Toripalimab (nasopharyngeal carcinoma)

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

EXTRACT

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Patient and family involvement

No feedback was received within the framework of this dossier assessment.

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Part I: Benefit assessment

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I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AWMF	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (Association of the Scientific Medical Societies)
CTCAE	Common Terminology Criteria for Adverse Events
EBV	Epstein-Barr virus
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
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)
IWRS	interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
NHS	National Health Service
NPC	nasopharyngeal carcinoma
PD-1	programmed cell death 1
PFS	progression-free survival
PT	Preferred Term
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-κB ligand
RCT	randomized controlled trial
RECIST v1.1	Response Evaluation Criteria in Solid Tumours Version 1.1
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SmPC	summary of product characteristics
WHO	World Health Organization

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 toripalimab (in combination with cisplatin and gemcitabine). 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 14 January 2026.

Research question

The aim of this report is to assess the added benefit of toripalimab, in combination with cisplatin and gemcitabine (hereinafter referred to as 'toripalimab + cisplatin + gemcitabine'), compared with cisplatin and gemcitabine (hereinafter referred to as 'cisplatin + gemcitabine') as the appropriate comparator therapy (ACT) for the first-line treatment of adult patients with recurrent, not amenable to 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 toripalimab + cisplatin + gemcitabine

Therapeutic indication	**ACT[a]**
Adult patients with recurrent, not amenable to surgery or radiotherapy, or metastatic nasopharyngeal carcinoma 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 authorisation for this therapeutic indication. According to the G-BA, in accordance with the generally recognised 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. Randomised controlled trials (RCTs) were used to derive the added benefit.

Study pool and study design

The JUPITER-02 study was used for the benefit assessment. This study is a completed, double-blind, multicentre RCT comparing toripalimab + cisplatin + gemcitabine versus placebo + cisplatin + gemcitabine. It exclusively included Asian adult patients aged up to 75 years with recurrent, not amenable to surgery or radiotherapy, or metastatic NPC, and who had not previously received any systemic chemotherapy 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 at study entry.

A total of 289 patients were included and randomly allocated in a 1:1 ratio either to treatment with toripalimab + cisplatin + gemcitabine (N = 146) or placebo + cisplatin + gemcitabine (N = 143). Randomisation was stratified by ECOG PS (0 versus 1) and disease stage (recurrent versus metastatic).

Treatment with toripalimab in the intervention arm was carried out in compliance with the summary of product characteristics (SmPC). In both study arms, the chemotherapy regimen consisted of cisplatin + gemcitabine. The chemotherapy regimen was administered over 6 cycles. Following completion of chemotherapy, treatment with toripalimab or placebo was to continue for up to a maximum of 2 years or until unacceptable toxicity, disease progression, withdrawal of consent, at the discretion of the investigator, death or the end of the trial.

The primary outcome in JUPITER-02 was progression-free survival (PFS). Patient-relevant secondary outcomes were overall survival, outcomes on morbidity, health-related quality of life and adverse events (AEs).

Limitation of the JUPITER-02 study

Consolidating radiotherapy

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. Likewise, 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 the 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 the JUPITER-02 study, around 40% of patients had newly diagnosed metastatic NPC. However, according to the study design, any concomitant anticancer treatment, including radiotherapy, was prohibited during the study. No further information was available on the approach used in the study in situations where consolidating locoregional radiotherapy was indicated in accordance with the guideline recommendations, or on the proportion of patients in the study who might have benefited

from such treatment. The absence of consolidating radiotherapy may have an impact on various patient-relevant outcomes, including overall survival; this was taken into account in the assessment of the certainty of conclusions of the study results.

Palliative radiotherapy and the availability of bisphosphonates

The S3 guideline on supportive therapy for oncological patients recommends treatment with bisphosphonates or the receptor activator of NF-κB ligand (RANK-L) inhibitor denosumab to prevent complications associated with bone metastases, taking into account the specific entity in question. Palliative radiotherapy for bone metastases is also recommended. This can be conducted in parallel with treatment using bisphosphonates or RANK-L inhibitors. According to the study design, concomitant treatment with bisphosphonates for the management of bone metastases was permitted, whilst treatment with the RANK-L inhibitor denosumab was not permitted. Patients who had received denosumab prior to enrolment had to switch to a bisphosphonate instead during the study. No further information was available on how many patients had received denosumab before the start of the study. Overall, it remained unclear why some of the patients with bone metastases did not receive bisphosphonates during the course of the study. There were also uncertainties as to the extent to which unrestricted use of palliative radiotherapy was allowed in the JUPITER-02 study. In JUPITER-02, palliative radiotherapy (e.g. for the treatment of bone metastases) was permitted, provided that the lesion was a non-target lesion. No information was available regarding the location of the target lesions.

Transferability to the German health care context

The JUPITER-02 study was conducted exclusively in Asia. The proportion of patients with type I was just 1%, whilst the proportion with type II and type III was around 93%. Furthermore, around two-thirds of the patients had an EBV infection (EBV DNA ≥2000 IU/mL). Given the negligible proportion of type I NPC compared with non-endemic regions, and the relatively high proportion of cases associated with EBV, uncertainties remained as to whether the results were fully transferable to the German health care context.

Summary

The uncertainties described above regarding consolidating radiotherapy, supportive concomitant therapies and the transferability to the German health care context may have an impact on various outcome categories and resulted in a limited certainty of conclusions of the results.

Data cuts

The JUPITER-02 study is complete and 4 data cuts were available. For this benefit assessment, the results from the fourth data cut were used for overall survival, as this was the final prespecified analysis. For the outcomes on morbidity, health-related quality of life and side

effects, the results from the most recent data cut-offs were used at which these data were still recorded (the second data cut for the outcomes on morbidity and health-related quality of life, and the third data cut for the outcomes on side effects).

Subsequent therapies

In the JUPITER-02 study, subsequent antineoplastic therapies were permitted without restrictions in both study arms. At the time of the final analysis of the outcome overall survival, 56% of the patients in the intervention arm and 74% of the patients in the comparator arm had received at least one subsequent antineoplastic therapy. The company did not provide any data on the proportion of patients with disease progression for this timepoint. It therefore remained unclear how many patients had a potential need for subsequent therapy. In both treatment arms, chemotherapy was the most commonly used first antineoplastic subsequent therapy. Furthermore, 13% of the patients in the intervention arm and 20% of the patients in the comparator arm received immunotherapy as the first subsequent therapy. 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 JUPITER-02 were deprived of effective subsequent therapies to any relevant extent.

Risk of bias

The risk of bias across outcomes was rated as low for JUPITER-02.

The results on overall survival had a low risk of bias. The risk of bias in the results on symptoms, health-related quality of life and side effects was assessed as high due to incomplete observation for potentially informative reasons, with different lengths of follow-up observation. Another reason for the high risk of bias in the results on symptoms and health-related quality of life was the lack of blinding in the presence of subjective recording of outcomes following the unblinding of the study at the first data cut-off.

No suitable data were available for discontinuation due to AEs, immune-mediated SAEs and immune-mediated severe AEs.

Summary assessment of the certainty of conclusions

Irrespective of the high risk of bias for all outcomes except overall survival, there were relevant uncertainties regarding consolidating radiotherapy, restrictions to supportive concomitant therapies and the transferability to the German health care context. 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 JUPITER-02 study.

Results

Mortality

Overall survival

With regard to the overall survival outcome, a statistically significant difference in favour of toripalimab + cisplatin + gemcitabine compared with placebo + cisplatin + gemcitabine was shown when the total population was considered. In addition, there was an effect modification by the characteristic 'disease stage'. There is a hint of an added benefit of toripalimab + cisplatin + gemcitabine in comparison with the ACT for patients with recurrent NPC. For patients with metastatic NPC, there is no hint of an added benefit of toripalimab + cisplatin + gemcitabine in comparison with the ACT. An added benefit for these patients is therefore not proven.

Morbidity

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

Fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, dry mouth (xerostomia), senses problems, speech problems, cough, feeling ill, problems with mouth opening (trismus), pain, sticky saliva, problems with swallowing, problems with teeth, use of a feeding tube

No statistically significant difference between the treatment groups was found for any of the outcomes of fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation and diarrhoea (recorded using the EORTC QLQ-C30), as well as dry mouth (xerostomia), senses problems, speech problems, cough, feeling ill, problems with mouth opening (trismus), pain, sticky saliva, problems with swallowing, problems with teeth, use of a feeding tube (recorded using the EORTC QLQ-H&N35). There is no hint of an added benefit of toripalimab + cisplatin + gemcitabine in comparison with the ACT for any of the outcomes; an added benefit is therefore not proven for these outcomes.

Health-related quality of life

Global health status, physical functioning, role functioning, social functioning, trouble with social eating, trouble with social contact, and less sexuality

No statistically significant difference was found between the treatment groups for any of the following outcomes: global health status, physical functioning, role functioning, social functioning (assessed using the EORTC QLQ-C30), as well as trouble with social eating, trouble with social contact, and less sexuality (assessed using the EORTC QLQ-H&N35). There is no hint of an added benefit of toripalimab + cisplatin + gemcitabine in comparison with the ACT for any of the outcomes; an added benefit is therefore not proven for these outcomes.

Emotional functioning and cognitive functioning (assessed using the EORTC QLQ-C30)

For the outcomes of emotional functioning and cognitive functioning of the EORTC QLQ-C30, no statistically significant difference between the treatment arms was found when considering the total population. However, in each case, there is an effect modification by the characteristic of sex. There is a hint of an added benefit of toripalimab + cisplatin + gemcitabine in comparison with the ACT for women. For men, there is no hint of an added benefit of toripalimab + cisplatin + gemcitabine in comparison with the ACT. An added benefit for men is therefore not proven.

Side effects

SAEs and severe AEs

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

Discontinuation due to AEs, immune-mediated SAEs and immune-mediated severe AEs

No suitable data were available for any of the outcomes of discontinuation due to AEs, immune-mediated SAEs and immune-mediated severe AEs. There is no hint of greater or lesser harm of toripalimab + cisplatin + gemcitabine in comparison with the ACT for these outcomes; greater or lesser harm is therefore not proven for these outcomes.

Pneumonia (PT, severe AEs)

With regard to the pneumonia outcome, a statistically significant difference to the disadvantage of toripalimab + cisplatin + gemcitabine compared with placebo + cisplatin + gemcitabine was shown when the total population was considered. In addition, there was an effect modification by the characteristic ‘disease stage’. There is a hint of greater harm of toripalimab + cisplatin + gemcitabine in comparison with the ACT for patients with recurrent NPC. For patients with metastatic NPC, there is no hint of greater or lesser harm of toripalimab + cisplatin + gemcitabine in comparison with the ACT. Greater or lesser harm for this group is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

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

Overall, both positive and negative effects of toripalimab + cisplatin + gemcitabine were shown in comparison with the ACT. Due to the effect modification in the outcome of overall survival by the characteristic of disease stage (recurrent versus metastatic), the results on the added benefit of toripalimab + cisplatin + gemcitabine in comparison with the ACT are derived separately below, based on disease stage:

Patients with metastatic NPC

Neither positive nor negative effects were shown for patients with metastatic NPC. For the outcomes that represent individual aspects of health-related quality of life (emotional functioning and cognitive functioning), it remained unclear – due to the effect modification by the characteristic of sex – whether there were any effects in the subpopulation of patients with metastatic NPC. Furthermore, there was a lack of appropriate analyses of various AE outcomes, such as discontinuation due to AEs, immune-mediated SAEs and immune-mediated severe AEs. Overall, given the available data, an added benefit is not proven for patients with metastatic NPC.

Patients with recurrent NPC

For patients with recurrent NPC, there is a hint of a major added benefit for the outcome of overall survival. This contrasts with a hint of greater harm of major extent in the 'serious/severe side effects' outcome category for the outcome pneumonia. For the outcomes that represent individual aspects of health-related quality of life (emotional functioning and cognitive functioning), there was an effect modification by the characteristic of sex. Due to this effect modification, it remained unclear whether there were any effects in the subpopulation of patients with recurrent NPC. No suitable data were available for discontinuation due to AEs, immune-mediated SAEs and immune-mediated severe AEs. Overall, there is a hint of a considerable added benefit for patients with recurrent NPC.

[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 lesser benefit). For further details see [1,2].

Summary

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

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

Table 3: Toripalimab + cisplatin + gemcitabine – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adult patients with recurrent, not amenable to surgery or radiotherapy, or metastatic nasopharyngeal carcinoma (NPC) in first-line treatment	cisplatin in combination with gemcitabine[b, c]	▪ Patients with metastatic NPC: added benefit not proven[d] ▪ Patients with recurrent NPC: hint of considerable added benefit[d]

a. Presented is the ACT specified by the G-BA.
b. Gemcitabine does not have a marketing authorisation for this therapeutic indication. According to the G-BA, in accordance with the generally recognised 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 JUPITER-02 study included only patients with an ECOG PS of 0 or 1, and only 3 patients (1%) with keratinising type I NPC. It remains unclear whether the observed effects can be transferred to patients with ECOG PS ≥2 or with type I NPC.

ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; NPC: nasopharyngeal carcinoma

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 toripalimab, in combination with cisplatin and gemcitabine (hereinafter referred to as 'toripalimab + cisplatin + gemcitabine'), compared with cisplatin and gemcitabine (hereinafter referred to as 'cisplatin + gemcitabine') as the appropriate comparator therapy (ACT) for the first-line treatment of adult patients with recurrent, not amenable to 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 toripalimab + cisplatin + gemcitabine

Therapeutic indication	**ACT**[a]
Adult patients with recurrent, not amenable to surgery or radiotherapy, or metastatic nasopharyngeal carcinoma 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 authorisation for this therapeutic indication. According to the G-BA, in accordance with the generally recognised 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. Randomised 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 toripalimab (status: 15 October 2025)
- Bibliographical literature search on toripalimab (last search on 13 November 2025)
- Search of trial registries / trial results databases for studies on toripalimab (last search on 15 October 2025)
- Search on the G-BA website for toripalimab (last search on 17 October 2025)

To check the completeness of the study pool:

- Search of trial registries for studies on toripalimab (last search on 27 January 2026); 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: toripalimab + cisplatin + gemcitabine vs. cisplatin + gemcitabine

Study	Study category			Available sources		
	Study for the marketing authorisation 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])
JS001-015-III-NPC (JUPITER-02[d])	Yes	Yes	No	Yes [3]	Yes [4]	Yes [5-7]

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.

ACT: appropriate comparator therapy; CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomised 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: toripalimab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine (multipage table)

Study	Study design	Population	Interventions (number of randomised patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
JUPITER-02	RCT, double-blind[b], parallel	Adult patients up to 75 years of age, with ▪ recurrent, not amenable to surgery or radiotherapy, or metastatic[c] NPC ▪ no previous systemic chemotherapy of recurrent or metastatic NPC ▪ ECOG PS ≤1	toripalimab + cisplatin + gemcitabine (N = 146) placebo + cisplatin + gemcitabine (N = 143)	Screening: 28 days Treatment: ▪ cisplatin + gemcitabine: 6 cycles of 3 weeks each, or until unacceptable toxicity, disease progression[d] or withdrawal of consent ▪ toripalimab/placebo: for a maximum of 2 years or until unacceptable toxicity, disease progression[d], withdrawal of consent, at the discretion of the investigator, death or end of study Observation[e]: Outcome-specific, at most until death, withdrawal of consent or end of study	35 centres in China, Singapore, Taiwan 10/2018–11/2022 Data cut-offs[f]: 30 May 2020 (primary PFS interim analysis[g]) 8 June 2021 (additional PFS analysis[h]) 8 May 2022 (final safety analysis[i]) 18 November 2022 (final analysis of overall survival[j])	Primary: PFS Secondary: overall survival, morbidity, health-related quality of life, AEs

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

Study	Study design	Population	Interventions (number of randomised 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. The study was unblinded after the first data cut-off (30 May 2020). c. Primarily metastatic (stage IVB as defined by the UICC and the AJCC, eighth edition). d. Toripalimab or placebo maintenance therapy could be continued beyond IRC-confirmed disease progression as per RECIST v1.1 at any timepoint, provided there was a clinical benefit and in the absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression, as determined by the investigator. e. Outcome-specific information is described in Table 8. f. In addition, following the completion of the study, several unplanned post hoc analyses were conducted to assess long-term overall survival over a period of 6 years (based on recordings by the investigator). g. Planned after the occurrence of 130 progression events. h. Conducted at the originally planned time for the PFS interim analysis (approximately 18 months after randomisation of the first patient) i. Unplanned data cut-off; see the Section on data cuts in Section I 3.2.2. j. Planned after the occurrence of 130 deaths. AE: adverse event; AJCC: American Joint Committee on Cancer; ECOG PS: Eastern Cooperative Oncology Group Performance Status; IRC: Independent Review Committee; N: number of randomised patients; NPC: nasopharyngeal carcinoma; RCT: randomised controlled trial; RECIST v1.1: Response Evaluation Criteria in Solid Tumours version 1.1; UICC: Union for International Cancer Control					

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

Study	Intervention	Comparison
JUPITER-02	6 cycles of 3 weeks toripalimab 240 mg, IV, on Day 1 of a cycle + chemotherapy: ▫ cisplatin 80 mg/m^2, IV, on Day 1 of a cycle ▫ gemcitabine 1000 mg/m^2, IV, on Days 1 + 8 of a cycle followed by toripalimab 240 mg, IV, on Day 1 of a 3-week cycle up to a maximum of 2 years	6 cycles of 3 weeks placebo, IV, on Day 1 of a cycle + chemotherapy: ▫ cisplatin 80 mg/m^2, IV, on Day 1 of a cycle ▫ gemcitabine 1000 mg/m^2, IV, on Days 1 + 8 of a cycle followed by placebo, IV, on Day 1 of a 3-week cycle up to a maximum of 2 years
	Dose modification: ▪ toripalimab/placebo: no dose reduction permitted; treatment interruption due to AEs permitted for up to 56 days[a]; chemotherapy could be continued ▪ gemcitabine/cisplatin: a maximum of 2 dose reductions permitted; no dose increase permitted after a dose reduction; interruptions of up to 42 days permitted due to AEs; toripalimab/placebo could be continued ▪ Treatment interruptions of chemotherapy and of toripalimab/placebo in the event of overlapping toxicities	
	Disallowed prior treatment ▪ Systemic chemotherapy for metastatic or recurrent disease ▪ Therapies targeting PD-1, PD-L1 or cytotoxic T-lymphocyte-associated protein 4 receptor ▪ Immunotherapy within 4 weeks or 5 half-lives (whichever is shorter) prior to randomisation ▪ Systemic corticosteroids (>10 mg daily prednisone equivalent) within 4 weeks prior to randomisation or other systemic immunosuppressive medications within 2 weeks prior to randomisation[b] ▪ Antineoplastic traditional herbal medicine within 4 weeks before randomisation	
	Allowed concomitant treatment ▪ Palliative radiotherapy for non-target lesions, e.g. the treatment of bone metastases ▪ Topical or systemic corticosteroids, mycophenolate or TNFα inhibitors for the treatment of immune-mediated and/or infusion-related AEs[c] ▪ Premedication with antihistamines from Cycle 2 onwards ▪ Symptomatic treatment of infusion-related reactions following standard therapy (including supplemental oxygen and β_2-adrenergic agonists) **Disallowed concomitant treatment** ▪ Any concomitant anticancer treatment (including chemotherapy, hormonal therapy, immunotherapy, radiotherapy, investigational agents or herbal therapy) ▪ denosumab[d] ▪ Steroids to premedicate patients with contrast allergy or impaired renal function for CT scans with contrast ▪ Traditional herbal medicines	

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

Study	Intervention	Comparison
a. A treatment interruption due to AEs of >56 days generally led to treatment discontinuation. b. Acute, low-dose, systemic immunosuppressant medications (e.g. a one-time dose of dexamethasone for nausea) before study start allowed, following approval by the medical monitor. c. Had to be tapered gradually to non-immunosuppressive doses (≤10 mg/day of prednisone or equivalent) before the next toripalimab/placebo administration. d. Patients who had received denosumab prior to enrolment had to receive a bisphosphonate instead during the study. AE: adverse event; CT: computed tomography; IV: intravenous; NPC: nasopharyngeal carcinoma; PD-1: programmed cell death protein-1; PD-L1: programmed death-ligand 1; RCT: randomised controlled trial; TNF: tumour necrosis factor		

I 3.2.1 Study design

JUPITER-02 is a completed, double-blind, multicentre RCT comparing toripalimab + cisplatin + gemcitabine versus placebo + cisplatin + gemcitabine. The study exclusively included Asian adult patients aged up to 75 years with recurrent, not amenable to surgery or radiotherapy, or metastatic NPC, and who had not previously received any systemic chemotherapy 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 at study entry.

A total of 289 patients were included and randomly allocated in a 1:1 ratio either to treatment with toripalimab + cisplatin + gemcitabine (N = 146) or placebo + cisplatin + gemcitabine (N = 143). Randomisation was stratified by ECOG PS (0 versus 1) and disease stage (recurrent versus metastatic).

Treatment with toripalimab in the intervention arm was carried out in accordance with the summary of product characteristics (SmPC) [8]. In both study arms, the chemotherapy regimen consisted of cisplatin + gemcitabine. Neither drug has marketing authorisation for this therapeutic indication; consequently, the SmPCs do not provide any direct recommendations regarding the dosage or duration of treatment [9,10]. There are no German guidelines for the treatment of NPC. International guidelines recommend chemotherapy with cisplatin and gemcitabine for this therapeutic indication. The dosage and treatment regimen for cisplatin + gemcitabine in the JUPITER-02 pivotal study were in line with those in the studies referred to in the guidelines [11-17], as well as with the treatment guideline issued by the National Health Service (NHS) [18], which the company cited in Module 3 A. The chemotherapy regimen was administered over 6 cycles. Following completion of chemotherapy, treatment with toripalimab or placebo was to continue for up to a maximum of 2 years or until unacceptable toxicity, disease progression, withdrawal of consent, at the

discretion of the investigator, death or the end of the trial. However, treatment with toripalimab or placebo could be continued beyond radiologically confirmed disease progression (as per Response Evaluation Criteria in Solid Tumours version 1.1 [RECIST v1.1]), provided there was continued clinical benefit and in the absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression, as determined by the investigator.

The primary outcome in JUPITER-02 was progression-free survival (PFS). Patient-relevant secondary outcomes were overall survival, outcomes on morbidity, health-related quality of life and adverse events (AEs).

I 3.2.2 Data cuts

The JUPITER-02 study is complete and 4 data cuts were available:

- First data cut (30 May 2020): primary PFS interim analysis, planned after the occurrence of 130 progression events; the study was unblinded after the first data cut-off
- Second data cut (8 June 2021): additional PFS analysis, conducted at the originally planned time for the PFS interim analysis (18 months after randomisation of the first patient)
- Third data cut (8 May 2022): unplanned final safety analysis
- Fourth data cut (18 November 2022): final analysis of overall survival, scheduled to take place after 130 deaths, coinciding with the end of the study (last patient last visit)

Furthermore, the study documents indicate that, following the final data cut-off on 18 November 2022 and the end of the study, the investigators continued to collect data on overall survival, and that this data was analysed on several unplanned occasions, most recently on 24 June 2025, according to the company.

In Module 4 A, the company presented results on all data cuts for overall survival. For this benefit assessment, the results from the fourth data cut were used, as this was the final prespecified analysis.

For the morbidity and health-related quality of life outcomes, the company presented results on the first and second data cuts. For the side effect outcomes, the company presented results on the first, second and third data cuts. Consequently, contrary to the module requirements for the final data cut (fourth data cut dated 18 November 2022), only analyses of overall survival were available, but not of the other outcomes. The company did not justify this. However, this approach was appropriate in the given situation. This is explained below.

With regard to the outcomes in the side effects category at the third data cut-off, no patients were still under observation (see Section I 3.2.3), and therefore no further events could occur, because the final dose of toripalimab was administered on 18 November 2021.

With regard to the morbidity and health-related quality of life outcomes, the company stated in Module 4 A that these were recorded and analysed until the second data cut-off. However, this was not apparent from the study documents, so it remained unclear whether any further recordings took place after the second data cut-off. The final patient was enrolled in the JUPITER-02 study in January 2020. Consequently, all patients had been under observation for at least 17 months at the second data cut-off. This corresponds to the recording of the EORTC QLQ-C30 and EORTC QLQ-H&N35 questionnaires at Cycle 24, by which time 69 versus 9 patients (intervention versus comparator arm) had completed a questionnaire, according to the company. Furthermore, in most items in the EORTC QLQ-C30 and EORTC QLQ-H&N35, a first deterioration occurred at an early stage (see I Appendix B.2 and I Appendix B.3 of the full dossier assessment). Overall, given the available data, even if data had been recorded beyond the second data cut-off, it is unlikely that an analysis of the outcomes relating to morbidity and health-related quality of life at a later timepoint would have led to any relevant changes in the effect estimates.

For the purposes of this benefit assessment, the analyses on the third data cut were therefore used for the side effect outcomes, whilst the analyses on the second data cut were used for the morbidity and health-related quality of life outcomes.

I 3.2.3 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: toripalimab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine

Study **Outcome category** **Outcome**	**Planned follow-up**
JUPITER-02	
Mortality	
Overall survival	Until death, withdrawal of consent or end of study
Morbidity	
Symptoms (EORTC QLQ-C30 and EORTC QLQ-H&N35)[a]	Until unacceptable toxicity, disease progression, death or withdrawal of consent
Health-related quality of life (EORTC QLQ-C30 and EORTC QLQ-H&N35)[a]	Until unacceptable toxicity, disease progression, death or withdrawal of consent
Side effects	
All outcomes in the side effects category	Up to 60 days after the last dose of the study medication

a. According to the different information provided by the company in Module 4 A: recording and analysis up to the second data cut-off; this is not apparent from the study documents.

AE: adverse event; 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: randomised controlled trial

The observation periods for the outcomes of the categories 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 60 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.

I 3.2.4 Patient characteristics

Table 9 shows the patient characteristics of the included study.

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

Study Characteristic Category	toripalimab + cisplatin + gemcitabine N[a] = 146	placebo + cisplatin + gemcitabine N[a] = 143
JUPITER-02		
Age [years], mean (SD)	46 (11)	50 (10)
Sex [F/M],%	15/85	19/81
Family origin, n (%)		
White	0 (0)	0 (0)
Black or African American	0 (0)	0 (0)
Asian	146 (100)	143 (100)
Other	0 (0)	0 (0)
Disease duration: time between first diagnosis and randomisation [years], mean (SD)	ND	ND
ECOG PS at baseline according to IWRS, n (%)		
0	83 (57)	80 (56)
1	63 (43)	63 (44)
Current or past cigarette consumption, n (%)		
Yes	76 (52)	59 (41)
No	70 (48)	84 (59)
Histology, n (%)		
Non-keratinising undifferentiated (WHO type III)	131 (90)	130 (91)
Non-keratinising differentiated (WHO type II)	2 (1)	6 (4)
Keratinising squamous cell carcinoma (WHO type I)	1 (<1)	2 (1)
NPC, unclassified	2 (1)	1 (<1)
Non-keratinising carcinoma, unclassified	10 (7)	3 (2)
Other	0 (0)	1 (<1)
Disease stage at baseline according to CRF, n (%)		
Recurrent	85 (58)	87 (61)
Type of recurrence[b]		
Local recurrence only	19 (13)	20 (14)
Distant recurrence	66 (45)	65 (46)
Unknown[c]	0 (0)	2 (1)
Primary metastatic	61 (42)	56 (39)

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

Study Characteristic Category	toripalimab + cisplatin + gemcitabine N[a] = 146	placebo + cisplatin + gemcitabine N[a] = 143
Location of metastases at baseline[d], n (%)		
Liver	61 (42)	57 (40)
Lung	59 (40)	56 (39)
Bone	60 (41)	55 (39)
Other	123 (84)	124 (87)
Any previous anticancer therapy, n (%)		
Radiotherapy	85 (58)	87 (61)
Simultaneous chemotherapy and radiotherapy	65 (45)	68 (48)
Neoadjuvant	54 (37)	49 (34)
Adjuvant	24 (16)	21 (15)
Surgery	38 (26)	43 (30)
EBV DNA level, n (%)		
<2000 IU/mL	54 (37)	54 (38)
≥2000 IU/mL	92 (63)	89 (62)
Treatment discontinuation, n (%)[e]	94 (64)[f]	112 (78)[f]
Study discontinuation, n (%)[g]	70 (48)	86 (60)

a. Number of randomised patients who received at least one dose of the respective treatment.
b. Local recurrence only was defined as stage I to stage IVA, whilst distant recurrence was defined as stage IVB, based on the disease stage at the time the consent form was signed.
c. The 2 patients were not diagnosed with NPC. One patient was diagnosed with bowel cancer and one with rhabdomyosarcoma.
d. The metastatic organ is based on any occurrence of lesion location of the target lesion or non-target lesions at screening.
e. Common reasons for treatment discontinuation in the intervention arm vs. control arm were the following (percentages based on randomised patients): disease progression (38% vs. 62%), AEs (11% vs. 4%). Furthermore, 36% vs. 22% of the patients completed treatment as planned.
f. Institute's calculations.
g. Frequent reasons for study discontinuation in the intervention arm vs. the control arm (percentages refer to randomised patients and the 18 November 2022 data cut): withdrawal of consent (3% vs. 1%), lost to follow-up (5% vs. 6%). The data additionally include patients who died during the course of the study (39% vs. 53%). In addition, 52% vs. 40% of the patients completed the study as planned.

AE: adverse event; CRF: case report form; EBV: Epstein-Barr virus; ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; IWRS: interactive web response system; M: male; n: number of patients in the category; N: number of randomised patients; ND: no data; NPC: nasopharyngeal carcinoma; RCT: randomised controlled trial; SD: standard deviation; WHO: World Health Organization

The patient characteristics were largely balanced between the 2 treatment arms of JUPITER-02. The mean age of the patients was 46 versus 50 years, most of them were male (85% versus 81%) and all patients were of Asian family origin. In both study arms, the majority of patients

had non-keratinising undifferentiated NPC (World Health Organization [WHO] type III) (90% versus 91%). In around two-thirds of patients, the Epstein-Barr virus (EBV) DNA titre was ≥2000 IU/mL. Approximately 40% of patients were in the primary metastatic stage at baseline.

Treatment was discontinued more frequently in the comparator arm (78%) than in the intervention arm (64%). In both study arms, the main reason for premature treatment discontinuation was disease progression (62% in the comparator arm versus 38% in the intervention arm). 48% of patients in the intervention arm and 60% of those in the comparator arm discontinued the study. These data also included patients who died during the course of the study (39% versus 53%).

I 3.2.5 Limitations of the JUPITER-02 study

Consolidating radiotherapy

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. Likewise, 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 the 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 [14]. This recommendation is based on the results of a randomised study involving patients with de novo metastatic NPC [19].

In the JUPITER-02 study, around 40% of patients had newly diagnosed metastatic NPC. However, according to the study design, any concomitant anticancer treatment, including radiotherapy, was prohibited during the study. This was reflected in the results of the study. Only 2 patients (<1%) received concomitant radiotherapy during the study (1 for the treatment of bone lesions and 1 as palliative radiotherapy). No further information was available on the approach used in the study in situations where consolidating locoregional radiotherapy was indicated in accordance with the guideline recommendations, or on the proportion of patients in the study who might have benefited from such treatment. The absence of consolidating radiotherapy may have an impact on various patient-relevant outcomes, including overall survival; this was taken into account in the assessment of the certainty of conclusions of the study results.

Palliative radiotherapy and the availability of bisphosphonates

The S3 guideline on supportive therapy for oncological patients recommends treatment with bisphosphonates or the receptor activator of NF-κB ligand (RANK-L) inhibitor denosumab to prevent complications associated with bone metastases, taking into account the specific

entity in question [20]. Palliative radiotherapy for bone metastases is also recommended. This can be conducted in parallel with treatment using bisphosphonates or RANK-L inhibitors.

According to the study design, concomitant treatment with bisphosphonates for the management of bone metastases was permitted, whilst treatment with the RANK-L inhibitor denosumab was not permitted. Patients who had received denosumab prior to enrolment had to switch to a bisphosphonate instead during the study. No further information was available on how many patients had received denosumab before the start of the study. At baseline, 40% of the patients included in the study had bone metastases, and 24% received bisphosphonates as concomitant treatment during the course of the study. Overall, it remained unclear why some of the patients with bone metastases did not receive bisphosphonates during the course of the study.

There were also uncertainties as to the extent to which unrestricted use of palliative radiotherapy was allowed in the JUPITER-02 study. In JUPITER-02, palliative radiotherapy (e.g. for the treatment of bone metastases) was permitted, provided that the lesion was a non-target lesion. No information was available regarding the location of the target lesions. In total, only one patient received palliative radiotherapy during the course of the study (see above).

Transferability to the German health care context

According to the WHO, NPC can be classified into 3 histology subtypes: keratinising (type I), non-keratinising differentiated (type II) and non-keratinising undifferentiated (type III). The frequencies of these subtypes vary from region to region. In Asia, around 97% of tumours are classified as types II and III, and there is a strong association with EBV [21-23]. Various studies carried out in non-endemic areas showed that the proportion of type I NPC in these regions was around 12% [24,25].

The JUPITER-02 study was conducted exclusively in Asia. The proportion of patients with type I was just 1%, whilst the proportion with type II and type III was around 93%. Furthermore, around two-thirds of the patients had an EBV infection (EBV DNA ≥2000 IU/mL). According to the information provided by the company in Module 4 A, there was no indication of reduced effectiveness of toripalimab for type I (see the company's further comments on this in Section I 3.2.9). Given the negligible proportion of type I NPC compared with non-endemic regions, and the relatively high proportion of cases associated with EBV, uncertainties remained as to whether the results were fully transferable to the German health care context.

Summary

The uncertainties described above regarding consolidating radiotherapy, supportive concomitant therapies and the transferability to the German health care context may have an

impact on various outcome categories and resulted in a limited certainty of conclusions of the results (see Section I 4.2).

I 3.2.6 Information on the course of the study

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

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

Study **Duration of the study phase** **Outcome category / outcome**	**toripalimab + cisplatin + gemcitabine** **N[a] = 146**	**placebo + cisplatin + gemcitabine** **N[a] = 143**
JUPITER-02		
Treatment duration [months][b]		
Median [min; max]	15.1 [0.7; 24.7]	8.6 [0.7; 23.3]
Mean (SD)	14.8 (8.8)	9.5 (5.0)
Observation period [months]		
Overall survival[c]		
Median [min; max]	36.7 [1.0; 47.4]	31.0 [0.2; 48.3]
Mean (SD)	31.5 (12.6)	28.7 (13.0)
Symptoms, health-related quality of life (EORTC QLQ-C30, EORTC QLQ-H&N35)[d]		
Median [min; max]	14.6 [0.03; 24.1]	7.9 [0.03; 22.6]
Mean (SD)	14.2 (8.8)	8.9 (5.1)
Side effects[e]		
Median [min; max]	16.4 [1.0; 26.0]	9.9 [0.2; 24.6]
Mean (SD)	16.1 (8.9)	10.8 (5.1)

a. Number of randomised patients who received at least one dose of the respective treatment.
b. The conversion from weeks to months was carried out by IQWiG (weeks x 7 x 12 / 365.25).
c. Defined as the time from randomisation until death, the end of the study or the date of the data cut-off, whichever occurred first. The information is based on the data cut from 18 November 2022.
d. At the 8 June 2021 data cut-off.
e. At the 8 May 2022 data cut-off.

CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; max: maximum; min: minimum; N: number of analysed patients; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-H&N35: Quality of Life Questionnaire-Head and Neck Cancer 35; RCT: randomised controlled trial; SD: standard deviation

In JUPITER-02, the median treatment duration was about 6 months longer in the intervention arm than in the comparator arm (15.1 months versus 8.6 months).

At the time of the final analysis of overall survival (data cut-off on 18 November 2022), the median and mean observation period for the outcome of overall survival was comparable between the 2 treatment arms. By contrast, the median observation periods for the other outcomes in the categories of morbidity and health-related quality of life / side effects differed notably from one another, as the median observation periods in the comparator arm corresponded to 54.1% and 60.4%, respectively, of the medians in the intervention arm. Furthermore, the observation periods for these outcomes were shorter in both arms than the observation period for overall survival, as they were linked to the end of treatment (plus 60 days for side effects).

I 3.2.7 Information on subsequent therapies

Table 11 shows the subsequent therapies patients received after discontinuing the study medication.

Table 11: Information on subsequent antineoplastic therapies (≥2% of the patients in ≥1 treatment arm) – RCT, direct comparison: toripalimab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine (multipage table)

Study **Drug class**[b] **Drug**	**Patients with subsequent therapy n (%)**[a]	
	toripalimab + cisplatin + gemcitabine **N = 146**	**placebo + cisplatin + gemcitabine** **N = 143**
JUPITER-02		
Patients with at least one subsequent therapy (data cut: 18 November 2022)	82 (56)	106 (74)
First subsequent therapy		
Pyrimidine analogues	36 (25)	64 (45)
capecitabine	21 (14)	41 (29)
gimeracil; oteracil; tegafur	7 (5)	8 (6)
gemcitabine	2 (1)	4 (3)
tegafur; uracil	2 (1)	3 (2)
tegafur	1 (<1)	3 (2)
Monoclonal antibodies	19 (13)	28 (20)
camrelizumab	6 (4)	11 (8)
monoclonal antibodies	4 (3)	6 (4)
sintilimab	3 (2)	3 (2)
nimotuzumab	1 (<1)	4 (3)
toripalimab	3 (2)	1 (<1)
Taxanes	13 (9)	25 (18)
paclitaxel	4 (3)	11 (8)
docetaxel	2 (1)	7 (5)
nab-paclitaxel	4 (3)	5 (4)
paclitaxel liposome	3 (2)	2 (1)
Protein kinase inhibitors	16 (11)	15 (11)
apatinib mesylate	11 (8)	10 (7)
apatinib	1 (<1)	4 (3)
famitinib	3 (2)	0 (0)
Platinum compounds	7 (5)	22 (15)
cisplatin	5 (3)	11 (8)
nedaplatin	0 (0)	7 (5)
Therapeutic group not further classified (ATC)	11 (8)	10 (7)
Radiotherapy	6 (4)	9 (6)
Investigational product	5 (3)	1 (<1)

Table 11: Information on subsequent antineoplastic therapies (≥2% of the patients in ≥1 treatment arm) – RCT, direct comparison: toripalimab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine (multipage table)

Study Drug class[b] Drug	Patients with subsequent therapy n (%)[a]	
	toripalimab + cisplatin + gemcitabine N = 146	placebo + cisplatin + gemcitabine N = 143
a. Subsequent therapies were classified in accordance with WHODrug Global Mar2020. In the summary by ATC drug class and preferred drug name, each patient was counted only once, even in case of multiple events. b. In accordance with the information provided by the company in Module 4 A, the next higher available level was used where the ATC drug class at level 4 was not available. ATC: Anatomical Therapeutic Chemical classification; n: number of patients with subsequent therapy; N: number of analysed patients; nab: albumin-bound nanoparticles; RCT: randomised controlled trial; WHO: World Health Organization		

In the JUPITER-02 study, subsequent antineoplastic therapies were permitted without restrictions in both study arms.

At the time of the final analysis of the outcome overall survival (data cut-off on 18 November 2022), 56% of the patients in the intervention arm and 74% of the patients in the comparator arm had received at least one subsequent antineoplastic therapy. The company did not provide any data on the proportion of patients with disease progression for this data cut. It therefore remained unclear how many patients had a potential need for subsequent therapy. The percentages for the subsequent therapies given below each refer to the total number of randomised patients.

In both treatment arms, chemotherapy was the most commonly used first antineoplastic subsequent therapy (pyrimidine analogues, taxanes, platinum compounds). Furthermore, 13% of the patients in the intervention arm and 20% of the patients in the comparator arm received immunotherapy as the first subsequent therapy. The data on all subsequent therapies showed that the proportion of patients receiving immunotherapy as subsequent therapy increased over time in both treatment arms (32% versus 40%). In addition, 6 versus 9 patients received radiotherapy as subsequent therapy.

According to international guidelines, there is no standard treatment for second- and third-line therapy in the given therapeutic indication [11,14,15]. 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 JUPITER-02 were deprived of effective subsequent therapies to any relevant extent.

I 3.2.8 Risk of bias across outcomes (study level)

Table 12 shows the risk of bias across outcomes (risk of bias at study level).

Table 12: Risk of bias across outcomes (study level) – RCT, direct comparison: toripalimab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine

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			
JUPITER-02	Yes	Yes	Yes[a]	Yes[a]	Yes	Yes	Low

a. Unblinding in accordance with the protocol following the first PFS interim analysis (first data cut-off: 30 May 2020) for both patients and treating staff. In principle, bias arising from knowledge of group allocation is possible at the outcome level.

PFS: progression-free survival; RCT: randomised controlled trial

The risk of bias across outcomes was rated as low for JUPITER-02.

I 3.2.9 Transferability of the study results to the German health care context

The company described that the results of the JUPITER-02 study were transferable to the German health care context. It justified this by referring to the assessment by the European Medicines Agency (EMA), which granted marketing authorisation for toripalimab in Europe on the basis of the study data. According to the company, the marketing authorisation was based on the fact that the biological characteristics of NPC and the mechanism of action of programmed cell death 1 (PD-1) inhibitors such as toripalimab were comparable across populations and effective regardless of ethnic origin, a finding that had already been confirmed in numerous tumour entities worldwide. It added that the survival advantages observed in the study were consistent with the results for other immune checkpoint inhibitors, such as nivolumab and pembrolizumab, which were also used successfully in European populations. It also pointed out that, whilst the keratinising subtype of NPC, which is more common in Europe than in Asia, was under-represented in the study, there was no indication of reduced efficacy in this population.

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 3.2.5.

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 (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥3)
  - Discontinuation due to AEs
  - Immune-mediated SAEs
  - Immune-mediated severe AEs (CTCAE grade ≥3)
  - Other specific AEs, if any

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

Table 13 shows for which outcomes data were available in the included study.

Table 13: Matrix of outcomes – RCT, direct comparison: toripalimab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine

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	Immune-mediated severe AEs[a]	Pneumonia (PT, severe AEs[a])
JUPITER-02	Yes	Yes	Yes	Yes	Yes	No[b]	No[b]	No[b]	Yes

a. Severe AEs are operationalised as CTCAE grade ≥3 AEs.
b. No suitable data available; for justification 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: randomised controlled trial; SAE: serious adverse event

Notes on outcomes

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

Operationalisation 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 A post hoc responder analyses for the time to first deterioration and to the first improvement of ≥10 points. Due to the expected progressive course of the disease in the given therapeutic indication, analyses of the first deterioration were relevant for this benefit assessment.

Symptoms recorded using the EORTC QLQ-H&N35

For the patient-reported outcomes of symptoms, the company presented in Module 4 A 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’). The EORTC QLQ-H&N35 also includes 4 additional 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.

Outcomes in the category of side effects

Operationalisation of discontinuation due to AEs

In Module 4 A, the company showed only those AEs that led to treatment discontinuation of toripalimab or placebo, whilst events that led to discontinuation of the chemotherapy components were not taken into account. This approach was not appropriate, and the relevant operationalisation ('discontinuation of at least one drug component') was not available for the benefit assessment. In accordance with the module template, the overall rate of discontinuations due to AEs must be provided in full. For this reason, the results of the JUPITER-02 study presented in Module 4 A were not considered suitable for the outcome 'discontinuation due to AEs' and were not taken into account in the assessment.

Operationalisation of immune-mediated AEs (SAEs and severe AEs)

The outcomes immune-mediated AEs (SAEs and severe AEs [CTCAE grade ≥3]) are of particular importance for the assessment of an immune checkpoint inhibitor such as toripalimab. The significance of these AEs specific to immune checkpoint inhibitors is generally acknowledged and is also reflected, for example, in the fact that the Association of the Scientific Medical Societies (AWMF) included a separate chapter on the prevention, diagnosis and treatment of immune-mediated AEs in the current version of its guideline on supportive therapy for oncological patients [20]. Immune-mediated AEs (SAEs and severe AEs) are patient-relevant outcomes for the assessment of immune checkpoint inhibitors, which were routinely used in the past when assessing drugs in this class.

In Module 4 A, the company did not provide any results on the overall rates for immune-mediated AEs (SAEs and severe AEs). Instead, in Module 4 A, it merely presented, in isolation, the results relating to immune-mediated myocarditis and hepatic impairment as a priori defined AEs of special interest (AESIs), each of which was derived from one Preferred Term (PT) of the Medical Dictionary for Regulatory Activities (MedDRA). There was therefore no comprehensive representation of the overall rate of immune-mediated AEs.

The study documents also contained results relating to immune-mediated AEs recorded by the investigator and to immune-mediated AEs determined by the sponsor. The immune-mediated AEs determined by the sponsor were initially identified on the basis of a predefined PT list, in accordance with the information provided in the clinical study report; however, in subsequent steps, they were linked to various prerequisites (direct association with the study medication, treatment with systemic corticosteroids).

Neither of the 2 operationalisations was suitable for the benefit assessment in this form. By linking the recording of immune-mediated AEs to prerequisites (treatment with systemic corticosteroids or investigator assessment) the complete and adequate representation of

immune-mediated AEs was not guaranteed. Overall, therefore, no suitable data were available for the assessment.

For a comprehensive benefit assessment, it would instead be necessary to perform an analysis of all occurred events in accordance with the predefined list of MedDRA PTs for immune-mediated AEs described in the study documentation, taking into account all relevant events, irrespective of any additional prerequisites. Furthermore, given the differences in the observation periods between the 2 treatment arms (see Section I 3.2.6), time-to-event analyses should be provided for the immune-mediated AEs (SAEs and severe AEs).

I 4.2 Risk of bias

Table 14 describes the risk of bias for the results of the relevant outcomes.

Table 14: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: toripalimab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine

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	Immune-mediated severe AEs[a]	Pneumonia (PT, severe AEs[a])
JUPITER-02	L	L	H[b, c]	H[b, c]	H[b]	H[b]	–[d]	–[d]	–[d]	H[b]

a. Severe AEs are operationalised as CTCAE grade ≥3 AEs.
b. Incomplete observations for potentially informative reasons with different lengths of follow-up observation.
c. Following unblinding (30 May 2020), lack of blinding in the presence of subjective recording of outcomes.
d. No suitable data available; for the reasoning, see Section I 4.1 of this dossier assessment.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; H: high; L: low; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-H&N35: Quality of Life Questionnaire-Head and Neck Cancer 35; RCT: randomised controlled trial; SAE: serious adverse event

The results on overall survival had a low risk of bias.

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. The main reason for this was the incomplete observation for potentially informative reasons with different lengths of follow-up observation. This was primarily due to treatment interruptions caused by disease

progression and the resulting discontinuation of follow-up. Furthermore, the unblinding of the study at the first data cut-off on 30 May 2020 resulted in the loss of blinding in the presence of subjective recording of outcomes from that point onwards. It can be inferred from the study documents that, at the time of unblinding, chemotherapy treatment had been completed for all patients and that the patients had already been under observation for at least 5 months; this corresponds to approximately 9 recordings of the patient-reported outcomes. This aspect therefore only had an effect later on in recording and did not apply to all patients.

The risk of bias in the results for the outcome category side effects 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.

No suitable data were available for discontinuation due to AEs, immune-mediated SAEs and immune-mediated severe AEs (see Section I 4.1). The risk of bias was therefore not assessed.

Summary assessment of the certainty of conclusions

Irrespective of the high risk of bias for all outcomes except overall survival, there were relevant uncertainties regarding consolidating radiotherapy, restrictions to supportive concomitant therapies and the transferability to the German health care context (see Section I 3.2.5). 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 JUPITER-02 study.

I 4.3 Results

Table 15 summarises the results of the comparison between toripalimab + cisplatin + gemcitabine and placebo + cisplatin gemcitabine in patients with recurrent, not amenable to 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 on 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) in I Appendix C of the full dossier assessment.

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: toripalimab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine (multipage table)

Study Outcome category Outcome	toripalimab + cisplatin + gemcitabine		placebo + cisplatin + gemcitabine		toripalimab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine
	L	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]
JUPITER-02					
Mortality (18 November 2022)					
Overall survival	146	NA [38.7; NC] 57 (39.0)	143	33.7 [27.0; 44.2] 76 (53.1)	0.63 [0.45; 0.89]; 0.008
Morbidity (8 June 2021)					
Symptoms (EORTC QLQ-C30 – time to first deterioration[b])					
Fatigue	145	2.4 [1.4; 3.3] 86 (59.3)	143	1.6 [1.4; 2.4] 91 (63.6)	0.90 [0.67; 1.21]; 0.453
Nausea and vomiting	145	1.9 [1.4; 2.2] 99 (68.3)	143	1.6 [1.4; 2.1] 100 (69.9)	0.91 [0.69; 1.21]; 0.484
Pain	145	–[c] 58 (40.0)	143	NA [4.1; NC] 63 (44.1)	0.82 [0.58; 1.18]; 0.279
Dyspnoea	145	16.2 [5.8; NC] 66 (45.5)	143	6.7 [4.1; 17.5] 70 (49.0)	0.83 [0.59; 1.18]; 0.288
Insomnia	145	NA [11.6; NC] 59 (40.7)	143	NA [4.9; NC] 59 (41.3)	0.86 [0.60; 1.25]; 0.420
Appetite loss	145	2.3 [1.4; 4.8] 83 (57.2)	143	2.1 [1.5; 2.3] 90 (62.9)	0.86 [0.64; 1.17]; 0.294
Constipation	145	NA [4.8; NC] 60 (41.4)	143	10.0 [4.2; NC] 65 (45.5)	0.87 [0.61; 1.24]; 0.428
Diarrhoea	145	NA [20.3; NC] 48 (33.1)	143	NA [14.1; NC] 37 (25.9)	1.17 [0.76; 1.81]; 0.472
Symptoms (EORTC QLQ-H&N35 – time to first deterioration[b])					
Dry mouth (xerostomia)	145	NA [8.0; NC] 57 (39.3)	143	NA 47 (32.9)	1.14 [0.77; 1.68]; 0.512
Senses problems	145	3.3 [2.6; 5.1] 85 (58.6)	143	3.2 [2.2; 4.7] 82 (57.3)	0.99 [0.73; 1.34]; 0.911
Speech problems	145	3.7 [2.9; 4.0] 91 (62.8)	143	2.2 [1.6; 4.3] 88 (61.5)	0.88 [0.66; 1.18]; 0.388
Cough	145	NA [11.7; NC] 57 (39.3)	143	6.4 [3.8; NC] 68 (47.6)	0.74 [0.52; 1.06]; 0.088

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: toripalimab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine (multipage table)

Study **Outcome category** **Outcome**	**toripalimab + cisplatin + gemcitabine**		**placebo + cisplatin + gemcitabine**		**toripalimab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine**
	L	**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]**
Feeling ill	145	NA [4.2; NC] 61 (42.1)	143	8.8 [2.4; NC] 66 (46.2)	0.82 [0.57; 1.16]; 0.253
Problems with mouth opening (trismus)	145	22.0 [10.0; NC] 58 (40.0)	143	NA [9.4; NC] 58 (40.6)	0.84 [0.58; 1.22]; 0.344
Pain	145	NA 44 (30.3)	143	NA [11.5; NC] 51 (35.7)	0.81 [0.54; 1.21]; 0.299
Sticky saliva	145	NA [8.5; NC] 59 (40.7)	143	NA [3.5; NC] 63 (44.1)	0.80 [0.56; 1.15]; 0.221
Problems with swallowing	145	NA 48 (33.1)	143	NA [8.0; NC] 55 (38.5)	0.74 [0.50; 1.10]; 0.135
Problems with teeth	145	NA [6.3; NC] 56 (38.6)	143	20.1 [8.8; NC] 52 (36.4)	1.09 [0.75; 1.60]; 0.649
Use of a feeding tube	145	NA 11 (7.6)	143	NA 8 (5.6)	1.36 [0.54; 3.38]; 0.514
Use of nutritional supplements (supplementary information)	*145*	*NA [19.8; NC]* *55 (37.9)*	*143*	*NA [3.5; NC]* *58 (40.6)*	–
Use of painkillers (supplementary information)	*145*	*NA* *30 (20.7)*	*143*	*NA* *18 (12.6)*	–
Weight gain (supplementary information)	*145*	*3.9 [3.2; 4.80]* *103 (71.0)*	*143*	*4.4 [3.8; 5.3]* *87 (60.8)*	–
Weight loss (supplementary information)	*145*	*NA [19.3; NC]* *50 (34.5)*	*143*	*NA [16.8; NC]* *46 (32.2)*	–

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: toripalimab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine (multipage table)

Study Outcome category Outcome	toripalimab + cisplatin + gemcitabine		placebo + cisplatin + gemcitabine		toripalimab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine
	L	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 (8 June 2021)					
EORTC QLQ-C30 – time to first deterioration[d]					
Global health status	145	9.0 [2.9; NC] 67 (46.2)	143	NA [4.0; NC] 63 (44.1)	1.05 [0.75; 1.49]; 0.762
Physical functioning	145	3.0 [2.3; 4.3] 82 (56.6)	143	2.3 [2.1; 3.0] 92 (64.3)	0.85 [0.63; 1.15]; 0.291
Role functioning	145	2.8 [1.4; 4.1] 89 (61.4)	143	2.3 [1.5; 3.3] 91 (63.6)	0.97 [0.72; 1.30]; 0.784
Emotional functioning	145	NA [3.8; NC] 61 (42.1)	143	13.8 [4.3; NC] 60 (42.0)	1.05 [0.73; 1.50]; 0.812
Cognitive functioning	145	3.0 [2.1; 4.4] 91 (62.8)	143	2.9 [2.1; 4.3] 86 (60.1)	1.02 [0.76; 1.37]; 0.926
Social functioning	145	3.9 [2.8; 11.2] 79 (54.5)	143	NA [4.8; NC] 61 (42.7)	1.32 [0.94; 1.85]; 0.108
EORTC QLQ-H&N – time to first deterioration[b]					
Trouble with social eating	145	8.8 [3.1; NC] 69 (47.6)	143	3.5 [2.3; NC] 74 (51.7)	0.85 [0.61; 1.18]; 0.298
Trouble with social contact	145	3.3 [2.2; 9.4] 78 (53.8)	143	2.2 [2.0; 3.5] 90 (62.9)	0.75 [0.55; 1.01]; 0.053
Less sexuality	145	3.0 [2.3; 5.3] 80 (55.2)	143	3.5 [2.1; 6.0] 79 (55.2)	1.02 [0.75; 1.40]; 0.904
Side effects (8 May 2022)					
AEs[e] (supplementary information)	146	0.03 [0.03; 0.07] 146 (100)	143	0.1 [0.03; 0.1] 143 (100)	–
SAEs[e]	146	NA [6.2; NC] 63 (43.2)	143	NA [5.1; NC] 61 (42.7)	0.98 [0.69; 1.39]; 0.897
Severe AEs[e, f]	146	0.7 [0.4; 0.9] 131 (89.7)	143	0.7 [0.5; 0.8] 129 (90.2)	1.04 [0.82; 1.33]; 0.739
Discontinuation due to AEs	No suitable data[g]				
Immune-mediated AEs (supplementary information)	No suitable data[g]				

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: toripalimab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine (multipage table)

Study **Outcome category** **Outcome**	**toripalimab + cisplatin + gemcitabine**		**placebo + cisplatin + gemcitabine**		**toripalimab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine**
	L	**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]**
Immune-mediated SAEs	No suitable data[g]				
Immune-related severe AEs[f]	No suitable data[g]				
Pneumonia (PT, severe AEs[f])	146	NA 17 (11.6)	143	NA 5 (3.5)	3.29 [1.21; 8.97]; 0.014[h]

a. HR and CI: Cox proportional hazards model, p-value: log-rank test, each stratified by ECOG PS (0 or 1) and disease stage (recurrent or metastatic) at baseline.
b. A score 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 of the full dossier assessment).
d. A score decrease of ≥10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
e. Presented are AEs, SAEs, severe AEs excluding the 'disease progression' PT.
f. Operationalised as CTCAE grade ≥3.
g. For an explanation, see Section I 4.1.
h. The effect estimation and testing shown in Figure 32 in the full dossier assessment differ from the information presented here. It is assumed that the deviations result from an unstratified model.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; ECOG PS: Eastern Cooperative Oncology Group Performance Status; 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: randomised controlled trial; SAE: serious adverse event

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

Overall survival

With regard to the overall survival outcome, a statistically significant difference in favour of toripalimab + cisplatin + gemcitabine compared with placebo + cisplatin + gemcitabine was shown when the total population was considered. In addition, there was an effect modification by the characteristic 'disease stage' (see Section I 4.4). There is a hint of an added benefit of toripalimab + cisplatin + gemcitabine in comparison with the ACT for patients with recurrent NPC. For patients with metastatic NPC, there is no hint of an added benefit of toripalimab + cisplatin + gemcitabine in comparison with the ACT. An added benefit for these patients is therefore not proven.

Morbidity

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

Fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, dry mouth (xerostomia), senses problems, speech problems, cough, feeling ill, problems with mouth opening (trismus), pain, sticky saliva, problems with swallowing, problems with teeth, use of a feeding tube

No statistically significant difference between the treatment groups was found for any of the outcomes of fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation and diarrhoea (recorded using the EORTC QLQ-C30), as well as dry mouth (xerostomia), senses problems, speech problems, cough, feeling ill, problems with mouth opening (trismus), pain, sticky saliva, problems with swallowing, problems with teeth, use of a feeding tube (recorded using the EORTC QLQ-H&N35). There is no hint of an added benefit of toripalimab + cisplatin + gemcitabine in comparison with the ACT for any of the outcomes; an added benefit is therefore not proven for these outcomes.

Health-related quality of life

Global health status, physical functioning, role functioning, social functioning, trouble with social eating, trouble with social contact, and less sexuality

No statistically significant difference was found between the treatment groups for any of the following outcomes: global health status, physical functioning, role functioning, social functioning (assessed using the EORTC QLQ-C30), as well as trouble with social eating, trouble with social contact, and less sexuality (assessed using the EORTC QLQ-H&N35). There is no hint of an added benefit of toripalimab + cisplatin + gemcitabine in comparison with the ACT for any of the outcomes; an added benefit is therefore not proven for these outcomes.

Emotional functioning and cognitive functioning (assessed using the EORTC QLQ-C30)

For the outcomes of emotional functioning and cognitive functioning of the EORTC QLQ-C30, no statistically significant difference between the treatment arms was found when

considering the total population. In each case, there was an effect modification by the characteristic of sex, however (see Section I 4.4). There is a hint of an added benefit of toripalimab + cisplatin + gemcitabine in comparison with the ACT for women. For men, there is no hint of an added benefit of toripalimab + cisplatin + gemcitabine in comparison with the ACT. An added benefit for men is therefore not proven.

Side effects

SAEs and severe AEs

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

Discontinuation due to AEs, immune-mediated SAEs and immune-mediated severe AEs

No suitable data were available for any of the outcomes of discontinuation due to AEs, immune-mediated SAEs and immune-mediated severe AEs. There is no hint of greater or lesser harm of toripalimab + cisplatin + gemcitabine in comparison with the ACT for these outcomes; greater or lesser harm is therefore not proven for these outcomes.

Pneumonia (PT, severe AEs)

With regard to the pneumonia outcome, a statistically significant difference to the disadvantage of toripalimab + cisplatin + gemcitabine compared with placebo + cisplatin + gemcitabine was shown when the total population was considered. In addition, there was an effect modification by the characteristic 'disease stage' (see Section I 4.4). There is a hint of greater harm of toripalimab + cisplatin + gemcitabine in comparison with the ACT for patients with recurrent NPC. For patients with metastatic NPC, there is no hint of greater or lesser harm of toripalimab + cisplatin + gemcitabine in comparison with the ACT. Greater or lesser harm for this group is therefore not proven.

I 4.4 Subgroups and other effect modifiers

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

- Age (≤50 versus >50 years)
- Sex (male versus female)
- Disease stage according to an interactive web response system (IWRS) (recurrent vs. metastatic)

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. Moreover, for binary data, there have to 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 16. The Kaplan-Meier curves on the subgroup results are presented in I Appendix B.5 of the full dossier assessment.

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

Study Outcome Characteristic Subgroup	toripalimab + cisplatin + gemcitabine		placebo + cisplatin + gemcitabine		toripalimab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine	
	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]
JUPITER-02						
Mortality (18 November 2022)						
Overall survival						
Disease stage according to the IWRS						
Recurrent	83	NA [41.5; NC] 28 (33.7)	82	27.4 [21.4; 39.0] 51 (62.2)	0.45 [0.28; 0.71]	<0.001
Metastatic	63	NA [31.9; NC] 29 (46.0)	61	44.3 [30.3; NC] 25 (41.0)	1.09 [0.64; 1.86]	0.748
Total					Interaction[b]:	0.010
Health-related quality of life (8 June 2021)						
EORTC QLQ-C30 – time to first deterioration[c]						
Emotional functioning						
Sex						
Male	123	NA [3.3; NC] 54 (43.9)	116	NA [8.5; NC] 44 (37.9)	1.26 [0.85; 1.88]	0.253
Female	22	NA [4.4; NC] 7 (31.8)	27	2.5 [2.1; 4.3] 16 (59.3)	0.25 [0.10; 0.65]	0.002
Total					Interaction[b]:	0.004
Cognitive functioning						
Sex						
Male	123	2.6 [1.5; 3.6] 79 (64.2)	116	3.8 [2.1; 6.9] 66 (56.9)	1.27 [0.92; 1.77]	0.145
Female	22	6.8 [1.6; NC] 12 (54.5)	27	1.5 [0.8; 2.8] 20 (74.1)	0.35 [0.17; 0.76]	0.005
Total					Interaction[b]:	0.003

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

Study Outcome Characteristic Subgroup	toripalimab + cisplatin + gemcitabine		placebo + cisplatin + gemcitabine		toripalimab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine	
	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]
Side effects (8 May 2022)						
Pneumonia (PT, severe AEs[d])						
Disease stage according to the IWRS						
Recurrent	83	NA 13 (15.7)	82	NA 1 (1.2)	13.0 [1.69; 99.46]	0.001
Metastatic	63	NA 4 (6.3)	61	NA 4 (6.6)	0.85 [0.21; 3.48]	0.825
Total					Interaction[b]:	0.034

a. HR and CI: Cox proportional hazards model, p-value: log-rank test; each unstratified.
b. Based on an interaction test (interaction term: subgroup * treatment) in a stratified Cox proportional hazards model; stratified by ECOG PS (0 or 1) and disease stage (recurrent or metastatic) at baseline.
c. A decrease of ≥10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
d. Severe AEs are operationalised as CTCAE grade ≥3 AEs.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; IWRS: interactive web response system; 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; RCT: randomised controlled trial

Mortality

Overall survival

There is a statistically significant effect modification by the characteristic of disease stage for the outcome of overall survival. A statistically significant difference in favour of toripalimab + cisplatin + gemcitabine compared with placebo + cisplatin + gemcitabine was shown for patients with recurrent NPC. There is therefore a hint of an added benefit of toripalimab + cisplatin + gemcitabine in comparison with the ACT for patients with recurrent NPC.

However, no statistically significant difference between the treatment arms was found for patients with metastatic NPC. There is no hint of an added benefit of toripalimab + cisplatin +

gemcitabine in comparison with the ACT for this subgroup; an added benefit is therefore not proven for patients with metastatic NPC.

Health-related quality of life

Emotional functioning and cognitive functioning (assessed using the EORTC QLQ-C30)

For each of the outcomes of emotional functioning and cognitive functioning (each assessed using the EORTC QLQ-C30), there was a statistically significant effect modification by the characteristic of sex. In each case, a statistically significant difference in favour of toripalimab + cisplatin + gemcitabine compared with placebo + cisplatin + gemcitabine was shown for women. For women, there is a hint of an added benefit of toripalimab + cisplatin + gemcitabine in comparison with the ACT for these outcomes.

For men, however, no statistically significant difference was shown between the treatment arms. For these outcomes, there is no hint of an added benefit of toripalimab + cisplatin + gemcitabine in comparison with the ACT for this subgroup; an added benefit is therefore not proven for men.

Side effects

Pneumonia (PT, severe AEs)

There was an effect modification by the characteristic of disease stage for the outcome pneumonia. A statistically significant difference to the disadvantage of toripalimab + cisplatin + gemcitabine compared with placebo + cisplatin + gemcitabine was shown for patients with recurrent NPC. For this subgroup, there is a hint of greater harm of toripalimab + cisplatin + gemcitabine in comparison with the ACT for these outcomes.

However, no statistically significant difference between the treatment arms was found for patients with metastatic NPC. There is no hint of greater or lesser harm of toripalimab + cisplatin + gemcitabine in comparison with the ACT for this subgroup; greater or lesser harm is therefore not proven for patients with metastatic NPC.

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 17).

Table 17: Extent of added benefit at outcome level: toripalimab + cisplatin + gemcitabine vs. cisplatin + gemcitabine (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**toripalimab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine** **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		
Disease stage according to the IWRS		
Recurrent	NA vs. 27.4 months HR: 0.45 [0.28; 0.71]; p <0.001 Probability: hint	Outcome category: mortality CI_u <0.85 Added benefit, extent: major
Metastatic	NA vs. 44.3 months HR: 1.09 [0.64; 1.86]; p = 0.748	Lesser benefit not proven / added benefit not proven

Table 17: Extent of added benefit at outcome level: toripalimab + cisplatin + gemcitabine vs. cisplatin + gemcitabine (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**toripalimab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Outcomes with shortened observation period		
Morbidity		
Symptoms (EORTC QLQ-C30 – time to first deterioration)		
Fatigue	2.4 vs. 1.6 months HR: 0.90 [0.67; 1.21]; p = 0.453	Lesser benefit not proven / added benefit not proven
Nausea and vomiting	1.9 vs. 1.6 months HR: 0.91 [0.69; 1.21]; p = 0.484	Lesser benefit not proven / added benefit not proven
Pain	– vs. NA HR: 0.82 [0.58; 1.18]; p = 0.279	Lesser benefit not proven / added benefit not proven
Dyspnoea	16.2 vs. 6.7 months HR: 0.83 [0.59; 1.18]; p = 0.288	Lesser benefit not proven / added benefit not proven
Insomnia	NA vs. NA HR: 0.86 [0.60; 1.25]; p = 0.420	Lesser benefit not proven / added benefit not proven
Appetite loss	2.3 vs. 2.1 months HR: 0.86 [0.64; 1.17]; p = 0.294	Lesser benefit not proven / added benefit not proven
Constipation	NA vs. 10.0 months HR: 0.87 [0.61; 1.24]; p = 0.428	Lesser benefit not proven / added benefit not proven
Diarrhoea	NA vs. NA HR: 1.17 [0.76; 1.81]; p = 0.472	Lesser benefit not proven / added benefit not proven
Symptoms (EORTC QLQ-H&N35 – time to first deterioration)		
Dry mouth (xerostomia)	NA vs. NA HR: 1.14 [0.77; 1.68]; p = 0.512	Lesser benefit not proven / added benefit not proven
Senses problems	3.3 vs. 3.2 months HR: 0.99 [0.73; 1.34]; p = 0.911	Lesser benefit not proven / added benefit not proven

Table 17: Extent of added benefit at outcome level: toripalimab + cisplatin + gemcitabine vs. cisplatin + gemcitabine (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**toripalimab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Speech problems	3.7 vs. 2.2 months HR: 0.88 [0.66; 1.18]; p = 0.388	Lesser benefit not proven / added benefit not proven
Cough	NA vs. 6.4 months HR: 0.74 [0.52; 1.06]; p = 0.088	Lesser benefit not proven / added benefit not proven
Feeling ill	NA vs. 8.8 months HR: 0.82 [0.57; 1.16]; p = 0.253	Lesser benefit not proven / added benefit not proven
Problems with mouth opening (trismus)	22.0 months vs. NA HR: 0.84 [0.58; 1.22]; p = 0.344	Lesser benefit not proven / added benefit not proven
Pain	NA vs. NA HR: 0.81 [0.54; 1.21]; p = 0.299	Lesser benefit not proven / added benefit not proven
Sticky saliva	NA vs. NA HR: 0.80 [0.56; 1.15]; p = 0.221	Lesser benefit not proven / added benefit not proven
Problems with swallowing	NA vs. NA HR: 0.74 [0.50; 1.10]; p = 0.135	Lesser benefit not proven / added benefit not proven
Problems with teeth	NA vs. 20.1 months HR: 1.09 [0.75; 1.60]; p = 0.649	Lesser benefit not proven / added benefit not proven
Use of a feeding tube	NA vs. NA HR: 1.36 [0.54; 3.38]; p = 0.514	Lesser benefit not proven / added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 – time to first deterioration		
Global health status	9.0 months vs. NA HR: 1.05 [0.75; 1.49]; p = 0.762	Lesser benefit not proven / added benefit not proven
Physical functioning	3.0 vs. 2.3 months HR: 0.85 [0.63; 1.15]; p = 0.291	Lesser benefit not proven / added benefit not proven

Table 17: Extent of added benefit at outcome level: toripalimab + cisplatin + gemcitabine vs. cisplatin + gemcitabine (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**toripalimab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Role functioning	2.8 vs. 2.3 months HR: 0.97 [0.72; 1.30]; p = 0.784	Lesser benefit not proven / added benefit not proven
Emotional functioning Sex Male	NA vs. NA HR: 1.26 [0.85; 1.88]; p = 0.253	Lesser benefit not proven / added benefit not proven
Female	NA vs. 2.5 months HR: 0.25 [0.10; 0.65]; p = 0.002 Probability: hint	Outcome category: health-related quality of life CI_u <0.75, risk ≥5% Added benefit, extent: major
Cognitive functioning Sex Male	2.6 vs. 3.8 months HR: 1.27 [0.92; 1.77]; p = 0.145	Lesser benefit not proven / added benefit not proven
Female	6.8 vs. 1.5 months HR: 0.35 [0.17; 0.76]; p = 0.005 Probability: hint	Outcome category: health-related quality of life 0.75 ≤ CI_u <0.90 Added benefit, extent: considerable
Social functioning	3.9 months vs. NA HR: 1.32 [0.94; 1.85]; p = 0.108	Lesser benefit not proven / added benefit not proven
EORTC QLQ-H&N35 – time to first deterioration		
Trouble with social eating	8.8 vs. 3.5 months HR: 0.85 [0.61; 1.18]; p = 0.298	Lesser benefit not proven / added benefit not proven
Trouble with social contact	3.3 vs. 2.2 months HR: 0.75 [0.55; 1.01]; p = 0.053	Lesser benefit not proven / added benefit not proven
Less sexuality	3.0 vs. 3.5 months HR: 1.02 [0.75; 1.40]; p = 0.904	Lesser benefit not proven / added benefit not proven

Table 17: Extent of added benefit at outcome level: toripalimab + cisplatin + gemcitabine vs. cisplatin + gemcitabine (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**toripalimab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Side effects		
SAEs	NA vs. NA HR: 0.98 [0.69; 1.39]; p = 0.897	Greater/lesser harm not proven
Severe AEs	0.7 vs. 0.7 months HR: 1.04 [0.82; 1.33]; p = 0.739	Greater/lesser harm not proven
Discontinuation due to AEs	No suitable datac	Greater/lesser harm not proven
Immune-mediated SAEs	No suitable datac	Greater/lesser harm not proven
Immune-mediated severe AEs	No suitable data[c]	Greater/lesser harm not proven
Pneumonia (severe AEs) Disease stage according to the IWRS Recurrent	NA vs. NA HR: 13.0 [1.69; 99.46]; HR: 0.08 [0.01; 0.59][d]; p = 0.001 Probability: hint	Outcome category: serious/severe side effects CI_u <0.75, risk ≥5% Greater harm, extent: major
Metastatic	NA vs. NA HR: 0.85 [0.21; 3.48]; p = 0.825	Greater/lesser harm not proven

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. See Section I 4.1 for the reasoning.
d. Institute's calculation; reversed direction of effect to enable the use of limits to derive the extent of added benefit.

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; IWRS: interactive web response system; 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 18 summarises the results taken into account for the overall conclusion on the extent of the added benefit.

Table 18: Positive and negative effects from the assessment of toripalimab + cisplatin + gemcitabine in comparison with cisplatin + gemcitabine

Positive effects	Negative effects
Outcomes with observation over the entire study duration	
Mortality ▪ Overall survival ▫ Disease stage according to the IWRS (recurrent) Hint of an added benefit – extent: major	–
Outcomes with shortened observation period	
Health-related quality of life ▪ Emotional functioning ▫ Sex (female) Hint of an added benefit – extent: major ▪ Cognitive functioning ▫ Sex (female) Hint of an added benefit – extent: considerable	–
–	Serious/severe side effects ▪ Pneumonia (severe AEs) ▫ Disease stage according to the IWRS (recurrent) Hint of greater harm – extent: major
No suitable data were available for discontinuation due to AEs, immune-mediated SAEs and immune-mediated severe AEs.	
AE: adverse event; IWRS: Interactive Web Response System; SAE: serious adverse event	

Overall, both positive and negative effects of toripalimab + cisplatin + gemcitabine were shown in comparison with the ACT. Due to the effect modification in the outcome of overall survival by the characteristic of disease stage (recurrent versus metastatic), the results on the added benefit of toripalimab + cisplatin + gemcitabine in comparison with the ACT are derived separately below, based on disease stage:

Patients with metastatic NPC

Neither positive nor negative effects were shown for patients with metastatic NPC. For the outcomes that represent individual aspects of health-related quality of life (emotional functioning and cognitive functioning), it remained unclear – due to the effect modification by the characteristic of sex – whether there were any effects in the subpopulation of patients with metastatic NPC. Furthermore, there was a lack of appropriate analyses of various AE outcomes, such as discontinuation due to AEs, immune-mediated SAEs and immune-mediated severe AEs. Overall, given the available data, an added benefit is not proven for patients with metastatic NPC.

Patients with recurrent NPC

For patients with recurrent NPC, there is a hint of a major added benefit for the outcome of overall survival. This contrasts with a hint of greater harm of major extent in the 'serious/severe side effects' outcome category for the outcome pneumonia. For the outcomes that represent individual aspects of health-related quality of life (emotional functioning and cognitive functioning), there was an effect modification by the characteristic of sex. Due to this effect modification, it remained unclear whether there were any effects in the subpopulation of patients with recurrent NPC. No suitable data were available for discontinuation due to AEs, immune-mediated SAEs and immune-mediated severe AEs. Overall, there is a hint of a considerable added benefit for patients with recurrent NPC.

Summary

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

The result of the assessment of the added benefit of toripalimab + cisplatin + gemcitabine in comparison with the ACT is summarised in Table 19.

Table 19: Toripalimab + cisplatin + gemcitabine – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adult patients with recurrent, not amenable to surgery or radiotherapy, or metastatic nasopharyngeal carcinoma (NPC) in first-line treatment	cisplatin in combination with gemcitabine[b, c]	▪ Patients with metastatic NPC: added benefit not proven[d] ▪ Patients with recurrent NPC: hint of considerable added benefit[d]

a. Presented is the ACT specified by the G-BA.
b. Gemcitabine does not have a marketing authorisation for this therapeutic indication. According to the G-BA, in accordance with the generally recognised 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 JUPITER-02 study included only patients with an ECOG PS of 0 or 1, and only 3 patients (1%) with keratinising type I NPC. It remains unclear whether the observed effects can be transferred to patients with ECOG PS ≥2 or with type I NPC.

ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; NPC: nasopharyngeal carcinoma

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

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.

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