controlled trial		

Table 12: Information on subsequent antineoplastic therapies of patients from the comparator arm who switched treatment – RCT (multipage table)

Study Type of therapy Drug class	Patients with subsequent therapy n (%) ^a
	N = 69
RATIONALE 309	
Any subsequent systemic therapy	43 (62.3)
Chemotherapy ^b	31 (72.1)
nab-paclitaxel	12 (27.9)
capecitabine	8 (18.6)
carboplatin	8 (18.6)
cisplatin	6 (14.0)
docetaxel	6 (14.0)
paclitaxel	5 (11.6)
nedaplatin	4 (9.3)
fluorouracil	2 (4.7)

Table 12: Information on subsequent antineoplastic therapies of patients from the comparator arm who switched treatment – RCT (multipage table)

Study	Patients with subsequent therapy n (%) ^a
Type of therapy	N = 69
Drug class	
Immunotherapy ^b	25 (58.1)
toripalimab	8 (18.6)
sintilimab	6 (14.0)
camrelizumab	4 (9.3)
Ibi 310	3 (7.0)
Shr 1701	3 (7.0)
tislelizumab	3 (7.0)
nivolumab	2 (4.7)
Targeted therapy ^b	12 (27.9)
catequentinib hydrochloride	4 (9.3)
nimotuzumab	2 (4.7)
rivoceranib mesylate	2 (4.7)
Chinese herb medicine ^b	2 (4.7)
Antibody-drug conjugate ^b	2 (4.7)
Mrg 003	2 (4.7)
Other ^b	5 (11.6)
Antineoplastic agents	2 (4.7)
Any subsequent non-systemic therapy	15 (21.7)
Surgery ^c	3 (20.0)
Radiotherapy ^c	13 (86.7)
a. Subsequent therapies used by ≥ 2 patients. Each patient was counted only once in each category. It is unclear to which lines of treatment the information provided by the company refers, and whether / in what combinations the listed drugs were administered. b. Percentages for the drug classes and the drugs listed below: Institute's calculation, based on the number of patients with any subsequent systemic therapy. c. Percentages are calculated by the Institute, based on the number of patients with any non-systemic subsequent therapy. n: number of patients with subsequent therapy; N: number of analysed patients; nab: albumin-bound nanoparticles; RCT: randomized controlled trial	

Table 11 and Table 12 are based on the company's presentation in Module 4 B. The company did not specify which line(s) of treatment its information related to, nor whether the drugs were used in combination. When presenting subsequent therapies of the overall population, the company excluded patients from the comparator arm who received tislelizumab as part of the treatment switch (see the paragraph on limitations of the RATIONALE 309 study in Section I 3.2).

In RATIONALE 309, subsequent antineoplastic therapies were permitted without restrictions in both study arms. When considering the 69 patients who received tislelizumab monotherapy following radiographic disease progression, it was apparent that more patients in the comparator arm received subsequent systemic therapy than in the intervention arm: 78 (60%) versus 101 (77%). It was assumed that most patients with disease progression (87 versus 104) received subsequent therapy.

Apart from tislelizumab, chemotherapy and immunotherapy were the most commonly used subsequent systemic therapies in both study arms. In addition, 7 versus 5 patients received Chinese herb medicine as subsequent therapies. It was unclear whether these were administered on their own or in combination with conventional medical treatment. In the given therapeutic indication, treatment with herbal remedies alone is not standard practice in Germany. The proportion of 62% of patients receiving subsequent systemic therapy following tislelizumab monotherapy given as part of treatment switch, as well as the distribution of the drug classes administered, were comparable to those in the intervention and comparator arms. According to international guidelines, there is no standard treatment for second- and third-line therapy in the given therapeutic indication [11,12,17]. Treatment options listed include immunotherapy and chemotherapy, as well as radiotherapy or surgical resection for the treatment of metastases. In the absence of specific recommendations in the guidelines, it was overall not assumed that patients in RATIONALE 309 were deprived of effective subsequent therapies to any relevant extent.

Risk of bias across outcomes (study level)

Table 13 shows the risk of bias across outcomes (risk of bias at study level).

Table 13: Risk of bias across outcomes (study level) – RCT, direct comparison: tislelizumab + gemcitabine + cisplatin vs. placebo + gemcitabine + cisplatin

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	Absence of other aspects	Risk of bias at study level
			Patients	Treating staff			
RATIONALE 309	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes is rated as low for the RATIONALE 309 study.

Transferability of the study results to the German health care context

The company described that the results of the RATIONALE 309 study were transferable to the German health care context due to the SmPC-compliant use of tislelizumab and the patient characteristics. To show this transferability, it compared age, sex distribution and risk factors of the study population with those of the patient population in non-endemic areas. According to the company, a bimodal age distribution can be observed in non-endemic areas, with the first peak among adolescents and young adults and the second peak from the age of 65 onwards. The median age of the study population, at 50 years, was therefore slightly below the second peak, the company explained. According to the company, the high proportion of men in the study population (78%) was consistent with the sex distribution within the German patient population. Furthermore, the company cited genetic factors that are associated with the development of NPC and pointed out that these are not genetic predispositions that occur exclusively in the Asian population and that the results are therefore, in principle, transferable to the German population. The company named chronic infection with the Epstein-Barr virus (EBV) as another additional risk factor, and added that the dominant genotype of EBV is the same in Europe and South-East Asia. It also referred to smoking as a risk factor and quoted the proportions of current smokers and former smokers in each study arm.

The company did not provide any further information on the transferability of the study results to the German health care context. For the transferability of the study results, see also the section regarding limitations of the study in Section I 3.2.

I 4 Results on added benefit

I 4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
 - Overall survival
- Morbidity
 - Symptoms
 - recorded using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and the EORTC Quality of Life Questionnaire-Head and Neck Cancer 35 (QLQ-H&N35)
- Health-related quality of life
 - recorded using the EORTC QLQ-C30 and QLQ-H&N35
- Side effects
 - Serious AEs (SAEs)
 - Severe AEs (CTCAE grade ≥ 3)
 - Discontinuation due to AEs
 - Immune-mediated SAEs
 - Immune-mediated severe AEs (CTCAE grade ≥ 3)
 - Fever (PT, AE)

The selection of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 B).

Table 14 shows for which outcomes data were available in the included study.

Table 14: Matrix of outcomes – RCT, direct comparison: tislelizumab + gemcitabine + cisplatin vs. placebo + gemcitabine + cisplatin

Study	Outcomes								
	Overall survival	Symptoms (EORTC QLQ-C30 and QLQ-H&N35)	Health-related quality of life (EORTC QLQ-C30 and QLQ-H&N35)	SAEs	Severe AEs ^a	Discontinuation due to AEs	Immune-mediated SAEs ^b	Immune-mediated severe AEs ^{a, b}	Fever (PT, AE)
RATIONALE 309	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
a. Severe AEs are operationalized as CTCAE grade ≥ 3 AEs. b. The operationalization as per prespecified PT collections of the company were used in each case, without applying any further criteria. For a detailed description of the operationalization, see Section I 4.1. AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-H&N35: Quality of Life Questionnaire-Head and Neck Cancer 35; RCT: randomized controlled trial; SAE: serious adverse event									

Notes on outcomes

Overall survival

To investigate the potential influence of treatment switching (from placebo to tislelizumab), the company presented sensitivity analyses for the outcome overall survival, using the rank preserving structural failure time (RPFST) and two-stage methods. The presented sensitivity analyses were not relevant for the dossier assessment, as these analyses were based on unverifiable assumptions and, furthermore, there was insufficient information available regarding the practical implementation of these methods [18].

Patient-reported outcomes on symptoms and health-related quality of life

Operationalization of patient-reported outcomes

For each of the patient-reported outcomes in the categories of morbidity and health-related quality of life (EORTC QLQ-C30 and QLQ-H&N35) the company presented in Module 4 B post hoc responder analyses for the time to 1st deterioration and, as a supporting analysis, the mean change from baseline, using a mixed-effects model with repeated measures (MMRM) analysis. The responder analyses of the time to 1st deterioration were used in this benefit assessment.

In RATIONALE 309, analyses of the time to confirmed deterioration were prespecified for individual outcomes, including general health status (assessed using the EORTC QLQ-C30). In this context, a confirmed deterioration was defined as a deterioration of ≥ 10 points at 2 consecutive recordings, or at a single recording followed by death within 3 weeks. Confirmed deterioration is generally relevant in terms of content and is desirable for all scales of an instrument, as it represents a more lasting change than a single deterioration. However, the company did not provide this information in Module 4 B. Given the differences in the observation periods between the study arms, the company's approach is initially comprehensible. However, the analyses of the time to confirmed deterioration may still be suitable for the benefit assessment despite the different observation periods, as both study arms had comparable response rates for both questionnaires up to around Month 8. The period of 8 months covers the majority of the median observation periods for the patient-reported outcomes (see Table 10). However, results of the time-to-event analyses, including the corresponding Kaplan-Meier curves, would be required to be able to make a conclusive assessment of whether the analyses relating to confirmed deterioration were suitable. These data were not available in the company's dossier, however.

Symptoms recorded using the EORTC QLQ-H&N35

For the patient-reported outcomes of symptoms, the company presented in Module 4 B results for the 15 scales recorded with the EORTC QLQ-H&N35. These include single-item and multi-item scales; the occurrence of most of the items are assessed on a scale from 1 ('not at all') to 4 ('very much'). In Module 4 A, the company presented results on only 14 of these scales. No results were available for the scale 'sticky saliva', which is based on a single item. The recording and analysis of this item were not prespecified in the RATIONALE 309 study.

On the other hand, the company also presented results in Module 4 B for the 'sense of smell' item, which, together with taste problems, forms part of the multi-item scale for senses problems [19]. The company did not justify this approach. The questionnaires recorded as part of the patient-reported outcomes were to be recorded and analysed in accordance with the relevant scoring manuals. The results relating to the sense of smell were therefore not taken into account in the benefit assessment.

The EORTC QLQ-H&N35 also includes 4 scales with uncertain patient relevance. These are the scales for use of painkillers, use of nutritional supplements, weight loss and weight gain. These scales simply involve a yes/no question to determine whether patients have taken painkillers or nutritional supplements in the past 7 days, or whether they have gained or lost weight, without asking them to assess the associated burden. For this reason, these scales are shown only as supplementary information.

Analysis of patient-reported outcomes

According to the company, all patients were included in the analyses of patient-reported outcomes. At the same time, however, the company stated that patients with no baseline value or no value in the further course of the study were censored at the time of randomization. These patients were therefore de facto not included in the analysis. The exact number of these patients cannot be determined. However, based on the information on the response rates, e.g. to the EORTC QLQ-C30, the number of patients included in the analysis was considered to be sufficiently large (approx. 93% in the intervention arm and 98% in the comparator arm) for the analysis to be used for the benefit assessment.

Operationalization of immune-mediated adverse events

In the RATIONALE 309 study, immune-mediated AEs were identified on the basis of predefined Preferred Terms (PTs) from the Medical Dictionary for Regulatory Activities (MedDRA). PTs with confirmed immune-mediated aetiology (according to the company) were classified directly as immune-mediated AEs. PTs that the company had predefined as potentially immune-mediated were only to be documented as immune-mediated AEs once they met prerequisites such as treatment with systemic steroids or other immunosuppressants, or following an assessment by the investigators. The company presented the corresponding analyses in Module 4 B. These analyses were not usable for this benefit assessment. By linking the recording of immune-mediated AEs to the prerequisites listed above, such as the treatment initiated, the adequate representation of immune-mediated AEs was not guaranteed.

In Appendix G to Module 4 B, the company provided further analyses based on all predefined PTs, irrespective of whether the prerequisites were met. The underlying PTs were divided into 9 categories. The categories included were assessed as appropriate for an approximation to immune-mediated AEs. The PT lists did contain events that are not suitable for representing patient-relevant immune-mediated AEs (e.g. laboratory results). However, an analysis of the events observed in the study that were included in the analyses of severe (CTCAE grade ≥ 3) and serious immune-mediated AEs revealed that these were based exclusively on relevant PTs (Table 25 and Table 26 of the full dossier assessment). The analyses presented in Appendix G were therefore used as a sufficient approximation to represent the immune-mediated AEs that occurred.

I 4.2 Risk of bias

Table 15 describes the risk of bias for the results of the relevant outcomes.

Table 15: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: tislelizumab + gemcitabine + cisplatin vs. placebo + gemcitabine + cisplatin

Study	Study level	Outcomes								
		Overall survival	Symptoms (EORTC QLQ-C30 and QLQ-H&N35)	Health-related quality of life (EORTC QLQ-C30 and QLQ-H&N35)	SAEs	Severe AEs ^a	Discontinuation due to AEs	Immune-mediated SAEs ^b	Immune-mediated severe AEs ^{a, b}	Fever (PT, AE)
RATIONALE 309	N	H ^c	H ^d	H ^d	H ^d	H ^d	L ^e	H ^d	H ^d	H ^d
a. Severe AEs are operationalized as CTCAE grade ≥ 3 AEs. b. The operationalization as per prespecified PT collections of the company were used in each case, without applying any further criteria. For a detailed description of the operationalization, see Section I 4.1. c. A high proportion of patients in the comparator arm who switched to treatment with tislelizumab during the course of the study (52.3%) d. Incomplete observations for potentially informative reasons with different lengths of follow-up observation. e. Despite a low risk of bias, the certainty of results for the outcome of discontinuation due to AEs is assumed to be limited (see Section I 4.2). AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; H: high; L: low, P: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-H&N35: Quality of Life Questionnaire-Head and Neck Cancer 35; RCT: randomized controlled trial; SAE: serious adverse event										

The results on overall survival showed a high risk of bias because a high proportion of patients (52%) switched from the comparator arm to treatment with tislelizumab (see also Section I 3.2 on treatment switching).

The risk of bias for the results on symptoms and health-related quality of life, recorded using the EORTC QLQ-C30 and the EORTC QLQ-H&N35, was assessed as high. Follow-up for these outcomes was planned until the end of treatment. The observation period was thus controlled by treatment discontinuation. The proportions and reasons for this varied to some extent between the study arms (disease progression: 57% in the intervention arm and 69% in the comparator arm; withdrawal of consent: 20% in the intervention arm and 17% in the comparator arm; AEs: 9% in the intervention arm and 4% in the comparator arm). Notable was the high proportion of patients who withdrew their consent during the course of the study, but the reasons for withdrawal were unknown. Due to a possible association between the reason for treatment discontinuation and the outcomes, incomplete observations for potentially informative reasons were present.

The risk of bias in the results for the outcome category side effects, excluding discontinuation due to AEs, was assessed as high in each case due to incomplete observations for potentially informative reasons, as previously described for the outcomes relating to symptoms and health-related quality of life.

Although the risk of bias for the outcome discontinuation due to AEs was low, the certainty of results for this outcome was limited. Premature treatment discontinuation for reasons other than AEs is a competing event for the outcome discontinuation due to AEs to be recorded. This means that, although AEs that would have led to discontinuation of therapy may occur after discontinuation for other reasons, the criterion discontinuation is no longer applicable to them. It was impossible to estimate how many AEs this affected.

Summary assessment of the certainty of conclusions

Independent of the high risk of bias for all outcomes except discontinuation due to AEs, there were relevant uncertainties regarding the restrictions around supportive concomitant therapies (see Section I 3.2). Consequently, the certainty of conclusions for all outcomes was limited. Thus, at most hints, e.g. of an added benefit, can be derived for all outcomes on the basis of the effects shown in the RATIONALE 309 study.

I 4.3 Results

Table 16 summarizes the results of the comparison between tislelizumab + gemcitabine + cisplatin and placebo + gemcitabine + cisplatin in patients with recurrent, not amenable to curative surgery or radiotherapy, or metastatic NPC. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

The Kaplan-Meier curves for the time-to-event analyses are presented in I Appendix B of the full dossier assessment, and the results on common AEs, SAEs and severe AEs (CTCAE grade ≥ 3), common immune-mediated AEs, immune-mediated SAEs, immune-mediated severe AEs (CTCAE grade ≥ 3) and discontinuations due to AEs can be found in I Appendix C of the full dossier assessment.

Table 16: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: tislelizumab + gemcitabine + cisplatin vs. placebo + gemcitabine + cisplatin (multipage table)

Study Outcome category Outcome	tislelizumab + gemcitabine + cisplatin		placebo + gemcitabine + cisplatin		tislelizumab + gemcitabine + cisplatin vs. placebo + gemcitabine + cisplatin
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value ^a
RATIONALE 309					
Mortality					
Overall survival	131	45.3 [33.4; NC] 55 (42.0)	132	31.8 [25.0; NC] 64 (48.5)	0.73 [0.51; 1.05]; 0.084
Morbidity					
Symptoms (EORTC QLQ-C30 – time to 1st deterioration) ^b					
Fatigue	131	1.4 [0.8; 2.3] 92 (70.2)	132	2.2 [2.0; 3.8] 84 (63.6)	1.18 [0.87; 1.59]; 0.307
Nausea and vomiting	131	2.6 [2.2; 5.2] 78 (59.5)	132	3.5 [2.2; 10.4] 74 (56.1)	1.04 [0.75; 1.43]; 0.801
Pain	131	17.2 [7.8; 24.4] 59 (45.0)	132	8.4 [6.2; 19.6] 62 (47.0)	0.82 [0.57; 1.18]; 0.280
Dyspnoea	131	22.6 [12.5; NC] 52 (39.7)	132	13.7 [11.1; NC] 45 (34.1)	1.08 [0.72; 1.63]; 0.705
Insomnia	131	27.6 [10.8; NC] 49 (37.4)	132	NA [10.3; NC] 44 (33.3)	0.98 [0.64; 1.48]; 0.914
Appetite loss	131	2.4 [2.1; 3.9] 80 (61.1)	132	3.4 [2.2; 4.6] 74 (56.1)	1.15 [0.83; 1.57]; 0.405
Constipation	131	— ^c 53 (40.5)	132	— ^c 52 (39.4)	0.94 [0.64; 1.38]; 0.727
Diarrhoea	131	NA [30.4; NC] 34 (26.0)	132	NA 27 (20.5)	1.15 [0.68; 1.93]; 0.607
Symptoms (EORTC QLQ-H&N35 – time to 1st deterioration) ^b					
Pain	131	NA [24.9; NC] 44 (33.6)	132	— ^c 35 (26.5)	1.18 [0.75; 1.86]; 0.469
Dysphagia	131	NA [22.5; NC] 41 (31.3)	132	NA [11.1; NC] 37 (28.0)	0.97 [0.61; 1.53]; 0.887
Senses problems	131	10.8 [4.8; 33.8] 64 (48.9)	132	10.8 [6.2; NC] 57 (43.2)	1.11 [0.77; 1.61]; 0.570

Table 16: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: tislelizumab + gemcitabine + cisplatin vs. placebo + gemcitabine + cisplatin (multipage table)

Study Outcome category Outcome	tislelizumab + gemcitabine + cisplatin		placebo + gemcitabine + cisplatin		tislelizumab + gemcitabine + cisplatin vs. placebo + gemcitabine + cisplatin
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value ^a
Speech problems	131	NA 24 (18.3)	132	27.5 [16.1; NC] 27 (20.5)	0.77 [0.44; 1.36]; 0.365
Problems with teeth	131	20.0 [12.0; 44.0] 54 (41.2)	132	13.1 [7.9; 38.9] 54 (40.9)	0.83 [0.57; 1.22]; 0.346
Problems with mouth opening	131	24.6 [13.8; NC] 46 (35.1)	132	15.6 [10.4; 21.9] 44 (33.3)	0.80 [0.52; 1.23]; 0.305
Dry mouth	131	— ^c 49 (37.4)	132	NA [15.6; NC] 36 (27.3)	1.31 [0.85; 2.02]; 0.223
Cough	131	33.6 [14.6; NC] 44 (33.6)	132	16.4 [11.1; NC] 40 (30.3)	0.93 [0.60; 1.45]; 0.755
Feeling ill	131	13.1 [5.2; NC] 60 (45.8)	132	18.9 [10.6; NC] 41 (31.1)	1.51 [1.01; 2.26]; 0.043
Feeding tube	131	NA [42.3; NC] 4 (3.1)	132	NA 7 (5.3)	0.33 [0.09; 1.20]; 0.080
<i>Use of painkillers (supplementary information)</i>	131	NA 22 (16.8)	132	NA 29 (22.0)	—
<i>Use of nutritional supplements (supplementary information)</i>	131	NA 42 (32.1)	132	NA 32 (24.2)	—
<i>Weight loss (supplementary information)</i>	131	NA [13.1; NC] 46 (35.1)	132	— ^c 39 (29.5)	—
<i>Weight gain (supplementary information)</i>	131	6.4 [5.0; 8.0] 72 (55.0)	132	5.1 [4.1; 6.5] 68 (51.5)	—

Table 16: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: tislelizumab + gemcitabine + cisplatin vs. placebo + gemcitabine + cisplatin (multipage table)

Study Outcome category Outcome	tislelizumab + gemcitabine + cisplatin		placebo + gemcitabine + cisplatin		tislelizumab + gemcitabine + cisplatin vs. placebo + gemcitabine + cisplatin
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value ^a
Health-related quality of life					
EORTC QLQ-C30 – time to 1st deterioration ^d					
Global health status	131	10.8 [4.0; NC] 61 (46.6)	132	6.6 [3.6; 15.0] 67 (50.8)	0.84 [0.59; 1.20]; 0.336
Physical functioning	131	10.8 [4.1; 18.8] 67 (51.1)	132	6.6 [3.8; NC] 61 (46.2)	1.03 [0.73; 1.46]; 0.862
Role functioning	131	5.2 [2.5; NC] 66 (50.4)	132	7.6 [4.9; 33.5] 65 (49.2)	1.03 [0.73; 1.46]; 0.859
Emotional functioning	131	NA [18.8; NC] 46 (35.1)	132	NA [19.1; NC] 34 (25.8)	1.30 [0.83; 2.04]; 0.244
Cognitive functioning	131	6.0 [3.8; 18.9] 68 (51.9)	132	8.4 [5.1; NC] 60 (45.5)	1.08 [0.76; 1.53]; 0.674
Social functioning	131	5.2 [2.5; 13.2] 72 (55.0)	132	10.4 [4.4; NC] 60 (45.5)	1.23 [0.87; 1.73]; 0.251
EORTC QLQ-H&N35 – time to 1st deterioration ^b					
Trouble with social eating	131	28.2 [8.4; NC] 53 (40.5)	132	13.6 [10.4; NC] 47 (35.6)	1.10 [0.74; 1.64]; 0.651
Trouble with social contact	131	NA 38 (29.0)	132	27.5 [16.4; NC] 37 (28.0)	0.90 [0.57; 1.43]; 0.658
Less sexuality	131	3.7 [2.3; 10.8] 74 (56.5)	132	5.2 [3.4; 8.7] 73 (55.3)	1.09 [0.78; 1.51]; 0.675

Table 16: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: tislelizumab + gemcitabine + cisplatin vs. placebo + gemcitabine + cisplatin (multipage table)

Study Outcome category Outcome	tislelizumab + gemcitabine + cisplatin		placebo + gemcitabine + cisplatin		tislelizumab + gemcitabine + cisplatin vs. placebo + gemcitabine + cisplatin
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value ^a
Side effects					
AEs (supplementary information)	133	0.1 [0.1; 0.1] 133 (100)	130	0.1 [0.1; 0.1] 129 (99.2)	–
SAEs	133	44.6 [22.7; NC] 47 (35.3)	130	NA [11.9; NC] 46 (35.4)	0.81 [0.54; 1.23]; 0.328
Severe AEs ^e	133	0.7 [0.5; 1.0] 113 (85.0)	130	0.7 [0.5; 0.9] 111 (85.4)	1.00 [0.77; 1.30]; 0.988
Discontinuation due to AEs	133	NA 22 (16.5)	130	NA 14 (10.8)	1.29 [0.65; 2.56]; 0.469
Immune-mediated AEs (supplementary information) ^f	133	6.2 [4.6; 14.8] 75 (56.4)	130	13.0 [6.7; NC] 56 (43.1)	–
Immune-mediated SAEs ^f	133	NA 5 (3.8)	130	NA 1 (0.8)	4.44 [0.52; 38.04]; 0.137
Immune-mediated severe AEs ^{e, f}	133	NA 7 (5.3)	130	NA 1 (0.8)	6.98 [0.86; 56.74]; 0.034 ^g
Fever (PT, AE)	133	NA [34.5; NC] 35 (26.3)	130	NA 13 (10.0)	2.56 [1.34; 4.88]; 0.003
a. HR and CI: Cox proportional hazards model, p-value: log-rank test; each stratified by sex and the presence of liver metastases. b. An increase of ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100). c. Median time [95% CI] to event cannot be meaningfully interpreted. The long median observation periods evident in the Kaplan-Meier curves occur following a plateau phase, in conjunction with very small numbers of patients at risk, and therefore have no informative value (see I Appendix B.2 of the full dossier assessment). d. A decrease of ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100). e. Operationalized as CTCAE grade ≥ 3. f. The operationalization as per prespecified PT collections of the company were used in each case, without applying any further criteria. For a detailed description of the operationalization, see Section I 4.1. g. Discrepancy between p-value and CI due to different calculation methods.					

Table 16: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: tislelizumab + gemcitabine + cisplatin vs. placebo + gemcitabine + cisplatin (multipage table)

Study Outcome category Outcome	tislelizumab + gemcitabine + cisplatin		placebo + gemcitabine + cisplatin		tislelizumab + gemcitabine + cisplatin vs. placebo + gemcitabine + cisplatin
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value ^a
AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-H&N35: Quality of Life Questionnaire-Head and Neck Cancer 35; RCT: randomized controlled trial					

On the basis of the available information, no more than hints, e.g. of an added benefit, can be determined for all outcomes. The reasons for this are set out in Section I 4.2.

Mortality

No significant difference between the treatment groups was found for the outcome overall survival. There is no hint of an added benefit of tislelizumab + gemcitabine + cisplatin in comparison with the ACT; an added benefit is therefore not proven.

Morbidity

Symptoms (recorded using the EORTC QLQ-C30 and QLQ-H&N35)

Nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, pain, dysphagia, senses problems, problems with teeth, problems with mouth opening, dry mouth, coughing and feeding tube

No statistically significant difference between the treatment groups was found for the outcomes of nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation and diarrhoea (recorded using the EORTC QLQ-C30), as well as pain, dysphagia, senses problems, problems with teeth, problems with mouth opening, coughing and feeding tube (recorded using the EORTC QLQ-H&N35). There is no hint of an added benefit of tislelizumab + gemcitabine + cisplatin in comparison with the ACT for any of the outcomes; an added benefit is therefore not proven for these outcomes.

Fatigue

For the outcome fatigue of the EORTC QLQ-C30, no statistically significant difference between the treatment arms was found when considering the total population. There was an effect modification by the characteristic of age, however (see Section I 4.4). There is a hint of lesser benefit of tislelizumab + gemcitabine + cisplatin in comparison with the ACT for patients ≥ 65 years of age. For patients < 65 years of age, there is no hint of an added benefit or of lesser benefit of tislelizumab + gemcitabine + cisplatin in comparison with the ACT. An added benefit for patients < 65 years of age is therefore not proven.

Speech problems

For the outcome 'speech problems' of the EORTC QLQ-H&N35, no statistically significant difference between the treatment arms was found when considering the total population. There was an effect modification by the characteristic 'presence of liver metastases', however (see Section I 4.4). There is a hint of an added benefit of tislelizumab + gemcitabine + cisplatin in comparison with the ACT for patients with liver metastases. For patients without liver metastases, there is no hint of an added benefit or of lesser benefit of tislelizumab + gemcitabine + cisplatin in comparison with the ACT. An added benefit for patients without liver metastases is therefore not proven.

Feeling ill

For the outcome 'feeling ill' of the EORTC QLQ-H&N35, a statistically significant difference between the treatment arms was found when considering the total population, which was no more than marginal, however. There was an effect modification by the characteristic 'presence of liver metastases' (see Section I 4.4). There is a hint of lesser benefit of tislelizumab + gemcitabine + cisplatin in comparison with the ACT for patients without liver metastases. For patients with liver metastases, there is no hint of an added benefit or of lesser benefit of tislelizumab + gemcitabine + cisplatin in comparison with the ACT. An added benefit for patients with liver metastases is therefore not proven.

Health-related quality of life

No statistically significant difference was found between the treatment arms for any of the following outcomes: general health status, physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning (assessed using the EORTC QLQ-C30), trouble with social eating, trouble with social contact and less sexuality (assessed using the EORTC QLQ-H&N35). In each case, there is no hint of an added benefit of tislelizumab + gemcitabine + cisplatin in comparison with the ACT; an added benefit is therefore not proven.

Side effects

SAEs, severe AEs, and discontinuation due to AEs

There was no statistically significant difference between the treatment arms for any of the outcomes of SAEs, severe AEs or discontinuation due to AEs. There is no hint of greater or lesser harm of tislelizumab + gemcitabine + cisplatin in comparison with the ACT for any of the outcomes; greater or lesser harm is therefore not proven for these outcomes.

Immune-mediated SAEs

No statistically significant difference between the treatment arms was shown for the outcome of immune-mediated SAEs. There is no hint of greater or lesser harm of tislelizumab + gemcitabine + cisplatin in comparison with the ACT; an added benefit is therefore not proven.

Immune-mediated severe AEs

A statistically significant difference to the disadvantage of tislelizumab + gemcitabine + cisplatin compared with placebo + gemcitabine + cisplatin was shown for the outcome of immune-mediated severe AEs. There is therefore a hint of greater harm of tislelizumab + gemcitabine + cisplatin in comparison with the ACT.

Fever (AE)

A statistically significant difference to the disadvantage of tislelizumab + gemcitabine + cisplatin compared with placebo + gemcitabine + cisplatin was shown for the outcome fever. There was an effect modification by the characteristic 'liver metastases' (see Section I 4.4). There is a hint of greater harm of tislelizumab + gemcitabine + cisplatin in comparison with the ACT for patients without liver metastases. There is no hint of greater or lesser harm of tislelizumab + gemcitabine + cisplatin in comparison with the ACT for patients with liver metastases; greater or lesser harm is therefore not proven for this group.

I 4.4 Subgroups and other effect modifiers

The following subgroup characteristics were taken into account for this benefit assessment:

- Age (< 65 years versus ≥ 65 years)
- Sex (male versus female)
- Presence of liver metastases (yes versus no)

According to the study documentation, the characteristic 'presence of liver metastases' (yes versus no) was defined as a stratification characteristic in the RATIONALE 309 study, but was not planned as a subgroup characteristic. However, it is the only one that represents the severity of the disease in a meaningful way. The prespecified subgroup characteristic 'metastatic status' (liver versus other organs) was reformulated during the course of the study

to 'presence of liver metastases' (yes versus no), as patients without metastases were also included in the study. This reasoning is understandable. Furthermore, the respective subgroups largely comprised the same patients (56 versus 70 / 56 versus 69 [liver versus other organs], and 56 versus 75 / 56 versus 76 [liver metastases yes versus no]).

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

The results are presented in Table 17. The Kaplan-Meier curves on the subgroup results are presented in I Appendix B.5 of the full dossier assessment.

Table 17: Subgroups (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: tislelizumab + gemcitabine + cisplatin vs. placebo + gemcitabine + cisplatin (multipage table)

Study Outcome Characteristic Subgroup	tislelizumab + gemcitabine + cisplatin		placebo + gemcitabine + cisplatin		tislelizumab + gemcitabine + cisplatin vs. placebo + gemcitabine + cisplatin	
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI] ^a	p-value ^a
RATIONALE 309						
Morbidity						
Symptoms (EORTC QLQ-C30 – time to 1st deterioration)^b						
Fatigue						
Age						
< 65 years	121	2.1 [0.9; 3.5] 82 (67.8)	120	2.2 [1.0; 5.2] 75 (62.5)	1.09 [0.79; 1.49]	0.610
≥ 65 years	10	0.7 [0.7; 0.8] 10 (100.0)	12	2.2 [0.9; 3.8] 9 (75.0)	5.88 [1.99; 17.32]	< 0.001
Total					Interaction:	0.046 ^c
Symptoms (EORTC QLQ-H&N35 – time to 1st deterioration)^b						
Speech problems						
Sex (supplementary information) ^d						
Male	103	NA 21 (20.4)	103	NA [22.0; NC] 18 (17.5)	1.05 [0.56; 1.99]	0.879
Female	28	NA [17.2; NC] 3 (10.7)	29	NA [4.9; NC] 9 (31.0)	0.17 [0.04; 0.81]	0.011
Total					Interaction:	0.028 ^c
Presence of liver metastases						
Yes	56	NA 4 (7.1)	56	NA [10.8; NC] 14 (25.0)	0.21 [0.07; 0.65]	0.004
No	75	NA [26.0; NC] 20 (26.7)	76	27.5 [16.1; NC] 13 (17.1)	1.40 [0.69; 2.82]	0.354
Total					Interaction:	0.005 ^c

Table 17: Subgroups (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: tislelizumab + gemcitabine + cisplatin vs. placebo + gemcitabine + cisplatin (multipage table)

Study Outcome	tislelizumab + gemcitabine + cisplatin		placebo + gemcitabine + cisplatin		tislelizumab + gemcitabine + cisplatin vs. placebo + gemcitabine + cisplatin	
Characteristic Subgroup	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI] ^a	p-value ^a
Feeling ill						
Presence of liver metastases						
Yes	56	NA [6.7; NC] 20 (35.7)	56	10.6 [8.4; NC] 21 (37.5)	0.87 [0.46; 1.62]	0.647
No	75	5.2 [3.5; 26.0] 40 (53.3)	76	18.9 [18.9; NC] 20 (26.3)	2.17 [1.27; 3.73]	0.004
Total					Interaction:	0.044 ^c
Side effects						
Fever (PT, AE)						
Presence of liver metastases						
Yes	56	NA [34.5; NC] 12 (21.4)	56	NA 9 (16.1)	1.39 [0.58; 3.32]	0.472
No	77	NA [29.3; NC] 23 (29.9)	74	NA 4 (5.4)	5.29 [1.88; 15.37]	< 0.001
Total					Interaction:	0.042 ^c
a. HR and CI: Cox proportional hazards model, p-value: log-rank test; each unstratified. b. An increase of ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100). c. p-value based on the interaction term in the Cox proportional hazards model, adjusted for subgroup and treatment*subgroup. d. For an explanation of why this effect is shown as supplementary information, see Section I 4.4. AE: adverse event; CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-H&N35: Quality of Life Questionnaire-Head and Neck Cancer 35; RCT: randomized controlled trial						

Morbidity (symptoms)

Fatigue (recorded with the EORTC QLQ-C30)

For the outcome fatigue (recorded with the EORTC QLQ-C30), there was a statistically significant effect modification by the characteristic age. A statistically significant difference to

the disadvantage of tislelizumab + gemcitabine + cisplatin compared with placebo + gemcitabine + cisplatin was shown for patients ≥ 65 years of age. There is a hint of lesser benefit of tislelizumab + gemcitabine + cisplatin in comparison with the ACT for patients ≥ 65 years of age.

However, no statistically significant difference between the treatment arms was found for patients < 65 years. There is no hint of an added benefit or lesser benefit of tislelizumab + gemcitabine + cisplatin in comparison with the ACT for this subgroup; an added benefit is therefore not proven for patients < 65 years.

Speech problems (recorded using the EORTC QLQ-H&N35)

There were statistically significant effect modifications by the characteristics of sex and presence of liver metastases for the outcome speech problems (recorded using the EORTC QLQ-H&N35). As can be seen from Table 17, quantitative and qualitative effect modifications by the characteristic of liver metastases were shown across several outcomes, which were largely in the same direction. By contrast, an effect modification by the characteristic of sex occurred only once for this outcome. Consequently, in the given situation, only the effect modification by the presence of liver metastases was considered for the outcome of speech problems.

A statistically significant difference in favour of tislelizumab + gemcitabine + cisplatin compared with placebo + gemcitabine + cisplatin was shown for patients with liver metastases. There is a hint of an added benefit of tislelizumab + gemcitabine + cisplatin in comparison with the ACT for patients with liver metastases.

However, no statistically significant difference between the treatment arms was found for patients without liver metastases. There is no hint of an added benefit of or lesser benefit of tislelizumab + gemcitabine + cisplatin in comparison with the ACT for this subgroup; an added benefit is therefore not proven for patients without liver metastases.

Feeling ill (recorded using the EORTC QLQ-H&N35)

There was a statistically significant effect modification by the characteristic 'presence of liver metastases' for the outcome feeling ill (recorded using the EORTC QLQ-H&N35).

A statistically significant difference to the disadvantage of tislelizumab + gemcitabine + cisplatin compared with placebo + gemcitabine + cisplatin was shown for patients without liver metastases. There is a hint of lesser benefit of tislelizumab + gemcitabine + cisplatin in comparison with the ACT for patients without liver metastases.

However, no statistically significant difference between the treatment arms was found for patients with liver metastases. There is no hint of an added benefit or lesser benefit of

tislelizumab + gemcitabine + cisplatin in comparison with the ACT for this subgroup; an added benefit is therefore not proven for patients with liver metastases.

Fever (AE)

There was a statistically significant effect modification by the characteristic 'presence of liver metastases' for the outcome fever (AE). A statistically significant difference to the disadvantage of tislelizumab + gemcitabine + cisplatin compared with placebo + gemcitabine + cisplatin was shown for patients without liver metastases. There is a hint of lesser benefit of tislelizumab + gemcitabine + cisplatin in comparison with the ACT for this subgroup.

However, no statistically significant difference between the treatment arms was found for patients with liver metastases. There is no hint of an added benefit or lesser benefit of tislelizumab + gemcitabine + cisplatin in comparison with the ACT for this subgroup; an added benefit is therefore not proven for patients with liver metastases.

I 5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the IQWiG General Methods [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

I 5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was assessed based on the results presented in Chapter I 4 (see Table 18).

Determination of the outcome category for symptom outcomes

For the symptom outcomes below, it cannot be inferred from the dossier whether they are serious/severe or non-serious/non-severe. Reasoning is provided for the classification of these outcomes.

Fatigue (recorded using the EORTC QLQ-C30), speech problems and feeling ill (each recorded using the EORTC QLQ-H&N35)

Insufficient information was available to classify the severity categories for the outcomes fatigue (recorded using the EORTC QLQ-C30), speech problems and feeling ill (each recorded using the EORTC QLQ-H&N35). These outcomes were therefore each assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Table 18: Extent of the added benefit at outcome level: tislelizumab + gemcitabine + cisplatin vs. gemcitabine + cisplatin (multipage table)

Outcome category Outcome Effect modifier Subgroup	tislelizumab + gemcitabine + cisplatin vs. placebo + gemcitabine + cisplatin Median time to event (months) Effect estimation [95% CI]; p-value Probability ^a	Derivation of extent ^b
Outcomes with observation over the entire study duration		
Mortality		
Overall survival	45.3 vs. 31.8 months HR: 0.73 [0.51; 1.05]; p = 0.084	Lesser benefit not proven / added benefit not proven
Outcomes with shortened observation period		
Morbidity		
Symptoms (EORTC QLQ-C30 – time to 1st deterioration)		
Fatigue		
Age		
< 65 years	2.1 vs. 2.2 months HR: 1.09 [0.79; 1.49]; p = 0.610	Lesser benefit not proven / added benefit not proven
≥ 65 years	0.7 vs. 2.2 months HR: 5.88 [1.99; 17.32] HR: 0.17 [0.06; 0.50] ^c ; p < 0.001 Probability: hint	Outcome category: non-serious / non-severe symptoms / late complications CI _u < 0.80 Lesser benefit, extent: considerable
Nausea and vomiting	2.6 vs. 3.5 months HR: 1.04 [0.75; 1.43]; p = 0.801	Lesser benefit not proven / added benefit not proven
Pain	17.2 vs. 8.4 months HR: 0.82 [0.57; 1.18]; p = 0.280	Lesser benefit not proven / added benefit not proven
Dyspnoea	22.6 vs. 13.7 months HR: 1.08 [0.72; 1.63]; p = 0.705	Lesser benefit not proven / added benefit not proven
Insomnia	27.6 months vs. NA HR: 0.98 [0.64; 1.48]; p = 0.914	Lesser benefit not proven / added benefit not proven
Appetite loss	2.4 vs. 3.4 months HR: 1.15 [0.83; 1.57]; p = 0.405	Lesser benefit not proven / added benefit not proven
Constipation	– HR: 0.94 [0.64; 1.38]; p = 0.727	Lesser benefit not proven / added benefit not proven

Table 18: Extent of the added benefit at outcome level: tislelizumab + gemcitabine + cisplatin vs. gemcitabine + cisplatin (multipage table)

Outcome category Outcome Effect modifier Subgroup	tislelizumab + gemcitabine + cisplatin vs. placebo + gemcitabine + cisplatin Median time to event (months) Effect estimation [95% CI]; p-value Probability ^a	Derivation of extent ^b
Diarrhoea	NA vs. NA HR: 1.15 [0.68; 1.93]; p = 0.607	Lesser benefit not proven / added benefit not proven
Symptoms (EORTC QLQ-H&N35 – time to 1st deterioration)		
Pain	NA vs. - HR: 1.18 [0.75; 1.86]; p = 0.469	Lesser benefit not proven / added benefit not proven
Dysphagia	NA vs. NA HR: 0.97 [0.61; 1.53]; p = 0.887	Lesser benefit not proven / added benefit not proven
Senses problems	10.8 vs. 10.8 months HR: 1.11 [0.77; 1.61]; p = 0.570	Lesser benefit not proven / added benefit not proven
Speech problems Presence of liver metastases Yes	NA vs. NA HR: 0.21 [0.07; 0.65]; p = 0.004 Probability: hint	Outcome category: non-serious / non-severe symptoms / late complications CI _u < 0.80 Added benefit, extent: considerable
No	NA vs. 27.5 months HR: 1.40 [0.69; 2.82]; p = 0.354	Lesser benefit not proven / added benefit not proven
Problems with teeth	20.0 vs. 13.1 months HR: 0.83 [0.57; 1.22]; p = 0.346	Lesser benefit not proven / added benefit not proven
Problems with mouth opening	24.6 vs. 15.6 months HR: 0.80 [0.52; 1.23]; p = 0.305	Lesser benefit not proven / added benefit not proven
Dry mouth	– vs. NA HR: 1.31 [0.85; 2.02]; p = 0.223	Lesser benefit not proven / added benefit not proven
Cough	33.6 vs. 16.4 months HR: 0.93 [0.60; 1.45]; p = 0.755	Lesser benefit not proven / added benefit not proven

Table 18: Extent of the added benefit at outcome level: tislelizumab + gemcitabine + cisplatin vs. gemcitabine + cisplatin (multipage table)

Outcome category Outcome Effect modifier Subgroup	tislelizumab + gemcitabine + cisplatin vs. placebo + gemcitabine + cisplatin Median time to event (months) Effect estimation [95% CI]; p-value Probability ^a	Derivation of extent ^b
Feeling ill		
Presence of liver metastases		
Yes	NA vs. 10.6 months HR: 0.87 [0.46; 1.62]; p = 0.647	Lesser benefit not proven / added benefit not proven
No	5.2 vs. 18.9 HR: 2.17 [1.27; 3.73] HR: 0.46 [0.27; 0.79] ^c ; p = 0.004 Probability: hint	Outcome category: non-serious / non-severe symptoms / late complications CI ₀ < 0.80 Lesser benefit, extent: considerable
Feeding tube	NA vs. NA HR: 0.33 [0.09; 1.20]; p = 0.080	Lesser benefit not proven / added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 – time to 1st deterioration		
Global health status	10.8 vs. 6.6 months HR: 0.84 [0.59; 1.20]; p = 0.336	Lesser benefit not proven / added benefit not proven
Physical functioning	10.8 vs. 6.6 months HR: 1.03 [0.73; 1.46]; p = 0.862	Lesser benefit not proven / added benefit not proven
Role functioning	5.2 vs. 7.6 months HR: 1.03 [0.73; 1.46]; p = 0.859	Lesser benefit not proven / added benefit not proven
Emotional functioning	NA vs. NA HR: 1.30 [0.83; 2.04]; p = 0.244	Lesser benefit not proven / added benefit not proven
Cognitive functioning	6.0 vs. 8.4 months HR: 1.08 [0.76; 1.53]; p = 0.674	Lesser benefit not proven / added benefit not proven
Social functioning	5.2 vs. 10.4 months HR: 1.23 [0.87; 1.73]; p = 0.251	Lesser benefit not proven / added benefit not proven

Table 18: Extent of the added benefit at outcome level: tislelizumab + gemcitabine + cisplatin vs. gemcitabine + cisplatin (multipage table)

Outcome category Outcome Effect modifier Subgroup	tislelizumab + gemcitabine + cisplatin vs. placebo + gemcitabine + cisplatin Median time to event (months) Effect estimation [95% CI]; p-value Probability ^a	Derivation of extent ^b
EORTC QLQ-H&N35 – time to 1st deterioration		
Trouble with social eating	28.2 vs. 13.6 months HR: 1.10 [0.74; 1.64]; p = 0.651	Lesser benefit not proven / added benefit not proven
Trouble with social contact	NA vs. 27.5 months HR: 0.90 [0.57; 1.43]; p = 0.658	Lesser benefit not proven / added benefit not proven
Less sexuality	3.7 vs. 5.2 months HR: 1.09 [0.78; 1.51]; p = 0.675	Lesser benefit not proven / added benefit not proven
Side effects		
SAEs	44.6 months vs. NA HR: 0.81 [0.54; 1.23]; p = 0.328	Lesser benefit not proven / added benefit not proven
Severe AEs	0.7 vs. 0.7 months HR: 1.00 [0.77; 1.30]; p = 0.988	Lesser benefit not proven / added benefit not proven
Discontinuation due to AEs	NA vs. NA HR: 1.29 [0.65; 2.56]; p = 0.469	Lesser benefit not proven / added benefit not proven
Immune-mediated SAEs	NA vs. NA HR: 4.44 [0.52; 38.04]; p = 0.137	Greater/lesser harm not proven
Immune-mediated severe AEs	NA vs. NA HR: 6.98 [0.86; 56.74]; p = 0.034 Probability: hint	Outcome category: serious/severe side effects Greater harm, extent: minor ^d

Table 18: Extent of the added benefit at outcome level: tislelizumab + gemcitabine + cisplatin vs. gemcitabine + cisplatin (multipage table)

Outcome category Outcome Effect modifier Subgroup	tislelizumab + gemcitabine + cisplatin vs. placebo + gemcitabine + cisplatin Median time to event (months) Effect estimation [95% CI]; p-value Probability ^a	Derivation of extent ^b
Fever (AE) Presence of liver metastases Yes	NA vs. NA HR: 1.39 [0.58; 3.32]; p = 0.472	Lesser benefit not proven / added benefit not proven
No	NA vs. NA HR: 5.29 [1.88; 15.37] HR: 0.19 [0.07; 0.53] ^c p < 0.001 Probability: hint	Outcome category: non-serious/non-severe side effects CI _u < 0.80 Lesser benefit, extent: considerable
a. Probability provided if there is a statistically significant and relevant effect. b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u). c. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit. d. Discrepancy between CI and p-value. The result of the statistical test is decisive for the derivation of the added benefit. Its extent is rated as minor. AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; NA: not achieved; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-H&N35: Quality of Life Questionnaire-Head and Neck Cancer 35; SAE: serious adverse event		

I 5.2 Overall conclusion on added benefit

Table 19 summarizes the results taken into account for the overall conclusion on the extent of the added benefit.

Table 19: Positive and negative effects from the assessment of tislelizumab + gemcitabine + cisplatin in comparison with gemcitabine + cisplatin

Positive effects	Negative effects
Outcomes with shortened observation period	
	Non-serious/non-severe symptoms/late complications - Fatigue - Age (≥ 65 years): hint of lesser benefit – extent: considerable - Feeling ill - Presence of liver metastases (no): hint of lesser benefit – extent: considerable
Non-serious/non-severe symptoms/late complications - Speech problems - Presence of liver metastases (yes): hint of an added benefit – extent: considerable	
	Serious/severe side effects - Immune-mediated severe AEs - hint of greater harm – extent: minor
	Non-serious/non-severe side effects - Fever (AE) - Presence of liver metastases (no): hint of greater harm – extent: considerable
AE: adverse event	

Overall, there are both positive and negative effects of tislelizumab + gemcitabine + cisplatin in comparison with gemcitabine + cisplatin. For the overall population, there is a negative effect in the category of severe/serious side effects: For immune-mediated severe AEs, there is a hint of greater harm of minor extent of tislelizumab + gemcitabine + cisplatin compared with gemcitabine + cisplatin; however, only a few events occurred.

For various subgroups, there are negative effects and one positive effect for outcomes in the categories of non-severe / non-serious symptoms / late complications and side effects. The effects are particularly evident here depending on the presence of liver metastases. For patients without liver metastases, there are hints of a lesser benefit of considerable extent in feeling ill and fever. For patients with liver metastases, there is, in contrast, a hint of an added benefit of considerable extent in speech problems. Furthermore, there is a disadvantage of considerable extent of tislelizumab + gemcitabine + cisplatin compared with gemcitabine + cisplatin in fatigue for patients ≥ 65 years. For no patient group are there any effects sufficient for the derivation of an added benefit or lesser benefit.

In summary, an added benefit of tislelizumab + gemcitabine + cisplatin versus the ACT, gemcitabine + cisplatin, is not proven for the first-line treatment of patients with recurrent, not amenable to curative surgery or radiotherapy, or metastatic NPC.

The result of the assessment of the added benefit of tislelizumab + gemcitabine + cisplatin in comparison with the ACT is summarized in Table 20.

Table 20: Tislelizumab + gemcitabine + cisplatin – probability and extent of added benefit

Therapeutic indication	ACT ^a	Probability and extent of added benefit
Adult patients with recurrent, not amenable to curative surgery or radiotherapy, or metastatic nasopharyngeal carcinoma (NPC) in first-line treatment	cisplatin in combination with gemcitabine ^{b, c}	Added benefit not proven ^d
a. Presented is the ACT specified by the G-BA. b. Gemcitabine does not have a marketing authorization for this therapeutic indication. According to the G-BA, in accordance with the generally recognized state of medical knowledge, it must be established in the overall assessment that the off-label use of cisplatin in combination with gemcitabine is generally preferable to the medicinal products previously approved in the therapeutic indication. c. According to the G-BA, based on the available evidence, the administration of consolidating locoregional radiotherapy is recommended, particularly depending on the response to systemic therapy. Radiotherapy should be made available to eligible patients as part of a clinical study. d. The RATIONALE 309 study included only patients with an ECOG-PS of 0 or 1. It remains unclear whether the observed effects are transferable to patients with an ECOG PS $\geq$ 2. ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee		

The assessment described above differs from that of the company, which claimed a hint of a non-quantifiable added benefit in the first-line treatment of patients with recurrent, not amenable to curative surgery or radiotherapy, or metastatic NPC.

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. 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: 02.10.2025]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_version-7-0.pdf.
2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. *Biom J* 2016; 58(1): 43-58. <https://doi.org/10.1002/bimj.201300274>.
3. BeiGene. A Phase 3, Multicenter, Double-Blind, Randomized, Placebo-controlled Study to Compare the Efficacy and Safety of Tislelizumab (BGB-A317) Combined With Gemcitabine Plus Cisplatin Versus Placebo Combined With Gemcitabine Plus Cisplatin as First-Line Treatment for Recurrent or Metastatic Nasopharyngeal Cancer; Clinical Study Report [unpublished]. 2024.
4. BeiGene. Tislelizumab Combined With Chemotherapy Versus Chemotherapy Alone in Recurrent or Metastatic Nasopharyngeal Cancer (NPC) (RATIONALE-309) [online]. 2025 [Accessed: 23.10.2025]. URL: <https://clinicaltrials.gov/study/NCT03924986>.
5. Yang Y, Pan J, Chen N et al. Effects of tislelizumab on health-related quality of life in patients with recurrent or metastatic nasopharyngeal cancer. *Head Neck* 2024; 46(9): 2301-2314. <https://doi.org/10.1002/hed.27785>.
6. Yang Y, Pan J, Wang H et al. Tislelizumab plus chemotherapy as first-line treatment for recurrent or metastatic nasopharyngeal cancer: A multicenter phase 3 trial (RATIONALE-309). *Cancer Cell* 2023; 41(6): 1061-1072.e4. <https://doi.org/10.1016/j.ccell.2023.04.014>.
7. BeOne Medicines. Tevimbra 100 mg Konzentrat zur Herstellung einer Infusionslösung [online]. 10.2025 [Accessed: 12.12.2025]. URL: <https://www.fachinfo.de/>.
8. Teva. Cisplatin Teva 1 mg/ml Konzentrat zur Herstellung einer Infusionslösung [online]. 02.2025 [Accessed: 17.10.2025]. URL: <https://www.fachinfo.de/>.
9. AqVida. Fachinformation Gemcitabin AqVida 38 mg/ml Pulver zur Herstellung einer Infusionslösung. 01.2025.
10. National Comprehensive Cancer Network. Head and Neck Cancers; NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines); Version 1.2026 [online]. 2025 [Accessed: 11.12.2025]. URL: <https://www.nccn.org>.

11. Bossi P, Chan AT, Even C et al. ESMO-EURACAN Clinical Practice Guideline update for nasopharyngeal carcinoma: adjuvant therapy and first-line treatment of recurrent/metastatic disease. *Ann Oncol* 2023; 34(3): 247-250.
<https://doi.org/10.1016/j.annonc.2022.11.011>.
12. Bossi P, Chan AT, Licitra L et al. Nasopharyngeal carcinoma: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up 2020. *Ann Oncol* 2021; 32(4): 452-465. <https://doi.org/10.1016/j.annonc.2020.12.007>.
13. Jin Y, Shi YX, Cai XY et al. Comparison of five cisplatin-based regimens frequently used as the first-line protocols in metastatic nasopharyngeal carcinoma. *J Cancer Res Clin Oncol* 2012; 138(10): 1717-1725. <https://doi.org/10.1007/s00432-012-1219-x>.
14. Hong S, Zhang Y, Yu G et al. Gemcitabine Plus Cisplatin Versus Fluorouracil Plus Cisplatin as First-Line Therapy for Recurrent or Metastatic Nasopharyngeal Carcinoma: Final Overall Survival Analysis of GEM20110714 Phase III Study. *J Clin Oncol* 2021; 39(29): 3273-3282.
<https://doi.org/10.1200/JCO.21.00396>.
15. Zhang L, Huang Y, Hong S et al. Gemcitabine plus cisplatin versus fluorouracil plus cisplatin in recurrent or metastatic nasopharyngeal carcinoma: a multicentre, randomised, open-label, phase 3 trial. *Lancet* 2016; 388(10054): 1883-1892.
[https://doi.org/10.1016/S0140-6736\(16\)31388-5](https://doi.org/10.1016/S0140-6736(16)31388-5).
16. Leitlinienprogramm Onkologie. S3-Leitlinie Supportive Therapie bei onkologischen PatientInnen; Langversion 1.3; AWMF-Registernummer: 032/054OL [online]. 2020 [Accessed: 13.11.2025]. URL: https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Supportivtherapie/Version_1/LL_Supportiv_Langversion_1.3.pdf.
17. National Comprehensive Cancer N. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Head and Neck Cancers. Version 4.2025. 2025.
18. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Treatment Switching in onkologischen Studien; Arbeitspapier [online]. 2018 [Accessed: 11.11.2025]. URL: https://www.iqwig.de/download/ga14-04_treatment-switching-in-onkologischen-studien_arbeitspapier_v1-0.pdf.
19. European Organisation for Research and Treatment of Cancer. EORTC QLQ-C30 Scoring Manual [online]. 2001 [Accessed: 13.11.2025]. URL: <https://qol.eortc.org/manual/scoring-manual/>.

The full report (German version) is published at
<https://www.iqwig.de/en/projects/a25-119.html>.