Medicinrådet

Bilag til Medicinrådets vurdering af toripalimab i kombination med cisplatin og gemcitabin til førstelinje-behandling af recidiverende eller metastatisk kræft i næsesvælget

Patienter, som ikke er egnede til kirurgi eller strålebehandling

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. toripalimab
2. Forhandlingsnotat fra Amgros vedr. toripalimab
3. Ansøgers endelige ansøgning vedr. toripalimab

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March 30, 2026

Mars 2026

Vedrørende: Vurderingsrapport for toripalimab (Loqtorzi) i kombination med cisplatin og gemcitabin til førstelinjebehandling af recidiverende eller metastatisk nasofaryngealt karcinom (NPC)

LEO Pharma takker for muligheden for at afgive bemærkninger til Medicinrådets udkast til vurderingsrapport.

Overordnet set finder vi, at vurderingsrapporten giver en retvisende og balanceret fremstilling af evidensgrundlaget, og vi noterer os særligt følgende centrale vurderinger:

- At datagrundlaget samlet set vurderes som robust med få væsentlige usikkerheder
- At de identificerede usikkerheder, herunder vedrørende studiepopulationens karakteristika, ikke vurderes at være af afgørende betydning for den forventede effekt i dansk klinisk praksis
- At der dokumenteres en klinisk relevant effekt på både progressionsfri overlevelse (PFS) og samlet overlevelse (OS), med vedvarende adskillelse mellem behandlingsarmene
- At en lavere andel patienter i interventionsarmen modtog efterfølgende behandling sammenlignet med komparatorarmen
- Vi finder det positivt, at Medicinrådet således anerkender både den kliniske effekt og relevansen af evidensen i en dansk kontekst.

Populationsdækning uafhængigt af PD-L1-status
Toripalimab i kombination med cisplatin og gemcitabin er godkendt til behandling af voksne patienter med recidiverende eller metastatisk NPC uden selektion på baggrund af PD-L1-status. Dette indebærer, at behandlingen er relevant for hele patientpopulationen, i modsætning til visse øvrige immunterapier, hvor anvendelsen er begrænset til patienter med PD-L1-positiv sygdom.

Vedrørende pembrolizumab som sammenligningsgrundlag
Det fremgår af vurderingsrapporten, at pembrolizumab anvendes i dansk klinisk praksis til nogle patienter med recidiverende eller metastatisk planocellulær hoved- og halskræft med PD-L1 CPS ≥1, og at resultater fra KEYNOTE-048 derfor inddrages i vurderingen.
Samtidig fremgår det eksplicit, at KEYNOTE-048 ikke inkluderede patienter med nasofaryngealt karcinom (NPC).

På den baggrund finder vi det væsentligt at understrege, at evidensgrundlaget for pembrolizumab ikke er baseret på patienter med NPC, og at sammenligningen derfor bør fortolkes som en kontekstualisering i forhold til beslægtet sygdomsområde snarere end en direkte evidensbaseret sammenligning i NPC.
Medicinrådet anfører, at dansk klinisk praksis er baseret på internationale retningslinjer, såsom ESMO og NCCN. I den forbindelse bemærkes det, at toripalimab i kombination med cisplatin og

gemcitabin i ESMO-retningslinjerne er anbefalet i første linje til patienter med recidiverende eller metastatisk NPC, mens pembrolizumab monoterapi er anbefalet i anden linje på baggrund af KEYNOTE-122. Ligeledes er toripalimab i kombination med cisplatin og gemcitabin angivet som "preferred" i NCCN-retningslinjerne, mens pembrolizumab er opført under "other recommended regimens".

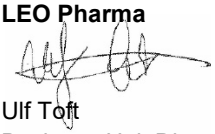
Det bemærkes endvidere, at toripalimab i kombination med cisplatin og gemcitabin er godkendt af EMA til behandling af NPC uafhængigt af PD-L1-ekspression, mens pembrolizumab er godkendt til behandling af patienter, hvis tumorer udtrykker PD-L1 med CPS ≥ 1. Behandling med toripalimab kræver således ikke PD-L1-testning.

Dette muliggør, at Anti-PD-1-immunterapi også kan tilbydes de PD-L1-negative patienter, som tidligere ikke har kunnet få denne type behandling. Derudover er en hurtigere behandlingsstart essentiel for onset af behandlingseffekten og formentlig også for patienternes overordnede kliniske outcome. Endelig bør fraværet af forsinkende stratifikation optimere klinikkens arbejdsgange, idet alle patienter får adgang til samme behandling uden yderligere test-afhængige trin."

Vi håber, at disse perspektiver kan indgå som et konstruktivt bidrag i DMC's endelige anbefaling, da de både afspejler den gældende internationale evidens for NPC og samtidig peger på forhold, der kan være til fordel for både patienterne og den daglige kliniske praksis.

Afsluttende bemærkninger
Samlet set vurderer vi, at vurderingsrapporten understøtter, at toripalimab i kombination med cisplatin og gemcitabin udgør en relevant og veldokumenteret behandlingsmulighed til patienter med recidiverende eller metastatisk NPC i Danmark.
LEO Pharma står naturligvis til rådighed for eventuelle uddybninger.

Med venlig hilsen
LEO Pharma



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31.03.2026

LSC/DBS

Forhandlingsnotat

Dato for behandling i Medicinrådet	29.04.2026
Leverandør	LEO Pharma
Lægemiddel	Loqtorzi (toripalimab)
Ansøgt indikation	Toripalimab i kombination med cisplatin og gemcitabin, er indiceret til førstelinjebehandling af voksne patienter med recidiverende eller metastatisk nasofaryngealt karcinom, som ikke kan behandles med kirurgi eller strålebehandling.
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris på Loqtorzi (toripalimab):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Loqtorzi	240 mg (1 stk.)	64.930,00	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling.

Det betyder, at hvis Medicinrådet ikke anbefaler Loqtorzi, indkøbes lægemidlet til AIP.

Aftaleforhold

Amgros vil indgå en aftale på Loqtorzi der løber fra 01.05.2026 indtil 31.12.2026 med mulighed for forlængelse i 12 måneder.

Denne aftale vil have samme betingelser og løbe i samme periode som de øvrige immunterapier, det vil sige at aftalen gælder frem til den 31.12.2026 med mulighed for forlængelse. Der er inkluderet mulighed for prisregulering i aftalen.

Konkurrencesituationen

Loqtorzi er en ny immunterapi. Udover denne indikation, er Loqtorzi under vurdering i Medicinrådet til indikationen spiserørskræft.

Platinbaseret kemoterapi betragtes som førstelinjebehandling med ikke-kurativt intenderet sigte, til patienter med recidiverende eller metastatisk nasofaryngealt karcinom (NPC). Patienter, hvis tumorer udtrykker PD-L1 med CPS ≥ 1, kan behandles med Keytruda (pembrolizumab) som monoterapi eller i kombination med kemoterapi.

Tabel 2 viser de årlige lægemiddeludgifter på hhv. Loqtorzi og Keytruda.

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient pr. år

Lægemiddel	Styrke (paknings-størrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Loqtorzi	240 mg (1 stk.)	240 mg hver 3. uge, i.v.	[redacted]	[redacted]
Keytruda	25 mg/ml (4 ml)	4 mg/kg* hver 6. uge, i.v.	[redacted]	[redacted]

*Kropsvægt 70 kg. jf. Fagudvalget vedr. hoved- og halskræft.

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Anbefalet	Link til vurdering
England	Under vurdering	Link til status
Sverige	Anbefalet	Link til vurdering

Opsummering

[redacted]

Application for the assessment of Toripalimab (LOQTORZI®) for recurrent or metastatic Nasopharyngeal Carcinoma (NPC)

Color of highlighted text	Definition of highlighted text
	Confidential information

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Abbreviations

AE: Adverse Event
AEs: Adverse Events
AWMSG: All Wales Medicines Strategy Group
CADTH: Canadian Agency for Drugs and Technologies in Health
CI: Confidence Interval
DCO: Data Cut-Off
ECOG PS: Eastern Cooperative Oncology Group Performance Status
EBV: Epstein–Barr Virus
EMA: European Medicines Agency
EQ-5D: EuroQol 5-Dimension Questionnaire
EORTC: European Organisation for Research and Treatment of Cancer
HRQoL: Health-Related Quality of Life
HTA: Health Technology Assessment
ICER: Incremental Cost-Effectiveness Ratio

ITT: Intention-to-Treat
KM: Kaplan–Meier
MMRM: Mixed Model for Repeated Measures
NA: Not Applicable
NCPE: National Centre for Pharmacoeconomics
NICE: National Institute for Health and Care Excellence
NPC: Nasopharyngeal Carcinoma
ORR: Objective Response Rate
OS: Overall Survival
PD: Progressive Disease
PD-L1: Programmed Cell Death Ligand 1
PFS: Progression-Free Survival
PRO: Patient-Reported Outcome
QoL: Quality of Life
SAE: Serious Adverse Event
SD: Standard Deviation
SE: Standard Error
SMC: Scottish Medicines Consortium
SOC: Standard of Care

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	LOQTORZI®
Generic name	Toripalimab
Therapeutic indication as defined by EMA	The EMA indication: • Loqtorzi, in combination with cisplatin and gemcitabine, (LCG) is indicated for the first-line treatment of adult patients with recurrent, not amenable to surgery or radiotherapy, or metastatic nasopharyngeal carcinoma. • Loqtorzi, in combination with cisplatin and paclitaxel, is indicated for the first-line treatment of adult patients with unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma.
Marketing authorization holder in Denmark	Topalliance Biosciences Europe Limited
ATC code	L01FF13
Combination therapy and/or co-medication	Loqtorzi should be administered in combination with cisplatin and gemcitabine.
(Expected) Date of EC approval	19 September 2024
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	No
Other indications that have been evaluated by the DMC (yes/no)	No
Joint Nordic assessment (JNHB)	Are the current treatment practices similar across the Nordic countries (DK, FI, IS, NO, SE)? No

	Sweden: There are no separate guidelines for NPC in Sweden. Treatment is primarily radiation therapy and/or induction chemotherapy (cisplatin-gemcitabine). Norway: Patients below 70 years of age should have concomitant chemotherapy weekly cisplatin 40 mg/m2, maximum 70 mg per time, or every three weeks 100 mg/m2 (all stages with potential exception of T1N0N0). Locally advanced disease can benefit from neoadjuvant chemotherapy with gemcitabine or cisplatin before chemotherapy.(1) Finland: Finland has national guidelines for NPC prepared by the Finnish Society for Head and Neck Oncology who's guideline recommends induction chemotherapy with gemcitabine–cisplatin in stage III–IV disease and in metastatic settings, particularly when systemic therapy is effective in low-volume disease (2). Is the product suitable for a joint Nordic assessment? No. In Denmark, Sweden, and Norway, specific assessment pathways exist for PD-(L)1 inhibitors, which do not require a full joint assessment.
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	240 mg toripalimab per vial, contained in 6 mL of solution. This corresponds to a concentration of 40 mg/mL.

2. Summary table

Summary	
Indication relevant for the assessment	Loqtorzi, in combination with cisplatin and gemcitabine (LCG), is indicated for the first-line treatment of adult patients with recurrent, not amenable to surgery or radiotherapy, or metastatic nasopharyngeal carcinoma (NPC). The second part of the EMA indication has been excluded from this application, as treatment with toripalimab is not intended for this patient population in Denmark at this time.
Dosage regiment and administration	Toripalimab 240 mg intravenously on Day 1 in combination with cisplatin 80 mg/m2 on Day 1 and gemcitabine 1 000 mg/m2 on Days 1 and 8 every 3 weeks for up to 6 cycles, followed by toripalimab 240 mg once every 3 weeks
Choice of comparator	Placebo intravenously on Day 1 in combination with cisplatin 80 mg/m2 on Day 1 and gemcitabine 1 000 mg/m2 on Days 1 and 8 every 3 weeks for up to 6 cycles, followed by placebo once every 3 weeks.
Prognosis with current treatment (comparator)	There is no specific study available on patients with *recurrent, not amenable to surgery or radiotherapy, or metastatic* NPC. But a Danish study of patients diagnosed with biopsy-proven NPC living in Denmark from 2000 to 2018 found that the 5-year overall (OS) and disease-specific survival (DSS) were 56 and 66%. Tumor EBV-status was determined in 221 patients, of whom 160 (72%) tested positive. (3)
Type of evidence for the clinical evaluation	Head-to-head study

Most important efficacy endpoints (Difference/gain compared to comparator)

Outcome measure	Loqtorzi + cisplatin + gemcitabine (n=146)	Placebo + cisplatin + gemcitabine (n=143)	Difference or HR (95% CI)	*P* value
Progression-free survival, median (95% CI), month	21.4 (11.7 to NE)[a]	8.2 (7.0 to 9.8) [a]	HR, 0.52 (0.37-0.73)[b]	<.001[c]

Summary				
Overall survival, median (95% CI), month	64.8 (38.8 to NE) [a]	33.7 (26.7 to 44.2)[a]	HR, 0.63 (0.45-0.89)[b]	.008 [c]
ORR (complete response + partial response), n/total (%), [95% CI]	115/146 (78.8) [71.2, 85.1][d]	96/143 (67.1) [58.8, 74.8][d]	Difference, 11.4 [1.7, 21.2][e]	.02[f]

Source of table: (4)
Data cut-off date: June 24, 2025, for overall survival (extended OS-data), and June 8, 2021, for PFS and ORR.
[a] The confidence interval for the median survival was computed using the Brookmeyer-Crowley method with log-log transformation.
[b] Computed from the Cox proportional hazards regression model, stratified by the baseline Eastern Cooperative Oncology Group performance status (0 vs 1) and the baseline disease stage (recurrent vs primary metastatic).
[c] Computed from the log-rank test, stratified by the baseline Eastern Cooperative Oncology Group performance status (0 vs 1) and the baseline disease stage (recurrent vs primary metastatic).
[d] Confidence interval was computed using the Clopper-Pearson method.
[e] Computed using the Mantel-Haenszel method, stratified by the baseline Eastern Cooperative Oncology Group performance status (0 vs 1) and baseline disease stage (recurrent vs primary metastatic)
[f] Computed from the Cochran-Mantel-Haenszel test, stratified by the baseline Eastern Cooperative Oncology Group performance status (0 vs 1) and baseline disease stage (recurrent vs primary metastatic)

Most important serious adverse events for the intervention and comparator

Adverse event	Toripalimab + gemcitabine-cisplatin (n=146)	Placebo + gemcitabine-cisplatin (n=143)
Any serious adverse event, n (%)	64 (43.8)	62 (43.4)
Blood and lymphatic		

Summary			
	system disorders Thrombocytopenia Anaemia Leukopenia Neutropenia	21 (14.4) 13 (8.9) 12 (8.2) 15 (10.3)	23 (16.1) 14 (9.8) 13 (9.1) 9 (6.3)
	Infections and infestations Pneumonia	14 (9.6)	5 (3.5)
Impact on health-related quality of life	Clinical documentation: N/A Not recorded in Jupiter-02 Health economic model: N/A		
Type of economic analysis that is submitted	N/A		
Data sources used to model the clinical effects	N/A		
Data sources used to model the health-related quality of life	N/A		
Life years gained	N/A		
QALYs gained	N/A		
Incremental costs	N/A		
ICER (DKK/QALY)	N/A		
Uncertainty associated with the ICER estimate	N/A		
Number of eligible patients in Denmark	Incidence: Approximately 15 new cases per year. Prevalence: N/A		
Budget impact (in year 5)	N/A		

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

Nasopharyngeal carcinoma (NPC) is an epithelial malignancy that develops in the tissue lining the upper part of the throat and behind the nose (i.e., the nasopharynx) and is distinct from other types of cancer that affect this region, such as esophageal cancer and head and neck cancers (including laryngeal).(5) NPC is differentiated from other subtypes of head and neck cancer with the highest metastatic potential, as demonstrated by many patients with the disease experiencing recurrence and/or metastasis.(6)

The disease typically progresses from the primary site in the nasopharynx to regional lymph nodes, with the retropharyngeal nodes being the most common site of initial metastasis. As the disease advances, it can spread to involve surrounding structures including the skull base, leading to cranial nerve palsies. In later stages, distant metastasis commonly affects the bones, lungs, and liver.(7)

3.1.1 Pathophysiology

The precise etiology of NPC is complex and not fully understood.(5) NPC has a distinct pathophysiology characterized by a complex interplay of viral infection, genetic alterations, and immune evasion mechanisms, all of which contribute to its development and progression.(5) There exist four histological subtypes of NPC, as classified by the WHO: keratinizing (type I), non-keratinizing differentiated (type II), non-keratinizing undifferentiated (type III) and basaloid squamous cell carcinoma.(8)

In non-endemic areas such as Denmark, keratinizing NPC is more common than in endemic areas, although the reported frequencies between keratinizing and non-keratinizg subtypes in non-endemic populations remain variable. (9-16) Keratinizing NPCs are typically associated with tobacco and alcohol exposure and poorer outcomes (9-13), while non-keratinizing, both differentiated and undifferentiated, types are often associated with Epstein-Barr Virus (EBV) (17). A Danish study finds that the majority of nasopharyngeal carcinoma (NPC) cases are undifferentiated carcinomas (74%), followed by differentiated non-keratinizing Squamous Cell Carcinoma (SCC) (9%), non-keratinizing SCC not otherwise specified (NOS) (4%), and keratinizing tumors (2%), with a small proportion of basaloid subtypes (0.5%) (3).

EBV infection represents the primary etiological factor in NPC pathogenesis, with an estimated 84.6% of all NPC cases worldwide being associated with EBV infection.(18) Non-endemic regions (such as Europe and the US) still report around 75% of cases of

NPC to be present with EBV infection.(19) EBV establishes latent infection in nasopharyngeal epithelial cells, expressing viral proteins that drive oncogenic transformation.(20) In addition, host genetic factors, particularly certain human leukocyte antigen (HLA)-A and HLA-B class I alleles, are pivotal, and a first-degree family history of NPC significantly increases risk.(21)

NPC can be characterized by multiple genomic aberrations that complement viral oncogenesis, including chromosomal abnormalities (deletions in 3p, 9p, 11q; amplifications in 1q, 3q, 8q), somatic mutations in tumor suppressor genes and epigenetic silencing of critical regulatory genes through DNA hypermethylation. These alterations are essential for NPC development and progression.(7)

NPC employs complementary immune evasion mechanisms, including recruitment of immunosuppressive cells, production of immunosuppressive cytokines, downregulation of antigen presentation machinery, and activation of additional immune checkpoints. A key player in the immune escape of NPC is PD-L1. Accordingly, PD-L1 expressed on NPC cells binds to the PD-1 receptor on T cells, creating an immunosuppressive environment that impairs immune surveillance by inhibiting T cell activation and cytotoxicity.(22) The interaction between PD-L1 on tumor cells and PD-1 on T cells leads to inhibition of T cell receptor signaling, suppression of T cell activation, proliferation, and cytokine production, development of T cell exhaustion characterized by progressive loss of effector functions, and impaired cytotoxic activity against tumor cells.(22)

It is known that EBV presence is strongly associated with a majority of NPC cases globally, and with EBV also inducing a high level of PD-L1 tumor expression (as well as EBV antigens aiding in immune escape), there exists a therapeutic opportunity to explore the role of anti-PD-1 antibodies to treat advanced NPC.(18, 23)

3.1.2 The clinical presentation/symptoms of the condition.

Patients can have variable presentations depending on the area of disease involvement. Broadly, the presentation of NPC can be categorized into four groups: nasal symptoms, otological symptoms, neurological symptoms, and nodal involvement:(24, 25)

Nasal symptoms: Around 80% of the individuals suffering from the disease present with nasal symptoms including nasal obstruction (usually on one side), epistaxis (nosebleeds), and post-nasal drip.(25, 26)

Otological symptoms: these symptoms are secondary to the tumor obstructing the Eustachian tube and can include conductive hearing loss, middle ear effusion or aural fullness. Half of patients with NPC have some form of otological complaint during the disease, as caused by obstruction of the Eustachian tube.(25)

Neurological symptoms: An estimated range of 10–20% of people with NPC may present with neurological symptoms due to cranial neuropathies.(25, 27) If persistent, these neuropathies could significantly impair vision (including double vision) and cause numbness in the bottom half of the face which may impact a person's ability to talk, breathe or swallow.(26-28)

Nodal involvement: one of the most common presenting features of NPC is an enlarged cervical lymph node. Lymph nodes of the apex of the posterior triangle and the upper jugular are commonly involved at the initial stages of disease, along with retropharyngeal nodes. Supraclavicular nodes are the last nodes to be affected and are a sign of advanced disease. (25)

Additional symptoms can include neck mass, tinnitus, headaches, double vision, numbness in the bottom part of the face, swallowing problems, and a hoarse voice.(26)

It is often difficult to recognize NPC because the symptoms are similar to other, less serious conditions. NPC can also remain asymptomatic in many patients until it reaches an advanced stage.(26, 29) Hence, NPC typically presents with nonspecific symptoms, which often leads to delayed diagnosis, with approximately 70% of patients presenting with locally advanced disease.(7)

Advanced (recurrent/metastatic) NPC):
In patients with advanced (recurrent/metastatic) NPC, the most common clinical manifestations are bloody nasal discharge and headache, reported in one study as present in 37.9% and 31.1% of patients, respectively (N=351).(7, 30) Ear symptoms and headaches are also more common in recurrent NPC compared with the primary form of the disease, and remains not uncommon for patients to experience dysfunction of cranial nerves, muscles or adjacent organs of the nasopharynx following their invasion by the tumor.(31) Patients with cervical lymph node metastasis at first diagnosis are more likely to have a recurrence with a neck mass.(32, 33)

3.1.3 Patient prognosis

In a Danish study of patients diagnosed with biopsy-proven NPC living in Denmark from 2000 to 2018, the 5-year overall (OS) and disease-specific survival (DSS) were 56 and 66%. Tumor EBV-status was determined in 221 patients, of whom 160 (72%) tested positive. (3)

3.1.4 The influence of the condition on the patients' functioning and health-related quality of life.

Limited information is available on the impact of NPC itself on a patient's HRQoL, as many studies focus on the side effects and burden of the current standard of care rather than the burden of the disease itself.

People with recurrent or metastatic NPC experience significant quality of life impairments due to both disease progression and treatment-related toxicities.(7) NPC and its treatment are associated with a range of symptoms and create a profound humanistic burden extending beyond the patient to their caregivers. Physical impacts include persistent olfactory dysfunction and swallowing difficulties, while emotional and social wellbeing are compromised through psychological distress and disrupted relationships.(34-37) The multifaceted symptom burden, dominated by pain, speech problems, and dysphagia, significantly impairs daily functioning, with extensive requirements for pain management and substantial activity limitations. This burden

cascades to caregivers, who experience anxiety, depression, and sleep disturbances directly linked to patients' symptom intensity and increasing care requirements.(38-40)

3.2 Patient population

The present application targets patients with recurrent, not amenable to surgery or radiotherapy, or metastatic nasopharyngeal carcinoma.

There are no specific Danish studies of patients with recurrent, not amenable to surgery or radiotherapy, or metastatic nasopharyngeal carcinoma. However, a recent Danish study identified NPC in 394 patients corresponding to age-standardized incidence rates of 0.5 and 0.2 per 100,000 in men and women, respectively. The male-to-female ratio was 2.6:1 and the median age at diagnosis was comparable in men and women (56 years). The majority of patients were diagnosed with undifferentiated carcinoma (292, 74%), followed by differentiated non-keratinizing SCC (34, 9%), non-keratinizing SCC NOS (16, 4%), keratinizing SCC (9, 2%), and basaloid SCC (2, 0.5%). In 41 (10%) patients the histology was unknown. The majority of patients were diagnosed in locally advanced stages (stage III–IVa, 63%), and lymph node involvement was observed in 73%. Primary metastatic disease was found in 29 (7%) patients.(3)

In a Nordic population-based cohort of 344 NPC patients (diagnosed 2005–2009), recurrence was common: 18.9% developed distant recurrence, 16% local recurrence and 9.9% neck recurrence. At the end of follow-up, only 50% had no evidence of disease. These findings support that a substantial proportion of NPC patients will require management in a recurrent/metastatic setting. (41)

As NPC occurs endemically in certain regions of the world, including southern China and Southeast Asia, North Africa and the Inuit, Greenlanders contribute a significant number of cases annually in Denmark. (42).

The latest DAHANCA data on incident cases in Denmark are shown in Table 1, corresponding to an average of approximately 29 new cases per year. (43) No source of prevalence in Denmark have been identified.

Table 1 Incidence and prevalence of NPC in the past 5 years (43)

Year	2020	2021	2022	2023	2024
Incidence in Denmark	22	35	29	25	33
Prevalence in Denmark	N/A	N/A	N/A	N/A	N/A
Global prevalence (per 100 000) (44)		6.14			

Based on clinical expert judgement informed by recurrence patterns in Nordic data, approximately 50% of incident NPC cases are expected to be treated in the recurrent/metastatic setting. This corresponds to approximately 14–15 patients per year (29 × 0.50 ≈ 14.5). The estimated eligible population is presented in Table 2.

Table 2 Estimated number of patients eligible for treatment (source: clinical expert judgement)

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of incident patients in Denmark who are eligible for treatment in the coming years	~15	~15	~15	~15	~15

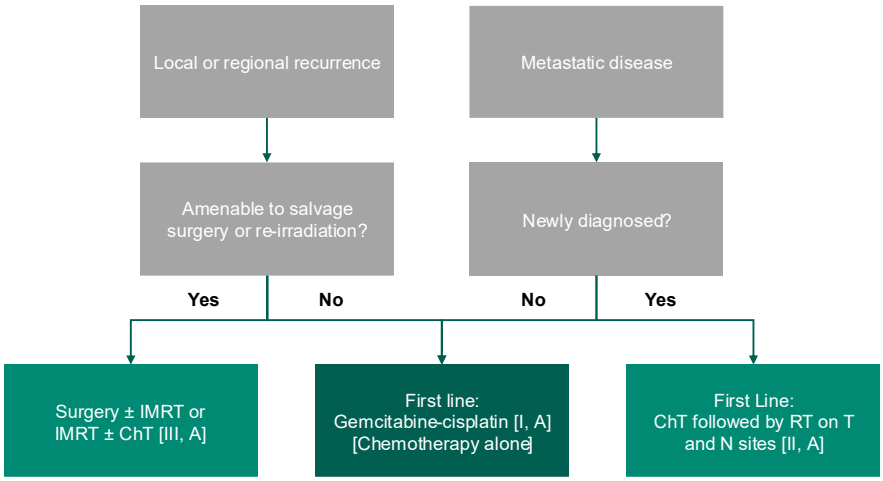
3.3 Current treatment options

The current Danish national guideline for pharyngeal and laryngeal cancer (2014 revision) does not provide specific recommendations for the management of recurrent, not amenable to surgery or radiotherapy or metastatic NPC. Consequently, clinical practice in Denmark has relied on international guidelines (e.g. ESMO, NCCN) and evidence from pivotal studies, where platinum-based chemotherapy has been considered standard first-line treatment in this setting. (5)

Potential treatment options for patients with recurrent or metastatic NPC include surgical resection and re-irradiation with or without chemotherapy.(31) For adult patients with recurrent or metastatic NPC who are unable to undergo surgical resection or re-irradiation, treatment options have been historically limited to chemotherapy alone.

The current treatment algorithm is illustrated in the diagram below.

Figure 1 Current treatment algorithm for recurrent and/or metastatic NPC



Following publication of the KEYNOTE-048 trial in 2020, pembrolizumab—either as monotherapy or in combination with platinum and 5-fluorouracil for patients with PD-L1 expression ≥1—has also been used in Danish clinical practice for patients with nasopharyngeal carcinoma, despite NPC patients not being included in the pivotal trial.

Few patients receive platinum-based chemotherapy in combination with 5-fluorouracil and cetuximab (the EXTREME regimen)

3.3.1 Prognosis with current treatment

As mentioned in section 3.1.2 a Danish study found the 5-year overall (OS) and disease-specific survival (DSS) to be 56 and 66%. Tumor EBV-status was determined in 221 patients, of whom 160 (72%) tested positive. (3) In the study, patients receiving radical radiotherapy were treated according to the principles of DAHANCA, i.e. by treating the gross tumor volume (GTV) and high-dose clinical target volume 1 (CTV1) to 66–68 Gy in 33–34 fractions of 2 Gy. Five fractions per week were used through 2002, and since 2003, a moderately accelerated schedule with six fractions/ week. Patients in good performance status were offered concurrent chemotherapy with weekly cisplatin 40 mg/m2 during the whole inclusion period, but only routinely from 2006 and onwards. (3)

3.4 The intervention

An overview of the information regarding Loqtorzi can be found in the table below.

Overview of intervention	
Indication relevant for the assessment	Loqtorzi, in combination with cisplatin and gemcitabine (LCG), is indicated for the first-line treatment of adult patients with recurrent, not amenable to surgery or radiotherapy, or metastatic nasopharyngeal carcinoma. The second part of the EMA indication has been excluded from this application, as treatment with toripalimab is not intended for this patient population in Denmark at this time.
ATMP	N/A
Method of administration	Intravenously
Dosing	Toripalimab 240 mg on Day 1 in combination with cisplatin 80 mg/m2 on Day 1 and gemcitabine 1 000 mg/m2 on Days 1 and 8 every 3 weeks for up to 6 cycles, followed by toripalimab 240 mg once every 3 weeks (5)
Dosing in the health economic model (including relative dose intensity)	N/A

Overview of intervention	
Should the medicine be administered with other medicines?	Yes, in combination with chemotherapy (cisplatin and gemcitabine)
Treatment duration / criteria for end of treatment	Treatment with toripalimab combined with chemotherapy is to be received until progressive disease, unacceptable toxicity, noncompliance, withdrawal of consent, or a maximum of six cycles of chemotherapy, whichever occurs first during the 'chemotherapy' phase. During the 'post-chemotherapy' phase, patients should continue receiving their allocated treatment until unacceptable toxicity, progressive disease, withdrawal of consent, investigator's judgment or a maximum of 2 years' of treatment (including chemotherapy and post-chemotherapy phase). The median treatment duration was 65.70 weeks in the toripalimab group and 37.30 weeks in the placebo group. The median exposure to cisplatin in the toripalimab group and placebo group was 18.30 weeks and 18.40 weeks respectively, and for gemcitabine, was 19.30 and 19.60 weeks, in the toripalimab and placebo groups, respectively. (4) (45)
Necessary monitoring, both during administration and during the treatment period	Early identification and management of immune-related adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Patients should be monitored closely for symptoms and signs of immune-related adverse reactions. Clinical chemistries including liver enzymes, creatinine, and thyroid function should be evaluated at baseline and periodically during treatment. In cases of suspected immune-related adverse reactions, appropriate workup should be initiated to exclude alternative aetiologies, including infection. Medical management should be instituted promptly, including specialty consultation as appropriate.(46)
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	There are no additional diagnostic tests or methods required for patient selection that are not already part of standard clinical practice in Denmark.
Package size(s)	240 mg toripalimab per vial, contained in 6 mL of solution. This corresponds to a concentration of 40 mg/mL.

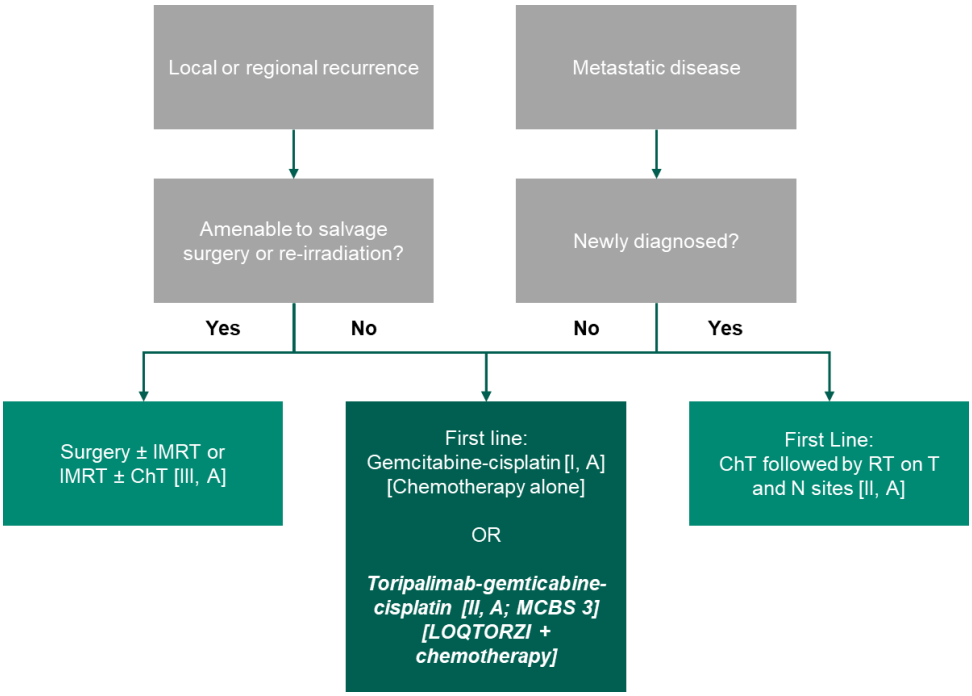
3.4.1 Description of ATMP

N/A

3.4.2 The intervention in relation to Danish clinical practice

As mentioned in section 3.3 the potential treatment options in Denmark for patients with recurrent or metastatic NPC include surgical resection and re-irradiation with or without chemotherapy.(31) However, some patients are not amenable to surgery or radiotherapy, for these and metastatic nasopharyngeal carcinoma (NPC), platinum-based chemotherapy has been considered standard first-line treatment in this setting. I.e. in the Danish clinical setting, the treatment options has been historically limited to chemotherapy alone.(5, 31) Hence, the LOQTORZI intervention will not replace existing medicines in this Danish clinical practice but will be an additional treatment option in the treatment algorithm, as it is to be offered as a supplement to chemotherapy for patients with recurrent or metastatic NPC not amenable to surgery or radiotherapy. See figure below.

Figure 2 **Treatment algorithm for recurrent and/or metastatic NPC**



3.5 Choice of comparator(s)

In the JUPITER-02 trial, the toripalimab intervention is compared against placebo in combination with gemcitabine and cisplatin, with both treatment arms administered as first-line treatment in patients with histologically or cytologically confirmed disease. Dosage in the study was as follows:

Placebo intravenously on Day 1 in combination with cisplatin 80 mg/m2 on Day 1 and gemcitabine 1 000 mg/m2 on Days 1 and 8 every 3 weeks for up to 6 cycles, followed by placebo once every 3 weeks. (4)

This regimen is considered the relevant comparator in Danish clinical practice. Although some patients may receive pembrolizumab, its use is off-label in this indication and is therefore not considered an appropriate comparator.

Overview of comparator	
Generic name	Cisplatin, gemcitabin
ATC code	L01XA01, L01BC05
Mechanism of action	Cisplatin: Cisplatin acts via non-cell cycle-specific cytotoxicity, which is achieved through the covalent binding of platinum to the purine bases guanine and adenine. This covalent binding leads to intra-strand and inter-strand crosslinks causing subsequent strand breaks. While DNA repair mechanisms are at play, cells often undergo apoptotic or non-apoptotic cell death due to remnant damaged DNA, RNA, and proteins (47). Gemcitabin: Gemcitabine (2'-deoxy-2',2'-difluorocytidine monohydrochloride isomer) is a novel analog of deoxycytidine that inhibits DNA synthesis. Gemcitabine triphosphate, the active metabolite after cellular uptake, competitively inhibits DNA chain elongation, leading to DNA fragmentation and cell death.(48)
Method of administration	Cisplatin: Cisplatin can be administered as an injectable agent both intravenously and as an intra-arterial agent (49). Gemcitabin: Gemcitabin is administered intravenously.
Dosing	Cisplatin: 80 mg/m2 on Day 1 Gemcitabine 1 000 mg/m2 on Days 1 and 8 every 3 weeks for up to 6 cycles Followed by placebo once every 3 weeks.
Dosing in the health economic model (including relative dose intensity)	N/A
Should the medicine be administered with other medicines?	**Cisplatin:** Yes – Gemcitabine **Gemcitabine:** Yes - should be administered together with Cisplatin. **Placebo:** Yes, with Cisplatin and Gemcitabine.
Treatment duration/ criteria for end of treatment	Until progressive disease, unacceptable toxicity, noncompliance, withdrawal of consent, or a maximum of six cycles of chemotherapy, whichever occurred first during the 'chemotherapy' phase.

Overview of comparator	
Need for diagnostics or other tests (i.e. companion diagnostics)	None
Package size(s)	240 mg concentrate for solution for infusion

3.6 Cost-effectiveness of the comparator(s)

The comparator regimen, placebo in combination with gemcitabine and cisplatin, has not been specifically evaluated or recommended by the Danish Medicines Council (DMC) for NPC. However, it can reasonably be assumed to be cost-effective, as this regimen has constituted standard clinical practice for many years and both gemcitabine and cisplatin are off-patent, low-cost medicines.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

In this section, we define the efficacy outcomes considered relevant and necessary to evaluate the effect of LOQTORZI vs. comparators and describe the rationale for the chosen efficacy outcomes.

Table 3 Efficacy outcome measures relevant for the application (4, 50, 51)

Outcome measure	Time point* Source: (4) (50, 51)	Definition	How was the measure investigated/method of data collection
Progression Free Survival (PFS)	Data cut-off: June 8, 2021, with a median follow-up time of 21.82 months	PFS is defined as the time from randomization to the occurrence of disease progression, as determined by IRC per RECIST v1.1 or death from any cause, whichever occurred first.	Blinded independent central review per RECIST (Response Evaluation Criteria in Solid Tumors) version 1.1 and irRECIST. PFS was performed on all randomized patients (i.e., ITT) irrespective of whether the assigned treatment was actually received.
Overall survival (OS)	Data cut-off: Pre defined: November 18, 2022, with a median survival	OS is defined as the time from randomization to	Data from participants who were alive at the time of the OS

Outcome measure	Time point* Source: (4) (50, 51)	Definition	How was the measure investigated/method of data collection
	follow-up of 36.0 months. Post hoc: June 24, 2025 (68 months after last enrollment)	death from any cause.	analysis were censored as of the last date they were known to be alive. OS was performed on all randomized patients (i.e., ITT) irrespective of whether the assigned treatment was actually received. Analyses were performed for OS rates at 1 year and 2 years after randomization. Kaplan-Meier curve was used to estimate median OS along with 95% CI in each arm.
Objective Response Rate (ORR)	Data cut-off: June 8, 2021, with a median follow-up time of 21.82 months	Defined as the proportion of participants who had an objective response. An objective response was defined as either a complete response (CR) or a partial response (PR), durable for at least 4 weeks per RECIST v1.1. Participants not meeting these criteria, including participants without any post baseline tumor assessments, were considered non-responders.	Blinded independent central review per RECIST (Response Evaluation Criteria in Solid Tumors) version 1.1 and irRECIST - tested hierarchically under a 2-sided α level of .05. ORR analyses were performed on all randomized patients who have measurable disease at baseline. ORR was determined along with 95% CI.
Disease control rate (DCR)	Data cut-off: June 8, 2021, with a median	Defined as the proportion of subjects with	Blinded independent central review per RECIST (Response

Outcome measure	Time point* Source: (4) (50, 51)	Definition	How was the measure investigated/method of data collection
	follow-up time of 21.82 months	confirmed CR or PR as their best response or confirmed stable disease (maintained for at least 6 weeks) per RECIST v1.1.	Evaluation Criteria in Solid Tumors) version 1.1 and irRECIST. DCR analyses were performed on all randomized patients who have measurable disease at baseline. DCR was determined along with 95% CI. Kaplan-Meier curve was used to estimate median DoR along with 95% CI in each arm.
Duration of response (DoR)	Data cut-off: June 8, 2021, with a median follow-up time of 21.82 months	Defined as the date from the first occurrence of a CR or PR (whichever status was recorded first) until the first date that progressive disease or death was documented, whichever occurred first. DoR was assessed only in participants who had a confirmed CR or PR per RECIST v1.1. Participants who had not progressed or died at the time of final analysis of PFS were censored at the time of last tumor assessment date. If no tumor assessments were performed after the date of the first occurrence of a CR or PR, DoR was censored on the	Blinded independent central review per RECIST (Response Evaluation Criteria in Solid Tumors) version 1.1 and irRECIST. DOR analyses were performed on the subset of patients who achieve an objective response.

Outcome measure	Time point* Source: (4) (50, 51)	Definition	How was the measure investigated/method of data collection
		date of the first occurrence of a CR or PR plus 1 day.	

* Time point for data collection used in analysis (follow up time for time-to-event measures)
Source: (45)

Validity of outcomes
Progression Free Survival (PFS)

PFS is a well-established endpoint for survival in cancer and NPC studies, frequently utilized by the Danish Medicines Council (DMC) in health economic models(52-55). PFS is widely recognized as a reliable primary endpoint and serves as a surrogate for overall survival (OS) in NPC studies (56) (57) (58, 59). Several randomized trials and meta-analyses in NPC have used PFS as a primary endpoint, supporting its role as a valid surrogate outcome (4, 60).

Overall survival (OS)

OS is considered the gold-standard endpoint for oncology trials and serves as the most compelling endpoint to demonstrate the benefits of novel therapeutics. Regulatory approval and patient reimbursement globally depend on OS results combined with patient-reported outcomes. These tendencies also apply to NPC studies, and several studies have investigated OS among NPC patients(60, 61). Additionally, DMC recommendations have included OS as a relevant endpoint(54).

ORR

ORR is a well-recognized marker of antitumor activity (62, 63). ORR is relevant in the recurrent/metastatic NPC setting, where rapid tumor shrinkage can relieve symptoms and improve quality of life (64-66).

DCR

DCR extends the assessment of therapeutic effect beyond tumor shrinkage alone. This endpoint is useful in NPC, where stabilizing disease may confer meaningful clinical benefit by delaying progression and preserving function. DCR has been consistently reported in immunotherapy and chemotherapy trials in NPC, reflecting its acceptance as a complementary measure to ORR (67-69).

DoR

DoR provides insight into the durability of tumor response once achieved, offering important context beyond initial response rates. In NPC, durable responses are relevant for immunotherapy, where long-lasting benefit has been observed despite modest ORR. DoR is therefore a valuable secondary endpoint in NPC trials, enabling assessment of sustained clinical benefit and informing long-term treatment value (70) (4, 71).

4. Health economic analysis N/A

N/A

4.1 Model structure

N/A

4.2 Model features

N/A

Table 4 Features of the economic model N/A

Model features	Description	Justification
Patient population		
Perspective		
Time horizon		
Cycle length		
Half-cycle correction		
Discount rate		
Intervention		
Comparator(s)		
Outcomes		

5. Overview of literature

5.1 Literature used for the clinical assessment

This section will present the literature used for clinical assessment.

The literature consists of a head-to-head international, multicenter, randomized, double-blind phase 3 study (4).

A systematic literature review (SLR) was conducted for the clinical assessment of Loqtorzi. The search was completed on the 3rd July 2025 for the original review, and 8th December 2025 for the update review. The SLR was adapted locally to only include toripalimab (Loqtorzi) in combination with cisplatin and gemcitabine as intervention.

The review led to 1 relevant study and 7 publications related to this study for the use of Loqtorzi in Denmark. The relevant literature included in the assessment of efficacy and safety can be seen in table Table 5.

Table 5 Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Chen, QY, Mai HQ, Chen DP, Hu CS, Yang K, Wen J et al. Four-year overall survival follow-up and dynamic EBV titer analysis of toripalimab versus placebo in combination with gemcitabine and cisplatin as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma (r/m NPC). Journal of Clinical Oncology. 2024;42(16) DOI:10.1200/JCO.2024.42.16_suppl.6039 (72)	JUPITER-02	NCT03581786	Start: 18. October 2018 (first written consent obtained) Completion: 18. November 2022 (last visit of the last patient) Data cut-off: OS : 09/01/24	Toripalimab plus gemcitabine-cisplatin vs. gemcitabine-cisplatin for recurrent or metastatic Nasopharyngeal Carcinoma
Mai HQ, Chen QY, Chen D, et al. Toripalimab Plus Chemotherapy for Recurrent or Metastatic Nasopharyngeal Carcinoma: The JUPITER-02 Randomized Clinical Trial. *Jama.* 2023;330(20):1961–1970. doi: 10.1001/jama.2023.20181 (4)			Start: 18. October 2018 (first written consent obtained) Completion: 18. November 2022 (last visit of the last patient) Data cut-off: PFS, DCR, ORR, DoR: 08/06/21 OS : 18/10/22 Safety data : 08/05/22	
Mai HQ, Chen QY, Chen D, et al. Toripalimab or placebo plus chemotherapy as first-line treatment in advanced nasopharyngeal carcinoma: a multicenter randomized phase 3 trial. *Nat Med.* 2021;27(9):1536–1543. doi: 10.1038/s41591-021-01444-0 (73)			Start: 18. October 2018 (first written consent obtained) Completion: 18. November 2022 (last visit of the last patient) Data cut-off: PFS : 30/05/2020 OS : 18/02/2021	

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Mai HQ, Chen QY, Chen D, Hu C, Yang K, Wen J et al. Final progression-free survival analysis of JUPITER-02, a randomized, double-blind, phase 3 study of toripalimab or placebo plus gemcitabine and cisplatin as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma. Cancer Research. 2022;82(12S): CT226. DOI:10.1158/1538-7445.AM2022-CT226 (74)			Start: 18. October 2018 (first written consent obtained) Completion: 18. November 2022 (last visit of the last patient) Data cut-off: PFS : 08/06/2021	
Mai HQ, Chen QY, Chen DP, Hu C, Yang K, Wen J et al. Final overall survival analysis of JUPITER-02: A phase 3 study of toripalimab versus placebo in combination with gemcitabine and cisplatin as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma (NPC). Journal of Clinical Oncology. 2023;41(16):6009 DOI: 10.1200/JCO.2023.41.16_suppl.6009 (75)			Start: 18. October 2018 (first written consent obtained) Completion: 18. November 2022 (last visit of the last patient) Data cut-off: OS : 18/11/2022	
Xu R, Mai H-Q, Chen Q-Y, Chen D, Hu C, Yang K, Wen J, Li J-G, Shi Y, Jin F, et al. JUPITER-02: Randomized, double-blind, phase III study of toripalimab or placebo plus gemcitabine and cisplatin as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma (NPC). Journal of Clinical Oncology. 202;39(18S):LBA2. DOI: 10.1200/JCO.2021.39.15_suppl.LBA2 (76)			Start: 18. October 2018 (first written consent obtained) Completion: 18. November 2022 (last visit of the last patient) Data cut-off: PFS, DCR, ORR, DoR: : 30/05/2020 (interim data cut-off) OS : 15/01/2021 (interim data cutoff)	

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Chen QY. Long term overall survival follow-up of toripalimab versus placebo in combination with gemcitabine and cisplatin as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma. ESMO Asia Conference 2025. Available from: https://oncologypro.esmo.org/congress-resources/esmo-asia-congress-2025?presentation=long_term_overall_survival_follow_up_of_toripalima (51)			Start: 18. October 2018 (first written consent obtained) Completion: 18. November 2022 (last visit of the last patient) Data cut-off: OS : 24/06/2025	

* If there are several publications connected to a trial, include all publications used.

5.2 Literature used for the assessment of health-related quality of life

N/A

Table 6 Relevant literature included for (documentation of) health-related quality of life N/A

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
N/A	N/A	N/A

5.3 Literature used for inputs for the health economic model

Table 7 Relevant literature used for input to the health economic model N/A

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
N/A	N/A	N/A	N/A

6. Efficacy

This section presents the evidence for the efficacy of Loqtorzi, in combination with cisplatin and gemcitabine (LCG) for adult patients with recurrent, not amenable to surgery or radiotherapy, or metastatic nasopharyngeal carcinoma, compared to cisplatin and gemcitabine alone (CG).

6.1 Efficacy of LCG compared to CG for adult patients with recurrent, not amenable to surgery or radiotherapy, or metastatic NPC

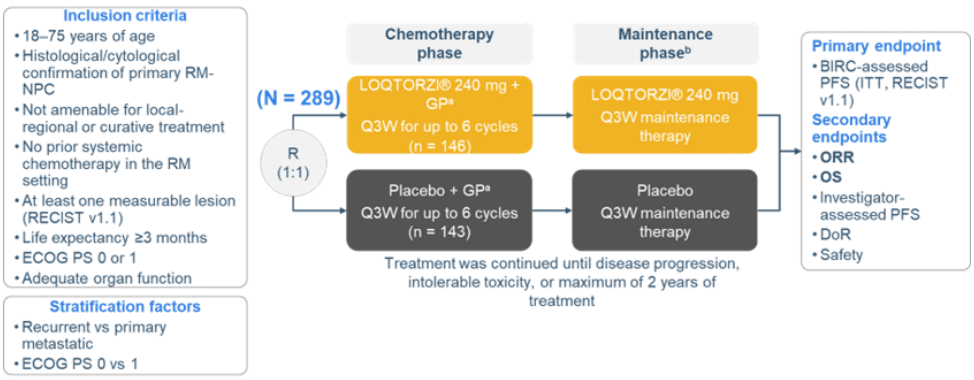
6.1.1 Relevant studies

The clinical evidence consists of the JUPITER-02 trial (NCT03581786): A randomized, placebo-controlled, multi-center, double-blind, phase III trial designed to investigate the efficacy and safety of toripalimab (in combination with gemcitabine and cisplatin) in patients with recurrent or metastatic NPC.

Efficacy and safety endpoints are presented according to the following data cut-offs:

- Progression-free survival and response outcomes are based on the data cut-off of 8 June 2021;
- Safety outcomes are based on the data cut-off of 8 May 2022;
- Overall survival is presented using the most recent extended follow-up (data cut-off 24 June 2025) when possible. Results from the prespecified final overall survival analysis (data cut-off 18 November 2022) are presented separately as confirmatory analyses.

Figure 3 Trial design schematic for the JUPITER-02 trial (4)



Abbreviations: BSC, best supportive care; d, day; ECOG, Eastern Cooperative Oncology Group; m, meter; mg, milligram; PD, progressive disease; QW3, once every 3 weeks.

Table 8 Overview of study design for studies included in the comparison (4, 51)

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
The Jupiter-02 trial "The Efficacy and Safety Study of TORIPALIMAB INJECTION Combined With Chemotherapy for Nasophapyngeal Cancer", NCT03581786. Mai HQ, Chen QY, Chen D, Hu C, Yang K, Wen J, Li J, Shi Y, Jin F, Xu R, Pan J, Qu S, Li P, Hu C, Liu YC, Jiang Y, He X, Wang HM, Lim WT, Liao W, He X, Chen X, Wang S, Yuan X, Li Q, Lin X, Jing S, Chen Y, Lu Y, Hsieh CY, Yang MH, Yen CJ, Samol J, Luo X, Wang X, Tang X, Feng H, Yao S, Keegan P, Xu RH. Toripalimab Plus Chemotherapy for Recurrent or Metastatic Nasopharyngeal Carcinoma: The JUPITER-02 Randomized Clinical	A randomized, placebo-controlled, multi-center, double blinded, Phase III study to determine the efficacy and safety of TORIPALIMAB INJECTIO (JS001) in combination with gemcitabine/cisplatin compared with placebo in combination with gemcitabine/cisplatin as first-line treatment in patients with histological/cytological confirmation of recurrent or metastatic NPC	Study Initiation Date: October 18, 2018 (first written consent obtained) Study Completion Date: November 18, 2022 (last visit of the last patient) Surviving patients who provided additional consent for the long-term trial	Patients eligible for the JUPITER-02 trial were between the ages of 18 and 75 years and were required to have histologically or cytologically confirmed primary recurrent or metastatic NPC, which was not amenable for local-regional or curative treatment and must have received no prior systemic chemotherapy in the recurrent or metastatic setting. Key inclusion criteria for the JUPITER-02 trial included: 1. Age ≥18 years and ≤75 years 2. Histological/cytological confirmation of NPC 3. Primarily metastatic (stage IVB as defined by the International Union against Cancer and American Joint Committee on Cancer staging system for	Toripalimab 240 mg intravenously on Day 1 in combination with cisplatin 80 mg/m2 on Day 1 and gemcitabine 1 000 mg/m2 on Days 1 and 8 every 3 weeks for up to 6 cycles, followed by toripalimab 240 mg once every 3 weeks.	Placebo in combination with gemcitabine and cisplatin. Dosage as follows: Placebo intravenously on Day 1 in combination with cisplatin 80 mg/m2 on Day 1 and gemcitabine 1 000 mg/m2 on Days 1 and 8 every 3 weeks for up to 6 cycles, followed by placebo once every 3 weeks.	Primary endpoints: • PFS, defined as the time from randomization to the occurrence of disease progression, as determined by IRC per RECIST v1.1 or death from any cause, whichever occurred first. Predefined data cut-off: June 8, 2021, with a median follow-up time of 21.82 months Secondary endpoints: • OS defined as the time from randomization to death from any cause. Data from participants who were alive at the time of the OS analysis were censored as of the last date they were known to be alive. Data cut-off: Pre defined: November 18, 2022, with a median survival follow-up of 36.0 months. Post hoc: June 24, 2025 (68 months after last enrollment)

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
Trial. JAMA. 2023 Nov 28;330(20):1961-1970. doi: 10.1001/jama.2023.20181. PMID: 38015220; PMCID: PMC10685882. Chen QY. Abstract 669M0: Long term overall survival follow-up of toripalimab versus placebo in combination with gemcitabine and cisplatin as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma. ESMO Asia Congress 2025.		were monitored for long-term survival follow-up until a cut-off date of June 24, 2025. (51)	NPC, eighth edition) or recurrent NPC that is not amenable for local-regional treatment or curative treatment 4. At least one measurable lesion according to RECIST version 1.1 5. Life expectancy ≥3 months Key exclusion criteria for the JUPITER-02 trial included: 1. History of severe hypersensitivity reactions to other monoclonal antibodies (mAbs) or any ingredient of JS001 2. Prior therapy targeting PD-1 receptor, or its ligand PD-L1, or cytotoxic T lymphocyte associated protein 4 (CTLA4) receptor			• ORR defined as the proportion of participants who had an objective response. An objective response was defined as either a complete response (CR) or a partial response (PR), durable for at least 4 weeks per RECIST v1.1. Participants not meeting these criteria, including participants without any post baseline tumor assessments, were considered non-responders. Predefined Data cut-off: June 8, 2021, with a median follow-up time of 21.82 months • Disease control rate (DCR), defined as the proportion of subjects with confirmed CR or PR as their best response or confirmed stable disease (maintained for at least 6 weeks) per RECIST v1.1. Predefined data cut-off: June 8, 2021, with a median follow-up time of 21.82 months • Duration of response (DoR), defined as the date from the first occurrence of a CR or PR

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
			3. Major surgical procedure other than for diagnosis of NPC within 28 days prior to randomization or anticipation of need for a major surgical procedure during the trial 4. History of hypersensitivity to gemcitabine or cisplatin or to any of the excipients 5. Female patients who were pregnant or refused to discontinue nursing			(whichever status was recorded first) until the first date that progressive disease or death was documented, whichever occurred first. DoR was assessed only in participants who had a confirmed CR or PR per RECIST v1.1. Participants who had not progressed or died at the time of final analysis of PFS were censored at the time of last tumor assessment date. If no tumor assessments were performed after the date of the first occurrence of a CR or PR, DoR was censored on the date of the first occurrence of a CR or PR plus 1 day. Predefined Data cut-off: June 8, 2021, with a median follow-up time of 21.82 months • Investigator-assessed PFS per RECIST v1.1 Predefined Data cut-off: June 8, 2021, with a median follow-up time of 21.82 months • Survival rates of PFS and OS. The 1- and 2-year OS rates and the investigator- and IRC-assessed 1- and 2-year PFS rates

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
						Predefined Data cut-off: June 8, 2021, with a median follow-up time of 21.82 months • PFS, ORR, DCR and DoR per irRECIST determined by the investigator and by the IRC. Predefined Data cut-off: June 8, 2021, with a median follow-up time of 21.82 months • Patient-Reported Outcome (PRO) using EORTC QLQ-C30, EORTC QLQ-H&N35 and ECOG performance status assessments Predefined Data cut-off: June 8, 2021, with a median follow-up time of 21.82 months • ADA formation Predefined Data cut-off: June 8, 2021, with a median follow-up time of 21.82 months

6.1.1.1 Subsequent treatment

A total of 188 (65.1%) patients received at least one subsequent anti-cancer therapy after study treatment (56.2% in the toripalimab plus chemotherapy arm and 74.1% in the placebo plus chemotherapy arm) (Table 9). The higher proportion observed in the placebo arm may be related to earlier discontinuation of study treatment in this group.

The most common subsequent systemic therapies were cytotoxic therapy (154 patients, 53.3%), PD-1/L1 inhibitors (97 patients, 33.6%), and protein kinase inhibitors (66 patients, 22.8%). Radiotherapy was administered to 41 patients (14.2%).

Among PD-1/L1 inhibitors, the most frequently used agents were camrelizumab (45 patients, 15.6%), toripalimab (31 patients, 10.7%), and sintilimab (17 patients, 5.9%). EGFR-targeting antibodies were administered to 26 patients (9.0%).

Table 9 Post anti-cancer therapies received (Intent-to-Treat population) on ATC-4-level

N (%)	Toripalimab + Chemotherapy N=146	Placebo + Chemotherapy N=143	Total Population N=289
New anti-cancer therapy	**82 (56.2)**	**106 (74.1)**	**188 (65.1)**
Systemic treatment	77 (52.7)	105 (73.4)	182 (63.0)
Radiotherapy	18 (12.3)	23 (16.1)	41 (14.2)
Systemic treatment	**77 (52.7)**	**105 (73.4)**	**182 (63.0)**
Cytotoxic Therapy	*55 (37.7)*	*99 (69.2)*	*154 (53.3)*
PD-1/L1 Inhibitors	*48 (32.9)*	*49 (34.3)*	*97 (33.6)*
CAMRELIZUMAB	21 (14.4)	24 (16.8)	45 (15.6)
TORIPALIMAB	14 (9.6)	17 (11.9)	31 (10.7)
SINTILIMAB	8 (5.5)	9 (6.3)	17 (5.9)
TISELIZUMAB	7 (4.8)	4 (2.8)	11 (3.8)
QL1706	3 (2.1)	3 (2.1)	6 (2.1)
SHR1701	3 (2.1)	1 (0.7)	4 (1.4)
PEMBROLIZUMAB	0	3 (2.1)	3 (1.0)
PENPULIMAB	0	2 (1.4)	2 (0.7)
NIVOLUMAB	1 (0.7)	1 (0.7)	2 (0.7)
DURVALUMAB	0	1 (0.7)	1 (0.3)
AVELUMAB	0	1 (0.7)	1 (0.3)
Protein Kinase Inhibitor	*28 (19.2)*	*38 (26.6)*	*66 (22.8)*
EGFR antibody	7 (4.8)	19 (13.3)	26 (9.0)

NIMOTUZUMAB	4 (2.7)	17 (11.9)	21 (7.3)
CETUXIMAB	2 (1.4)	1 (0.7)	3 (1.0)
MRG003	1 (0.7)	1 (0.7)	2 (0.7)
Other immunomodulators	*2 (1.4)*	*8 (5.6)*	*10 (3.5)*
Anti-angiogenic Agent (non-TKI)	*3 (2.1)*	*2 (1.4)*	*5 (1.7)*
Others	*9 (6.2)*	*4 (2.8)*	*13 (4.5)*
Unknown	*1 (0.7)*	*1 (0.7)*	*2 (0.7)*

Data cut-off: Nov 18, 2022.

6.1.2 Comparability of studies

N/A for head-to-head studies according to DMC guidelines.

6.1.2.1 Comparability of patients across studies

The efficacy of LCG compared to CG alone is based solely on JUPITER-02. Baseline patient characteristics from JUPITER-02 are shown in the table below.

Table 10 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety (4)

	Jupiter-02 (4) **No. (%)**	
	Loqtorzi + cisplatin + gemcitabine (n=146)	Placebo + cisplatin + gemcitabine (n=143)
Age, median (IQR), y	46 (38-53)	51 (43-57)
≤ 50	97 (66)	69 (48)
> 50	49 (34)	74 (52)
Sex		
Male	124 (85)	116 (81)
Female	22 (15)	27 (19)
Asian	146 (100)	143 (100)
Disease status		
Recurrent	85 (58)	87 (61)
Locally advanced, No./total (%)	19/85 (22)	20/87 (23)
With distal metastasis, No./total (%)	66/85 (78)	67/87 (77)
Primary metastatic[a]	61 (42)	56 (39)
ECOG PS score[b]		

	Jupiter-02 (4) No. (%)	
	Loqtorzi + cisplatin + gemcitabine (n=146)	Placebo + cisplatin + gemcitabine (n=143)
0	83 (57)	81 (57)
1	63 (43)	62 (43)
Histology		
Nonkeratinizing squamous cell carcinoma	145 (99)	140 (98)
Keratinizing squamous cell carcinoma	1 (1)	2 (1)
Other	0	1 (1)
Metastatic sites at baseline (ITT population)		
Liver	61 (42)	57 (40)
Bone	60 (41)	55 (39)
Lung	59 (40)	56 (39)
Current or former smoker	76 (52)	59 (41)
Current or former alcohol use	30 (21)	18 (13)
Prior treatment		
Radiation therapy	85 (58)	87 (61)
Concurrent chemotherapy to radiation	65 (45)	68 (48)
Neoadjuvant therapy	54 (37)	49 (34)
Surgery	38 (26)	43 (30)
Adjuvant therapy	24 (16)	21 (15)
Disease-free interval, y, No./total (%)[c]		
≤ 2	48/75 (64)	45/79 (57)
> 2	27/75 (36)	34/79 (43)
PD-L1 status positive, No./total (%)[d]	109/130 (84)	109/133 (82)
Baseline plasma EBV DNA copy No., IU/mL[e]		
<2000	54 (37)	54 (38)
≥2000	92 (63)	89 (62(

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intention to treat; PD-L1, programmed cell death ligand 1; EBV, Epstein-Barr virus.

[a] Primary metastatic disease is defined as de novo metastatic disease at the initial diagnosis.

[b] Scores range from 0 to 5, with 0 indicating no symptoms and higher scores indicating greater disability: 0: asymptomatic, 1: symptomatic but completely ambulatory, 2: symptomatic, in bed less than 50% during the day, 3: symptomatic, in bed more than 50% during the day but not bedbound, 4: bedbound, 5: death

[c] Evaluated among patients who had received definitive radiation or chemoradiation therapy as the last treatment before enrolling onto the current study. The disease-free interval was calculated from the end of definitive therapy to disease progression prior to the study treatments.

[d] Defined as 1% or more of tumor cells or 1% or more of immune cells expressing PD-L1 by JS311 IHC staining in a central laboratory.

[e] Determined by real-time quantitative reverse transcription polymerase chain reaction method with probes against EBV genes in a central laboratory.

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

The present application targets patients with recurrent, not amenable to surgery or radiotherapy, or metastatic nasopharyngeal carcinoma.

There are no specific Danish studies of patients with recurrent, not amenable to surgery or radiotherapy, or metastatic nasopharyngeal carcinoma. Hence the 'Value in Danish population' in the table below is based on this total of 394 patients identified with NPC between 2000-2018. For this reason, the population and data in the column showing values from the Jupiter-02 are not directly comparable, as these only show data on patients with recurrent, not amenable to surgery or radiotherapy, or metastatic nasopharyngeal carcinoma.

The pivotal JUPITER-02 trial enrolled a 100% Asian population, which reflects the geographic distribution of nasopharyngeal carcinoma (NPC). NPC is substantially more prevalent in endemic regions, particularly parts of Asia, and conducting a randomized phase III trial with sufficient statistical power therefore requires recruitment in regions with a higher disease incidence. In non-endemic regions such as Denmark, the underlying patient population is too small to enable timely enrollment of an adequately powered study of comparable design, making evidence generation in endemic regions both necessary and expected. As NPC occurs endemically in certain regions of the world, including the Inuit, Greenlanders contribute a significant number of cases annually in Denmark. (42)

Table 11 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (3) All patients (N = 394)	Value from Jupiter-02 study used in health economic model (4, 77)	
		Toripalimab + chemotherapy (n=146)	Placebo + chemotherapy (n=143)
Median age	56 years	46 years	51 years

Male (%)	72,3 %	85 %	81 %
	27,7 %		
T-classification [1]			
Tis	NR	0,7 %	0 %
T0	NR	13,7 %	13,3 %
T1	42,6 %	3,4 %	2,1 %
T2	21,8 %	6,8 %	5,6 %
T3	11,4 %	28,1 %	25,2 %
T4	22,1 %	30,8 %	28,7 %
Tx	NR	16,4 %	23,8 %
Unknown	2,0 %	0 %	1,4 %
N-classification [1]			
Nx	NR	15,8 %	23,1 %
N0	26,4 %	19,9 %	19,6 %
N1	24,6 %	10,3 %	9,8 %
N2	29,7 %	18,5 %	16,8 %
N3	18,8 %	31,5 %	26,6 %
N3a	NR	2,7 %	0 %
N3b	NR	1,4 %	2,8 %
Unknown	0,5 %	0 %	1,4 %
M-classification [1]			
M0	92,6 %	12,3 %	14,0 %
M1	7,4 %	87,7 %	84,6 %
Missing	0 %	0 %	1,4 %
Stage [1]			
I	10,9 %	0 %	0 %
II	18,8 %	2,1 %	2,1 %
III	31,2 %	2,7 %	2,1 %
IVa	31,5 %	8,2 %	9,8 %
IVb	7,4 %	87,0 %	84,6 %
Unknown/missing	0, 3 %	0 %	1,4 %
Histology			

Undifferentiated	74,1 %	89,7 %	90,9 %
Differentiated			
Differentiated non-keratinised	8,6 %	1,4 %	4,2 %
Keratinised	2,3 %	0,7 %	1,4 %
Basaloid	0,5 %	-	-
Non-karatinised (not classified)	4,1 %	6,8 %	2,1 %
Unknown/other	10,4 %	1,4 %	1,4 %
Smoking		Current/former smokers: 52 %	Current/former smokers: 41 %
Never	28,4 %		
Former	38,8 %		
Current	29,7 %		
Missing	3,0 %		

1) For Jupiter-02 data this is recorded at the time of inform consenting.

Efficacy – results per JUPITER-02

The proportion of patients that discontinued the study in each study arm and the reason for discontinuation is presented in the table below.

Table 12 Patient disposition in JUPITER-02 (78)

Patient disposition	Toripalimab + chemotherapy (n=146), n (%)	Placebo + chemotherapy (n=143), n (%)	Total (N=289), n (%)
Patients who had discontinued treatment and were under survival follow-up	0	0	0
Patients completed the trial	76 (52.1)	57 (39.9)	133 (46.0)
Patients discontinued from the trial	70 (47.9)	86 (60.1)	156 (54.0)
Primary reason for trial discontinuation			
Death	57 (39.0)	76 (53.1)	133 (46.0)
Withdrawal of consent	5 (3.4)	2 (1.4)	7 (2.4)
Lost to follow-up	7 (4.8)	8 (5.6)	15 (5.2)
Other	1 (0.7)	0	1 (0.3)
Follow-up time (months)			

N	146	143	289
Mean	31.51	28.73	30.14
SD	12.577	13.020	12.852
Minimum	1.0	0.2	0.2
Median	36.73	30.95	36.04
Maximum	47.4	48.3	48.3

Note: Follow-up time was defined as the time from randomization to death, date of end of trial, or the data cut-off date for the analysis, whichever occurred first and was calculated as (event date - randomization date + 1) / 30.4375 days in a month.
Abbreviations: N, number of patients; SD, standard deviation; ITT, intention-to-treat.
Source: (45)

Efficacy results from the ITT populations in the Jupiter-02 study are presented in this section.

Table 13 Overview of the efficacy results from the Jupiter-02 trial

Outcome measure	Loqtorzi + cisplatin + gemcitabine (n=146)	Placebo + cisplatin + gemcitabine (n=143)	Difference or HR (95% CI)	*P* value
Progression-free survival, median (95% CI), month	21.4 (11.7 to NE)[a]	8.2 (7.0 to 9.8)[a]	HR, 0.52 (0.37-0.73)[b]	<.001[c]
Overall survival, median (95% CI), month	64.8 (38.8 to NE)[a]	33.7 (26.7 to 44.2)[a]	HR, 0.63 (0.45-0.89)[b]	.008[c]
ORR (complete response + partial response), n/total (%), [95% CI]	115/146 (78.8) [71.2, 85.1][d]	96/143 (67.1) [58.8, 74.8][d]	Difference, 11.4 [1.7, 21.2][e]	.02[f]
DCR (complete response + partial response + stable disease), n/total (%) [95% CI]	129/146 (88.4) [82.0-93.1][d]	115/143 (80.4) [73.0-86.6][d]	Difference, 7.9 [-0.4 to 16.1][e]	.06[f]
DoR, median (95% CI), month [n]	18.0 (10.5, NE)[a] [n = 115]	6.0 (5.6, 8.3)[a] [n = 96]	HR, 0.49 (0.33-0.72)[g]	<0.001[h]

Abbreviations: NE, not estimable; RECIST, Response Evaluation Criteria in Solid Tumors.
Data cut-off date: June 24, 2025, for overall survival, and June 8, 2021, for all other results.
[a] The confidence interval for the median survival was computed using the Brookmeyer-Crowley method with log-log transformation.
[b] Computed from the Cox proportional hazards regression model, stratified by the baseline Eastern Cooperative Oncology Group performance status (0 vs 1) and the baseline disease stage (recurrent vs primary metastatic).
[c] Computed from the log-rank test, stratified by the baseline Eastern Cooperative Oncology Group performance status (0 vs 1) and the baseline disease stage (recurrent vs primary metastatic).

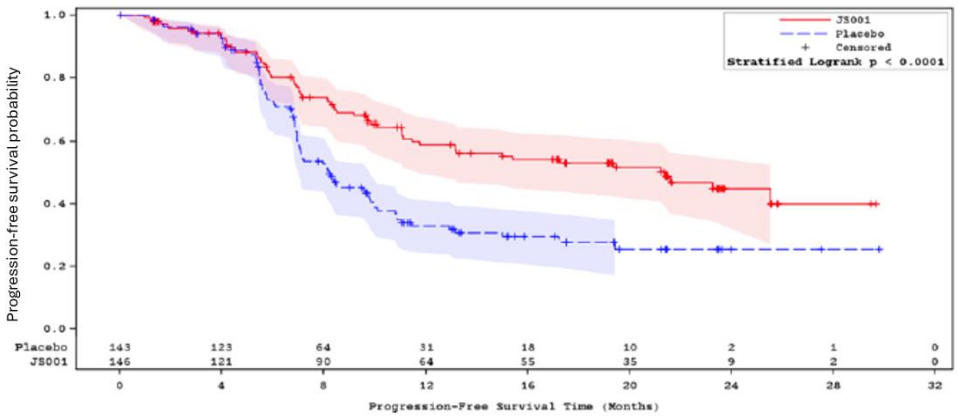
Outcome measure	Loqtorzi + cisplatin + gemcitabine (n=146)	Placebo + cisplatin + gemcitabine (n=143)	Difference or HR (95% CI)	*P* value

[d] Confidence interval was computed using the Clopper-Pearson method.
[e] Computed using the Mantel-Haenszel method, stratified by the baseline Eastern Cooperative Oncology Group performance status (0 vs 1) and baseline disease stage (recurrent vs primary metastatic)
[f] Computed from the Cochran-Mantel-Haenszel test, stratified by the baseline Eastern Cooperative Oncology Group performance status (0 vs 1) and baseline disease stage (recurrent vs primary metastatic)
[g] Computed from the unstratified Cox proportional hazards regression model
[h] Computed from the unstratified log-rank test

6.1.3.1 PFS

In the JUPITER-02 trial, a total of 289 randomized participants were evaluated by the IRC, among whom 150 (51.9%) experienced disease progression or death: 63 (43.2%) in the toripalimab group and 87 (60.8%) in the placebo group (data cut-off: June 8, 2021). Treatment with toripalimab plus chemotherapy reduced the absolute risk of progression or death by 17.6 percentage points compared with placebo plus chemotherapy (HR = 0.52; 95% CI, 0.374–0.726; P = <0.001) (Figure 4)(4).

Figure 4 IRC-Assessed Progression-free survival analyses in the ITT population in the JUPITER-02 trial (79)



Further details are reported in Table 14. Three-year PFS rates were not reported, as follow-up time was insufficient at the predefined data cut-off of 8 June 2021.

Table 14 IRC-Assessed Progression-free survival in Intent-to-Treat Population as of June 8, 2021 (79)

	Toripalimab + Chemo (N=146)	Placebo + Chemo (N=143)	Total (N=289)
Status, n (%)			
Events observed	63 (43.2)	87 (60.8)	150 (51.9)
Progressive disease	60 (41.1)	86 (60.1)	146 (50.5)

Death	3 (2.1)	1 (0.7)	4 (1.4)
Censored	83 (56.8)	56 (39.2)	139 (48.1)
No post-baseline tumor assessment	2 (1.4)	5 (3.5)	7 (2.4)
No disease progression or death at the time of analysis	47 (32.2)	14 (9.8)	61 (21.1)
Missing two or more consecutive tumor assessments[1]	14 (9.6)	7 (4.9)	21 (7.3)
Started new anti-cancer therapy prior to IRC-determined progression	20 (13.7)	30 (21.0)	50 (17.3)
Estimate of median PFS (months) (95% CI)[2]	21.4 (11.73, NE)	8.2 (7.03, 9.79)	10.8 (9.53, 13.17)
Stratified analysis[3] Estimate of hazard ratio (Toripalimab vs Placebo)[4] (95% CI) Nominal log-rank p-value (two-sided)		0.52 (0.374, 0.726) <0.0001	
Unstratified analysis Stratified analysis[3] Estimate of hazard ratio (Toripalimab vs Placebo)[4] (95% CI) Nominal log-rank p-value (two-sided)		0.52 (0.377, 0.727) 0.0002	
1-Year PFS Rate	59.0%	32.9%	46.2%
(95% CI)[5]	(49.72, 67.16)	(24.55, 41.53)	(39.72, 52.34)
Difference of 1-Year PFS Rates		26.1%	
(95% CI)[6]		(13.8, 38.3)	
2-Year PFS Rate	44.8%	25.4%	35.1%
(95% CI)[5]	(34.39, 54.71)	(16.95, 34.81)	(28.14, 42.10)
Difference of 2-Year PFS Rates		19.4%	
(95% CI)[6]		(5.7, 33.1)	

CI = confidence interval, IRC = independent review committee, IWRS = interactive web response system, NE = not estimable, PFS = progression- free survival, RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1,

Note: IRC-Assessed PFS is defined as the time from randomization until the earliest occurrence of disease progression, as determined by independent review committee from tumor assessments, per RECIST v1.1, or death from any cause, whichever occurs first.

Note: PFS (in month) = (event date or censoring date - randomization date + 1)/30.4375.

[1] For patients who had two or more consecutive missing tumor assessments due to COVID-19, but had subsequent tumor assessments with no immediate disease progression, the subsequent tumor assessments were used in the PFS analysis and those patients were not counted in this category.

[2] The Brookmeyer Crowley methodology was used to construct the 95% CI for the median PFS.

[3] The stratified analyses used ECOG performance status (0 vs. 1), and disease stage (recurrent vs. metastatic) as recorded in the IWRS.

[4] The hazard ratio was estimated with the use of the Cox proportional hazards model. Efron's method was used to handle ties.

[5] The 95% CI was estimated with use of the standard error derived from Greenwood's formula.
[6] The 95% CI was estimated with use of the normal approximation method.
Table 14.2.2.1 Listings 16.2.6.1, 16.2.6.2.1, 16.2.6.4.1, 16.2.6.5.1, and 16.2.6.6.1
Program Location: /projects/shenb237456/stats/primary/prog/tables/t_pfs.sas/23JUL2021/10:52
Database Cutoff Date: 08JUN2021 Extract Date: 20JUL2021

6.1.3.2 OS – extended analysis of June 24, 2025

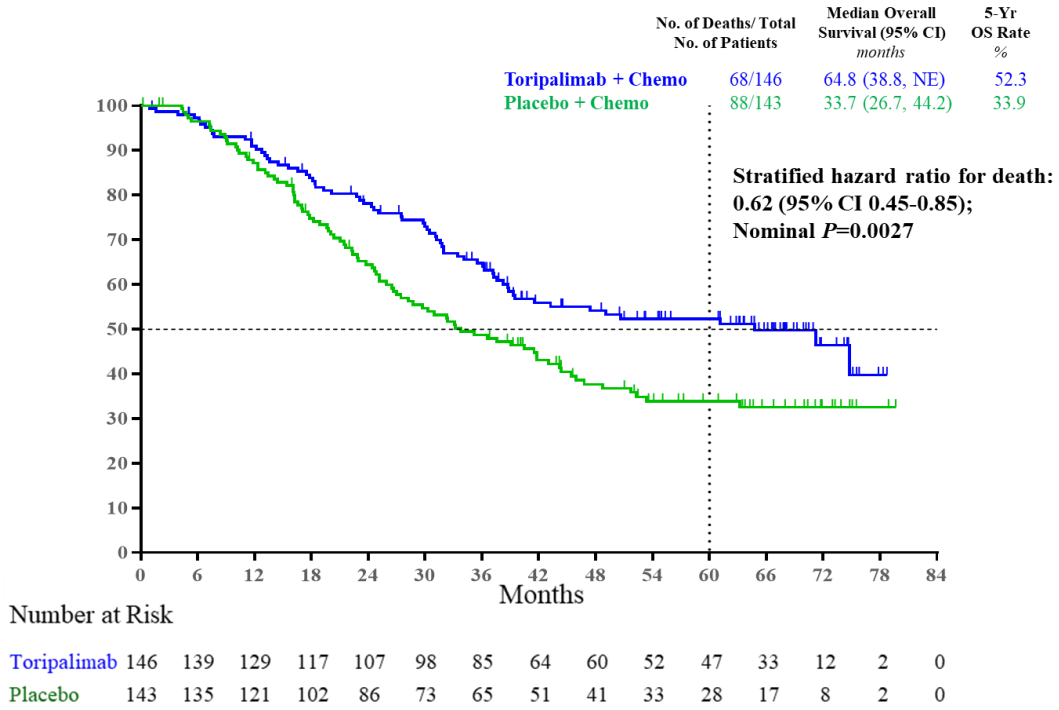
Based on a data cut-off of June 24, 2025, 68 months after the last enrollment, a long term OS follow up was conducted (51). By then 156 deaths had occurred, and median OS was 64.8 months for participants treated with toripalimab and 33.7 months for those receiving placebo. The hazard ratio (HR) for death was 0.62 (95% CI: 0.45–0.85; nominal p=0.0027).

The OS rates at 5 years were 52.3% vs 33.9% for the toripalimab and placebo groups, respectively.

Sensitivity analyses were performed to evaluate how post-progression immunotherapy influenced survival outcomes. Within the intent-to-treat cohort, after adjusting for post-progression anti–PD-(L)1 therapy, the HR was 0.52 (95% CI: 0.38–0.72), with a median OS of 61.0 months in the toripalimab group compared with 25.1 months in the placebo group. The improved HR in the adjusted analysis suggests that post-progression immunotherapy conferred a relatively greater survival advantage among patients in the placebo arm. (51)

In conclusion, treatment with toripalimab combined with GP chemotherapy provided a marked survival advantage over GP chemotherapy alone as a first-line option for recurrent or metastatic NPC (RM-NPC). Patients in the toripalimab arm achieved a median OS of 64.8 months, representing a 31-month improvement compared with GP alone. These findings indicate that toripalimab plus GP chemotherapy establishes a new benchmark for standard first-line care in RM-NPC. (51)

Figure 5 **Jupiter-02 Six-year overall survival follow-up (51)**



Notice, that a full six-year overall survival analysis was not conducted, as this was not pre-specified in the study protocol. Consequently, updated Kaplan–Meier estimates of OS at 1, 2, and 3 years are not available from the extended follow-up. Therefore, results from the pre-specified final overall survival analysis (data cut-off 18 November 2022) are also presented in the next section.

6.1.3.3 OS – prespecified final analysis

In the prespecified final OS analysis (data cut-off: November 18, 2022), with a median follow-up for survival of 36.0 months, a total of 133 overall survival (OS) events had occurred (57 in the toripalimab arm and 76 in the placebo arm), cf. (Table 15. Among patients still alive, the median follow-up duration was 39.6 months (range, 1.2–47.4) for the toripalimab arm and 39.9 months (range, 0.2–48.3) for the placebo arm. The median OS had not been reached in the toripalimab arm, whereas it was 33.7 months for the placebo arm.

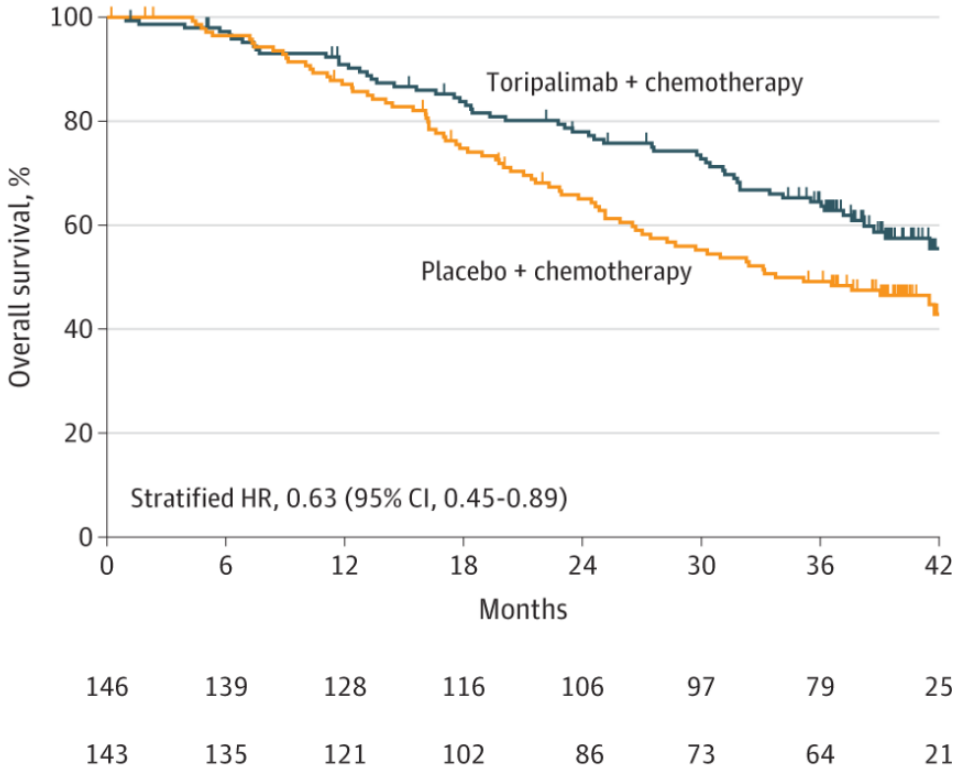
Table 15 **Overall Survival in Intent-to-Treat Population as of November 18, 2022 (78)**

Status, n (%)	Toripalimab + Chemo (N=146)	Placebo + Chemo (N=143)	Total (N=289)
Death	57 (39.0)	76 (53.1)	133 (46.0)
Censored	89 (61.0)	67 (46.9)	156 (54.0)
Alive	82 (56.2)	60 (42.0)	142 (49.1)
Lost to Follow-up	7 (4.8)	7 (4.9)	14 (4.8)
Unknown	0	0	0
Estimate of median OS (months)	NE	33.7	41.8

(95% CI)	(38.70, NE)	(27.01, 44.19)	(36.57, NE)
	Stratified analyses		
Estimate of HR (Stratified)	0.63 (0.446, 0.891)		
Log-rank p-value (Stratified)	0.008		
	Unstratified analyses		
Estimate of HR (Unstratified)	0.66 (0.465, 0.925)		
Log-rank p-value (Unstratified)	0.02		
1-Year OS Rate	90.9%	87.1%	89.1%
(95% CI)	(84.87, 94.62)	(80.36, 91.69)	(84.80, 92.17)
Difference	3.8%		
(95% CI)	(-3.5, 11.1)		
2-Year OS Rate	78.0%	65.1%	71.6%
(95% CI)	(70.18, 83.97)	(56.50, 72.44)	(65.93, 76.55)
Difference	12.9%		
(95% CI)	(2.3, 23.4)		
3-Year OS Rate	64.5%	49.2%	56.9%
(95% CI)	(55.86, 71.87)	(40.53, 57.32)	(50.83, 62.58)
Difference of 3-Year OS Rates	15.3%		
(95% CI)	(3.6, 26.9)		

Toripalimab demonstrated a significant OS advantage over placebo (HR, 0.63 [95% CI, 0.45–0.89]; two-sided P = .008), surpassing the predefined efficacy boundary (Figure 6 and Table 13). The OS rates at 1, 2, and 3 years were 90.9% vs 87.1%, 78.0% vs 65.1%, and 64.5% vs 49.2% for the toripalimab and placebo groups, respectively.

Figure 6 Overall Survival (predefined data cut-off of November 18, 2022) (4)



Note: The median overall survival was not reached (IQR, 27.6 months to not estimable) in the toripalimab group and was 33.7 (IQR, 17.8 to not estimable) months in the placebo group. Vertical ticks on curves indicate censored patients. Hazard ratios were stratified by baseline Eastern Cooperative Oncology Group performance status score (0 vs 1) and baseline disease stage (recurrent vs primary metastatic).

6.1.3.4 ORR

As of the data cut-off on June 8, 2021, the ICR-assessed objective response rates (ORR) were 78.8% in the toripalimab group (95% CI: 71.2- 85.1) and 67.1% in the placebo group (95% CI: 58.8- 74.8). The between-group difference was 11.4% (95% CI: 1.7-21.2), which was statistically significant (P = 0.02).

6.1.3.5 DCR

The CR rates evaluated by the IRC was twice as high in the toripalimab group compared with the placebo group—26.7% (95% CI: 82.0-93.1) versus 13.3% (95% CI: 73.0-86.6] The absolute difference of 7.9% (95% C:, –0.4-16.1) favored toripalimab but did not reach statistical significance (P = 0.06) (Table 13Table 13).

6.1.3.6 DoR

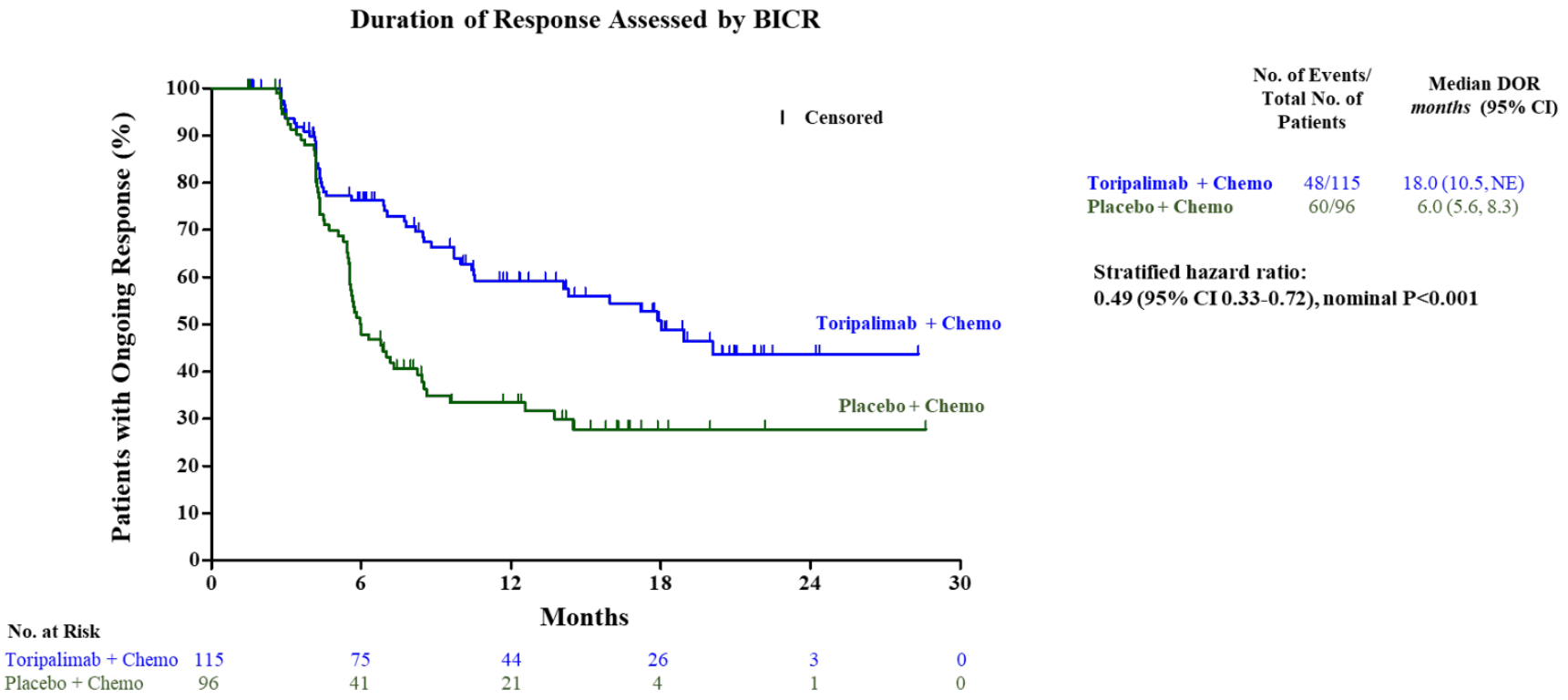
Responses were durable, with the ICR-assessed median duration of response reaching 18.0 months (95% CI, 10.5 to not estimable) in the toripalimab arm and 6.0 months (95% CI, 5.6–8.3) in the placebo arm (HR, 0.49 [95% CI, 0.33–0.72]) (Figure 7) (4).

6.1.3.7 EBV DNA Copy Number

Because latent EBV infection is critical to the development of NPC, the dynamic change of plasma EBV DNA copy number is closely related with response to chemotherapy, radiotherapy or immunotherapy (4).

Dynamic changes in plasma EBV DNA copy number were evaluated for their association with clinical outcomes (Figure 8). Among participants who had measurable EBV DNA copy number at baseline and at least one posttreatment assessment, all 107 patients (100%) in the toripalimab arm and 99 of 103 patients (96.1%) in the placebo arm showed a decline in EBV DNA levels following treatment. Of these, 103 of 107 patients (96.3%) receiving toripalimab and 87 of 103 (84.5%) receiving placebo achieved undetectable EBV DNA levels. Subsequently, EBV DNA levels rebounded in 39 of 107 patients (36.5%) in the toripalimab group and 58 of 101 (57.4%) in the placebo group. The median time from the lowest EBV DNA copy number to the rebound was 20.5 in the toripalimab arm vs 6.0 months in the placebo arm. In the toripalimab group, this rebound occurred a median of 1.9 months prior to investigator-assessed disease progression. The results suggest that EBV DNA copy number rebound might be used to predict disease progression (4).

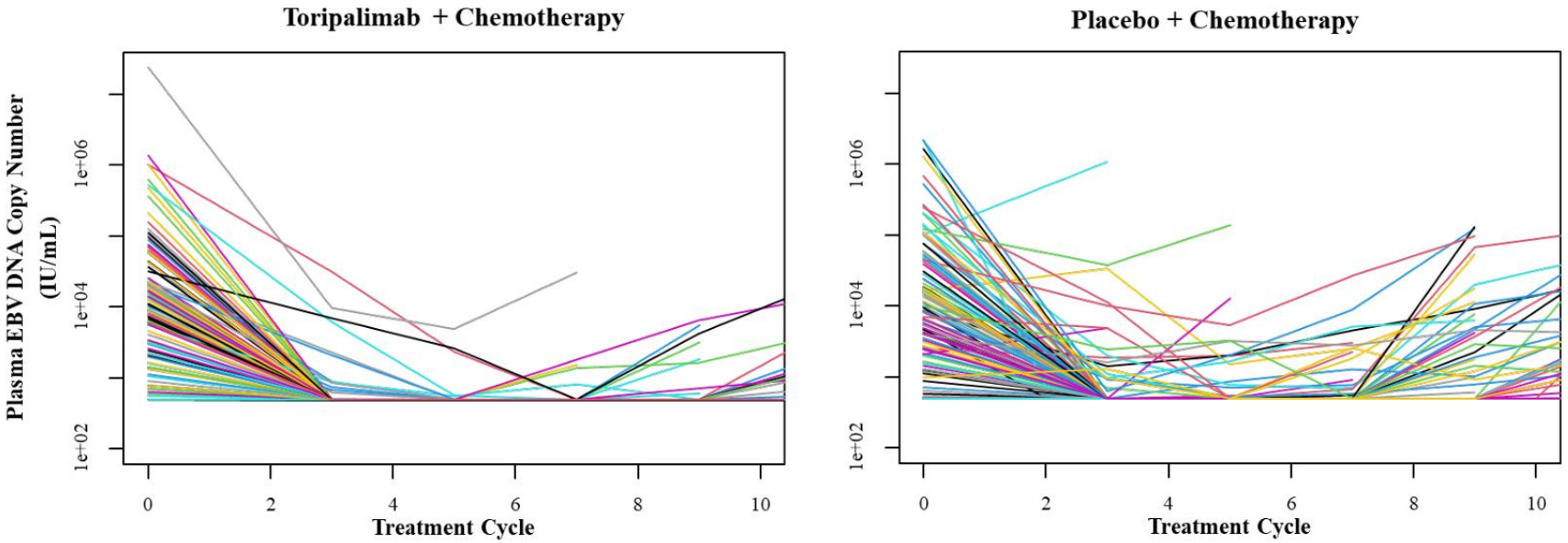
Figure 7 Duration of Response by Blinded Independent Central Review per RECIST v1.1. (4)(supplement 3)



Abbreviations: CI, confidence interval; DoR, duration of response; NE, not evaluated

Kaplan-Meier-estimated DoR curves as assessed by ICR according to RECIST v1.1. Censored patients are marked with " | " in the graph. The number of patients at risk at indicated time points shown below x-axis. The number of events, median DoR, and stratified hazard ratio for DoR were shown to the right of KaplanMeier curves. The cut-off date for DoR analysis is June 8, 2021.

Figure 8 **Dynamic Plasma EBV DNA Copy Numbers during the study (4) (supplement 3)**



Note: Longitudinal plasma samples were collected for dynamic EBV DNA copy number evaluation, including samples from baseline and multiple treatments cycles specified in the study protocol. Plasma EBV DNA copy number was determined by qRT-PCR method with probes against EBV genes in a central lab. The detection limit was 500 IU/mL. The EBV DNA copy number in the toripalimab group (LEFT) and the placebo group (RIGHT) over treatment cycles are shown.

7. Comparative analyses of efficacy N/A

N/A

7.1.1 Differences in definitions of outcomes between studies

N/A

7.1.2 Method of synthesis

N/A

7.1.3 Results from the comparative analysis

N/A

7.1.4 Efficacy – results per [outcome measure]

N/A

8. Modelling of efficacy in the health economic analysis N/A

N/A

8.1 Presentation of efficacy data from the clinical documentation used in the model

N/A

8.1.1 Extrapolation of efficacy data

N/A

8.1.1.1 Extrapolation of [effect measure 1]

N/A

Table 16 Summary of assumptions associated with extrapolation of effect measure N/A

Method/approach	Description/assumption
Data input	

Method/approach	Description/assumption
Model	
Assumption of proportional hazards between intervention and comparator	
Function with best AIC fit	
Function with best BIC fit	
Function with best visual fit	
Function with best fit according to evaluation of smoothed hazard assumptions	
Validation of selected extrapolated curves (external evidence)	
Function with the best fit according to external evidence	
Selected parametric function in base case analysis	
Adjustment of background mortality with data from Statistics Denmark	
Adjustment for treatment switching/cross-over	
Assumptions of waning effect	
Assumptions of cure point	

N/A

8.1.1.2 Extrapolation of [effect measure 2]

N/A

8.1.2 Calculation of transition probabilities

N/A

Table 17 Transitions in the health economic model N/A

Health state (from)	Health state (to)	Description of method	Reference
Disease-free survival			
Recurrence			
Health state/Transition			

N/A

8.2 Presentation of efficacy data from [additional documentation]

N/A

8.3 Modelling effects of subsequent treatments

N/A

8.4 Other assumptions regarding efficacy in the model

N/A

8.5 Overview of modelled average treatment length and time in model health state

N/A

Table 18 Estimates in the model N/A

	Modelled average [effect measure] (reference in Excel)	Modelled median [effect measure] (reference in Excel)	Observed median from relevant study

N/A

Table 19 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction (N/A

Treatment	Treatment length [months]	Health state 1 [months]	Health state 2 [months]

9. Safety

In this chapter, we present safety data on patients with recurrent, not amenable to surgery or radiotherapy, or metastatic nasopharyngeal carcinoma from the Jupiter-02 study.

9.1 Safety data from the clinical documentation

An overview of the safety events in the Jupiter-02 study is presented in Table 20. In Jupiter-02, safety analyses were performed on the safety population of 289 patients, which included all randomized patients who received any amount of study drug.

Only Treatment-Emergent Adverse Events are recorded (TEAEs) in the Jupiter-02 study. TEAEs are defined as TEAEs are adverse events that either start or worsen in severity on or after the date/time of first dose of study treatment and on or before 60 days after the date/time of last dose of study treatment. Hence, all data in the table below show different grades of TEAEs.

All patients experienced at least 1 treatment-emergent adverse event (TEAE). No novel safety signals were identified when toripalimab was compared with other drugs in the same class. (4)

Table 20 Overview of safety events (only TEAEs). Data cut-off May 08, 2022 – median treatment duration was 65.7 weeks in the toripalimab group and 37.3 weeks in the placebo group. (4) (supplement 3)

	Toripalimab + gemcitabine-cisplatin (n=146) (4)	Placebo + gemcitabine-cisplatin (n=143) (4)	Difference, % (95 % CI)
Number of adverse events, n	Not recorded	Not recorded	Not recorded
Number and proportion of patients with ≥1 adverse events, n (%)	146 (100%)	143 (100 %)	0.0 %-point

	Toripalimab + gemcitabine-cisplatin (n=146) (4)	Placebo + gemcitabine-cisplatin (n=143) (4)	Difference, % (95 % CI)
Number of serious adverse events*, n	Not recorded	Not recorded	Not recorded
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)[a]	64 (43.8%)	62 (43.4%)	+0.4 %-point
Number of CTCAE grade ≥ 3 events, n	Not recorded	Not recorded	Not recorded
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)[b]	131 (89.7%)	129 (90.2%)	-0.5 %-point
Number of adverse reactions, n	Not recorded	Not recorded	Not recorded
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	141 (96.6%)	139 (97.2%)	-0.6 %-point
Number and proportion of patients who had a dose reduction, n (%)	Toripalimab: Not recorded Gemcitabine: 71 (48.6%) Cisplatin: 59 (40.4%)	Gemcitabine: 74 (51.7%) Cisplatin: 62 (43.4%)	Gemcitabine: -3.1 %-point Cisplatin: -3.0 %-point
Number and proportion of patients who discontinue treatment regardless of reason, n (%) [c]	146 (100.0%)	143 (100.0%)	0.0 %-point
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	Withdrawal of: Toripalimab: 17 (11.6%) Gemcitabine: 20 (13.7%) Cisplatin: 27 (18.5%)	Withdrawal of: Study drug: 7 (4.9%) Gemcitabine: 16 (11.2%) Cisplatin: 19 (13.3%)	Toripalimab/study drug: +6.7 %-point Gemcitabine: +2.5 %-point

	Toripalimab + gemcitabine-cisplatin (n=146) (4)	Placebo + gemcitabine-cisplatin (n=143) (4)	Difference, % (95 % CI)
			Cisplatin: +5.2 %-point
Number and proportion of deaths related to adverse events, n (%)	5 (3.4)	4 (2.8)	+0.6 %-point
Number and proportion of immune-related adverse events	79 (54.1)	31 (21.7)	+32.4 (X – X)

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).
[a] Only treatment-emergent serious adverse events were recorded in the study, and hence the reported data in the table show treatment-emergent serious adverse events.
[b] Only treatment-emergent CTCAE grade ≥ 3 events were recorded in the study, and hence the reported data in the table show these.
[c] All patients had discontinued study treatment at the time of data cut-off. Discontinuation due to reaching the protocol-defined maximum treatment duration of 2 years occurred in 58 patients in the toripalimab arm and 34 patients in the placebo arm.
§ CTCAE v. 5.0 must be used if available.

Table 21 presents the frequency of all serious adverse events with frequency of ≥ 5% recorded in the Jupiter-02 study. A list of all serious adverse events observed in Jupiter-02 is presented in Appendix E.

Table 21 Serious adverse events. Data cut-off May 08, 2022 – median treatment duration was 65.7 weeks in the toripalimab group and 37.3 weeks in the placebo group. (77)

Adverse events	Toripalimab + gemcitabine-cisplatin (n=146)		Placebo + gemcitabine-cisplatin (n=143)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Any serious adverse event, n (%)	64 (43.8)	Not recorded	62 (43.4)	Not recorded
Blood and lymphatic system disorders				
Thrombocytopenia	[redacted]		[redacted]	
Anaemia				

Adverse events	Toripalimab + gemcitabine-cisplatin (n=146)	Placebo + gemcitabine-cisplatin (n=143)
Leukopenia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Infections and infestations		
Pneumonia	[redacted]	[redacted]

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

Table 22 Adverse events used in the health economic model N/A

Adverse events	Intervention	Comparator		
	Frequency used in economic model for intervention	**Frequency used in economic model for comparator**	**Source**	**Justification**
Adverse event, n (%)	N/A	N/A	N/A	N/A

9.2 Safety data from external literature applied in the health economic model

N/A

Table 23 Adverse events that appear in more than X % of patients N/A

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events
Adverse event, n	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

10. Documentation of health-related quality of life (HRQoL)

Table 24 Overview of included HRQoL instruments (80)

Measuring instrument	Source	Utilization
EORTC QLQ-C30	JUPITER-02	Clinical effectiveness
EORTC QLQ-H&N35	JUPITER-02	Clinical effectiveness

10.1 Presentation of EORTC QLQ

10.1.1 Study design and measuring instrument

JUPITER-02 was a randomized, placebo-controlled, multi-center, double blinded, Phase III. See section 6 for more details. Patient-reported outcomes (PROs) were prospectively collected in the JUPITER-02 trial as secondary outcomes in accordance with the study protocol and prespecified statistical analysis plan. Health-related quality of life (HRQoL) and disease-specific symptoms were assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and the EORTC QLQ-H&N35 head and neck cancer module, both of which are validated instruments for use in oncology and head and neck cancer populations.

The EORTC QLQ-C30 is a cancer-specific, multidimensional, self-administered, culturally adaptable tool. It assesses quality of life (QoL) through five functional scales (physical, role, cognitive, emotional, social), three symptom scales (fatigue, pain, nausea/vomiting), a global health/QoL scale, and single items for common symptoms. (81) All scales are scored from 0 to 100: higher functional and global health scores indicate better QoL; higher symptom scores indicate greater symptom burden. The global health/QoL scale is recommended as the summary measure. The EORTC QLQ-H&N35 is an additional supplemental module for head and neck cancer, focusing on relevant symptoms and side effects. (81) Raw questionnaire responses for EORTC QLQ-H&N35 were linearly transformed to a 0–100 scale, where higher scores for items indicate greater symptom burden.

PRO analyses were prespecified to be primarily descriptive and exploratory per protocol.

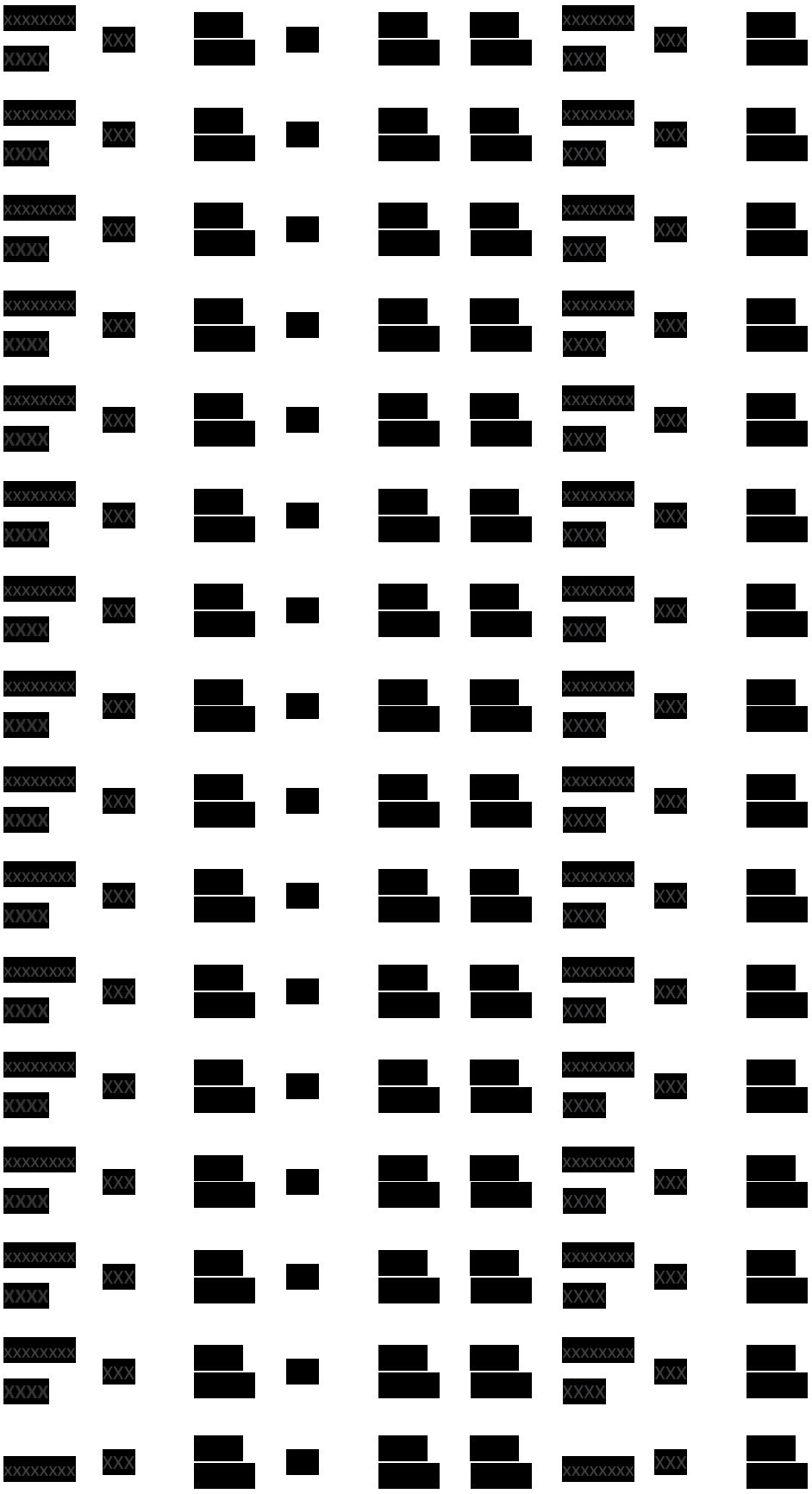
Observed mean scores and standard deviations were summarised by treatment arm at each scheduled assessment. To provide between-arm comparisons at individual time points, to populate DMC tables below, were performed using differences in observed mean scores with associated 95% confidence intervals and two-sided nominal p-values, based on available data at each visit.

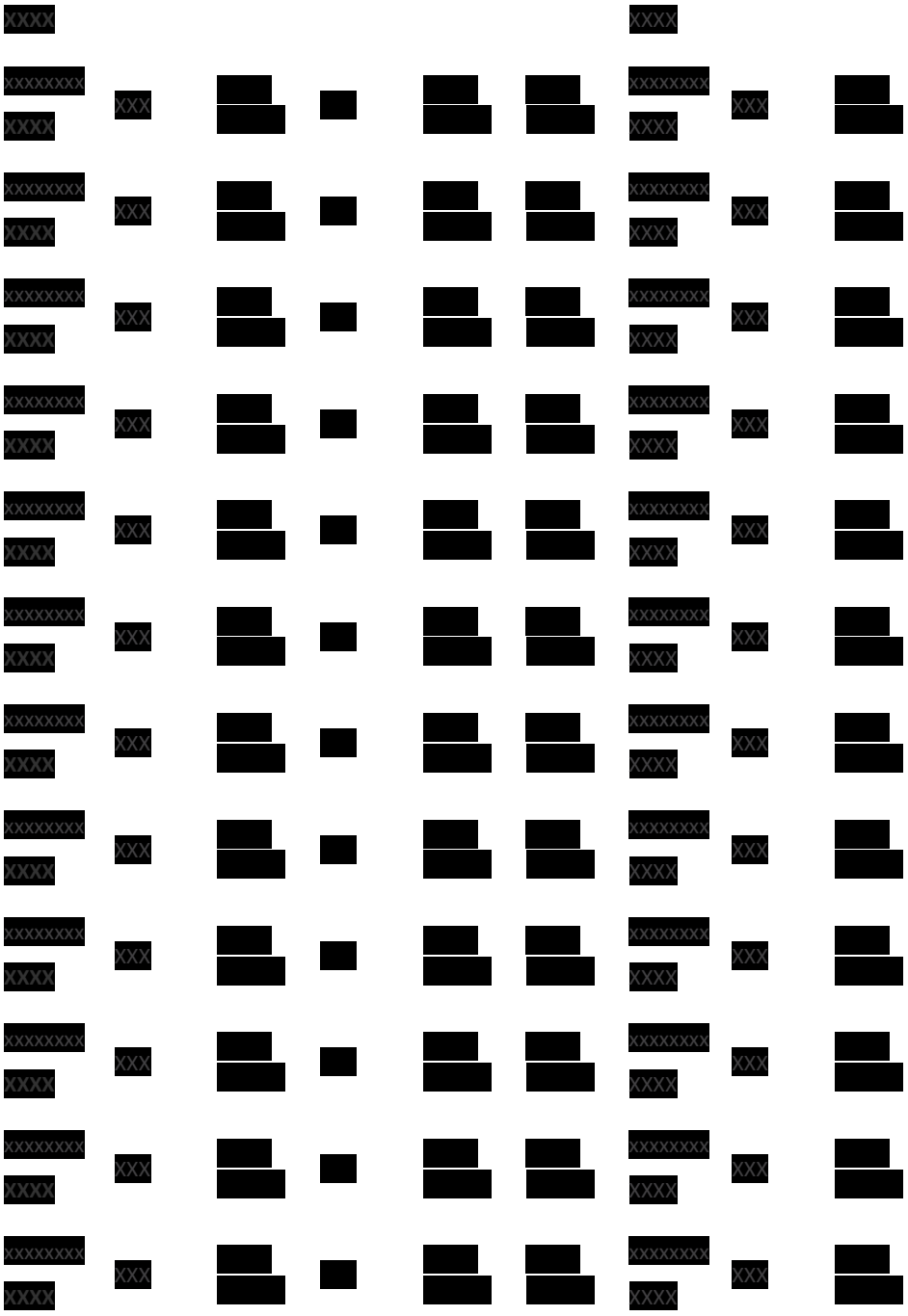
10.1.2 Data collection

This section describes the data collection for both EORTC QLQ-30 and EORTC QLQ-H&N35. The HRQoL was assessed at baseline and prior to dosing or any clinical activity at every treatment cycle. According to the protocol, PRO questionnaires were administered at baseline (prior to randomisation) and at prespecified on-treatment visits corresponding to each treatment cycle (Day 1), continuing until treatment discontinuation or study completion. Patients were instructed to complete the questionnaires before clinical assessments, laboratory procedures, or administration of study treatment at each visit, in order to minimise potential bias related to investigator interaction or treatment effects. Standardised written instructions were provided to patients, and site staff were trained in PRO administration procedures to ensure consistency across investigational sites.

Table 25 Pattern of missing data and completion for PRO instruments (80)

Time point	HRQoL population N		Missing N (%)		Expected to complete N		Completion N (%)	
	Number of patients at randomization		Number of patients for whom data is missing (% of patients at randomization)		Number of patients "at risk" at time point X		Number of patients who completed (% of patients expected to complete)	
	Int	Pla	Int	Pla	Int	Pla	Int	Pla
[redacted]								





10.1.3 HRQoL results

Mean changes from baseline for the EORTC QLQ-C30 global health/QoL for both treatment arms are presented in Figure 9.

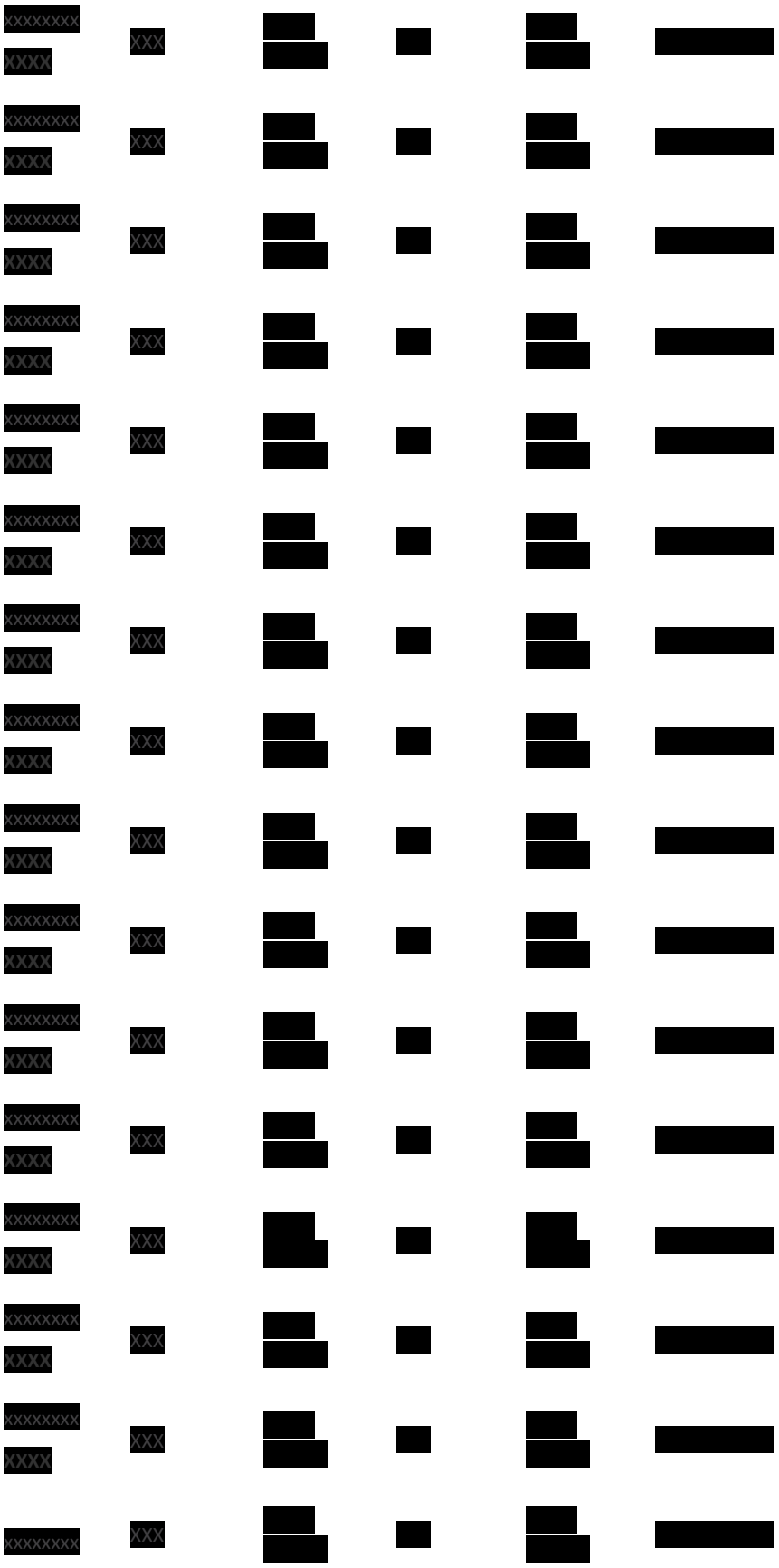
Separation of the curves at late timepoints is considered uninterpretable due to the limited number of completed questionnaires, particularly in the control (placebo plus chemotherapy) arm. Given the very high likelihood that data at later timepoints are not missing at random and are likely due to disease progression, death or adverse events that

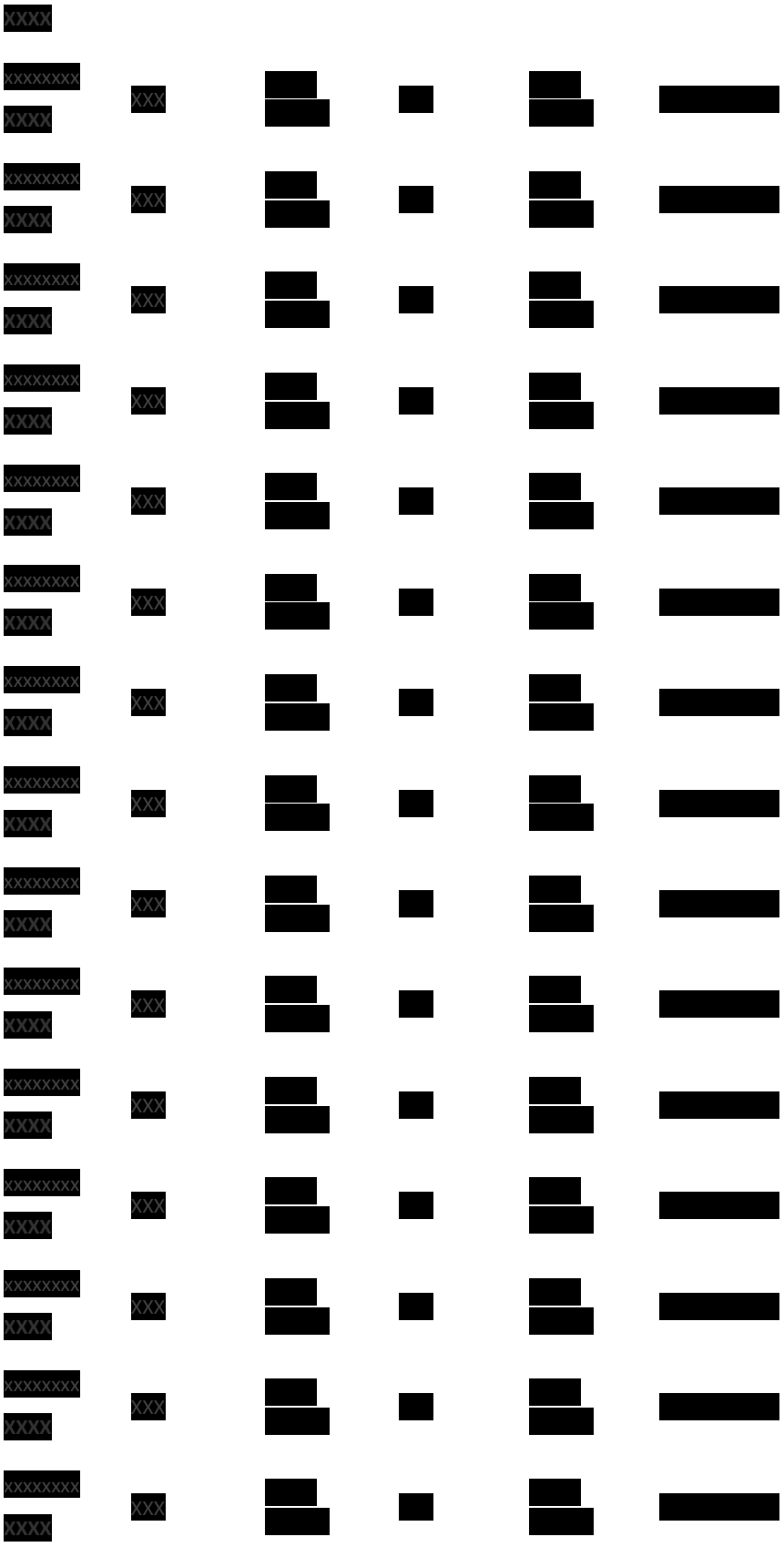
might be highly correlated with patients' quality of life; thus, more bias might be introduced in the QoL data at later timepoints.

The EORTC QLQ-C30 global health score at each treatment cycle are presented in Table 26. The difference per visit was calculated based on observed mean scores at each visit. Standard errors were estimated under the assumption of independent samples, and 95% confidence intervals were constructed using a normal approximation. Two-sided nominal p-values were calculated using z-tests. No adjustment for multiplicity or baseline values was applied.

Table 26 HRQoL EORTC QLQ-C30 (Global health status summary statistics (80)

	Intervention		Comparator		Intervention vs. comparator
Time point	Intervention N	Intervention Mean (SD)	Comparator N	Comparator Mean (SD)	Difference (95% CI) p-value
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]





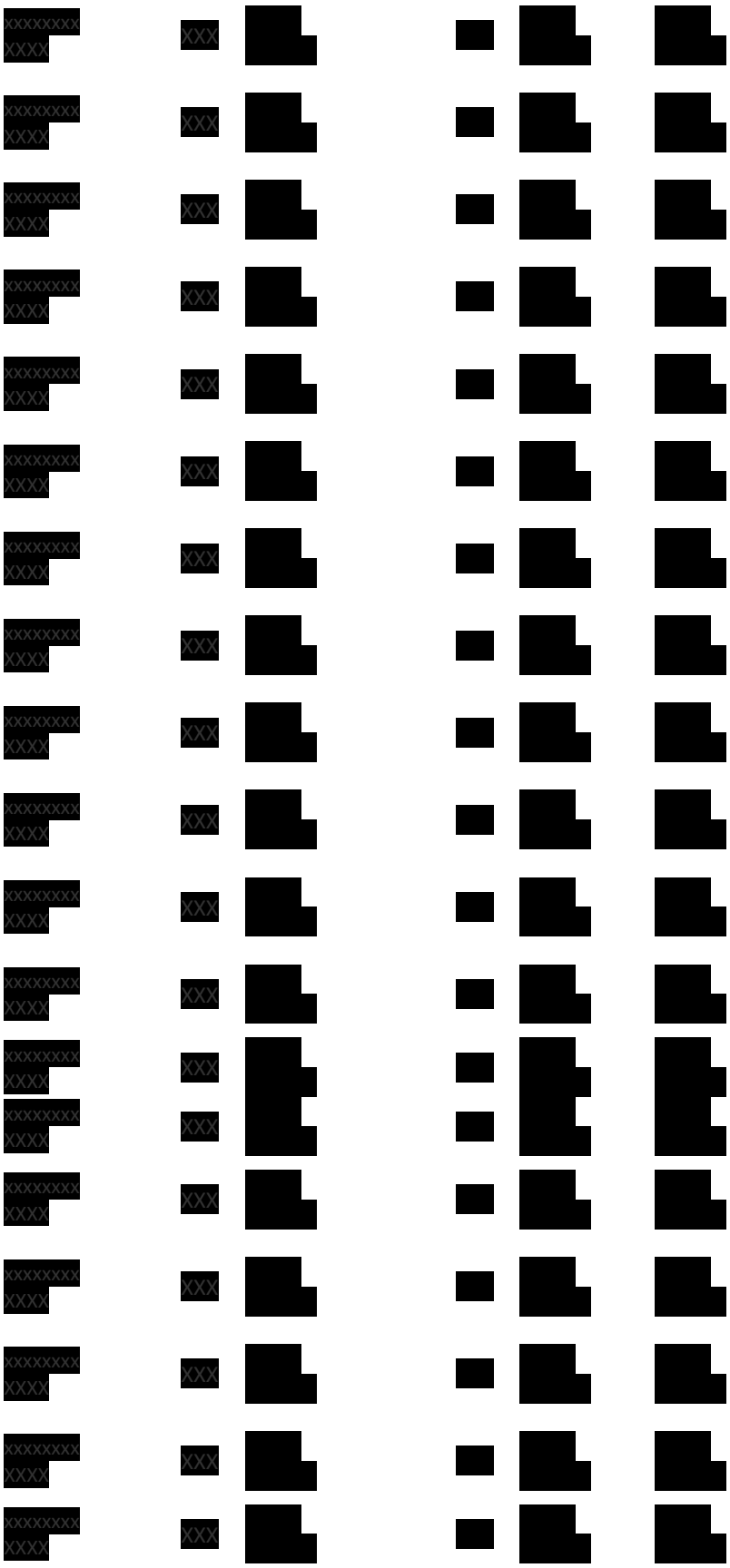
Similar data for the EORTC QLQ-C30 domains Pain, Swallowing, Senses problems (taste/smell), Speech problems, Social eating, Social contact, and Sexuality are shown in Figure 10-Figure 15 and Table 28-Table 32.

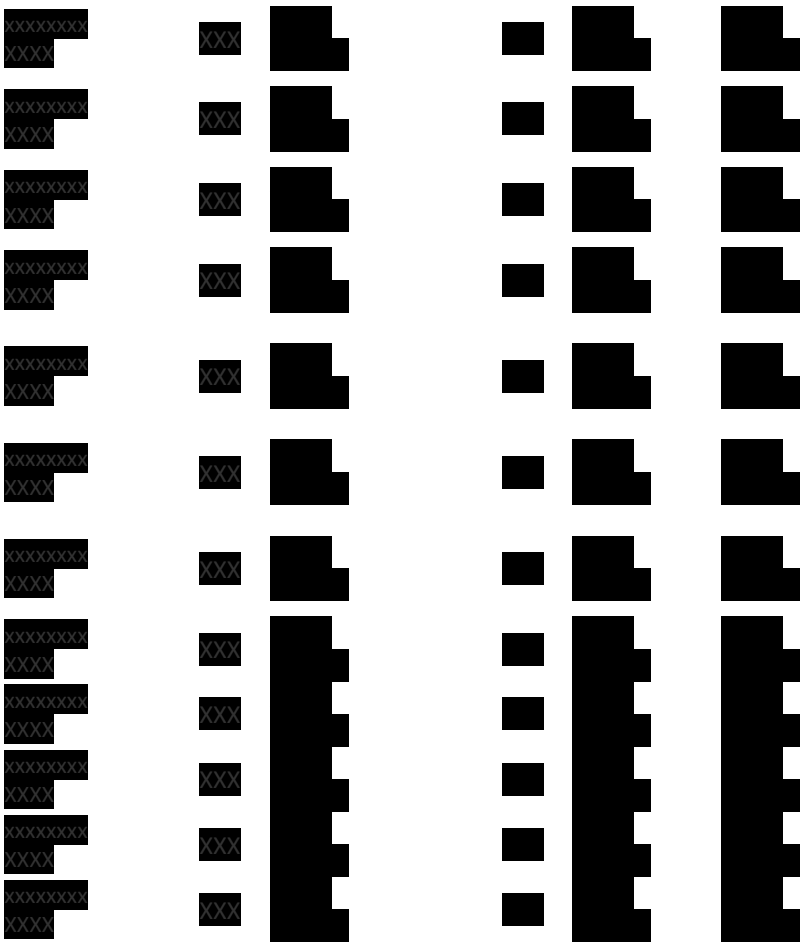
The mean change from baseline in the EORTC QLQ-H&N35 pain score stays close to zero in both treatment arms across most cycles, indicating little overall change in pain from baseline (Figure 10). The toripalimab and placebo curves track closely, and their 95% confidence intervals largely overlap at nearly all time points, suggesting no significant difference between treatments. Any fluctuations are small and not sustained; variability increases in later cycles as the number of patients decreases.

Figure 10 Mean change from baseline in EORTC QLQ-H&N35 (Pain) for both the intervention and comparator (80)

Table 27 HRQoL EORTC QLQ-H&N35 (Pain) (80)

	Intervention		Comparator		Intervention vs. comparator
Time point	Intervention N	Intervention Mean (SD)	Comparator N	Comparator Mean (SD)	Difference (95% CI), p-value
[redacted]					



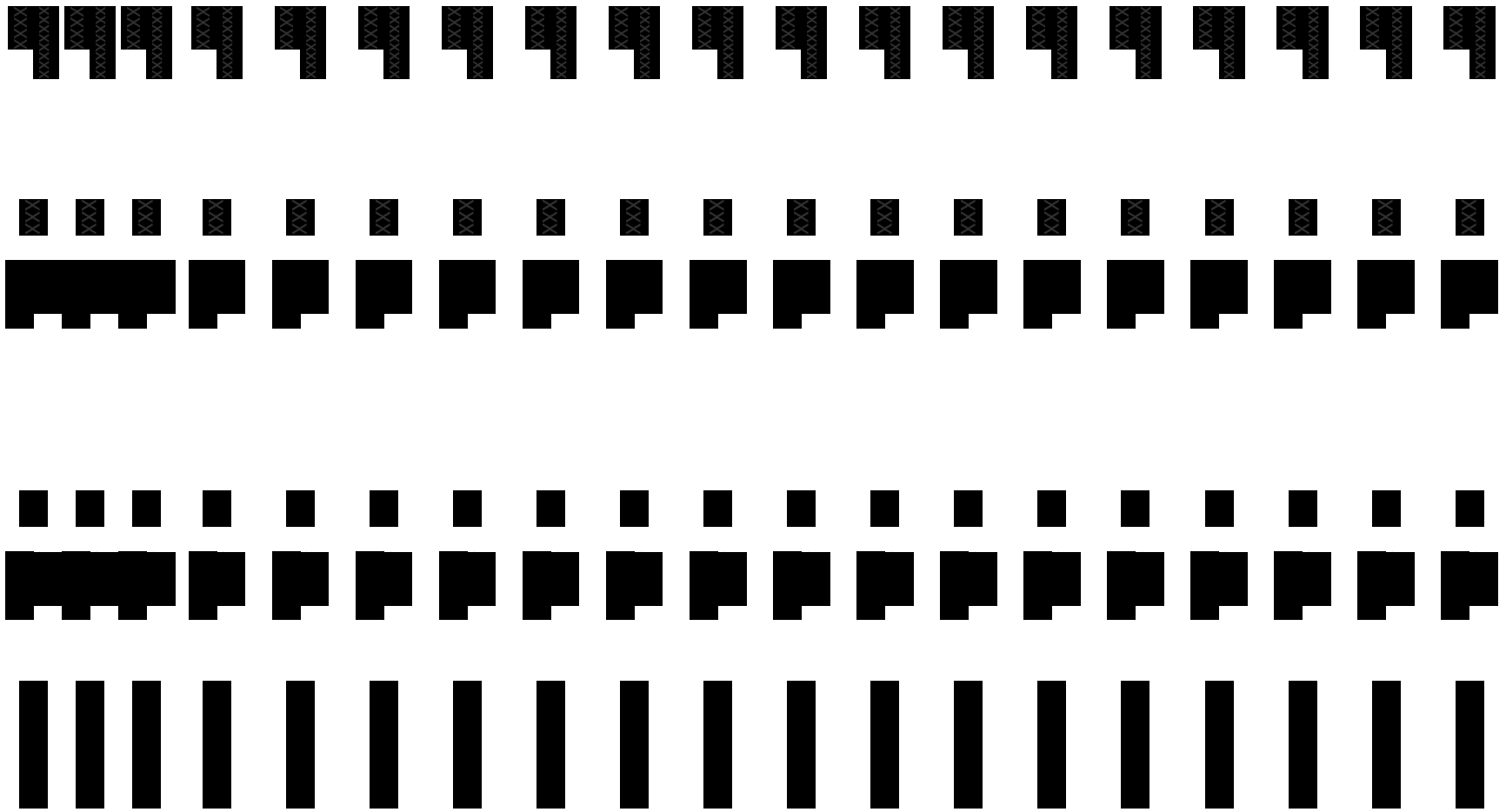


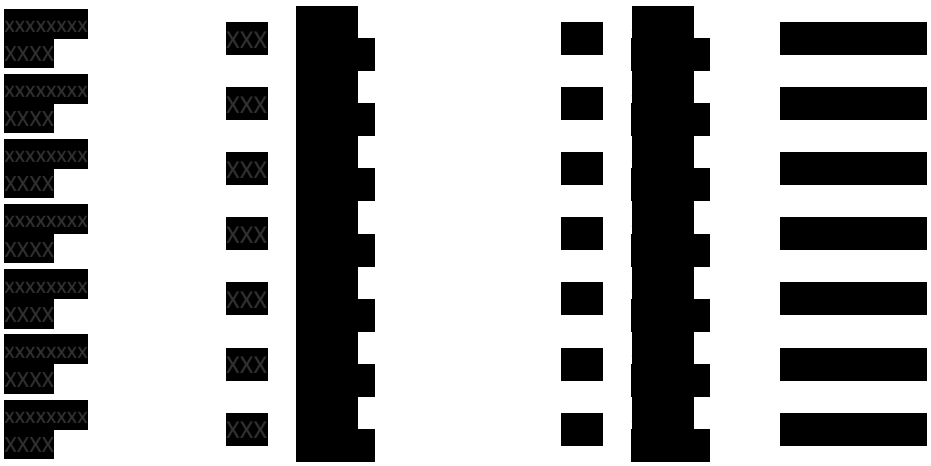
The mean change from baseline in the EORTC QLQ-H&N35 swallowing score remains close to zero in both groups across most cycles, indicating little overall change in swallowing symptoms (Figure 11). Placebo sits slightly above zero more often in early–mid cycles and shows a few upward spikes around the mid cycles; toripalimab trends a bit closer to zero/slightly negative. However, the toripalimab and placebo curves are very similar, with largely overlapping 95% confidence intervals at nearly all time points, suggesting no significant treatment difference. Fluctuations are small and not sustained; variability increases in later cycles as the number of patients declines.

Figure 11 Mean change from baseline in EORTC QLQ-H&N35 (Swallowing) for both the intervention and comparator (80)

Table 28 HRQoL EORTC QLQ-H&N35 (Swallowing) (80)

	Intervention		Comparator		Intervention vs. comparator
Time point	Intervention N	Intervention Mean (SD)	Comparator N	Comparator Mean (SD)	Difference (95% CI), p-value
[redacted]					





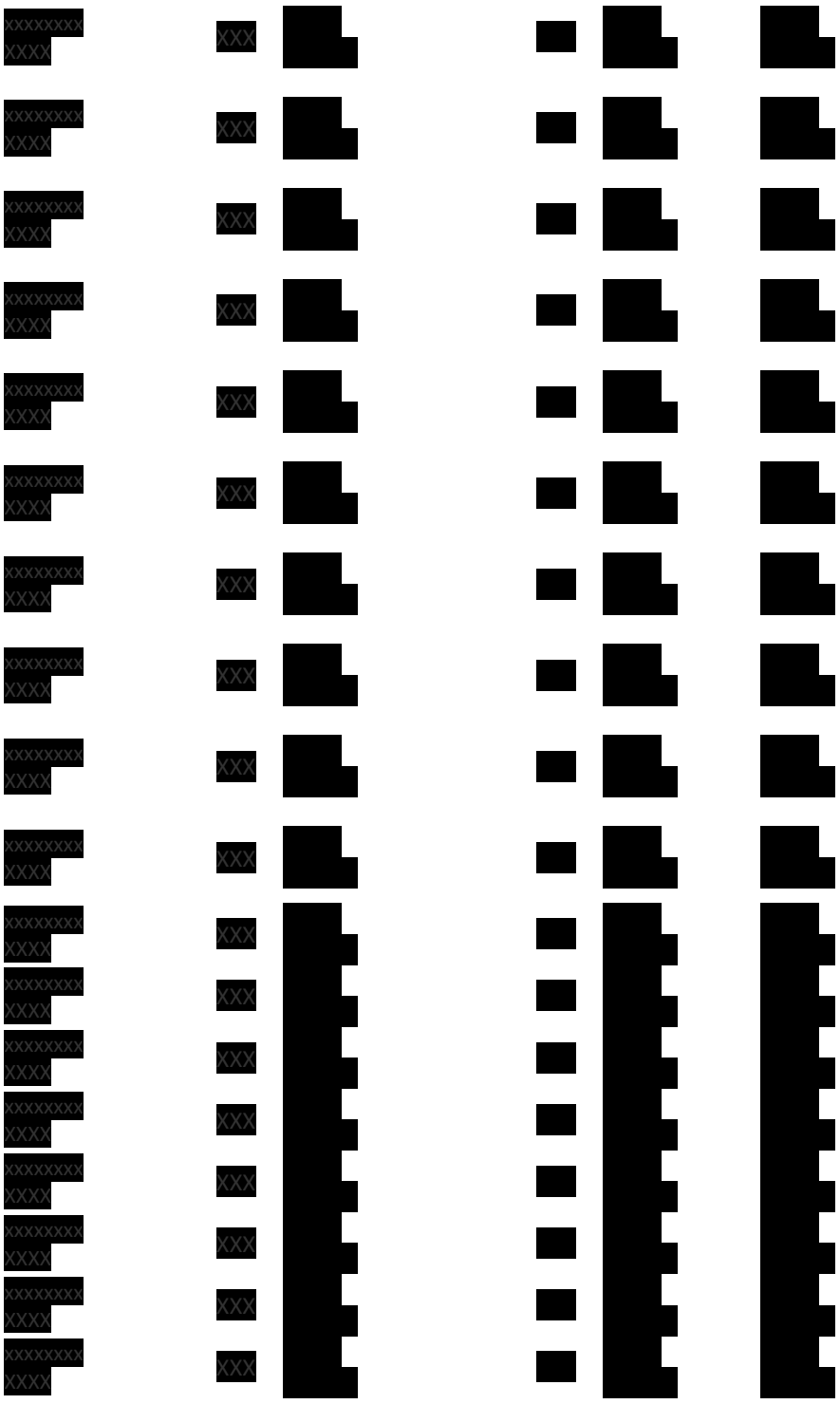
In the EORTC QLQ-H&N35 “Senses problems” scale, both groups show a gradual negative mean change from baseline over time (scores drift below zero), consistent with an overall improvement in this symptom (Figure 12). The toripalimab and placebo curves are closely aligned and their 95% CIs largely overlap across cycles, indicating no clear, significant or sustained between-arm difference. Any late-cycle divergences are small and imprecise, occurring when sample sizes are low, so variability increases toward the end.

Figure 12 Mean change from baseline in EORTC QLQ-H&N35 (Senses problems) for both the intervention and comparator (80)

Table 29 HRQoL EORTC QLQ-H&N35 (Senses problems) (80)

Intervention	Comparator	Intervention vs. comparator

Time point	Intervention N	Intervention Mean (SD)	Comparator N	Comparator Mean (SD)	Difference (95% CI), p-value
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]



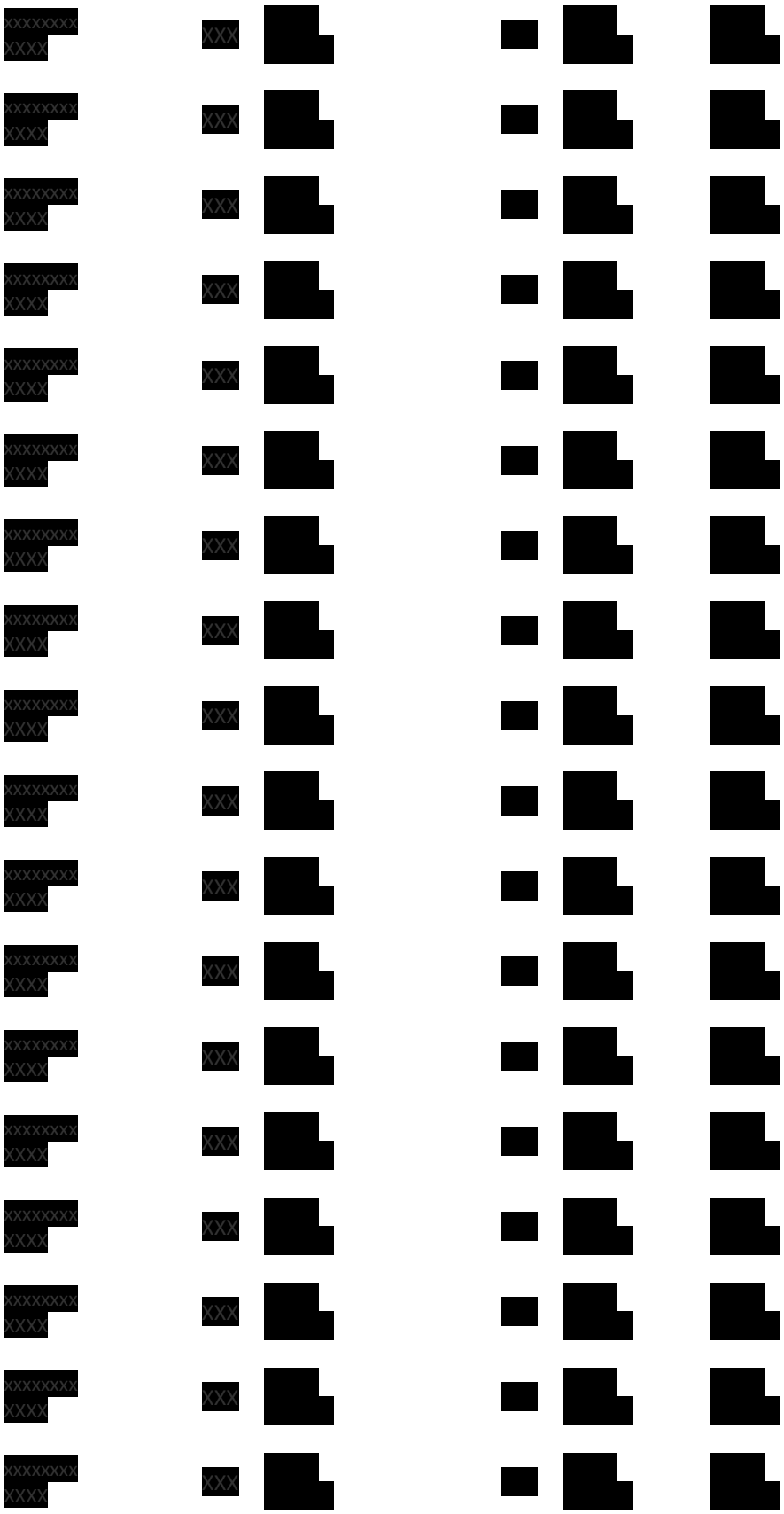
On the EORTC QLQ-H&N35 “Speech problems” score remains close to zero in both groups across for the first 20 cycles, indicating little overall change in speech problems (Figure 13). The two curves separate somewhat after the early cycles, but their 95% confidence intervals overlap at most time points, so a significant, clear, sustained between-arm difference is not established. Late-cycle divergences (placebo spikes above

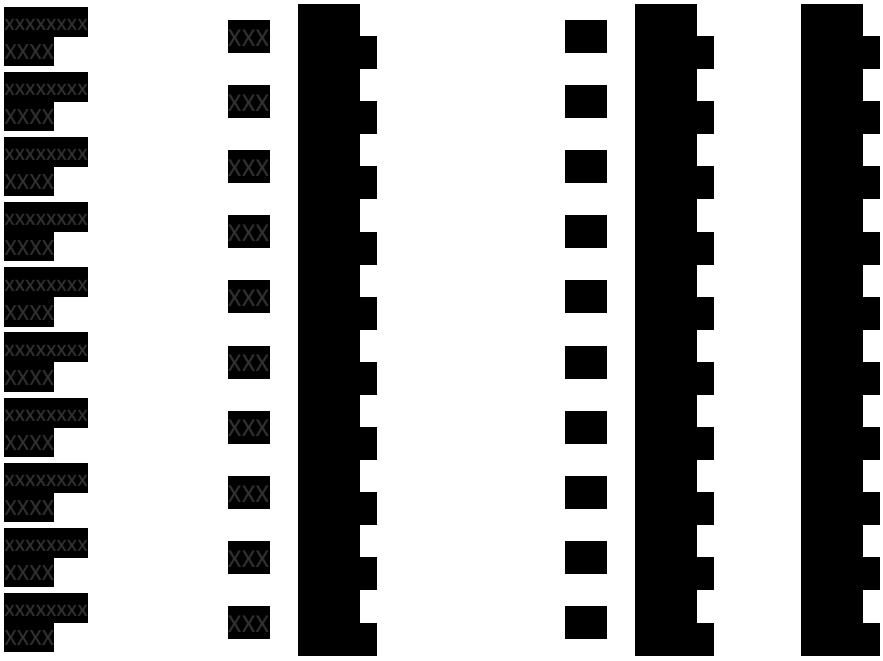
zero and a deeper drop for toripalimab) occur when patient numbers are low, so variability and uncertainty are high.

Figure 13 Mean change from baseline in EORTC QLQ-H&N35 (Speech problems) for both the intervention and comparator (80)

Table 30 HRQoL EORTC QLQ-H&N35 (Speech problems) (80)

	Intervention		Comparator		Intervention vs. comparator
Time point	Intervention N	Intervention Mean (SD)	Comparator N	Comparator Mean (SD)	Difference (95% CI), p-value
[redacted]					



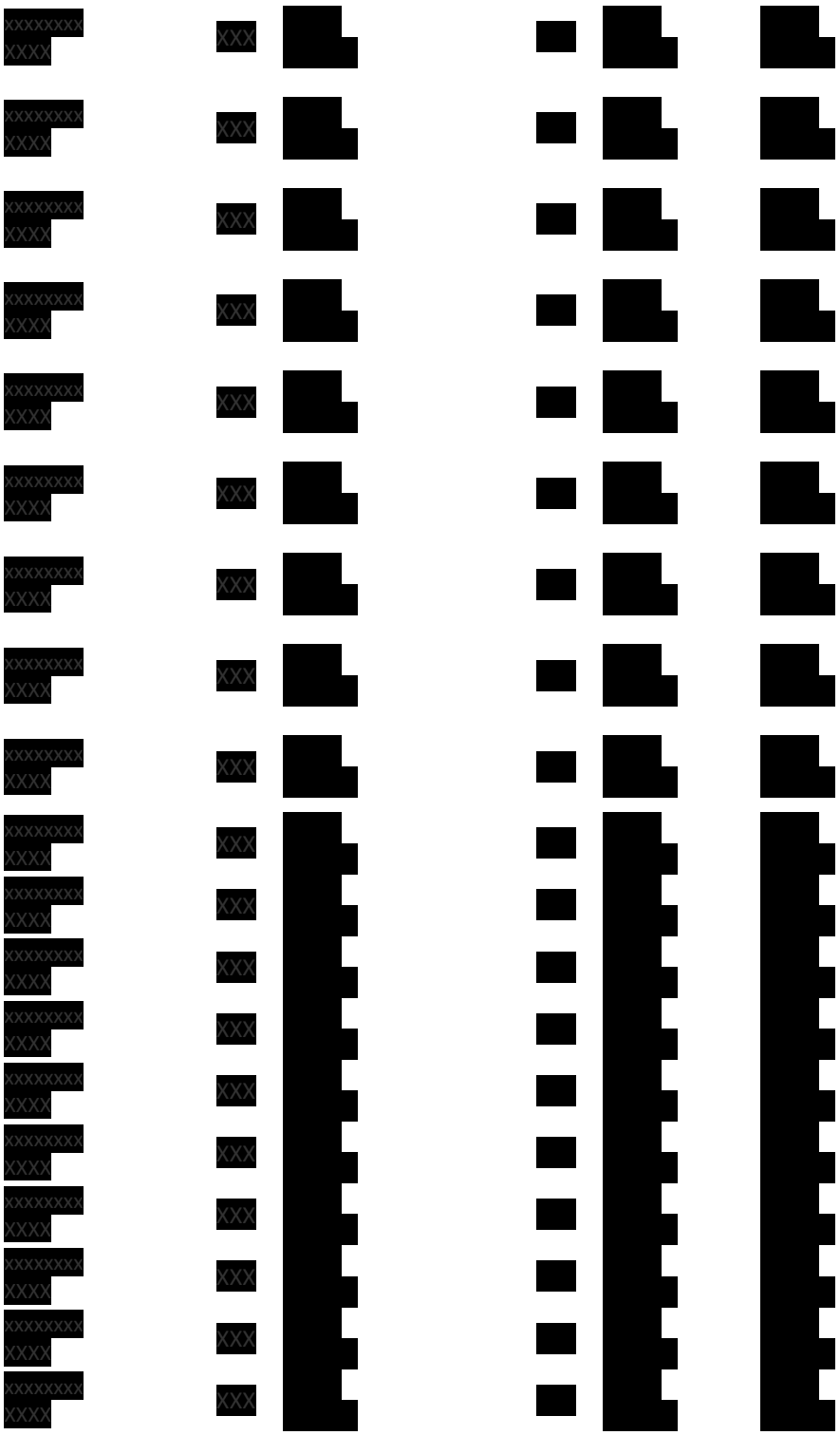


For the “Trouble with social eating” score, mean changes are small and similar between toripalimab and placebo across cycles. Across cycles, the 95% confidence intervals for toripalimab and placebo overlap at most time points. Hence overall, social eating symptoms remained near baseline with no clear treatment effect, and no consistent or clinically significant between-arm differences were observed.

Figure 14 Mean change from baseline in EORTC QLQ-H&N35 (Trouble with social eating) for both the intervention and comparator (80)

Table 31 HRQoL EORTC QLQ-H&N35 (Trouble with social eating) (80)

	Intervention		Comparator		Intervention vs. comparator
Time point	Intervention N	Intervention Mean (SD)	Comparator N	Comparator Mean (SD)	Difference (95% CI), p-value
[redacted]					



On the EORTC QLQ-H&N35 “Trouble with social contact,” both arms start near zero and over time toripalimab trends negative (improvement) while placebo hovers around zero/slightly positive (worsening) (Figure 15). The 95% confidence intervals mostly

overlap and widen in later cycles as patient numbers drop, so no significant between-arm difference is established.

Figure 15 Mean change from baseline in EORTC QLQ-H&N35 (Trouble with social contact) for both the intervention and comparator (80)

Table 32 HRQoL EORTC QLQ-H&N35 (Trouble with social contact) (80)

	Intervention		Comparator		Intervention vs. comparator
Time point	Intervention N	Intervention Mean (SD)	Comparator N	Comparator Mean (SD)	Difference (95% CI), p-value
[redacted]					
[redacted]					
[redacted]					
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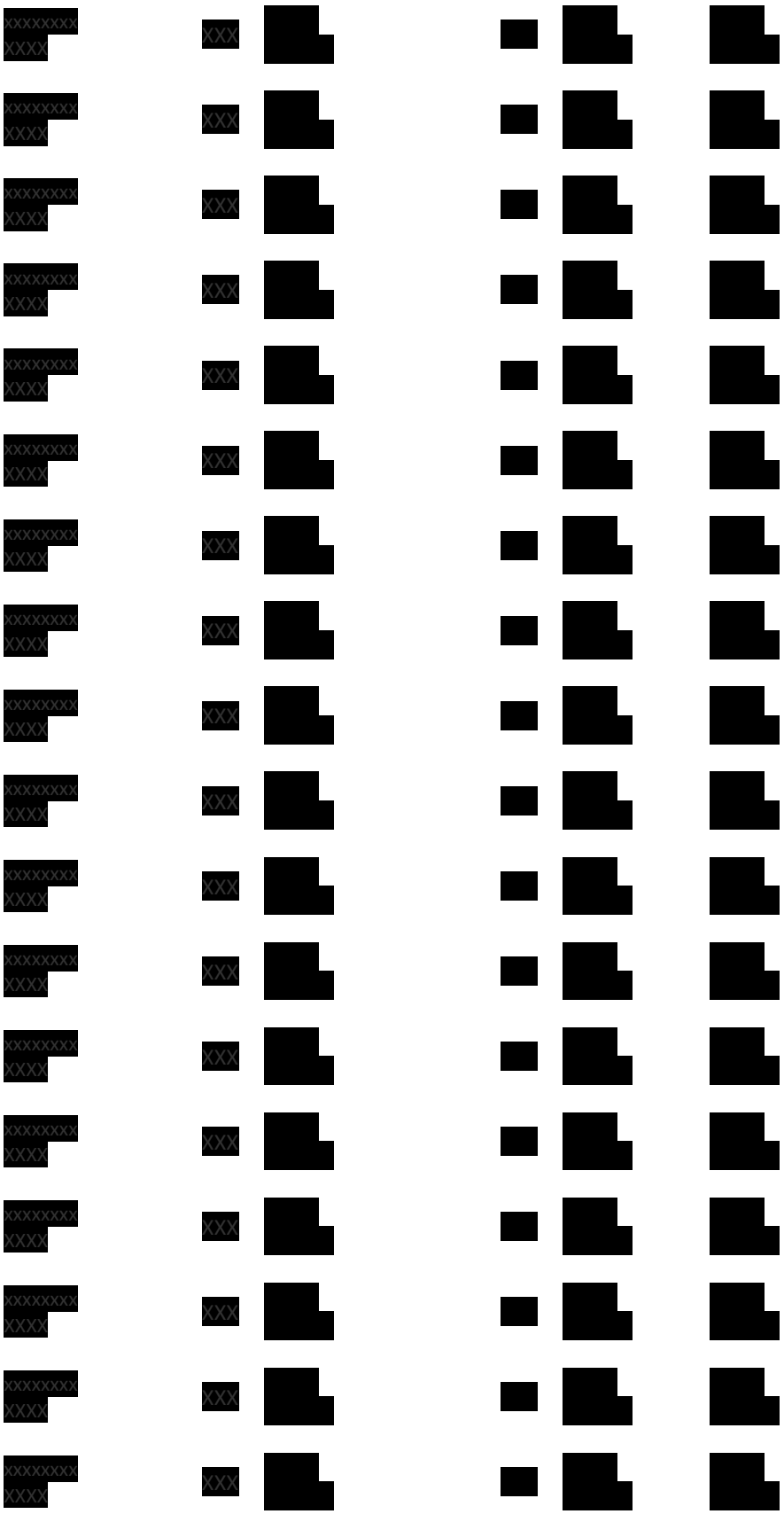
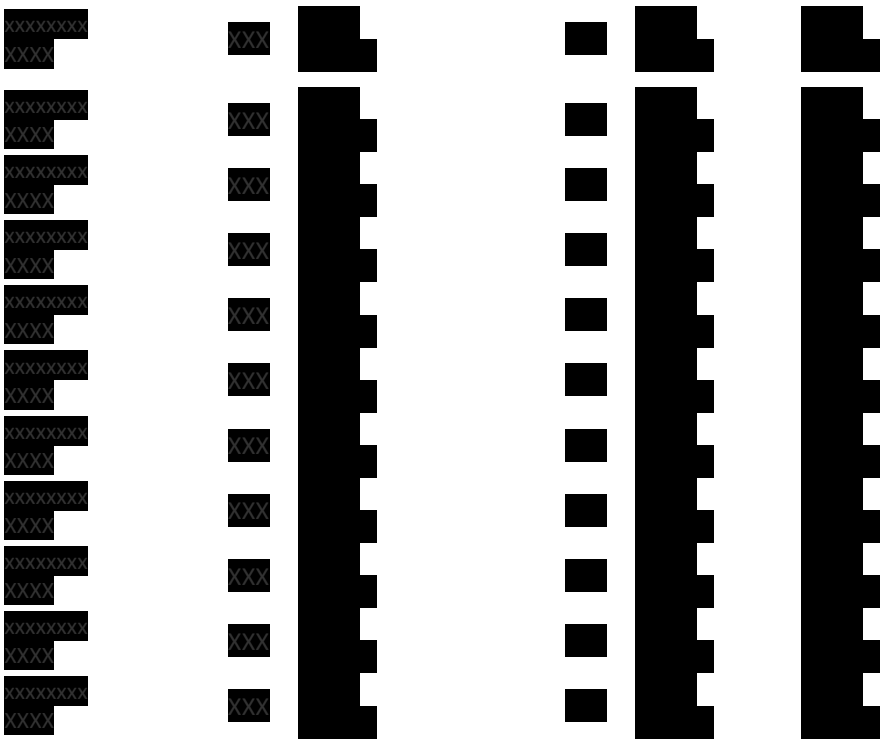
[redacted]					
[redacted]					





On EORTC QLQ–H&N35 “Less sexuality”, mean changes are small and similar between toripalimab and placebo across cycles. Across cycles, the 95% confidence intervals for toripalimab and placebo overlap at most time points. Hence overall, patients sexuality score remained near baseline with no clear treatment effect, and no consistent or clinically significant between-arm differences were observed. (Figure 16).

Figure 16 Mean change from baseline in EORTC QLQ-H&N35 (Less sexuality) for both the intervention and comparator (80)

Table 33 HRQoL EORTC QLQ-H&N35 (Less sexuality) (80)

	Intervention		Comparator		Intervention vs. comparator
Time point	Intervention N	Mean (SD)	Comparator N	Mean (SD)	Difference (95% CI), p-value
[redacted]					
[redacted]					
[redacted]					
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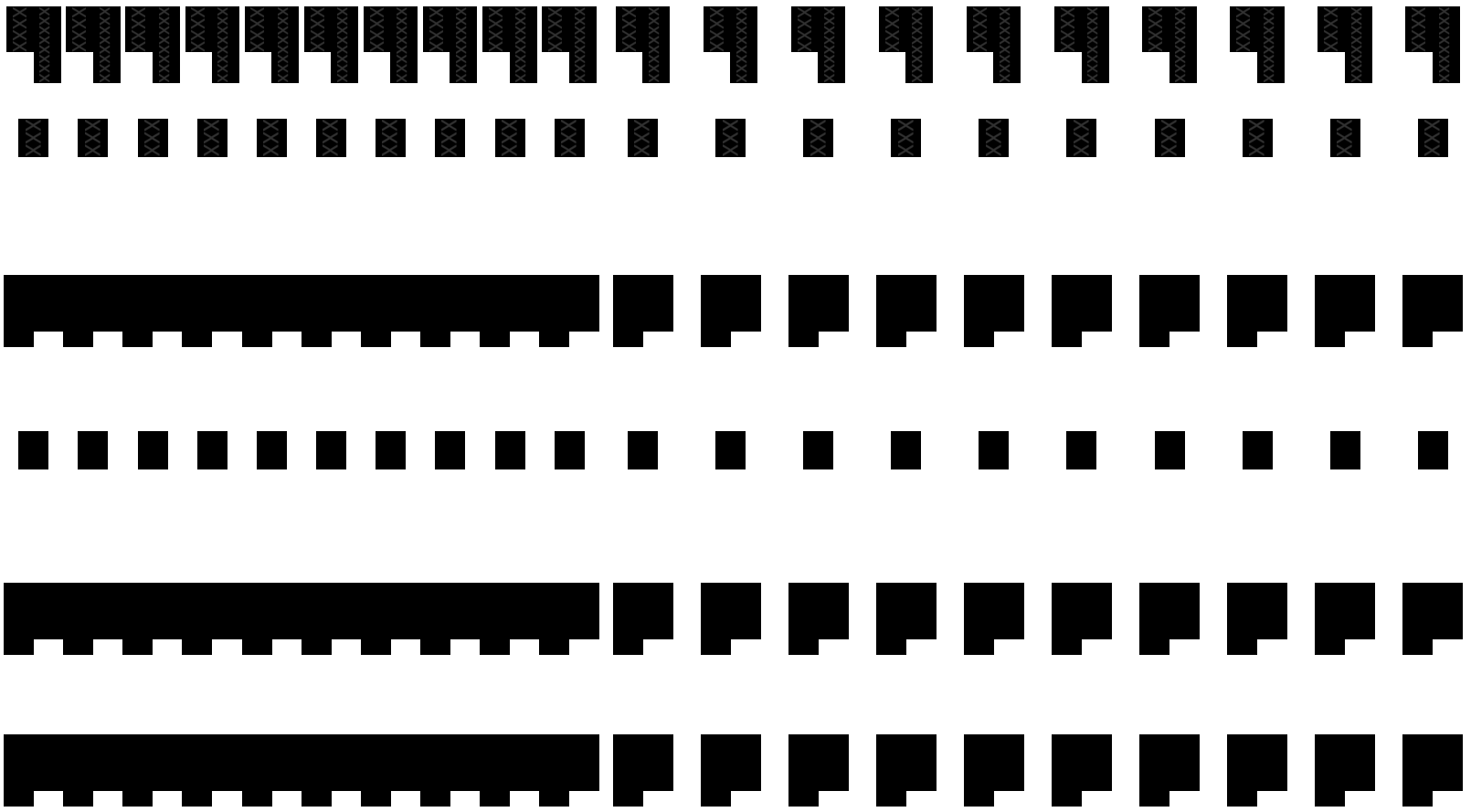

10.2 Health state utility values (HSUVs) used in the health economic model N/A

N/A

10.2.1 HSUV calculation

10.2.1.1 Mapping

10.2.2 Disutility calculation

10.2.3 HSUV results

Table 34 Overview of health state utility values N/A

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				

10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy N/A

N/A

10.3.1 Study design

10.3.2 Data collection

10.3.3 HRQoL Results

10.3.4 HSUV and disutility results

Table 35 Overview of health state utility values N/A

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				

...

Table 36 Overview of literature-based health state utility values N/A

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Study 2				
Study 3				
HSUV B				
...				
[Disutility A]				
...				

11. Resource use and associated costs

N/A

11.1 Medicines - intervention and comparator

N/A

Table 37 Medicines used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing

11.2 Medicines– co-administration

N/A

11.3 Administration costs

N/A

Table 38 Administration costs used in the model N/A

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference

11.4 Disease management costs

N/A

Table 39 Disease management costs used in the model N/A

Activity	Frequency	Unit cost [DKK]	DRG code	Reference

11.5 Costs associated with management of adverse events

N/A

Table 40 Cost associated with management of adverse events N/A

	DRG code	Unit cost/DRG tariff

11.6 Subsequent treatment costs

N/A

Table 41 Medicines of subsequent treatments N/A

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing

11.7 Patient costs

N/A

Table 42 Patient costs used in the model N/A

Activity	Time spent [minutes, hours, days]

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

N/A

12. Results

N/A

12.1 Base case overview

N/A

Table 43 Base case overview N/A

Feature	Description
Comparator	
Type of model	
Time horizon	
Treatment line	
Measurement and valuation of health effects	
Costs included	
Dosage of medicine	
Average time on treatment	

Parametric function for PFS

Parametric function for OS

Inclusion of waste

Average time in model health state

Health state 1

Health state 2

Health state 3

Death

12.1.1 Base case results

N/A

Table 44 Base case results, discounted estimates N/A

	[Intervention]	[Comparator]	Difference
Medicine costs			
Medicine costs – co-administration			
Administration			
Disease management costs			
Costs associated with management of adverse events			
Subsequent treatment costs			
Patient costs			
Palliative care costs			
Total costs			
Life years gained (health state A)			
Life years gained (health state B)			

Total life years

QALYs (state A)

QALYs (state B)

QALYs (adverse reactions)

Total QALYs

Incremental costs per life year gained

Incremental cost per QALY gained (ICER)

12.2 Sensitivity analyses

N/A

12.2.1 Deterministic sensitivity analyses

N/A

Table 45 One-way sensitivity analyses results N/A

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case					

N/A

12.2.2 Probabilistic sensitivity analyses

N/A

13. Budget impact analysis

N/A

Number of patients (including assumptions of market share)

Table 46 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share) N/A

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
			Non-recommendation		

Budget impact

Table 47 Expected budget impact of recommending the medicine for the indication N/A

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended					
The medicine under consideration is NOT recommended					
Budget impact of the recommendation					

14. List of experts

Overlæge Claus Andrup Kristensen, lægelig leder af Klinik for Hoved-Halskræft og Hudkræft, afdeling for kræftbehandling på Rigshospitalet

15. References

1. Helsedirektoratet. Hode-/halskreft - handlingsprogram - nasofarynks 2023 [Available from: https://www.helsedirektoratet.no/retningslinjer/hode-hals-kreft-handlingsprogram/nasofarynks/behandling.
2. Oncology FSfHaN. Hoitosuositus. 2024.
3. Schiess E, Jensen, Kristian, Kristensen, Morten, et al. . Epidemiology and treatment outcome of nasopharyngeal carcinoma in a low-incidence population – a DAHANCA analysis in Denmark 2000–2018. Acta Oncologica. 2024;63.
4. Mai HQ, Chen QY, Chen D, Hu C, Yang K, Wen J, et al. Toripalimab Plus Chemotherapy for Recurrent or Metastatic Nasopharyngeal Carcinoma: The JUPITER-02 Randomized Clinical Trial. Jama. 2023;330(20):1961–70.
5. Sinha S, Winters R, Gajra A. Nasopharyngeal Cancer. StatPearls. Treasure Island (FL)2025.
6. Toumi N, Ennouri S, Charfeddine I, Daoud J, Khanfir A. Prognostic factors in metastatic nasopharyngeal carcinoma. Brazilian Journal of Otorhinolaryngology. 2022;88(2):212–9.
7. Xu T, Tang J, Gu M, Liu L, Wei W, Yang H. Recurrent Nasopharyngeal Carcinoma: A Clinical Dilemma and Challenge. Current Oncology. 2013;20(5):406–19.
8. Lin W, Chen X, Huang Z, Ding Q, Yang H, Li Y, et al. Identification of novel molecular subtypes to improve the classification framework of nasopharyngeal carcinoma. British Journal of Cancer. 2024;130(7):1176–86.
9. Chang ET, Liu Z, Hildesheim A, Liu Q, Cai Y, Zhang Z, et al. Active and Passive Smoking and Risk of Nasopharyngeal Carcinoma: A Population-Based Case-Control Study in Southern China. Am J Epidemiol. 2017;185(12):1272–80.
10. Guo X, Johnson RC, Deng H, Liao J, Guan L, Nelson GW, et al. Evaluation of nonviral risk factors for nasopharyngeal carcinoma in a high-risk population of Southern China. Int J Cancer. 2009;124(12):2942–7.
11. Tsao SW, Yip YL, Tsang CM, Pang PS, Lau VM, Zhang G, et al. Etiological factors of nasopharyngeal carcinoma. Oral Oncol. 2014;50(5):330–8.
12. van Velsen JS, van der Vegt B, Plaat BEC, Langendijk JA, Epskamp-Kuijpers C, van Dijk BAC, et al. Nasopharyngeal carcinoma: nationwide trends in subtype-specific incidence and survival over 3 decades in a non-endemic area. J Cancer Res Clin Oncol. 2024;150(2):49.
13. Gille E, Näsman, A., Helmersson, M., Marsk, E., Mäkitie, A., Hammerstedt-Nordenvall, L. The burden and outcome of nasopharyngeal carcinoma in Sweden. Acta Oncologica. 2025;64:894–901.
14. Bossi P, Trama A, Bernasconi A, Grisanti S, Mohamad I, Galiana IL, et al. Nasopharyngeal cancer in non-endemic areas: Impact of treatment intensity within a large retrospective multicentre cohort. Eur J Cancer. 2021;159:194–204.
15. Ruuskanen M, Grenman R, Leivo I, Vahlberg T, Mäkitie A, Saarilahti K, et al. Outcome of nasopharyngeal carcinoma in Finland: A nationwide study. Acta Oncologica. 2018;57(2):251–6.
16. Ruuskanen MI, H.; Minn, H.; Vahlberg, T.; Randen-Brandy, R.; Hagström, J.; Syrjänen, S.; Leivo, I. Epstein-Barr virus and human papillomaviruses as favorable prognostic factors in nasopharyngeal carcinoma: A nationwide study in Finland. Head Neck. 2018;41(2):439–357.
17. American Cancer Society. What Is Nasopharyngeal Cancer? 2022 [Available from: https://www.cancer.org/cancer/types/nasopharyngeal-cancer/about/what-is-nasopharyngeal-cancer.html#:~:text=Non%2Dkeratinizing%20differentiated%20carcinoma%20is,is%20often%20associated%20with%20EBV.

18. de Martel C, Georges D, Bray F, Ferlay J, Clifford GM. Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis. Lancet Glob Health. 2020;8(2):e180–e90.
19. Wong Y, Meehan MT, Burrows SR, Doolan DL, Miles JJ. Estimating the global burden of Epstein-Barr virus-related cancers. J Cancer Res Clin Oncol. 2022;148(1):31–46.
20. Su ZY, Siak PY, Leong C-O, Cheah S-C. Nasopharyngeal Carcinoma and Its Microenvironment: Past, Current, and Future Perspectives. Frontiers in Oncology. 2022;Volume 12 - 2022.
21. Chang ET, Ye W, Zeng YX, Adami HO. The Evolving Epidemiology of Nasopharyngeal Carcinoma. Cancer Epidemiol Biomarkers Prev. 2021;30(6):1035–47.
22. Krishnan M, Jothi shanmugam A, Babu S. PD-L1 mediated immune escape in nasopharyngeal carcinoma: Impact of LMP1 and IFN-γ on immune surveillance. Oral Oncology Reports. 2024;12:100688.
23. Chen BJ, Chapuy B, Ouyang J, Sun HH, Roemer MG, Xu ML, et al. PD-L1 expression is characteristic of a subset of aggressive B-cell lymphomas and virus-associated malignancies. Clin Cancer Res. 2013;19(13):3462–73.
24. Amene C, Cosetti M, Ambekar S, Guthikonda B, Nanda A. Johann Christian Rosenmüller (1771-1820): A Historical Perspective on the Man behind the Fossa. J Neurol Surg B Skull Base. 2013;74(4):187–93.
25. Shah AB, Nagalli S. Nasopharyngeal Carcinoma. StatPearls. Treasure Island (FL)2025.
26. National Health Service. Nasopharyngeal cancer [Available from: https://www.nhs.uk/conditions/nasopharyngeal-cancer/.
27. Chow JCH, Lee A, Bao KKH, Cheung KM, Chan JCH, Tam AHP, et al. Cranial neuropathies in advanced nasopharyngeal carcinoma: Neurological recovery after modern radiotherapy and systemic chemotherapy. Radiotherapy and Oncology. 2021;163:221–8.
28. American Cancer Society. Signs and Symptoms of Nasopharyngeal Cancer [Available from: https://www.cancer.org/cancer/types/nasopharyngeal-cancer/detection-diagnosis-staging/signs-and-symptoms.html.
29. An G, Liu J, Lin T, He L, He Y. Global trends in research of nasopharyngeal carcinoma: a bibliometric and visualization analysis. Frontiers in Oncology. 2024;Volume 14 - 2024.
30. Li JX, Lu TX, Huang Y, Han F. Clinical characteristics of recurrent nasopharyngeal carcinoma in high-incidence area. ScientificWorldJournal. 2012;2012:719754.
31. Peng Z, Wang Y, Fan R, Gao K, Xie S, Wang F, et al. Treatment of Recurrent Nasopharyngeal Carcinoma: A Sequential Challenge. Cancers (Basel). 2022;14(17).
32. Li W, Lu H, Wang H, Zhang H, Sun X, Hu L, et al. Salvage Endoscopic Nasopharyngectomy in Recurrent Nasopharyngeal Carcinoma: Prognostic Factors and Treatment Outcomes. Am J Rhinol Allergy. 2021;35(4):458–66.
33. Liu YP, Wen YH, Tang J, Wei Y, You R, Zhu XL, et al. Endoscopic surgery compared with intensity-modulated radiotherapy in resectable locally recurrent nasopharyngeal carcinoma: a multicentre, open-label, randomised, controlled, phase 3 trial. Lancet Oncol. 2021;22(3):381–90.
34. Bramerson A, Nyman J, Nordin S, Bende M. Olfactory loss after head and neck cancer radiation therapy. Rhinology. 2013;51(3):206–9.
35. McDowell L, So N, Keshavarzi S, Xu W, Rock K, Chan B, et al. Sexual satisfaction in nasopharyngeal carcinoma survivors: Rates and determinants. Oral Oncology. 2020;109:104865.
36. Rieu R, Prestwich RJ, Paterson C, Vohra S, Swan A, Noble D, et al. A Multicenter Study of Clinician and Patient Reported Acute and Late Toxicity after Radical (Chemo)Radiotherapy for Non-Endemic Nasopharyngeal Cancer. International Journal of Radiation Oncology, Biology, Physics. 2023;117(2):e619.

37. Ursino S, Calistri E, De Felice F, Bonomo P, Desideri I, Franco P, et al. Patient-Reported Outcomes After Swallowing (SWOARs)-Sparing IMRT in Head and Neck Cancers: Primary Results from a Prospective Study Endorsed by the Head and Neck Study Group (HNSG) of the Italian Association of Radiotherapy and Clinical Oncology (AIRO). Dysphagia. 2023;38(1):159–70.
38. Bond SM, Hawkins DK, Murphy BA. Caregiver-reported neuropsychiatric symptoms in patients undergoing treatment for head and neck cancer: a pilot study. Cancer Nurs. 2014;37(3):227–35.
39. Mo Y, Lai X, Li L, Lu Y-z. Sleep, depression, and anxiety in family caregivers of nasopharyngeal carcinoma patients before therapy. Acta Psychologica. 2022;223:103504.
40. Tang Y, Hua Y, Huang X, Cao Y, Sun X. Psychological Burden of Patients with Head and Neck Cancer Undergoing Radiotherapy and Their Family Caregivers: A Cross-Sectional Survey. J Multidiscip Healthc. 2023;16:927–35.
41. Mäkitie A, Ruuskanen M, Bentzen J, Brun E, Gebre-Medhin M, Friesland S, et al. The management and survival outcomes of nasopharyngeal cancer in the Nordic countries*. Acta Oncologica. 2018;57(4):557–60.
42. DAHANCA. Nationale retningslinjer for udredning, behandling, rehabilitering og kontrolforløb for patienter med Pharynx- og Larynx-Cancer i Danmark. 2011.
43. DAHANCA.dk DHaNCG. Årsrapport 2024 for den kliniske kvalitetsdatabase DAHANCA. 2025.
44. Wu T, Miao W, Qukuerhan A, Alimu N, Feng J, Wang C, et al. Global, Regional, and National Burden of Nasopharyngeal Carcinoma from 1990 to 2021. The Laryngoscope. 2025;135(4):1409–18.
45. LEO Pharma. [Data on file] Addendum to Phase III Clinical Study Report of Toripalimab (Tuoyi®). 2023.
46. European Medicines Agency (EMA). Summary of Product Charateristics, LOQTORZI. 2024.
47. Gold J, A R. Cisplatin. Treasure Island (FL) [Internet]: StatPearls Publishing; 2023.
48. Ngan RK, Yiu HH, Lau WH, Yau S, Cheung FY, Chan TM, et al. Combination gemcitabine and cisplatin chemotherapy for metastatic or recurrent nasopharyngeal carcinoma: report of a phase II study. Ann Oncol. 2002;13(8):1252–8.
49. Gold JRA. Cisplatin. Treasure Island (FL) [Internet]: StatPearls Publishing; 2023.
50. LEO Pharma. [Data on file] Addendum to Phase III Clinical Study Report of Toripalimab (Tuoyi®). 2021.
51. Chen QY. Abstract 669M0: Long term overall survival follow-up of toripalimab versus placebo in combination with gemcitabine and cisplatin as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma. ESMO Asia Congress 2025. https://oncologypro.esmo.org/congress-resources/esmo-asia-congress-2025?presentation=long_term_overall_survival_follow_up_of_toripalima2025.
52. DMC. Medicinrådets anbefaling vedr. daratumumab i kombination med lenalidomid og dexamethason til behandling af patienter med nydiagnosticeret myelomatose, som ikke er kandidater til autolog stamcelletransplantation. 2024.
53. DMC. Medicinrådets anbefaling vedrørende daratumumab i kombination med bortezomib, melphalan og prednison til nydiagnosticerede patienter med knoglemarvskræft, som ikke er egnede til højdosiskemoterapi med stamcellestøtte. 2021.
54. Medicinrådet. Baggrund for Medicinrådets anbefaling vedrørende pembrolizumab som førstelinjebehandling af recidiverende eller metastatisk planocellulær hovedhalskræft. 2020.
55. Medicinrådet. Baggrund for Medicinrådets anbefaling vedrørende pembrolizumab som mulig standardbehandling til hoved-halskræft. 2019.

56. Rotolo F, Pignon J-P, Bourhis J, Marguet S, Leclercq J, Tong Ng W, et al. Surrogate End Points for Overall Survival in Loco-Regionally Advanced Nasopharyngeal Carcinoma: An Individual Patient Data Meta-analysis. JNCI: Journal of the National Cancer Institute. 2016;109(4).
57. Chen YP, Sun Y, Chen L, Mao YP, Tang LL, Li WF, et al. Surrogate endpoints for overall survival in combined chemotherapy and radiotherapy trials in nasopharyngeal carcinoma: Meta-analysis of randomised controlled trials. Radiother Oncol. 2015;116(2):157–66.
58. Ailawadhi S, Ogbonnaya A, Murty S, Cherepanov D, Schroader BK, Romanus D, et al. Duration of frontline therapy and impact on clinical outcomes in newly diagnosed multiple myeloma patients not receiving frontline stem cell transplant. Cancer Med. 2023;12(3):3145–59.
59. Chen Y-P, Yong Chen, Wen-Na Zhang, Shao-Bo Liang, Jing-Feng Zong, Lei Chen, Yan-Ping Mao, Ling-Long Tang, Wen-Fei Li, Xu Liu, Ying Guo, Ai-Hua Lin, Meng-Zhong Liu, Ying Sun, Jun Ma. Potential surrogate endpoints for overall survival in locoregionally advanced nasopharyngeal carcinoma: an analysis of a phase III randomized trial. Sci Rep. 2015;5.
60. Blanchard P LA, Carmel A, Wai Tong N, Ma J, Chan ATC, Hong RL, Chen MY, Chen L, Li WF, Huang PY, Kwong DLW, Poh SSX, Ngan R, Mai HQ, Ollivier C, Fountzilas G, Zhang L, Bourhis J, Aupérin A, Lacas B, Pignon JP; MAC-NPC collaborative Group. Meta-analysis of chemotherapy in nasopharynx carcinoma (MAC-NPC): An update on 26 trials and 7080 patients. Clinical and Translational Radiation Oncology. 2021;26(32):59–68.
61. Chen YP CY, Zhang WN, Liang SB, Zong JF, Chen L, Mao YP, Tang LL, Li WF, Liu X, Guo Y, Lin AH, Liu MZ, Sun Y, Ma J. Potential surrogate endpoints for overall survival in locoregionally advanced nasopharyngeal carcinoma: an analysis of a phase III randomized trial. Sci Rep. 2015;5.
62. Food and Drug Administration FDA. Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. 2018.
63. Jain A, Stebbing, Justin. The Relationship Between Response Rate and Survival Benefits in Randomized Immunotherapy Studies. Cancers (Basel). 2025;2(17).
64. Yan L RB, Hu R, Zhang H, Gou H. Are PD-1 inhibitors effective for recurrent/metastatic nasopharyngeal carcinoma? Meta-analysis and systematic review. Frontiers in Pharmacology. 2023;9(13).
65. Ma BBY LW, Goh BC, Hui EP, Lo KW, Pettinger A, Foster NR, Riess JW, Agulnik M, Chang AYC, Chopra A, Kish JA, Chung CH, Adkins DR, Cullen KJ, Gitlitz BJ, Lim DW, To KF, Chan KCA, Lo YMD, King AD, Erlichman C, Yin J, Costello BA, Chan ATC. Antitumor Activity of Nivolumab in Recurrent and Metastatic Nasopharyngeal Carcinoma: An International, Multicenter Study of the Mayo Clinic Phase 2 Consortium (NCI-9742). Journal of Clinical Oncology. 2018;10.
66. Wang FH WX, Feng J, Li Q, Xu N, Hu XC, Liao W, Jiang Y, Lin XY, Zhang QY, Yuan XL, Huang HX, Chen Y, Dai GH, Shi JH, Shen L, Yang SJ, Shu YQ, Liu YP, Wang W, Wu H, Feng H, Yao S, Xu RH. Efficacy, Safety, and Correlative Biomarkers of Toripalimab in Previously Treated Recurrent or Metastatic Nasopharyngeal Carcinoma: A Phase II Clinical Trial (POLARIS-02). Journal of Clinical Oncology. 2021;1.
67. Xu JY, Wei XL, Wang YQ, Wang FH. Current status and advances of immunotherapy in nasopharyngeal carcinoma. Ther Adv Med Oncol. 2022;14:17588359221096214.
68. Ma S-X, Zhou T, Huang Y, Yang Y-P, Zhan J-H, Zhang Y-X, et al. The efficacy of first-line chemotherapy in recurrent or metastatic nasopharyngeal carcinoma: a systematic review and metaanalysis. Annals of Translational Medicine. 2018;6(11):201.
69. Nakashima K, Horita N, Nagai K, Manabe S, Murakami S, Ota E, et al. Progression-Free Survival, Response Rate, and Disease Control Rate as Predictors of Overall Survival in Phase III Randomized Controlled Trials Evaluating the First-Line Chemotherapy

for Advanced, Locally Advanced, and Recurrent Non–Small Cell Lung Carcinoma. Journal of Thoracic Oncology. 2016;11(9):1574–85.
70. Siak PY, Heng WS, Teoh SSH, Lwin YY, Cheah S-C. Precision medicine in nasopharyngeal carcinoma: comprehensive review of past, present, and future prospect. Journal of Translational Medicine. 2023;21(1).
71. Hu C, Wang M, Wu C, Zhou H, Chen C, Diede S. Comparison of Duration of Response vs Conventional Response Rates and Progression-Free Survival as Efficacy End Points in Simulated Immuno-oncology Clinical Trials. JAMA Netw Open. 2021;4(5):e218175.
72. Chen Q-Y, Mai H-Q, Chen D-P, Hu C-s, Yang K, Wen J, et al. Four-year overall survival follow-up and dynamic EBV titer analysis of toripalimab versus placebo in combination with gemcitabine and cisplatin as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma (r/m NPC). Journal of Clinical Oncology. 2024;42(16_suppl):6039–.
73. Mai HQ, Chen QY, Chen D, Hu C, Yang K, Wen J, et al. Toripalimab or placebo plus chemotherapy as first-line treatment in advanced nasopharyngeal carcinoma: a multicenter randomized phase 3 trial. Nat Med. 2021;27(9):1536–43.
74. Mai HQ, Chen QY, Chen D, Hu C, Yang K, Wen J, et al. Abstract CT226: Final progression-free survival analysis of JUPITER-02, a randomized, double-blind, phase 3 study of toripalimab or placebo plus gemcitabine and cisplatin as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma. Cancer Res. 2022;82(12).
75. Mai H-Q, Chen Q-Y, Chen D-P, Hu C, Yang K, Wen J, et al. Final overall survival analysis of JUPITER-02: A phase 3 study of toripalimab versus placebo in combination with gemcitabine and cisplatin as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma (NPC). Journal of Clinical Oncology. 2023;41(16_suppl):6009–.
76. Xu R-h, Mai H-Q, Chen Q-Y, Chen D, Hu C, Yang K, et al. JUPITER-02: Randomized, double-blind, phase III study of toripalimab or placebo plus gemcitabine and cisplatin as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma (NPC). Journal of Clinical Oncology. 2021;39(18_suppl):LBA2–LBA.
77. LEO Pharma. [Data on file], Addendum 2 to Phase III Clinical Study Report of Toripalimab. 2022.
78. LEO Pharma. [Data on file] Addendum 3 to Phase III Clinical Study Report of Toripalimab (Tuoyi®). 2023.
79. LEO Pharma. [Data on file] Addendum 1 to Phase III Clinical Study Report of Toripalimab (Tuoyi®). 2021.
80. LEO Pharma. [Data on FIle] Phase III Clinical Study Report of Toripalimab (Tuoyi®). 2021.
81. European Organisation for Research and Treatment of Cancer. EORTC QLQ-C30 Scoring Manual. 2001.

Appendix A. Main characteristics of studies included

Table 48 Main characteristic of studies included (4)

Trial name: Jupiter-02 - A Phase III, Randomized, Placebo Controlled, Multicenter, Double-Blind Study Comparing Toripalimab Injection (JS001) Combined With Chemotherapy Versus Placebo Combined With Chemotherapy for Recurrent or Metastatic Nasopharyngeal Cancer	NCT number: NCT03581786
Objective	To determine the efficacy and safety of TORIPALIMAB INJECTIO (JS001) in combination with gemcitabine/cisplatin compared with placebo in combination with gemcitabine/cisplatin as first-line treatment in patients with histological/cytological confirmation of recurrent or metastatic NPC. The primary objective is to compare PFS as assessed by the IRC in ITT population (all randomized patients).
Publications – title, author, journal, year	Toripalimab Plus Chemotherapy for Recurrent or Metastatic Nasopharyngeal Carcinoma: The JUPITER-02 Randomized Clinical Trial. Mai HQ, Chen QY, Chen D, Hu C, Yang K, Wen J, Li J, Shi Y, Jin F, Xu R, Pan J, Qu S, Li P, Hu C, Liu YC, Jiang Y, He X, Wang HM, Lim WT, Liao W, He X, Chen X, Wang S, Yuan X, Li Q, Lin X, Jing S, Chen Y, Lu Y, Hsieh CY, Yang MH, Yen CJ, Samol J, Luo X, Wang X, Tang X, Feng H, Yao S, Keegan P, Xu RH. JAMA. 2023 Nov 28;330(20):1961-1970. doi: 10.1001/jama.2023.20181. PMID: 38015220; PMCID: PMC10685882. Toripalimab or placebo plus chemotherapy as first-line treatment in advanced nasopharyngeal carcinoma: a multicenter randomized phase 3 trial. Mai HQ, Chen QY, Chen D, Hu C, Yang K, Wen J, Li J, Shi YR, Jin F, Xu R, Pan J, Qu S, Li P, Hu C, Liu YC, Jiang Y, He X, Wang HM, Lim WT, Liao W, He X, Chen X, Liu Z, Yuan X, Li Q, Lin X, Jing S, Chen Y, Lu Y, Hsieh CY, Yang MH, Yen CJ, Samol J, Feng H, Yao S, Keegan P, Xu RH. Nat Med. 2021 Sep;27(9):1536-1543. doi: 10.1038/s41591-021-01444-0. Epub 2021 Aug 2.
Study type and design	A randomized, placebo-controlled, multi-center, double blinded, Phase III study. Patients were enrolled and randomized in a 1:1 ratio to the group of JS001 (Arm A) with gemcitabine and cisplatin or placebo (Arm B) with gemcitabine and cisplatin every 3 weeks (Q3W) in the 'during chemotherapy' phase. During the 'post-chemotherapy' phase, patients randomized to Arm A or Arm B continued treatment with JS001 or placebo as maintenance therapy Q3W until excessive toxicity or progressive disease, withdrawal of consent or Investigator's judgement or a maximum of 2 years. Tumor evaluation scans was performed at screening (as baseline) then every 6weeks in

Trial name: Jupiter-02 - A Phase III, Randomized, Placebo Controlled, Multicenter, Double-Blind Study Comparing Toripalimab Injection (JS001) Combined With Chemotherapy Versus Placebo Combined With Chemotherapy for Recurrent or Metastatic Nasopharyngeal Cancer	NCT number: NCT03581786

	the first 12 months then every 9 weeks thereafter until objective disease progression. The study is completed.
Sample size (n)	*289*
Main inclusion criteria	Key inclusion criteria for the JUPITER-02 trial included: 1. Age ≥18 years and ≤75 years 2. Histological/cytological confirmation of NPC 3. Primarily metastatic (stage IVB as defined by the International Union against Cancer and American Joint Committee on Cancer staging system for NPC, eighth edition) or recurrent NPC that is not amenable for local-regional treatment or curative treatment 4. At least one measurable lesion according to RECIST version 1.1 5. Life expectancy ≥3 months
Main exclusion criteria	Key exclusion criteria for the JUPITER-02 trial included: 1. History of severe hypersensitivity reactions to other monoclonal antibodies (mAbs) or any ingredient of JS001 2. Prior therapy targeting PD-1 receptor, or its ligand PD-L1, or cytotoxic T lymphocyte associated protein 4 (CTLA4) receptor 3. Major surgical procedure other than for diagnosis of NPC within 28 days prior to randomization or anticipation of need for a major surgical procedure during the trial 4. History of hypersensitivity to gemcitabine or cisplatin or to any of the excipients 5. Female patients who were pregnant or refused to discontinue nursing
Intervention	Toripalimab 240 mg on Day 1 in combination with cisplatin 80 mg/m2 on Day 1 and gemcitabine 1 000 mg/m2 on Days 1 and 8

Trial name: Jupiter-02 - A Phase III, Randomized, Placebo Controlled, Multicenter, Double-Blind Study Comparing Toripalimab Injection (JS001) Combined With Chemotherapy Versus Placebo Combined With Chemotherapy for Recurrent or Metastatic Nasopharyngeal Cancer	NCT number: NCT03581786

	every 3 weeks for up to 6 cycles, followed by toripalimab 240 mg once every 3 weeks (5) n=146
Comparator(s)	Placebo intravenously on Day 1 in combination with cisplatin 80 mg/m2 on Day 1 and gemcitabine 1 000 mg/m2 on Days 1 and 8 every 3 weeks for up to 6 cycles, followed by placebo once every 3 weeks. (4) n=143
Follow-up time	OS: Data cut-off (post-hoc analysis): June 24, 2025 (68 months after last enrollment) (51) Final pre defined data cut-off: November 18, 2022, with a median survival follow-up of 36.0 months. All other efficacy endpoints: Data cut-off: June 8, 2021, with a median follow-up time of 21.82 months. Safety endpoints: Data cut-off: May 8, 2022.
Is the study used in the health economic model?	N/A
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** Primary endpoints: • PFS, defined as the time from randomization to the occurrence of disease progression, as determined by IRC per RECIST v1.1 or death from any cause, whichever occurred first. Secondary endpoints: • OS defined as the time from randomization to death from any cause. Data from participants who were alive at the time of the OS analysis were censored as of the last date they were known to be alive. • ORR defined as the proportion of participants who had an objective response. An objective response was defined as either a complete response (CR) or a partial response (PR), durable for at least 4 weeks per RECIST v1.1. Participants not meeting these criteria, including participants without any post baseline tumor assessments, were considered non-responders. • Disease control rate (DCR), defined as the proportion of subjects with confirmed CR or PR as their best response or

confirmed stable disease (maintained for at least 6 weeks) per RECIST v1.1.

- Duration of response (DoR), defined as the date from the first occurrence of a CR or PR (whichever status was recorded first) until the first date that progressive disease or death was documented, whichever occurred first. DoR was assessed only in participants who had a confirmed CR or PR per RECIST v1.1. Participants who had not progressed or died at the time of final analysis of PFS were censored at the time of last tumor assessment date. If no tumor assessments were performed after the date of the first occurrence of a CR or PR, DoR was censored on the date of the first occurrence of a CR or PR plus 1 day.

Other endpoints:

- Investigator-assessed PFS per RECIST v1.1
- Survival rates of PFS and OS. The 1- and 2-year OS rates and the investigator- and IRC-assessed 1- and 2-year PFS rates
- PFS, ORR, DCR and DoR per irRECIST determined by the investigator and by the IRC.
- Patient-Reported Outcome (PRO) using EORTC QLQ-C30, EORTC QLQ-H&N35 and ECOG performance status assessments
- ADA formation

Method of analysis

The sample size calculation was based on the primary endpoint of IRC-PFS.(80) A total of 280 participants (140 per arm) were needed to observe 200 PFS events in order to detect the PFS improvement of HR=0.67 with 80% power at a two-sided significance level of 0.05.(80) This was expected to occur approximately 25 months after the first participant was randomized.(80) An interim analysis was planned when approximately 130 PFS events were observed.(80)

The enrolled population was defined as all participants who provided informed consent form (ICF) for this trial.(80) The intent-to-treat set (ITT) included all participants randomized.(80) The safety analysis set (SAS) included all participants who received any amount of toripalimab or placebo infusion.(80)

The non-parametric Kaplan-Meier method was used to estimate the PFS curve in each treatment arm.(80) The treatment difference in

PFS was assessed by the stratified log-rank test. A stratified Cox proportional hazard model was used to assess the magnitude of the treatment difference (i.e., HR) between the treatment arms.(80)

The same analysis methods for the primary objective were also applied to investigator-assessed OS and PFS.(80) Secondary analyses were performed for 1- and 2- year PFS rates and 1- and 2-year OS rates at 1 year and 2 years after randomization.(80) The number and proportion of participants with best overall response of confirmed complete response (CR), confirmed partial response (PR), stable disease (SD), or progressive disease were summarized. ORR and DCR were determined along with their respective 95% CI.(80) A Kaplan-Meier curve was used to estimate median DoR and OS along with their 95% CI in each arm.(80)

Subgroup analyses

Subgroup analyses sought to assess the consistency of the trial results in subgroups defined by demographics and baseline prognostic characteristics, the IRC-assessed PFS in these subgroups were examined. Summaries of PFS and OS results, including unstratified HR estimated from Cox proportional hazards models and Kaplan-Meier estimates of median PFS, were generated for each of the categorical variables. No formal statistical power calculations were performed for subgroup analyses.

The efficacy of toripalimab was supported by the analysis of PFS and OS across various subgroups in the JUPITER-02 trial population.

The different subgroups are listed below and were pre-specified:

Age <=50
Age >50

Sex: Female
Sex: Male

Baseline ECOG per CRF: 0
Baseline ECG per CRF: 1

Baseline ECOG per IWRS: 0
Baseline ECOG per IWRS: 1

Baseline disease stage per CRF: Recurrent
Baseline disease stage per CRF: Metastatic

Baseline disease stage per IWRS: Recurrent
Baseline disease stage per IWRS: Metastatic

Trial name: Jupiter-02 - A Phase III, Randomized, Placebo Controlled, Multicenter, Double-Blind Study Comparing Toripalimab Injection (JS001) Combined With Chemotherapy Versus Placebo Combined With Chemotherapy for Recurrent or Metastatic Nasopharyngeal Cancer	NCT number: NCT03581786

Baseline PD-L1 expression level:
TC ≥ 1 % or IC ≥ 1 %
TC < 1 % and IC < 1 %

Baseline EBV copy number: <500
Baseline EBV copy number: >=500
Baseline EBV copy number: <2000
Baseline EBV copy number: >=2000

(Plasma EBV DNA copy number was determined by qRT-PCR method with probes against EBV genes in a central lab.)

Post hoc sub groups analyses:

Disease-free interval (years): ≤ 2
Disease-free interval (years): >2

Source:(4)

Other relevant information

Appendix B. Efficacy results per study

Results per study

Table 49 Results per Jupiter-02, total population (ITT) (4) (78)

Results of Jupiter-02 (NCT03581786) (											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Progression-free survival, (median follow up time: 21.82 months)	**Toripalimab + gemcitabine-cisplatin**	146	21.4 (11.7 to NE)	13.2	NE	NE	HR: 0.52	0.37-0.73	<.001	The confidence interval for the median survival was computed using the Brookmeyer-Crowley method with log-log transformation. HR confidence interval was computed from the Cox proportional hazards regression model, stratified by the baseline Eastern Cooperative Oncology Group performance status (0 vs 1) and the baseline disease stage (recurrent vs primary metastatic). P-value computed from the log-rank test, stratified by the baseline Eastern Cooperative Oncology Group performance	(4) (45)
	Placebo + gemcitabine-cisplatin	143	8.2 (7.0 to 9.8)								

										status (0 vs 1) and the baseline disease stage (recurrent vs primary metastatic). No confidence interval or p-value was estimated for the absolute difference in median PFS, as this was not pre-specified and is not reported in the clinical study report.
Median overall survival (median follow up time: 36.0)	**Toripalimab + gemcitabine-cisplatin**	146	NE (38.7 to NE)	NE	NE	NE	HR: 0.63	0.45-0.89	.008	The confidence interval for the median overall survival was computed using the Brookmeyer-Crowley method with log-log transformation. HR confidence interval was computed from the Cox proportional hazards regression model, stratified by the baseline Eastern Cooperative Oncology Group performance status (0 vs 1) and the baseline disease stage (recurrent vs primary metastatic). P-value computed from the log-rank test, stratified by the baseline Eastern Cooperative Oncology Group performance status (0 vs 1) and the baseline disease stage (recurrent vs primary metastatic).
	Placebo + gemcitabine-cisplatin	143	33.7 (27.0 to 44.2)							

										An absolute difference in median overall survival is not reported, as the median was not reached in the toripalimab arm. Consequently, a meaningful estimate of the absolute difference and its confidence interval cannot be derived.
Objective response rate (complete response + partial response), No./total [%] (median follow up time: 21.82 months)	**Toripalimab + gemcitabine-cisplatin**	146	115/146 [78.8] (71.2-85.1)*	11.4	1.7-21.2	.02	NE	NE	NE	*Confidence interval was computed using the Clopper-Pearson method. Difference confidence interval was computed using the Mantel-Haenszel method, stratified by the baseline Eastern Cooperative Oncology Group performance status (0 vs 1) and the baseline disease stage (recurrent vs primary metastatic). p-value computed from the Cochran-Mantel-Haenszel test, stratified by the baseline Eastern Cooperative Oncology Group performance status (0 vs 1) and the baseline disease stage (recurrent vs primary metastatic).
	Placebo + gemcitabine-cisplatin	143	96/143 [67.1] (58.8-74.8)*							

										A relative treatment effect for objective response rate was not estimated, as the clinical study report reports ORR using absolute response rates and absolute differences with corresponding confidence intervals. Relative effect measures were not part of the pre-specified analyses.
Disease control rate (complete response + partial response + stable disease), No./total [%] (median follow up time: 21.82 months)	**Toripalimab + gemcitabine-cisplatin**	146	129/146 [88.4] (82.0-93.1)*	7.9	−0.4 to 16.1	.06	NE	NE	NE	*Confidence interval was computed using the Clopper-Pearson method. Difference confidence interval was computed using the Mantel-Haenszel method, stratified by the baseline Eastern Cooperative Oncology Group performance status (0 vs 1) and the baseline disease stage (recurrent vs primary metastatic). p-value computed from the Cochran-Mantel-Haenszel test, stratified by the baseline Eastern Cooperative Oncology Group performance status (0 vs 1) and the baseline disease stage (recurrent vs primary metastatic).
	Placebo + gemcitabine-cisplatin	143	115/143 [80.4] (73.0-86.6)*							

										A relative treatment effect for disease control rate was not estimated, as DCR was analysed and reported using absolute response rates and absolute differences only. Relative effect measures were not part of the pre-specified analyses.
Duration of response, median, mo (median follow up time: 21.82 months)	**Toripalimab + gemcitabine-cisplatin**	115	18.0 (10.5 to NE)	NE	NE	NE	0.49	0.33-0.72	<.001	The confidence interval for the duration of response result was computed using the Brookmeyer-Crowley method with log-log transformation. HR confidence interval was computed from the unstratified Cox proportional hazards regression model. p-value was computed from the unstratified log-rank test. An absolute difference in median duration of response was not estimated, as the median duration of response was not reached in the toripalimab arm. Consequently, a meaningful estimate of the absolute
	Placebo + gemcitabine-cisplatin	96	6.0 (5.6-8.3)							

difference and its confidence interval could not be derived.

Appendix C. Comparative analysis of efficacy N/A

((N/A

Table 50 Comparative analysis of studies comparing [intervention] to [comparator] for patients with [indication] N/A

Outcome	Studies included in the analysis	Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
		Difference	CI	P value	Difference	CI	P value		

(

Outcome	Studies included in the analysis	Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
		Difference	CI	P value	Difference	CI	P value		
								(	
								((	

Appendix D. Extrapolation N/A

N/A

D.1 Extrapolation of [effect measure 1]

D.1.1 Data input

D.1.2 Model

D.1.3 Proportional hazards

N/A

D.1.4 Evaluation of statistical fit (AIC and BIC)

N/A

D.1.5 Evaluation of visual fit

D.1.6 Evaluation of hazard functions

(N/A

D.1.7 Validation and discussion of extrapolated curves

D.1.8 Adjustment of background mortality

D.1.9 Adjustment for treatment switching/cross-over

D.1.10 Waning effect

D.1.11 Cure-point

D.2 Extrapolation of [effect measure 2]

N/A

Appendix E. Serious adverse events

Table 51 Serious Adverse Events Occurring in ≥ 1% of Patients (SS Population). Data cut-off May 08, 2022 – median treatment duration was 65.7 weeks in the toripalimab group and 37.3 weeks in the placebo group. (77)

Adverse events	Toripalimab + gemcitabine-cisplatin (n=146)	Placebo + gemcitabine-cisplatin (n=143)
	Number of patients with adverse events (%)	Number of patients with adverse events (%)
Any serious adverse event, n (%)	64 (43.8)	62 (43.4)
[redacted]		

Adverse events	Toripalimab + gemcitabine-cisplatin (n=146)	Placebo + gemcitabine-cisplatin (n=143)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

= number of events reporting in the specific category.
Note: Serious adverse events are classified according to the MedDRA version 23.0.
Source: (45)

Appendix F. Health-related quality of life N/A

N/A

Appendix G. Probabilistic sensitivity analyses N/A

N/A

Table 52. Overview of parameters in the PSA N/A

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Probabilities				
HSUV				
Costs				

Appendix H. Literature searches for the clinical assessment

H.1 Efficacy and safety of the intervention and comparator(s)

The objective was to perform SLRs to capture the available data on the following elements:

- Clinical effectiveness and safety data associated with 'toripalimab (LOQTORZI) in combination with cisplatin and gemcitabine' and comparator treatments in the management of recurrent and/or metastatic NPC
- Economic evaluations associated with the management of recurrent and/or metastatic NPC
- Costs and resource use associated with the management of recurrent and/or metastatic NPC
- Utility and QoL measures associated with recurrent and/or metastatic NPC

Searches in each of the following databases were conducted on the 3rd July 2025 for the original review, and 8th December 2025 for the update review.

Table 53 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion (original review)	Date of search completion (update review)
Embase	via Ovid.com	1974 to 02 July 2025 / 04 December 2025 (date limit applied 20250702-20251231)	03.07.2025	08.12.2025
Medline	MEDLINE ALL (including MEDLINE daily, MEDLINE ePub ahead of print, MEDLINE (R) In-Process & Other Non-Indexed Citations) (via Ovid.com)	1946 to 02 July 2025 / 05 December 2025 (date limit applied 20250702-20251231)	03.07.2025	08.12.2025
Cochrane Library database (CENTRAL)	via the Wiley online platform	6 of 12, June 2025 / 11 of 12, November 2025 (with limits: Publication Year from 2025 to 2025, with Cochrane Library	03.07.2025	08.12.2025

Database	Platform/source	Relevant period for the search	Date of search completion (original review)	Date of search completion (update review)
		publication date from Jul 2025 to Dec 2025, in Trials)		
Cochrane Library database (CDSR)	via the Wiley online platform	Issue 7 of 12, July 2025 / Issue 12 of 12, December 2025 (with limits: Publication Year from 2025 to 2025, with Cochrane Library publication date from Jul 2025 to Dec 2025, in Trials)	03.07.2025	08.12.2025
Centre for Reviews and Dissemination database (DARE)	via york.ac.uk/crd	Database inception to 03 July 2025 / inception to 08 December 2025 (no date limits applied)	03.07.2025	08.12.2025
Centre for Reviews and Dissemination database (NHS EED)	via york.ac.uk/crd	Database inception to 03 July 2025 / inception to 08 December 2025 (no date limits applied)	03.07.2025	08.12.2025
Centre for Reviews and Dissemination database (HTA database)	via york.ac.uk/crd	Database inception to 03 July 2025 / inception to 08 December 2025 (no date limits applied)	03.07.2025	08.12.2025

Abbreviations:
CENTRAL: Cochrane Central Register of Controlled Trials
CDSR: Cochrane Database of Systematic Reviews
DARE: Database of Abstracts of Reviews of Effects
NHS EED: NHS Economic Evaluation Database
HTA database: Health Technology Assessment database

Table 54 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
NICE, SMC, AWMSG, NCPE, CADTH	https://www.nice.org.uk/ https://www.scottishmedicines.org.uk/	In the search bar search for: Nasopharyngeal; naso-pharyngeal; nasopharynx = 24 unique hits Reviewed each hit for inclusion.	03.07/08.12.2025

Source name	Location/source	Search strategy	Date of search
	http://www.awmsg.org/ https://www.ncpe.ie/ https://www.cadth.ca/	Update review: NICE: 1 additional hit SMC/AWMSG/NCPE: 0 hits CADTH: 0 additional hits	
clinicaltrials.gov **clinicaltrialsregister.eu** **isrctn.com** **who.int/ictrp/en/**	https://clinicaltrials.gov https://www.clinicaltrialsregister.eu http://www.isrctn.com www.who.int/ictrp/en/	In the search bar search for: Nasopharyngeal; naso-pharyngeal; nasopharynx = 195 unique hits Reviewed each hit for inclusion (including using database filters, such as “with results”) Update review additional or updated hits re-reviewed: 64	03.07/08.12.2025

Abbreviations: NICE: National Institute for Health and Care Excellence
SMC: Scottish Medicines Consortium
AWMSG: All Wales Medicines Strategy Group
NCPE: National Centre for Pharmacoeconomics
CADTH: Canadian Agency for Drugs and Technologies in Health

Table 55 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
ISPOR (all meetings)	2025/2024/2023/2022: https://www.ispor.org/heor-resources/presentations-database/search Update review 2025 (addition of results from ISPOR Glasgow November 2025)	In the search bar search for: Nasopharyngeal; naso-pharyngeal; nasopharynx = 7 unique hits Reviewed each abstract identified for inclusion Update review: an additional 3 unique hits	Nasopharyngeal; naso-pharyngeal; nasopharynx	03.07/08.12.2025
ESMO + ESMO ASIA	ESMO ASIA 2025: https://oncologypro.esmo.org/congress-resources/esmo-asia-congress-2025 2025: https://www.sciencedirect.com/journal/annals-of-oncology/vol/36/suppl/S2 (Original review "Not yet available – congress is being held 17-21 October 2025") 2024: https://www.sciencedirect.com/journal/annals-of-oncology/vol/35/suppl/S2 2023: https://www.sciencedirect.com/journal/annals-of-oncology/vol/34/suppl/S2 2022: https://www.sciencedirect.com/journal/annals-of-oncology/vol/33/suppl/S7	In the titles on the webpage search for: Nasopharyngeal; naso-pharyngeal; nasopharynx = 2 unique hits Reviewed each abstract identified for inclusion Update review: an additional 49 unique hits (ESMO 2025), plus an additional 24 hits (ESMO ASIA 2025)	Nasopharyngeal; naso-pharyngeal; nasopharynx	03.07/08.12.2025
ASCO	2025: https://ascopubs.org/toc/jco/43/16_suppl https://ascopubs.org/toc/jco/43/17_suppl 2024: https://ascopubs.org/toc/j	In the search bar search for: Nasopharyngeal; naso-pharyngeal; nasopharynx = 241 unique hits	Nasopharyngeal; naso-pharyngeal; nasopharynx	03.07/08.12.2025

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
	co/42/17_suppl https://ascopubs.org/toc/jco/42/16_suppl 2023: https://ascopubs.org/toc/jco/41/16_suppl https://ascopubs.org/toc/jco/41/17_suppl 2022: https://ascopubs.org/toc/jco/40/16_suppl https://ascopubs.org/toc/jco/40/17_suppl Update review: next annual meeting not until 2026	Reviewed each abstract identified for inclusion		
ECHNO	ICHNO-ECHNO 2022: removed from the website and journal (https://www.estro.org/Congresses/Post-congress-information and https://www.thegreenjournal.com/issues) Abstract book: https://user-swndwmf.cld.bz/ICHNO-ECHNO-2022-Abstract-Book Update review: next meeting not until 2027	In the abstract book search for: Nasopharyngeal; naso-pharyngeal; nasopharynx = 17 unique hits Reviewed each abstract identified for inclusion	Nasopharyngeal; naso-pharyngeal; nasopharynx	03.07/08.12.2025
ICHNO	ICHNO 2024: https://www.estro.org/ESTRO/media/ESTRO/ICHNO-2024-Abstract-Book.pdf Update review: next meeting not until March 19th to 21st 2026	In the PDF search for: Nasopharyngeal; naso-pharyngeal; nasopharynx = 38 unique hits Reviewed each abstract identified for inclusion	Nasopharyngeal; naso-pharyngeal; nasopharynx	03.07/08.12.2025
AACR	2025: https://aacrjournals.org/cancerres/issue/85/8_Supplement_1	Use the search function for: Nasopharyngeal; naso-pharyngeal; nasopharynx = 80 unique hits	Nasopharyngeal; naso-pharyngeal; nasopharynx	03.07/08.12.2025

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
	https://aacrjournals.org/cancerres/issue/85/8_Supplement_2 2024: https://aacrjournals.org/cancerres/issue/84/6_Supplement https://aacrjournals.org/cancerres/issue/84/7_Supplement 2023: https://aacrjournals.org/cancerres/issue/83/7_Supplement https://aacrjournals.org/cancerres/issue/83/8_Supplement 2022: https://aacrjournals.org/cancerres/issue/82/12_Supplement Update review: next meeting not until April 17th to 22nd 2026	Reviewed each abstract identified for inclusion		
Multidisciplinary Head and Neck Cancers Symposium (MHNCS)	2024 and 2022: https://poster.astro.org/astro/#!*date=2022-01-01%2013:02:24,2025-06-25%2013:02:43*search=nasopharyngeal*browseby=8*listing=0*sortby=1 Update review: next meeting not until February 19th to 21st 2026	In the PDF search for: Nasopharyngeal; naso-pharyngeal; nasopharynx = 2 unique hits Reviewed each abstract identified for inclusion	Nasopharyngeal; naso-pharyngeal; nasopharynx	

H.1.1 Search strategies

In the following tables the exact search strings are documented, including results. Afterwards, inclusion and exclusion criteria for the search are specified.

Table 56 of search strategy table for MEDLINE via Ovid

No.	Query	Results per 03 jul 25	Results per update 08 dec 25
#1	exp Nasopharyngeal Neoplasms/ or (((nasopharyngeal or naso-pharyngeal or nasopharynx or epipharynx or rhinopharynx or rhinopharyngeal or rhino-pharyngeal or postnasal space or lymphoepithelial) adj4 (neoplasm* or cancer* or carcinoma* or tumour* or tumo* or lesion*)) or rhinopharyngioma or lymphoepithelioma or lympho-epithelioma or ((nasopharyngeal or naso-pharyngeal or nasopharynx) adj4 (SCC or squamous cell carcinoma*))).ti,ab.	29619	30224
#2	exp Neoplasm Metastasis/ or (metasta* or micromet* or reocurr* or reoccurr* or recurr* or recidive or regenerat* or relaps* or seeding or seeded or macromet* or oligomet* or spread* or carcinomatosis or carcinosis or disseminat* or migrat* or extranodal or extracapsular or deposit* or circulating or embolic or embolism* or high grade or invasive or return* or second*).ti,ab.	5979444	6137443
#3	1 and 2	12094	12383
#4	(toripalimab* or Loqtorzi* or chs 007* or chs007* or js 001* or js001* or tab 001* or tab001* or teripalimab* or teriprizumab* or toripalimab tpzi* or toripalimab-tpzi* or treipril* or treprizumab* or tripleitriumab* or triprizumab* or tuoyi* or 1924598-82-2*).ti,ab.	468	535
#5	Cisplatin/ or (cisplatin* or cis-diamminedichloroplatinum* or cis diamminedichloroplatinum* or "cis-dichlorodiammineplatinum(ii)" or cis-platinum or cis platinum* or cisplatinum* or dichlorodiammineplatinum* or (platinum adj2 diamminodichloride*) or platino* or abiplatin* or biocisplatinum* or biocysplatinum* or Blastolem* or briplatin* or cddp ti* or cis ddp* or cis diamine dichloroplatinum* or cis diamine* or (cis diammine adj2 dichloroplatinum*) or cis dichloridiammineplatinum* or cis dichloroadiamine* or cis dichlorodiamine* or cis dichlorodiammine* or cis dichlorodiamineplatinum* or cis dichlorodiammineplatinum* or cis platinous diamino dichloride* or "cis−platinum" or cismaplat* or cisplatyl* or citoplatino* or cytoplatin* or cytosplat* or diamine dichloroplatinum* or diaminodichloroplatinum* or diamminedichloroplatinum* or dichlorodiamine platinum* or docistin* or elvecis* or fauldiscipla* or kemoplat* or lederplatin* or liplacis* or lipoplatin* or mpi 5010* or mpi5010* or neoplatin* or niyaplat* or nk 801* or nk801* or noveldexis* or nsc 119875* or platamine* or platiblastin* or platidiam* or platimine* or platinex* or	97465	99181

No.	Query	Results per 03 jul 25	Results per update 08 dec 25
	platinil* or platinol* or platinoxan* or (platinum adj2 (diaminodichloride* or "(ii)diamino dichloride" or diamine dichloride* or diaminedichloride* or diamminedichloride*)) or platiran* or platistil* or platistin* or platosin* or randa* or romcis* or sicatem* or spi 077* or spi 77* or spi077* or spi77* or tecnoplatin* or tr 170* or tr170* or 15663-27-1* or 26035-31-4* or 96081-74-2*).ti,ab.		
#6	exp Nasopharyngeal Neoplasms/ or (((nasopharyngeal or naso-pharyngeal or nasopharynx or epipharynx or rhinopharynx or rhinopharyngeal or rhino-pharyngeal or postnasal space or lymphoepithelial) adj4 (neoplasm* or cancer* or carcinoma* or tumour* or tumo* or lesion*)) or rhinopharyngioma or lymphoepithelioma or lympho-epithelioma or ((nasopharyngeal or naso-pharyngeal or nasopharynx) adj4 (SCC or squamous cell carcinoma*))).ti,ab.	23197	23849
#7	Carboplatin/ or (carboplat* or "(1,1 cyclobutanedicarboxylato)diammineplatinum" or blastocarb* or boplatex* or carbosin* or carbotec* or carplan* or CBDCA* or "cis diammine 1,1 cyclobutanedicarboxylate platinum" or "cis diammine(1,1 cyclobutanedicarboxylato)platinum" or "cis diamminecyclobutane 1,1 dicarboxylatoplatinum" or "cis(diammino)(1,1 cyclobutanedicarboxylato)platinum" or cycloplatin* or "diammine cyclobutane 1,1 dicarboxylatoplatinum" or "cis-diammine(cyclobutanedicarboxylato)platinum ii" or "diamminecyclobutane 1,1 dicarboxylatoplatinum" or diamminecyclobutanedicarboxylatoplatinum* or erbakar* or ercar* or ifacap* or jm 8* or jm-8* or jm8* or kemocarb* or nsc 241240* or nsc-241240* or nsc241240* or oncocarbin* or paraplatin* or "platinum cis diammine 1,1 cyclobutanedicarboxylate" or "platinum cyclobutane 1,1 dicarboxylatediammine" or "platinum diamino 1,1 cyclobutanedicarboxylate" or "platinum diammine 1,1 cyclobutanedicarboxylate" or 41575-94-4* or nealorin* or neocarbo* or platinwas* or ribocarbo*).ti,ab.	22638	23116
#8	Fluorouracil/ or (fluorouracil* or fluoro uracil* or 5-fluorouracil* or 5fluoruracil* or 5 fluorouracil* or 5-fu* or 5fu* or 5 fu* or efudix* or efudex* or fluoro-uracile icn* or adrucil* or fluoroplex* or flurodex* or carac* or 5-hu hexal* or 5 hu hexal* or haemato-fu* or haemato fu* or neofluor* or onkofluor* or ribofluor* or fluracedyl* or 10318-20-4* or 51-21-8* or 57050-04-1* or 57172-36-8* or 68021-61-4* or "2,4 dihydroxy 5 fluoropyrimidine" or "2,4 dioxo 5 fluoropyrimidine" or "5 fluoracil" or "5 fluoro 1	85767	87444

No.	Query	Results per 03 jul 25	Results per update 08 dec 25
	hydro 2,4 pyrimidinedione" or "5 fluoro 1 hydropyrimidine 2,4 dione" or "5 fluoro 1,2,3,4 tetrahydropyrimidine 2,4 dione" or "5 fluoro 1,3 dihydro 2,4 pyrimidinedione" or "5 fluoro 1,3 dihydropyrimidine 2,4 dione" or "5 fluoro 1h 2,4 pyrimidinedione" or "5 fluoro 1h pyrimidine 2,4 dione" or "5 fluoro 2,4 pyrimidinedione" or "5 fluoro 2,4(1h,3h) pyrimidinedione" or "5 fluoropyrimidine 2,4 dione" or "5 fluoropyrimidine 2,4(1h,3h) dione" or "5 fluoruracil" or accusite* or actino-hermal* or agicil* or cinkef* or effluderm* or efflurak* or efurix* or eurofluor* or f6627* or fivoflu* or fluoroblastin* or fluoruracil* or fluouracil* or fluoxan* or flurablastin* or fluracil* or fluril* or fluro uracil* or fluroblastin* or ifacil* or nsc 18913* or nsc 19893* or nsc18913* or nsc19893* or oncofu* or ro 2 9757* or ro 2-9757* or ro2 9757* or ro2-9757* or tolak* or tolerak* or uflahex* or uraciflor* or utoral* or 1004-03-1* or 51-21-8*).ti,ab.		
#9	Nivolumab/ or (nivolumab* or mdx-1106* or mdx1106* or mdx 1106* or opdivo* or bms-936558* or bms936558* or bms 936558* or ono-4538* or ono4538* or ono 4538* or ba 1104* or ba1104* or cmab 819* or cmab819* or ly 01015* or ly01015* or mdx 1106* or mdx1106* or pbp 2101* or pbp2101* or xdivane* or "946414-94-4").ti,ab.	11604	12178
#10	(Pembrolizumab* or bcd 201* or bcd201* or keytruda* or lambrolizumab* or mk 3475* or mk3475* or pbp 2102* or pbp2102* or sch 900475* or sch900475* or xtrudane* or 1374853-91-4*).ti,ab.	10657	11439
#11	(Tislelizumab* or bgb a317* or bgba317* or bgn 1* or bgn1* or jhl 2108* or jhl2108* or tevimbra* or tilelizumab* or tirelizumab* or tizveni* or vdt 482* or vdt482* or 1858168-59-8*).ti,ab.	607	756
#12	4 and (5 or 6)	66	84
#13	5 and 6	6121	6307
#14	6 and 7	2059	2095
#15	8 and 5	12323	12438
#16	9 or 10 or 11 or 12 or 13 or 14 or 15	38006	39621
#17	3 and 16	551	563
#18	Randomized Controlled Trials as Topic/ or randomized controlled trial/ or Random Allocation/ or Double Blind	1404340	1423146

No.	Query	Results per 03 jul 25	Results per update 08 dec 25
	Method/ or Single Blind Method/ or clinical trial/ or exp Clinical Trials as topic/ or placebos/		
#19	(clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt.	1255108	1276442
#20	((clinical adj trial$) or ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)) or placebo$ or randomly allocated or (allocated adj2 random$) or (open-label or open label or extension)).mp.	1718387	1753779
#21	Or/18-20	2317982	2369084
#22	17 and 21	221	225
#23	limit 22 to dt=20250702-20251231	-	5

Table 57 of search strategy table for Embase via Ovid

No.	Query	Results per 03 jul 25	Results per update 08 dec 25
#1	exp nasopharynx tumor/ or (((nasopharyngeal or naso-pharyngeal or nasopharynx or epipharynx or rhinopharynx or rhinopharyngeal or rhino-pharyngeal or postnasal space or lymphoepithelial) adj4 (neoplasm* or cancer* or carcinoma* or tumour* or tumo* or lesion*)) or rhinopharyngioma or lymphoepithelioma or lympho-epithelioma or ((nasopharyngeal or naso-pharyngeal or nasopharynx) adj4 (SCC or squamous cell carcinoma*))).ti,ab.	42708	43956
#2	exp metastasis/ or Cancer recurrence/ or (metasta* or micromet* or reocurr* or reoccurr* or recurr* or recidive or regenerat* or relaps* or seeding or seeded or macromet* or oligomet* or spread* or carcinomatosis or carcinosis or disseminat* or migrat* or extranodal or extracapsular or deposit* or circulating or embolic or embolism* or high grade or invasive or return* or second*).ti,ab.	8335861	8595936
#3	1 and 2	19681	20288
#4	toripalimab/ or (toripalimab* or Loqtorzi* or chs 007* or chs007* or js 001* or js001* or tab 001* or tab001* or	3213	3667

No.	Query	Results per 03 jul 25	Results per update 08 dec 25
	teripalimab* or teriprizumab* or toripalimab tpzi* or toripalimab-tpzi* or treipril* or treprizumab* or tripleitriumab* or triprizumab* or tuoyi* or 1924598-82-2*).ti,ab.		
#5	Cisplatin/ or (cisplatin* or cis-diamminedichloroplatinum* or cis diamminedichloroplatinum* or "cis-dichlorodiammineplatinum(ii)" or cis-platinum or cis platinum* or cisplatinum* or dichlorodiammineplatinum* or (platinum adj2 diamminodichloride*) or platino* or abiplatin* or biocisplatinum* or biocysplatinum* or Blastolem* or briplatin* or cddp ti* or cis ddp* or cis diamine dichloroplatinum* or cis diamine* or (cis diammine adj2 dichloroplatinum*) or cis dichloridiammineplatinum* or cis dichloroadiamine* or cis dichlorodiamine* or cis dichlorodiammine* or cis dichlorodiamineplatinum* or cis dichlorodiammineplatinum* or cis platinous diamino dichloride* or "cis−platinum" or cismaplat* or cisplatyl* or citoplatino* or cytoplatin* or cytosplat* or diamine dichloroplatinum* or diaminodichloroplatinum* or diamminedichloroplatinum* or dichlorodiamine platinum* or docistin* or elvecis* or fauldiscipla* or kemoplat* or lederplatin* or liplacis* or lipoplatin* or mpi 5010* or mpi5010* or neoplatin* or niyaplat* or nk 801* or nk801* or noveldexis* or nsc 119875* or platamine* or platiblastin* or platidiam* or platimine* or platinex* or platinil* or platinol* or platinoxan* or (platinum adj2 (diaminodichloride* or "(ii)diamino dichloride" or diamine dichloride* or diaminedichloride* or diamminedichloride*)) or platiran* or platistil* or platistin* or platosin* or randa* or romcis* or sicatem* or spi 077* or spi 77* or spi077* or spi77* or tecnoplatin* or tr 170* or tr170* or 15663-27-1* or 26035-31-4* or 96081-74-2*).ti,ab.	257907	263282
#6	Gemcitabine/ or (Gemcit* or "2'-deoxy-2'-difluorocytidine" or "2' deoxy 2' difluorocytidine" or "2',2'-difluorodeoxycytidine" or "2',2'-difluoro-2'-deoxycytidine" or "2',2'-dfdc" or dfdcyd* or "ly 188011" or "188011, ly" or ly-188011* or gemzar* or "2'-deoxy-2',2''-difluorocytidine-5'-o-monophosphate" or "2' deoxy 2',2'' difluorocytidine 5' o monophosphate" or "hydrochloride,gemcitabine, (d-threo-pentafuranosyl)-isomer" or "2' deoxy 2',2' difluorocytidine" or "4 amino 1 (2 deoxy 2,2 difluoro beta dextro erythro pentofuranosyl)" or "4 amino 1 [3,3 difluoro 4 hydroxy 5" or "d 07001" or d07001* or difluorodeoxycytidine* or ff 10832* or ff10832* or gembin* or "gemci−cell" or gemcisela* or gemedac* or gemkabi* or gemliquid* or gemsol* or gemstad* or	88432	90955

No.	Query	Results per 03 jul 25	Results per update 08 dec 25
	gemtro* or getmisi* or gitrabin* or infugem* or "jnj 17000139" or jnj17000139* or ly188011* or ribozar* or solgekma* or tar 200* or tar200* or 103882-84-4* or 95058-81-4*).ti,ab.		
#7	Carboplatin/ or (carboplat* or "(1,1 cyclobutanedicarboxylato)diammineplatinum" or blastocarb* or boplatex* or carbosin* or carbotec* or carplan* or CBDCA* or "cis diammine 1,1 cyclobutanedicarboxylate platinum" or "cis diammine(1,1 cyclobutanedicarboxylato)platinum" or "cis diamminecyclobutane 1,1 dicarboxylatoplatinum" or "cis(diammino)(1,1 cyclobutanedicarboxylato)platinum" or cycloplatin* or "diammine cyclobutane 1,1 dicarboxylatoplatinum" or "cis-diammine(cyclobutanedicarboxylato)platinum ii" or "diamminecyclobutane 1,1 dicarboxylatoplatinum" or diamminecyclobutanedicarboxylatoplatinum* or erbakar* or ercar* or ifacap* or jm 8* or jm-8* or jm8* or kemocarb* or nsc 241240* or nsc-241240* or nsc241240* or oncocarbin* or paraplatin* or "platinum cis diammine 1,1 cyclobutanedicarboxylate" or "platinum cyclobutane 1,1 dicarboxylatediammine" or "platinum diamino 1,1 cyclobutanedicarboxylate" or "platinum diammine 1,1 cyclobutanedicarboxylate" or 41575-94-4* or nealorin* or neocarbo* or platinwas* or ribocarbo*).ti,ab.	104852	107780
#8	Fluorouracil/ or (fluorouracil* or fluoro uracil* or 5-fluorouracil* or 5fluoruracil* or 5 fluorouracil* or 5-fu* or 5fu* or 5 fu* or efudix* or efudex* or fluoro-uracile icn* or adrucil* or fluoroplex* or flurodex* or carac* or 5-hu hexal* or 5 hu hexal* or haemato-fu* or haemato fu* or neofluor* or onkofluor* or ribofluor* or fluracedyl* or 10318-20-4* or 51-21-8* or 57050-04-1* or 57172-36-8* or 68021-61-4* or "2,4 dihydroxy 5 fluoropyrimidine" or "2,4 dioxo 5 fluoropyrimidine" or "5 fluoracil" or "5 fluoro 1 hydro 2,4 pyrimidinedione" or "5 fluoro 1 hydropyrimidine 2,4 dione" or "5 fluoro 1,2,3,4 tetrahydropyrimidine 2,4 dione" or "5 fluoro 1,3 dihydro 2,4 pyrimidinedione" or "5 fluoro 1,3 dihydropyrimidine 2,4 dione" or "5 fluoro 1h 2,4 pyrimidinedione" or "5 fluoro 1h pyrimidine 2,4 dione" or "5 fluoro 2,4 pyrimidinedione" or "5 fluoro 2,4(1h,3h) pyrimidinedione" or "5 fluoropyrimidine 2,4 dione" or "5 fluoropyrimidine 2,4(1h,3h) dione" or "5 fluoruracil" or accusite* or actino-hermal* or agicil* or cinkef* or effluderm* or efflurak* or efurix* or eurofluor* or f6627* or fivoflu* or fluoroblastin* or fluoruracil* or fluouracil* or fluoxan* or flurablastin* or fluracil* or fluril* or fluro uracil* or fluroblastin* or ifacil* or nsc 18913* or nsc 19893* or	194309	199647

No.	Query	Results per 03 jul 25	Results per update 08 dec 25
	nsc18913* or nsc19893* or oncofu* or ro 2 9757* or ro 2-9757* or ro2 9757* or ro2-9757* or tolak* or tolerak* or uflahex* or uraciflor* or utoral* or 1004-03-1* or 51-21-8*).ti,ab.		
#9	Nivolumab/ or (nivolumab* or mdx-1106* or mdx1106* or mdx 1106* or opdivo* or bms-936558* or bms936558* or bms 936558* or ono-4538* or ono4538* or ono 4538* or ba 1104* or ba1104* or cmab 819* or cmab819* or ly 01015* or ly01015* or mdx 1106* or mdx1106* or pbp 2101* or pbp2101* or xdivane* or "946414-94-4").ti,ab.	51539	54291
#10	Pembrolizumab/ or (Pembrolizumab* or bcd 201* or bcd201* or keytruda* or lambrolizumab* or mk 3475* or mk3475* or pbp 2102* or pbp2102* or sch 900475* or sch900475* or xtrudane* or 1374853-91-4*).ti,ab.	54134	57836
#11	Tislelizumab/ or (Tislelizumab* or bgb a317* or bgba317* or bgn 1* or bgn1* or jhl 2108* or jhl2108* or tevimbra* or tilelizumab* or tirelizumab* or tizveni* or vdt 482* or vdt482* or 1858168-59-8*).ti,ab.	4019	4756
#12	4 and (5 or 6)	936	1079
#13	5 and 6	36506	37481
#14	6 and 7	21071	21470
#15	8 and 5	53650	54412
#16	9 or 10 or 11 or 12 or 13 or 14 or 15	163340	170132
#17	3 and 16	2934	3049
#18	Clinical Trial/ or Randomized Controlled Trial/ or controlled clinical trial/ or multicenter study/ or Phase 3 clinical trial/ or phase 4 clinical trial/ or exp RANDOMIZATION/ or Single Blind Procedure/ or Double Blind Procedure/ or Crossover Procedure/ or PLACEBO/ or Prospective Study/	3523618	3627595
#19	(randomi?ed controlled trial$ or rct or (random$ adj2 allocat$) or single blind$ or double blind$ or ((treble or triple) adj blind$) or placebo$ or open-label or open label or extension).mp.	2255348	2325751
#20	Or/18-19	4195137	4319766
#21	17 and 20	961	1013

No.	Query	Results per 03 jul 25	Results per update 08 dec 25
#22	limit 21 to dc=20250702-20251231	-	81

Table 58 of search strategy table for Cochrane Library (via Wiley online platform)

No.	Query	Results per 03 jul 25	Results per update 08 dec 25
#1	[mh "Nasopharyngeal Neoplasms"] or (((nasopharyngeal or naso-pharyngeal or nasopharynx or epipharynx or rhinopharynx or rhinopharyngeal or rhino-pharyngeal or postnasal space or lymphoepithelial) NEAR/4 (neoplasm* or cancer* or carcinoma* or tumour* or tumo* or lesion*)) or rhinopharyngioma or lymphoepithelioma or lympho-epithelioma or ((nasopharyngeal or naso-pharyngeal or nasopharynx) NEAR/4 (SCC or squamous cell carcinoma*))):ti,ab	2425	2505
#2	[mh "Neoplasm Metastasis"] or (metasta* or micromet* or reocurr* or reoccurr* or recurr* or recidive or regenerat* or relaps* or seeding or seeded or macromet* or oligomet* or spread* or carcinomatosis or carcinosis or disseminat* or migrat* or extranodal or extracapsular or deposit* or circulating or embolic or embolism* or high grade or invasive or return* or second*):ti,ab	765170	798664
#3	#1 and #2	1198	1259
#4	(toripalimab* or Loqtorzi* or "chs 007" or chs007* or "js 001" or js001* or "tab 001" or tab001* or teripalimab* or teriprizumab* or toripalimab tpzi* or toripalimab-tpzi* or treipril* or treprizumab* or tripleitriumab* or triprizumab* or tuoyi* or "1924598-82-2"):ti,ab	264	305
#5	[mh "Cisplatin"] or (cisplatin* or cis-diamminedichloroplatinum* or cis diamminedichloroplatinum* or "cis-dichlorodiammineplatinum(ii)" or cis-platinum or cis platinum* or cisplatinum* or dichlorodiammineplatinum* or (platinum NEAR/2 diamminodichloride*) or platino* or abiplatin* or biocisplatinum* or biocysplatinum* or Blastolem* or briplatin* or cddp ti* or cis ddp* or cis diamine dichloroplatinum* or cis diamine* or (cis diammine NEAR/2 dichloroplatinum*) or cis dichloridiammineplatinum* or cis dichloroadiamine* or cis dichlorodiamine* or cis dichlorodiammine* or cis dichlorodiamineplatinum* or cis dichlorodiammineplatinum* or cis platinous diamino	17652	17995

No.	Query	Results per 03 jul 25	Results per update 08 dec 25
	dichloride* or "cis−platinum" or cismaplat* or cisplatyl* or citoplatino* or cytoplatin* or cytosplat* or diamine dichloroplatinum* or diaminodichloroplatinum* or diamminedichloroplatinum* or dichlorodiamine platinum* or docistin* or elvecis* or fauldiscipla* or kemoplat* or lederplatin* or liplacis* or lipoplatin* or "mpi 5010" or mpi5010* or neoplatin* or niyaplat* or "nk 801" or nk801* or noveldexis* or "nsc 119875" or platamine* or platiblastin* or platidiam* or platimine* or platinex* or platinil* or platinol* or platinoxan* or (platinum NEAR/2 (diaminodichloride* or "(ii)diamino dichloride" or diamine dichloride* or diaminedichloride* or diamminedichloride*)) or platiran* or platistil* or platistin* or platosin* or randa* or romcis* or sicatem* or "spi 077" or "spi 77" or spi077* or spi77* or tecnoplatin* or "tr 170" or tr170* or "15663-27-1" or "26035-31-4" or "96081-74-2"):ti,ab		
#6	[mh "Gemcitabine"] or (Gemcit* or "2'-deoxy-2'-difluorocytidine" or "2' deoxy 2' difluorocytidine" or "2',2'-difluorodeoxycytidine" or "2',2'-difluoro-2'-deoxycytidine" or "2',2'-dfdc" or dfdcyd* or "ly 188011" or "188011, ly" or ly-188011* or gemzar* or "2'-deoxy-2',2''-difluorocytidine-5'-o-monophosphate" or "2' deoxy 2',2'' difluorocytidine 5' o monophosphate" or "hydrochloride,gemcitabine, (d-threo-pentafuranosyl)-isomer" or "2' deoxy 2',2' difluorocytidine" or "4 amino 1 (2 deoxy 2,2 difluoro beta dextro erythro pentofuranosyl)" or "4 amino 1 [3,3 difluoro 4 hydroxy 5" or "d 07001" or d07001* or difluorodeoxycytidine* or "ff 10832" or ff10832* or gembin* or "gemci−cell" or gemcisela* or gemedac* or gemkabi* or gemliquid* or gemsol* or gemstad* or gemtro* or getmisi* or gitrabin* or infugem* or "jnj 17000139" or jnj17000139* or ly188011* or ribozar* or solgekma* or "tar 200" or tar200* or "103882-84-4" or "95058-81-4"):ti,ab	7588	7792
#7	[mh "Carboplatin"] or (carboplat* or "(1,1 cyclobutanedicarboxylato)diammineplatinum" or blastocarb* or boplatex* or carbosin* or carbotec* or carplan* or CBDCA* or "cis diammine 1,1 cyclobutanedicarboxylate platinum" or "cis diammine(1,1 cyclobutanedicarboxylato)platinum" or "cis diamminecyclobutane 1,1 dicarboxylatoplatinum" or "cis(diammino)(1,1 cyclobutanedicarboxylato)platinum" or cycloplatin* or "diammine cyclobutane 1,1 dicarboxylatoplatinum" or "cis-diammine(cyclobutanedicarboxylato)platinum ii" or "diamminecyclobutane 1,1 dicarboxylatoplatinum" or diamminecyclobutanedicarboxylatoplatinum* or erbakar* or ercar* or ifacap* or "jm 8" or jm-8* or jm8* or kemocarb* or "nsc 241240" or nsc-241240* or nsc241240* or oncocarbin*	9311	9555

No.	Query	Results per 03 jul 25	Results per update 08 dec 25
	or paraplatin* or "platinum cis diammine 1,1 cyclobutanedicarboxylate" or "platinum cyclobutane 1,1 dicarboxylatediammine" or "platinum diamino 1,1 cyclobutanedicarboxylate" or "platinum diammine 1,1 cyclobutanedicarboxylate" or "41575-94-4" or nealorin* or neocarbo* or platinwas* or ribocarbo*):ti,ab		
#8	[mh "Fluorouracil"] or (fluorouracil* or fluoro uracil* or "5-fluorouracil" or 5fluoruracil* or "5 fluorouracil" or "5-fu" or 5fu* or "5 fu" or efudix* or efudex* or fluoro-uracile icn* or adrucil* or fluoroplex* or flurodex* or carac* or "5-hu hexal" or "5 hu hexal" or haemato-fu* or haemato fu* or neofluor* or onkofluor* or ribofluor* or fluracedyl* or "10318-20-4" or "51-21-8" or "57050-04-1" or "57172-36-8" or "68021-61-4" or "2,4 dihydroxy 5 fluoropyrimidine" or "2,4 dioxo 5 fluoropyrimidine" or "5 fluoracil" or "5 fluoro 1 hydro 2,4 pyrimidinedione" or "5 fluoro 1 hydropyrimidine 2,4 dione" or "5 fluoro 1,2,3,4 tetrahydropyrimidine 2,4 dione" or "5 fluoro 1,3 dihydro 2,4 pyrimidinedione" or "5 fluoro 1,3 dihydropyrimidine 2,4 dione" or "5 fluoro 1h 2,4 pyrimidinedione" or "5 fluoro 1h pyrimidine 2,4 dione" or "5 fluoro 2,4 pyrimidinedione" or "5 fluoro 2,4(1h,3h) pyrimidinedione" or "5 fluoropyrimidine 2,4 dione" or "5 fluoropyrimidine 2,4(1h,3h) dione" or "5 fluoruracil" or accusite* or actino-hermal* or agicil* or cinkef* or effluderm* or efflurak* or efurix* or eurofluor* or f6627* or fivoflu* or fluoroblastin* or fluoruracil* or fluouracil* or fluoxan* or flurablastin* or fluracil* or fluril* or fluro uracil* or fluroblastin* or ifacil* or "nsc 18913" or "nsc 19893" or nsc18913* or nsc19893* or oncofu* or "ro 2 9757" or "ro 2-9757" or "ro2 9757" or "ro2-9757" or tolak* or tolerak* or uflahex* or uraciflor* or utoral* or "1004-03-1" or "51-21-8"):ti,ab	15740	15960
#9	[mh "Nivolumab"] or (nivolumab* or mdx-1106* or mdx1106* or "mdx 1106" or opdivo* or bms-936558* or bms936558* or "bms 936558" or ono-4538* or ono4538* or "ono 4538" or "ba 1104" or ba1104* or "cmab 819" or cmab819* or "ly 01015" or ly01015* or "mdx 1106" or mdx1106* or "pbp 2101" or pbp2101* or xdivane* or "946414-94-4"):ti,ab	3529	3706
#10	(Pembrolizumab* or "bcd 201" or bcd201* or keytruda* or lambrolizumab* or "mk 3475" or mk3475* or "pbp 2102" or pbp2102* or "sch 900475" or sch900475* or xtrudane* or "1374853-91-4"):ti,ab	3990	4216
#11	(Tislelizumab* or "bgb a317" or bgba317* or "bgn 1" or bgn1* or "jhl 2108" or jhl2108* or tevimbra* or tilelizumab*	409	458

No.	Query	Results per 03 jul 25	Results per update 08 dec 25
	or tirelizumab* or tizveni* or "vdt 482" or vdt482* or "1858168-59-8"):ti,ab		
#12	#4 and (#5 or #6)	82	95
#13	#5 and #6	2723	2813
#14	#6 and #7	1323	1353
#15	#8 and #5	3116	3160
#16	#9 or #10 or #11 or #12 or #13 or #14 or #15	13337	13856
#17	#3 and #16	303	321
#18	#3 and #16 with Publication Year from 2025 to 2025, with Cochrane Library publication date Between Jul 2025 and Dec 2025, in Trials	-	15

Table 59 of search strategy table for the Database of Abstract Reviews of Effects, NHS Economic Evaluation Database, HTA Database (via York.ac.uk/crd interface)

No.	Query	Results per 03 jul 25	Results per update 08 dec 25
#1	MeSH DESCRIPTOR Nasopharyngeal Carcinoma EXPLODE ALL TREES	0	0
#2	MeSH DESCRIPTOR Nasopharyngeal Neoplasms EXPLODE ALL TREES	34	34
#3	(nasopharyngeal or naso-pharyngeal or nasopharynx or epipharynx or rhinopharynx or rhinopharyngeal or rhino-pharyngeal or postnasal space or lymphoepithelial)	93	93
#4	((neoplasm* or cancer* or carcinoma* or tumour* or tumo* or lesion*))	15115	15115
#5	#3 AND #4	54	54

No.	Query	Results per 03 jul 25	Results per update 08 dec 25
#6	(rhinopharyngioma or lymphoepithelioma or lympho-epithelioma)	0	0
#7	(nasopharyngeal or naso-pharyngeal or nasopharynx)	93	93
#8	(SCC or squamous cell carcinoma*)	200	200
#9	#7 AND #8	6	6
#10	#1 OR #2 OR #5 OR #9 OR #6	54	37

H.1.2 Systematic selection of studies

Methods followed were in line with the guidance provided by the National Institute for Health and Care Excellence (NICE) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. For each review, following the removal of duplicate records across the databases searched, two independent reviewers assessed the relevance of identified studies based on title and abstract for inclusion using the eligibility criteria. Disagreements were discussed and a third reviewer involved to resolve if required. For the update review duplicate database hits were also checked for between the original and update reviews.

Full text copies of all potentially relevant records were then obtained and evaluated in more detail against the eligibility criteria. This assessment was also undertaken by two independent reviewers, with disagreements discussed and a third reviewer involved to resolve if required.

For each review, data were extracted by one reviewer and checked by a second, into NICE submission template tables. A comprehensive critical appraisal of the included clinical studies was also conducted by one reviewer and checked by a second.

Table 60 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population	Patients diagnosed with untreated recurrent and/or metastatic NPC Recurrent and/or metastatic was assessed at full text review by either one of the following criteria:	Any other population, including but not limited to the following examples of ways different papers describe the population: • clearly states the patients were suitable for either radiation or surgery	No changes

	• Histologically or cytologically confirmed primary RM-NPC • Not amenable for radiotherapy or surgery • No prior systemic chemotherapy in the RM setting • For the recurrent NPC after curative treatment (including radiotherapy and/or induction, concurrent or adjuvant chemotherapy), the interval between recurrence and the last dose of previous radiotherapy or chemotherapy must be more than 6 months	• only describes the NPC with staging/advanced/locoregionally advanced/non-advanced etc. with no further detail on the three options listed in the inclusion criteria • subsequent line treatments (after first line) for the recurrent/metastatic form of the disease	
Intervention	• Toripalimab (Loqtorzi) in combination with cisplatin and gemcitabine • Gemcitabine and cisplatin combination • Gemcitabine and carboplatin combination • Fluorouracil and cisplatin combination • Nivolumab (alone or in combination with other chemotherapy treatments) • Pembrolizumab (alone or in combination with other chemotherapy treatments) • Tislelizumab (alone or in combination with other chemotherapy treatments)	Any other treatment, OR combination of relevant treatments, including but not limited to any treatments combined with: - Radiotherapy - Chemoradiotherapy - Surgery (either neoadjuvant, simultaneous or adjuvant)	Inclusion: Toripalimab (Loqtorzi) in combination with cisplatin and gemcitabine Exclusion: Any other treatment, OR combination of relevant treatments, including but not limited to any treatments combined with: - Radiotherapy - Chemoradiotherapy - Surgery (either neoadjuvant, simultaneous or adjuvant)

Comparators	No restriction, any or no comparator	No restriction	
Outcomes	Clinical efficacy or effectiveness: • Progression-free survival (including IRC-assessed/ Investigator-assessed/ Investigator-assessed PFS Rate/PFS Assessed Per irRECIST) • Overall survival (including OS rate) • Overall response rate (including IRC-assessed/ Investigator-assessed/ORR Assessed Per irRECIST) • Duration of response (including IRC-assessed/ Investigator-assessed/DoR Assessed Per irRECIST) • Complete response • Partial response • Stable disease • Disease progression • Disease control rate (including IRC-assessed/ Investigator-assessed/DCR Assessed Per irRECIST) • EORTC QLQ-C30 • EORTC QLQ-H&N35 • ECOG Performance Status Assessments	Those not listed in the inclusion criteria	No changes

	Safety: • Adverse events (including ECG tests and anti-drug antibodies, discontinuations and mortality)		
Study design/publication type	Randomised controlled trials	• Non-randomised controlled studies • Non-controlled studies • Animal studies • In-vitro studies • Pharmacokinetic studies • Editorials • Reviews • Letters • Comments • Notes • Erratum SLRs will be included at the abstract review stage, for handsearching of the reference lists, then excluded as primary publications.	No changes
Language restrictions	No restriction	No restriction	No changes
Publication date	No restriction; any study date	No restriction	No changes
Geographical location	No restriction	No restriction	No changes

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) diagram illustrated in Figure 17 presents how clinical references were reviewed and extracted. In the original review, the database searches retrieved 1539 references, of which 342 were duplicates. Of the 1197 titles and abstracts screened with the eligibility criteria, 1079 references did not meet the criteria. Hence, full texts of the remaining 118 references were retrieved and reviewed based on the eligibility criteria, plus two publications identified through grey literature searches. The 42 clinical publications extracted from were on 11 different studies – 31 were publications on the RCTs, and 11 were NMAs analysing the RCT data.

Local adaptations were then made, to ensure that the selected studies and reports were relevant for the clinical assessment of toripalimab. Thus, only 1 study remained (7 publications), with toripalimab as the intervention.

Figure 17 PRISMA diagram

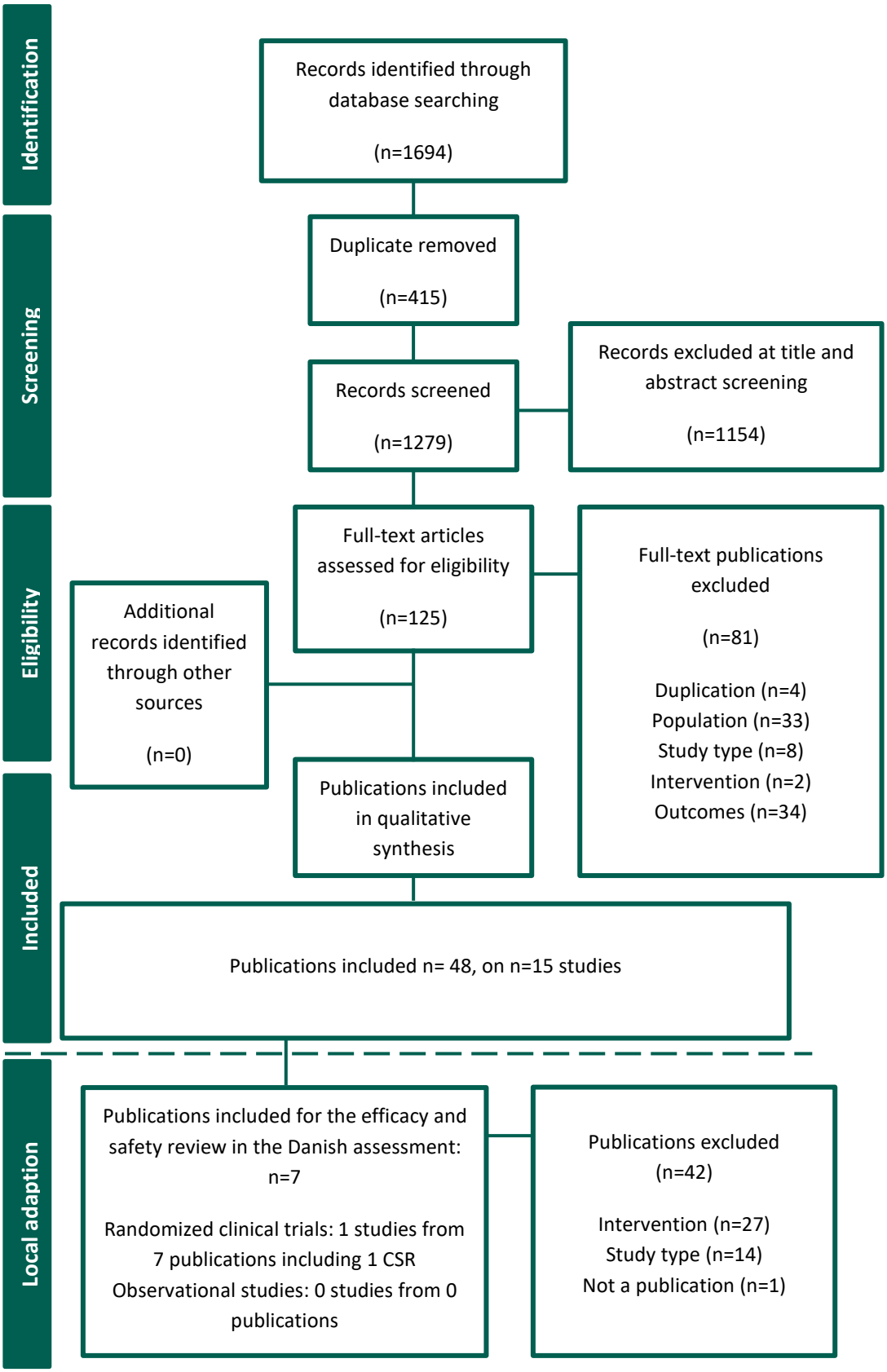

Table 61 Overview of study design for studies included in the analyses (4)

Study/ID	Study objective and design	Patient population	Intervention and compara-tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Jupiter-02/NCT03581786	A randomized, placebo-controlled, multi-center, double blinded, Phase III study to determine the efficacy and safety of TORIPALIMAB INJECTIO (JS001) in combination with gemcitabine/cisplatin compared with placebo in combination with gemcitabine/cisplatin as first-line treatment in patients with histological/cytological confirmation of recurrent or metastatic NPC	Patients eligible for the JUPITER-02 trial were between the ages of 18 and 75 years and were required to have histologically or cytologically confirmed primary recurrent or metastatic NPC, which was not amenable for local-regional or curative treatment and must have received no prior systemic chemotherapy in the recurrent or metastatic setting. Key inclusion criteria for the JUPITER-02 trial included: • Age ≥18 years and ≤75 years • Histological/cytological confirmation of NPC • Primarily metastatic (stage IVB as defined by the International Union against Cancer and American Joint Committee on Cancer staging system for NPC, eighth edition) or recurrent NPC that is not amenable for local-regional treatment or curative treatment	**Intervention:** Toripalimab 240 mg intravenously on Day 1 in combination with cisplatin 80 mg/m2 on Day 1 and gemcitabine 1 000 mg/m2 on Days 1 and 8 every 3 weeks for up to 6 cycles, followed by toripalimab 240 mg once every 3 weeks. **Comparator:** Placebo in combination with gemcitabine and cisplatin. Dosage as follows: Placebo intravenously on Day 1 in combination with cisplatin 80 mg/m2 on Day 1 and gemcitabine 1 000 mg/m2 on Days 1	• PFS, defined as the time from randomization to the occurrence of disease progression, as determined by IRC per RECIST v1.1 or death from any cause, whichever occurred first. Predefined data cut-off: June 8, 2021, with a median follow-up time of 21.82 months	• OS defined as the time from randomization to death from any cause. Data from participants who were alive at the time of the OS analysis were censored as of the last date they were known to be alive. Data cut-off: Pre defined: November 18, 2022, with a median survival follow-up of 36.0 months. Post hoc: June 24, 2025 (68 months after last enrollment) (51) • ORR defined as the proportion of participants who had an objective response. An objective response was defined as either a complete response (CR) or a partial response (PR), durable for at least 4 weeks per RECIST v1.1. Participants not meeting these criteria, including participants without any post baseline tumor assessments, were considered non-responders. Predefined Data cut-off: June 8, 2021, with a median follow-up time of 21.82 months • Disease control rate (DCR), defined as the proportion of subjects with confirmed CR or PR as their best response or confirmed stable

Study/ID	Study objective and design	Patient population	Intervention and compara-tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
	Objective: To assess the efficacy and safety of LCG vs CG in the first-line of patients with recurrent or metastatic NPC.	• At least one measurable lesion according to RECIST version 1.1 • Life expectancy ≥3 months Key exclusion criteria for the JUPITER-02 trial included: • History of severe hypersensitivity reactions to other monoclonal antibodies (mAbs) or any ingredient of JS001 • Prior therapy targeting PD-1 receptor, or its ligand PD-L1, or cytotoxic T lymphocyte associated protein 4 (CTLA4) receptor • Major surgical procedure other than for diagnosis of NPC within 28 days prior to randomization or anticipation of need for a major surgical procedure during the trial • History of hypersensitivity to gemcitabine or cisplatin or to any of the excipients • Female patients who were pregnant or refused to discontinue nursing	and 8 every 3 weeks for up to 6 cycles, followed by placebo once every 3 weeks.		disease (maintained for at least 6 weeks) per RECIST v1.1. Predefined data cut-off: June 8, 2021, with a median follow-up time of 21.82 months • Duration of response (DoR), defined as the date from the first occurrence of a CR or PR (whichever status was recorded first) until the first date that progressive disease or death was documented, whichever occurred first. DoR was assessed only in participants who had a confirmed CR or PR per RECIST v1.1. Participants who had not progressed or died at the time of final analysis of PFS were censored at the time of last tumor assessment date. If no tumor assessments were performed after the date of the first occurrence of a CR or PR, DoR was censored on the date of the first occurrence of a CR or PR plus 1 day. Predefined Data cut-off: June 8, 2021, with a median follow-up time of 21.82 months • Investigator-assessed PFS per RECIST v1.1 Predefined Data cut-off: June 8, 2021, with a median follow-up time of 21.82 months • Survival rates of PFS and OS. The 1- and 2-year OS rates and the investigator- and IRC-

Study/ID	Study objective and design	Patient population	Intervention and compara-tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
					assessed 1- and 2-year PFS rates Predefined Data cut-off: June 8, 2021, with a median follow-up time of 21.82 months • PFS, ORR, DCR and DoR per irRECIST determined by the investigator and by the IRC. Predefined Data cut-off: June 8, 2021, with a median follow-up time of 21.82 months • Patient-Reported Outcome (PRO) using EORTC QLQ-C30, EORTC QLQ-H&N35 and ECOG performance status assessments Predefined Data cut-off: June 8, 2021, with a median follow-up time of 21.82 months • ADA formation Predefined Data cut-off: June 8, 2021, with a median follow-up time of 21.82 months

H.1.3 Excluded fulltext references

The table below shows the references that were excluded during fulltext screening in the original review, the update review and local adaption.

Table 62 Clinical publications excluded from the original review (publications n=123)

ID	Reference details of publication	Reason for exclusion
#992 Mai 2023	Mai HQ, Chen QY, Chen D, Hu C, Yang K, Wen J, Li J, Shi Y, Jin F, Xu R, et al. Toripalimab Plus Chemotherapy for Recurrent or Metastatic Nasopharyngeal Carcinoma: The JUPITER-02 Randomized Clinical Trial. JAMA. 2023 Nov 28;330(20):1961-1970.	Duplicate
#1057 Nct 2019	NCT. Tislelizumab Combined With Chemotherapy Versus Chemotherapy Alone in Recurrent or Metastatic Nasopharyngeal Cancer (NPC). Available from: https://clinicaltrials.gov/ct2/show/NCT03924986	Duplicate
#1063 Nct 2020	NCT. Testing the Addition of an Anti-cancer Immune Therapy Drug (Nivolumab) to the Usual Chemotherapy Treatment (Cisplatin or Carboplatin With Gemcitabine) for Recurrent or Metastatic Nasopharyngeal Cancer. Available from: https://clinicaltrials.gov/ct2/show/NCT04458909	Duplicate
#1033 Muratori 2019	Muratori L, La Salvia A, Sperone P, Di Maio M. Target therapies in recurrent or metastatic head and neck cancer: state of the art and novel perspectives. A systematic review. Crit Rev Oncol Hematol. 2019;139:41–52.	Intervention
#1409 Yang 2021	Yang H, Lu Y, Xu Z, Wei M, Huang H. Gemcitabine plus platinum versus docetaxel plus platinum as first-line therapy for metastatic nasopharyngeal carcinoma: a randomized clinical study. Saudi J Med Med Sci. 2021;9(2):125–34.	Intervention
#312 Chan 2016	Chan ATC, Lee V, Ngan R, Ahn MJ, Ng QS, Hong RL, et al. 394TiP KEYNOTE-122: Phase 2 study of pembrolizumab versus standard-of-care chemotherapy in platinum-pretreated, recurrent or metastatic nasopharyngeal carcinoma. Ann Oncol. 2016;27:ix122.	Outcomes
#401 Chi 2016	ICTRP. The S-1 (AiYi) maintenance therapy with metastatic nasopharyngeal carcinoma received gemcitabine combined platinum chemotherapy randomized controlled multicenter clinical study. Available from: https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2007-001211-33-Outside-EU/EEA	Outcomes
#412 ChiCtr 2019	ICTRP. A randomized, multicenter, phase III trial for apatinib combined with 5-fluorouracil (5-fu) and cisplatin versus 5-fluorouracil and cisplatin for the treatment of recurrent or metastatic nasopharyngeal carcinoma. Available from: https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR1900020790	Outcomes
#413 ChiCtr 2019	ChiCtr. Camrelizumab in combination with gemcitabine plus cisplatin and SBRT for metastatic lesions versus gemcitabine plus cisplatin in the treatment of metastatic nasopharyngeal carcinoma: a prospective, phase III clinical trial. 2019. Available from: http://www.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR1900025341	Outcomes
#415 ChiCtr 2019	ICTRP. A randomized, controlled, multi-center clinical trial for albumin-bound paclitaxel plus cisplatin and capecitabine (Nab-TPC) versus gemcitabine plus cisplatin (GP) in patients with metastatic nasopharyngeal carcinoma. Available from: https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR1900027112	Outcomes
#740 Kct 2024	ICTRP. A RANDOMIZED PHASE II STUDY OF NIVOLUMAB VERSUS NIVOLUMAB AND BMS-986016 (RELATLIMAB) AS MAINTENANCE TREATMENT AFTER FIRST-LINE TREATMENT WITH PLATINUM-GEMCITABINE-NIVOLUMAB FOR PATIENTS	Outcomes

	WITH EPSTEIN-BARR VIRUS-ASSOCIATED RECURRENT/METASTATIC NASOPHARYNGEAL CARCINOMA. Available from: https://trialsearch.who.int/Trial2.aspx?TrialID=KCT0009487	
#1042 Nct 2008	NCT00697905. An Open Labeled, Multicentre, Randomized Phase II Trial of Combination Gemcitabine and Carboplatin Chemotherapy in Patients With Metastatic or Recurrent Nasopharyngeal Carcinoma. 2008. Available from: https://clinicaltrials.gov/study/NCT00697905	Outcomes
#1047 Nct 2012	NCT. A Randomized, Multicenter Phase III Clinical Trial Comparing Gemcitabine and Cisplatin With 5-Fluorouracil and Cisplatin in the Treatment of Recurrent or Metastatic Nasopharyngeal Carcinoma (NPC). Available from: https://clinicaltrials.gov/study/NCT01528618	Outcomes
#1049 Nct 2013	NCT01915134. A Prospective, Randomized, Controlled, Multicenter, Phase III Study of Stage ,Ö¢ Study of Gemcitabine Plus Cisplatin With or Without Endostatin to the Metastatic Nasopharyngeal Carcinoma. 2013. Available from: https://clinicaltrials.gov/study/NCT01915134	Outcomes
#1055 Nct 2018	NCT. Phase III Randomized Trial of Anlotinib Plus Gemcitabine/Cisplatin Vesus Placebo Plus Gemcitabine/Cisplatin in Previous Untreated Patients With Recurrent/Metastatic Nasopharyngeal Carcinoma. Available from: https://clinicaltrials.gov/study/NCT03601975	Outcomes
#1060 Nct 2019	NCT. A Randomised Phase II Study of Pembrolizumab With or Without Bevacizumab in Platinum-resistant Recurrent/Metastatic Nasopharyngeal Carcinoma. Available from: https://clinicaltrials.gov/study/NCT03813394	Outcomes
#1069 Nct 2021	NCT. A Randomized, Double-blind, Multi-center Phase III Study of Penpulimab (AK105) Combined With Chemotherapy Versus Placebo Combined With Chemotherapy in the First-line Treatment of Recurrent or Metastatic Nasopharyngeal Carcinoma. Available from: https://clinicaltrials.gov/study/NCT04974398	Outcomes
#1073 Nct 2022	NCT. KL-A167 Injection Combined With Cisplatin and Gemcitabine vs Placebo Combined With Cisplatin and Gemcitabine in the Treatment of Recurrent or Metastatic Nasopharyngeal Carcinoma: A Randomized, Double-blind, Placebo-controlled, Multicenter Phase III Clinical Trial. Available from: https://clinicaltrials.gov/study/NCT05294172	Outcomes
#1076 Nct 2022	NCT. Phase II Randomised Trial of Induction Gemcitabine and Cisplatin Versus Gemcitabine, Cisplatin, Pembrolizumab and Bevacizumab (GPPB) in Nasopharyngeal Cancer. Available from: https://clinicaltrials.gov/study/NCT05305131	Outcomes
#1078 Nct 2023	NCT. A Randomized Phase II Study of Nivolumab Versus Nivolumab and BMS-986016 (Relatlimab) as Maintenance Treatment After First-Line Treatment With Platinum-Gemcitabine-Nivolumab for Patients With Epstein-Barr Virus-Associated Recurrent/Metastatic Nasopharyngeal Carcinoma (REMAIN). Available from: https://clinicaltrials.gov/study/NCT06029270	Outcomes
#1084 Nct 2024	NCT. A Randomized, Controlled, Multicenter Clinical Study Comparing the Efficacy of Pembrolizumab in Combination With Nab-TPC Regimen Versus the GP Regimen in the First-Line Treatment of Nasopharyngeal Carcinoma With Bone Metastases.. Available from: https://clinicaltrials.gov/study/NCT06383780	Outcomes
#314 Ng 2016	Ng QS, Spreafico A, Lee V, Ngan RKC, To KF, Ahn MJ, Hong RL, Lin JC, Swaby RF, Chan ATC. KEYNOTE-122: phase 2 study of pembrolizumab versus standard-of-care chemotherapy in platinum-pretreated, recurrent or metastatic nasopharyngeal carcinoma. Ann Oncol. 2016;27(Suppl 8):viii15.	Outcomes
#1218 Spreafico 2016	Spreafico A, Lee V, Ngan RKC, To KF, Ahn MJ, Ng QS, et al. KEYNOTE-122: phase II study of pembrolizumab versus standard-of-care chemotherapy in platinum-pretreated, recurrent or metastatic nasopharyngeal carcinoma. Journal for ImmunoTherapy of Cancer 2016;4.	Outcomes

#1271 Toh 2018	Toh HC, Menezes J, et al. An open-label, randomized phase III trial of gemcitabine and carboplatin (GC) followed by Epstein-Barr virus-specific autologous cytotoxic T lymphocytes (EBV-CTLs) versus GC as front-line therapy for patients with advanced nasopharyngeal carcinoma (NPC). J Clin Oncol. 2018;36(15_suppl):6082.	Outcomes
#1422 Yang 2019	Yang Y, Huang Y, Fang W, Ma Y, Cai Q, Li ZM, et al. A multicenter, randomized, double-blind, placebo-controlled phase III study of anlotinib or placebo in combination with gemcitabine and cisplatin (GP) as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma (R/M NPC). J Clin Oncol. 2019;37.	Outcomes
#1478 Zhang 2014	Zhang L, Huang Y, Wu X, Liang W, Fang W, Hu Z, et al. A randomized, multicenter phase III clinical trial comparing gemcitabine and cisplatin with 5-fluorouracil and cisplatin in the treatment of recurrent or metastatic nasopharyngeal carcinoma. J Clin Oncol. 2014;32(15_suppl):TPS6098.	Outcomes
#1477 Zhang 2014	Zhang L, Huang Y, Wu X, Liang W, Fang W, Hu Z, Qin T. A randomized, multicenter phase III clinical trial comparing gemcitabine and cisplatin with 5-fluorouracil and cisplatin in the treatment of recurrent or metastatic nasopharyngeal carcinoma. Journal of Clinical Oncology. 2014;32(15):.	Outcomes
#24 NCT	NCT. An Open Labeled, Multicentre, Randomized Phase II Trial of Combination Gemcitabine and Carboplatin Chemotherapy in Patients With Metastatic or Recurrent Nasopharyngeal Carcinoma. Available from: https://clinicaltrials.gov/study/NCT00697905	Outcomes
#39 NCT	NCT. A Randomized, Multicenter Phase III Clinical Trial Comparing Gemcitabine and Cisplatin With 5-Fluorouracil and Cisplatin in the Treatment of Recurrent or Metastatic Nasopharyngeal Carcinoma (NPC). Available from: https://clinicaltrials.gov/study/NCT01528618	Outcomes
#42 NCT	NCT. Autologous Cytokine-Induced Killer Cell Transfusion in Combination With Gemcitabine Plus Cisplatin Regimen Chemotherapy for Metastatic Nasopharyngeal Carcinoma. Available from: https://clinicaltrials.gov/study/NCT01655628	Outcomes
#43 NCT	NCT. A Prospective,Randomized,Controlled,Multicenter,Phase III Study of Stage Ⅲ Study of Gemcitabine Plus Cisplatin With or Without Endostatin to the Metastatic Nasopharyngeal Carcinoma. Available from: https://clinicaltrials.gov/study/NCT01915134	Outcomes
#77 NCT	NCT.Phase III Randomized Trial of Anlotinib Plus Gemcitabine/Cisplatin Vesus Placebo Plus Gemcitabine/Cisplatin in Previous Untreated Patients With Recurrent/Metastatic Nasopharyngeal Carcinoma. Available from: https://clinicaltrials.gov/study/NCT03601975	Outcomes
#80 NCT	NCT. A Phase III, Randomized, Double-Blind, Multi-center Study to Investigate the Efficacy and Safety of Camrelizumab+Gemcitabine+Cisplatin Versus Placebo+Gemcitabine+Cisplatin in Subjects With Recurrent/Metastatic Nasopharyngeal Carcinoma. Available from: https://clinicaltrials.gov/study/NCT03707509	Outcomes
#91 NCT	NCT. A Randomised Phase II Study of Pembrolizumab With or Without Bevacizumab in Platinum-resistant Recurrent/Metastatic Nasopharyngeal Carcinoma. Available from: https://clinicaltrials.gov/study/NCT03813394	Outcomes
#140 NCT	NCT. KL-A167 Injection Combined With Cisplatin and Gemcitabine vs Placebo Combined With Cisplatin and Gemcitabine in the Treatment of Recurrent or Metastatic Nasopharyngeal Carcinoma: A Randomized, Double-blind, Placebo-controlled, Multicenter Phase III Clinical Trial. Available from: https://clinicaltrials.gov/study/NCT05294172	Outcomes
#151 NCT	NCT. A Randomized Phase II Study of Nivolumab Versus Nivolumab and BMS-986016 (Relatlimab) as Maintenance Treatment After First-Line Treatment With	Outcomes

	Platinum-Gemcitabine-Nivolumab for Patients With Epstein-Barr Virus-Associated Recurrent/Metastatic Nasopharyngeal Carcinoma (REMAIN). Available from: https://clinicaltrials.gov/study/NCT06029270	
#178 NCT	NCT. A Randomized, Controlled, Multicenter Clinical Study Comparing the Efficacy of Pembrolizumab in Combination With Nab-TPC Regimen Versus the GP Regimen in the First-Line Treatment of Nasopharyngeal Carcinoma With Bone Metastases. Available from: https://clinicaltrials.gov/study/NCT06383780	Outcomes
#266 Bourhis 2007	Bourhis J, Le Maître A, Baujat B, Audry H, Pignon J-P. Individual patients' data meta-analyses in head and neck cancer. Curr Opin Oncol. 2007;19(3):188-194.	Population
#283 Cai 2009	Cai ZW, Liu HF, Gan TQ, Lan D. Gemcitabine combined with cisplatin in treatment of lung metastases from nasopharyngeal carcinoma. Chin J Cancer Prev Treat. 2009;16(16):1256-1258.	Population
#286 Cao 2011	Cao K-J, Zhang A-L, Ma W-J, Huang P-Y, Luo D-H, Xia W-X. Nedaplatin or cisplatin combined with 5-fluorouracil for treatment of stage III-IVa nasopharyngeal carcinoma: a randomized controlled study. Zhonghua Zhong Liu Za Zhi. 2011;33(1):50-52.	Population
#310 Chan 2021	Chan ATC, Lee HFV, Hong R-L, Ahn M-J, Chong WQ, Kim S-B, Fuang HG, Caguioa PB, Ngamphaiboon N, Ho C, et al. 163P Health-related quality of life (HRQoL) with pembrolizumab (pembro) vs chemotherapy (chemo) in platinum-pretreated recurrent or metastatic (R/M) nasopharyngeal cancer (NPC): Phase III KEYNOTE-122 study. Ann Oncol. 2021 Dec;32(Suppl):S1452	Population
#316 Chan 2023	Chan ATC, Lee VHF, Hong R-L, Ahn M-J, Chong WQ, Kim S-B, Ho GF, Caguioa PB, Ngamphaiboon N, Ho C, et al. Pembrolizumab monotherapy versus chemotherapy in platinum-pretreated, recurrent or metastatic nasopharyngeal cancer (KEYNOTE-122): an open-label, randomized, phase III trial. Ann Oncol. 2023 Mar;34(3):251-261.	Population
#319 Chan 2023	Chan ATC, Lee VHF, Hong R-L, Ahn M-J, Chong WQ, Spreafico A, Kim S-B, Ho GF, Caguioa PB, Ngamphaiboon N, et al. Association of plasma Epstein-Barr virus DNA and clinical response in patients with recurrent and/or metastatic nasopharyngeal cancer treated with pembrolizumab or standard-of-care chemotherapy in KEYNOTE-122. Clin Cancer Res. 2023;29(18).	Population
#297 Chan 2021	Chan AT, Lee VHF, Hong R-L, Ahn M-J, Chong WQ, Kim S-B, Ho GF, Caguioa PB, Ngamphaiboon N, Ho C, et al. 858O Results of KEYNOTE-122: A phase III study of pembrolizumab (pembro) monotherapy vs chemotherapy (chemo) for platinum-pretreated, recurrent or metastatic (R/M) nasopharyngeal carcinoma (NPC). Ann Oncol. 2021 Sep;32(Suppl):S786.	Population
#328 Chan 2020	Chan SK, Choi CW, Chan SY, Tong CC, Lam KO, Kwong DLW, et al. 269MO Comparison of three induction chemotherapy regimens with gemcitabine plus cisplatin, cisplatin plus fluorouracil, and cisplatin plus capecitabine for locoregionally advanced nasopharyngeal carcinoma: A pooled analysis of two prospective studies. Ann Oncol. 2020 Nov;31(Suppl 4):S1348.	Population
#358 Chen 2019	Chen M, You R, You-Ping L, Huang P-Y, Zou X, Shen G-P, Zhang H-D. Chemotherapy plus local-regional radiotherapy versus chemotherapy alone in primary metastatic nasopharyngeal carcinoma: A randomized, open-label, phase III trial. Ann Oncol. 2019;30(Suppl 5):v449.	Population
#399 Chi 2015	ICTRP. Comparison the effects of different neoadjuvant chemotherapy regimen on acute toxicity, tumor response, and survival in patients with advanced nasopharyngeal carcinoma. Available from: https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR-IPR-15006378	Population
#414 ChiCtr 2019	ICTRP. Induction chemotherapy with GP versus TPF in III-IVA nasopharyngeal carcinoma: a randomized controlled trial. Available from: https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR1900022288	Population

#435 Chong 2024	Chong WQ, Low JL, Sooi K, Soo RA, Teo HL, Samol J, Goh G, Kong LR, DasGupta R, Chia S, et al. 848MO Phase II open-label randomized study of pembrolizumab with or without bevacizumab in platinum-resistant recurrent/metastatic nasopharyngeal carcinoma (R/M NPC). Ann Oncol. 2024;35(Suppl 5):S614.	Population
#430 Chong 2025	Chong WQ, Low JL, Tay JK, Le TBU, Goh GSQ, Sooi K, Teo HL, Cheo SW, Wong RTX, Samol J, et al. Pembrolizumab with or without bevacizumab in platinum-resistant recurrent or metastatic nasopharyngeal carcinoma: a randomised, open-label, phase 2 trial. Lancet Oncol. 2025;26(2):175–86.	Population
#523 EuctrOutsideEU/EEA 2012	ICTRP. International randomized study to evaluate the addition of docetaxel to the combination of cisplatin-5-fluorouracil (TCF) vs. cisplatin-5-fluorouracil (CF) in the induction treatment of nasopharyngeal carcinoma (NPC) in children and adolescents - Docetaxel Pediatric study in NPC. Available from: https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2007-001211-33-Outside-EU/EEA	Population
#525 Euctr 2021	ICTRP. Bempegaldesleukin with pembrolizumab in patients with PD-L1 (programmed cell death-ligand 1) positive Metastatic or Recurrent Head and Neck Squamous-Cell Carcinoma (HNSCC). Available from: https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2021-002461-18-HU	Population
#527 Euctr 2015	ICTRP. Ph 3 Trial of MK-3475 (Pembrolizumab) vs Standard Treatment in Recurrent/Metastatic Head and Neck Cancer. Available from: https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2014-001749-26-PL	Population
#707 Janopaul-Naylor 2024	Janopaul-Naylor JR, Boe L, Yu Y, Sherman EJ, Pfister DG, Lee NY, McBride S. Effect of time-of-day nivolumab and stereotactic body radiotherapy in metastatic head and neck squamous cell carcinoma: A secondary analysis of a prospective randomized trial. Head Neck. 2024;46(9):2292–2300.	Population
#823 Li 2012	Li JJ, Gu MF, Pan K, Liu LZ, Zhang H, Shen WX, Xia JC. Autologous cytokine-induced killer cell transfusion in combination with gemcitabine plus cisplatin regimen chemotherapy for metastatic nasopharyngeal carcinoma. J Immunother. 2012;35(2):189–95.	Population
#830 Li 2006	Li LB, Luo RC, Liao WJ, Zhang MJ, Luo YL, Miao JX. Clinical study of Photofrin photodynamic therapy for the treatment of relapse nasopharyngeal carcinoma. Photodiagnosis Photodyn Ther. 2006;3(4):266–71.	Population
#859 Li 2022	Li Z, Li C, Yang D, Song J, Liu T, Zhou Z, Zhou L, Kang M. Comparing the efficacy and safety of cisplatin and other platinum-based chemotherapies in locally advanced nasopharyngeal carcinoma: a systematic review and meta-analysis. BMC Cancer. 2022;22(1):616.	Population
#895 Liu 2024	Liu C, Li M, Liu X, Shi T, Wang Y, Sui C, Zhang W, Wang B. Evaluating the efficacy and safety of different neoadjuvant immunotherapy combinations in locally advanced HNSCC: a systematic review and meta-analysis. Front Immunol. 2024;15:1467306.	Population
#1053 Nct 2016	NCT02611960. A Two-Arm, Open-label, Randomized Phase II Study of Pembrolizumab (MK-3475) Monotherapy Versus Standard Chemotherapy in Platinum Pre-treated, Recurrent or Metastatic Nasopharyngeal Cancer (NPC) (Keynote-122). 2016. Available from: https://clinicaltrials.gov/study/NCT02611960	Population
#1105 Nl 2014	ICTRP. A Phase III Randomized Trial of MK-3475 (Pembrolizumab) versus Standard Treatment in Subjects with Recurrent or Metastatic Head and Neck Cancer. Available from: https://trialsearch.who.int/Trial2.aspx?TrialID=NL-OMON44471	Population
#1138 Pignon 2000	Pignon JP, Bourhis J, Domenge C, Designé LL. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. Lancet. 2000;355(9208):949–55.	Population

#1139 Pignon 2009	Pignon JP, Le Maitre A, Maillard E, Bourhis J, MACH-NC Collaborative Group, et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol. 2009;92(1):4–14.	Population
#1181 Saif 2019	Saif MW, Rajagopal S, Caplain J, Grimm E, Serebrennikova O, Das M, Tsichlis PN, Martell R. A phase I delayed-start, randomized and pharmacodynamic study of metformin and chemotherapy in patients with solid tumors. Cancer Chemother Pharmacol. 2019;84(6):1323–31.	Population
#1222 Srinivasmurthy 2025	Srinivasmurthy R, Nanda RK, Jones DT, Khalid T, Aboaid H, Ta J, Do K, Nguyen K, Fama KB, Aamer S, et al. Abstract B043: A systematic review and meta-analysis of randomized controlled trials to assess the risk of immune-related adverse effects (irAEs) in patients with locally advanced nasopharyngeal carcinoma treated with immune checkpoint inhibitors. Cancer Immunol Res. 2025;13(2_Suppl):B043.	Population
#1448 You 2020	You R, Liu YP, Huang PY, Zou X, Sun R, He YX, et al. Efficacy and safety of locoregional radiotherapy with chemotherapy vs chemotherapy alone in de novo metastatic nasopharyngeal carcinoma: a multicenter phase 3 randomized clinical trial. JAMA Oncol. 2020;6(9):1345–52.	Population
#1514 Zhao 2011	Zhao YY, Xue C, Hou X, Liao H, Li S, Zhao HY, et al. Changes of bone resorption marker (NTX) in chemotherapy plus zoledronic acid versus chemotherapy alone for nasopharyngeal cancer patients with bone metastases. Eur J Cancer. 2011;47(6):848–53.	Population
#1525 Zhong 2009	Zhong JH, Liu RL, Chen J, Hu XG, Wang LQ, Wang Y. Efficacy and adverse effects of gemcitabine plus cisplatin regimen and fluorouracil plus cisplatin regimen in treatment of advanced nasopharyngeal carcinoma: a meta-analysis. Academic Journal of Second Military Medical University 2009; 30(8): 926-931.	Population
#11	NCT. A Phase III Trial for Locally Recurrent, Previously Irradiated Head and Neck Cancer: Concurrent Re-Irradiation and Chemotherapy Versus Chemotherapy Alone. Available from: https://clinicaltrials.gov/study/NCT00113399	Population
#139	NCT. Phase II Randomised Trial of Induction Gemcitabine and Cisplatin Versus Gemcitabine, Cisplatin, Pembrolizumab and Bevacizumab (GPPB) in Nasopharyngeal Cancer. Available from: https://clinicaltrials.gov/study/NCT05305131	Population
#48	NCT. A Two-arm, Open-label, Randomized Phase III Study of Pembrolizumab (MK-3475) Monotherapy Versus Standard Chemotherapy in Platinum Pre-treated, Recurrent or Metastatic Nasopharyngeal Cancer (NPC) (Keynote-122). Available from: https://clinicaltrials.gov/study/NCT02611960	Population
#501 Delord 2017	Delord JP, Hollebecque A, De Boer JP, De Greve J, Machiels JPH, Leidner RS, Ferris RL, Rao S, Soumaoro I, Cao ZA, Kang H, Topalian SL. An open-label, multicohort, phase I/II study to evaluate nivolumab in patients with virus-associated tumors (CheckMate 358): Efficacy and safety in recurrent or metastatic (R/M) nasopharyngeal carcinoma (NPC). J Clin Oncol. 2017;35(15_suppl):6025.	Study design
#770 Kumar 2021	Kumar S, Noronha V, Patil V, Joshi A, Menon N, Prabhash K. Advances in pharmacotherapy for head and neck cancer. Expert Opin Pharmacother. 2021;22(15):2007–18.	Study design
#1014 Masterson 2020	Masterson L, Howard J, Gonzalez-Cruz J, Jackson C, Barnett C, Overton L, Liu H, Ladwa R, Simpson F, McGrath M, et al. Immune checkpoint inhibitors in advanced nasopharyngeal carcinoma: Beyond an era of chemoradiation? Int J Cancer. 2020;146(8):2305–14.	Study design
#1136 Peng 2023	Peng SH, Lin CH, Chen IC, Shen YC, Chang DY, Chen TWW, Huang SM, Hu FC, Lu YS. Disparity in survival benefits of pembrolizumab between Asian and non-Asian	Study design

	patients with advanced cancers: A systematic review and meta-regression analysis. Cancer Med. 2023;12(19):20035–51.	
#1242 Tan 2022	Tan LLY, Le QT, Lee NYY, Chua MLK. JUPITER-02 trial: advancing survival for recurrent metastatic nasopharyngeal carcinoma and next steps. Cancer Commun. 2021;42(1):56-59.	Study design
#1505 Zhang 2023	Zhang Y, Yao Q, Pan Y, Fang X, Xu H, Zhao T, et al. Efficacy and safety of PD-1/PD-L1 checkpoint inhibitors versus anti-PD-1/PD-L1 combined with other therapies for tumors: A systematic review. Cancers. 2023;15(3):682.	Study design
#185 The Medical Letter.	The Medical Letter. Toripalimab (Loqtorzi) for Nasopharyngeal Carcinoma (online only). Med Lett Drugs Ther. 2024 Jan 22;66(1694):e16-17.	Study design
#187 Liu 2024	Liu GY, Ye YF, Jiang YF, Chen GJ, Xia WX, Huang YS, et al. Nab-paclitaxel, cisplatin, and capecitabine versus cisplatin and gemcitabine as first line chemotherapy in patients with recurrent or metastatic nasopharyngeal carcinoma: randomised phase 3 clinical trial. BMJ. 2024;385.	Study design
U#66 Shi 2025	Shi Y, Mai H, Chen C, Wang Y, Li J, Jin H, Peng X, Zhang P, Qu S, Huang J, He YX. Tagitanlimab versus placebo in combination with gemcitabine and cisplatin as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma (R/M NPC): Results from a randomized, double-blind, phase 3 study. ASCO 2025.	Duplicate (of original review)
U#16 clinicaltrials.gov	NCT. A Randomized Phase II Study of Nivolumab Versus Nivolumab and BMS-986016 (Relatlimab) as Maintenance Treatment After First-Line Treatment With Platinum-Gemcitabine-Nivolumab for Patients With Epstein-Barr Virus-Associated Recurrent/Metastatic Nasopharyngeal Carcinoma (REMAIN). Available from: https://clinicaltrials.gov/study/NCT06029270	Outcomes
U#18 clinicaltrials.gov	NCT. Randomized Phase 2 Study of Nivolumab and Ipilimumab With or Without Cabozantinib in Patients With Advanced Nasopharyngeal Carcinoma That Have Progressed After Platinum Treatment and Immunotherapy. Available from: https://clinicaltrials.gov/study/NCT05904080	Outcomes
#534 Fang 2024	Fang WF, Pan J, Wang, H.; Qu, S.; Chen, N.; Chen, X.; Sun, Y.; He, X.; Hu, C.; Lin, L.; et al., Tislelizumab (TIS) plus chemotherapy (CT) vs placebo (PBO) plus CT as first-line (1L) treatment for recurrent or metastatic nasopharyngeal cancer (NPC): 3-year follow-up from the RATIONALE-309 study. Annals of Oncology. 2024;35(S4):S1554–S1555	Different intervention
#86 clinicaltrials.gov	NCT. A Phase 3, Multicenter, Double-Blind, Randomized, Placebo-Controlled Study to Compare the Efficacy and Safety of Tislelizumab (BGB-A317) Combined With Gemcitabine Plus Cisplatin Versus Placebo Combined With Gemcitabine Plus Cisplatin as First-Line Treatment for Recurrent or Metastatic Nasopharyngeal Cancer. Available from: https://clinicaltrials.gov/study/NCT03924986	Different intervention
#352 Chen 2024	Chen K, Li A, Xiong K, Zhou, H, Zhang, Q, Huang, Y, Zhang L et al. Benchmarking the transcriptomic predictive biomarkers for immunotherapy plus chemotherapy: Results from phase III RATIONALE-309 and ORIENT-11 randomized trials. Journal of Clinical Oncology. 2024;42(16)	Different intervention
#1427 Yang 2024	Yang Y, Pan J, Chen N, Guo Y, Huang X, Wu Y, Leaw S, Bai F, Wang Y, Zhao N, et al. Effects of tislelizumab on health-related quality of life in patients with recurrent or metastatic nasopharyngeal cancer. Head and Neck. 2024;46(9):2301-2314.	Different intervention
#1430 Yang 2022	Yang Y, Pan J, Chen N, Wu Y, Leaw S, Bai F, Wang Y, Zhao N, Tang B, Barnes G. 220O RATIONALE-309: Effects of tislelizumab on health-related quality of life (HRQoL) in patients with recurrent or metastatic nasopharyngeal cancer (R/M NPC). Annals of Oncology. 2022;33(S9):S1521.	Different intervention
#1432 Yang 2021	Yang Y, Pan J, Wang H, Qu S, Chen N, Chen X, Sun Y, He X, Hu C, Lin L, et al. 121O RATIONALE 309: a randomized, global, double-blind, phase III trial of tislelizumab	Different intervention

	(TIS) vs placebo, plus gemcitabine+cisplatin (GP), as first-line treatment for recurrent/metastatic nasopharyngeal cancer (RM-NPC). Annals of Oncology. 2021;32(S7):S1430.	
#1434 Yang 2023	Yang Y, Pan J, Wang H, Zhao Y, Qu S, Chen N, Chen X, Sun Y, He X, Hu C, et al. Tislelizumab plus chemotherapy as first-line treatment for recurrent or metastatic nasopharyngeal cancer: a multicenter phase 3 trial (RATIONALE-309). Cancer Cell. 2023;41(6):1061-1072.	Different intervention
#GL4 Zhang 2022	Zhang L, Yang Y, Pan J-j, et al. RATIONALE-309: updated progression-free survival (PFS), PFS after next line of treatment, and overall survival from a phase 3 double-blind trial of tislelizumab versus placebo, plus chemotherapy, as first-line treatment for recurrent/metastatic nasopharyngeal cancer. Journal of Clinical Oncology. 2022;40(36S):384950	Different intervention
#1424 Yang 2021	Yang Y, Qu S, Li J, Hu C, Xu M, Li W, Zhou T, Shen L, Wu H, Lang J, et al. Camrelizumab versus placebo in combination with gemcitabine and cisplatin as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma (CAPTAIN-1st): a multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol. 2021;22(8):1162-1174.	Different intervention
#1479 Zhang 2021	Zhang L, Yang Y, Qu S, Li J-G, Hu C, Xu M, Li W, Zhou T, Shen L, Wu H, et al. Camrelizumab versus placebo combined with gemcitabine and cisplatin for recurrent or metastatic nasopharyngeal carcinoma: a randomized, double-blind, phase 3 trial. Journal of Clinical Oncology. 2021;39(15S):	Different intervention
#1273 Toh 2024	Toh HC, Yang M-H, Wang H-M, Hsieh CY, Chitapanarux I, Ho KF, Hong R-L, Ang MK, Colevas AD, Sirachainan E, et al. Gemcitabine, carboplatin, and Epstein–Barr virus-specific autologous cytotoxic T lymphocytes for recurrent or metastatic nasopharyngeal carcinoma: VANCE, an international randomized phase III trial. Annals of Oncology. 2024;35(12):1181-1190.	Different intervention
#58 clinicaltrials.gov	NCT. A Multicentre, Randomized, Open-Label, Phase III Clinical Trial Of Gemcitabine And Carboplatin Followed By Epstein-Barr Virus-Specific Autologous Cytotoxic T Lymphocytes Versus Gemcitabine And Carboplatin As First Line Treatment For Advanced Nasopharyngeal Carcinoma(NPC) Patients. Available from: https://clinicaltrials.gov/study/NCT02578641	Different intervention
#1276 Toh 2022 VANCE, NCT20578641	Toh HC, Yang MH, Wang HM, Hsieh CY, Chitapanarux I, Ho KF, Hong RL, Ang MK, Colevas D, Sirachainan E, et al. 652O Randomized phase III VANCE study: Gemcitabine and carboplatin (GC) followed by Epstein Barr virus-specific autologous cytotoxic T lymphocytes (EBV-CTL) versus the same chemotherapy as first-line treatment for advanced nasopharyngeal carcinoma (NPC). Annals of Oncology. 2022;33(S7):S840.	Different intervention
#653 Hong 2021	Hong S, Zhang Y, Yu G, Peng P, Peng J, Jia J et al. Gemcitabine plus cisplatin versus fluorouracil plus cisplatin as first-line therapy for recurrent or metastatic nasopharyngeal carcinoma: final overall survival analysis of GEM20110714 phase III study. Journal Clinical Oncology.2021;39(29):3273-3282.	Different intervention
#647 Hong 2020 GEM20110714 NCT01528618	Hong, S, Huang Y, Yang Y, Yu G, Jia J, Peng J, et al. GEM20110714: Final overall survival results of the phase III study of first-line gemcitabine plus cisplatin versus fluorouracil plus cisplatin in recurrent or metastatic nasopharyngeal carcinoma. Journal Clinical Oncology. 2020;38(15).	Different intervention
#1474 Zhang 2016	Zhang L, Huang Y, Hong S, Yang Y, Yu G, Jia J, Peng P, Wu X, Lin Q, Xi X, et al. Gemcitabine plus cisplatin versus fluorouracil plus cisplatin in recurrent or metastatic nasopharyngeal carcinoma: a multicentre, randomised, open-label, phase 3 trial. Lancet. 2016;388(10054):1883-1892.	Different intervention

#1481 Zhang 2016	Zhang L, Yu G, Jia J, Peng P, Lin Q, Xi X, Peng J, Xu M, Chen D, Lu X, et al. Gemcitabine plus cisplatin (GP) versus 5-FU plus cisplatin (FP) as firstline treatment for recurrent or metastatic nasopharyngeal carcinoma (NPC): a randomized, openlabel, multicenter, phase III trial. Journal of Clinical Oncology. 2016;34(15S):	Different intervention
#102 clinicaltrials.gov	NCT. An Open-Label, Phase III Study of Platinum-Gemcitabine With or Without Nivolumab in the First-Line Treatment of Recurrent or Metastatic Nasopharyngeal Carcinoma. Available from: https://clinicaltrials.gov/study/NCT04458909	Different intervention
#190 Liu 2024	Liu G-Y, Ye Y-F, Jiang Y-F, Chen GJ, Xia W-X, Huang Y-S, Gao T-S, Liu Y-M, Hou Y-T, Li J-F, et al. Nab-paclitaxel, cisplatin, and capecitabine versus cisplatin and gemcitabine as first line chemotherapy in patients with recurrent or metastatic nasopharyngeal carcinoma: randomised phase 3 clinical trial. BMJ. 2024;385:e077890.	Different intervention
#384 Chen 2025	Hu C, Chen X, Xu T, Huang S, Liu F, Qu S, Chen L, Zhou P, Qu S, Ai X, et al. Abstract CT011: Penpulimab versus placebo in combination with chemotherapy as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma: a global, multicenter, randomized, double-blind, phase 3 trial (AK105-304). Cancer Research. 2025;85(8S2):CT011.	Different intervention
#639 Hirsch 2017	Hirsch L, Le Tourneau C. Gemcitabine plus cisplatine versus fluoro-uracile plus cisplatine dans les carcinomes nasopharyngés récidivants ou métastatiques : un essai de phase 3 randomisé, multicentrique, en ouvert. Oncologie. 2017;19:44-48.	Different intervention
#995 Mai 2024	Mai HQ, Han YQ, Wu GW, Yang KY, Chen CB, Wang M et al. A dose-exploring, randomized, open-label, Phase I study for toripalimab subcutaneous injection in patients with advanced nasopharyngeal carcinoma. Cancer Research. 2024;84(7S):CT113.	Study type
#1520 Zheng 2014	Zheng J, Lin J, Wang L, Zhou J, Xie B, Xu T, Zhang W. Metastatic nasopharyngeal carcinoma outcomes in patients on cisplatin with nolatrexed or 5-fluorouracil. Oncology Research and Treatment. 2014;37(10):540-544.	Different intervention
#GL1 Shi 2025	Shi Y, Mai H, Chen C, Wang Y, Li J, Jin H, Peng X, Zhang P, Qu S, Huang J, He YX. Tagitanlimab versus placebo in combination with gemcitabine and cisplatin as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma (R/M NPC): Results from a randomized, double-blind, phase 3 study. ASCO 2025.	Different intervention
U#82 Zheng 2024	Zheng S, Liu Y, Liu Z, Gao J, Gao L, Zhang M, Cao Y, Zhou S, Wu J, Xiang Li, et, al. 2164: A trial of low-dose 5-Fu and cisplatin and PD-1 in metastatic nasopharyngeal carcinoma (NCT04890522). Radiotherapy and Oncology. 2024;194(S1):S1380-S1382.	Different intervention
#83 clinicaltrials.gov	NCT. A Phase III, Randomized, Placebo Controlled, Multicenter, Double-Blind Study Comparing Toripalimab Injection (JS001) Combined With Chemotherapy Versus Placebo Combined With Chemotherapy for Recurrent or Metastatic Nasopharyngeal Cancer. Available from: https://clinicaltrials.gov/study/NCT03581786	Not a publication
#279 Cai 2025	Cai T, Lin C, Li Q, Mo J, Zheng J, Zhou J. Efficacy and safety of first-line treatments for recurrent or metastatic nasopharyngeal carcinoma: a systematic review and network meta-analysis. Frontiers in Immunology. 2025;16:1485609.	Study type
#610 Guven 2024	Guven DC, Stephen B, Sahin TK, Cakir IY, Aksoy S. Immunotherapy in the first-line treatment of advanced nasopharyngeal carcinoma: a systematic review and meta-analysis. The Laryngoscope. 2024;134(1): 7-17.	Study type
#619 Han 2023	Han J, Zeng N, Tian K, Liu Z, She L, Wang Z et al. First-line immunotherapy combinations for recurrent or metastatic nasopharyngeal carcinoma: an updated network meta-analysis and cost-effectiveness analysis. Head & Neck. 2023;45(9):2246-2258.	Study type

#1225 Sun 2024	Sun H, Bu F, Li L, Zhang X, Xin X, Yan J, Huang T. Efficacy and safety of immune checkpoint inhibitors combined with chemotherapy as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma: A network meta-analysis of randomized controlled trials. The Annals of Pharmacotherapy. 2024 Apr;58(4):349–59.	Study type
#1313 Wang 2024	Wang S, Huang X, Li R, Zhou Z, Kang M. Immune checkpoint inhibitor combined with chemotherapy versus chemotherapy alone in the first-line treatment for recurrent or metastatic nasopharyngeal carcinoma: a meta-analysis of random controlled trials. European Archives of Oto-Rhino-Laryngology. 2024;281(10):5111-5118.	Study type
U#78 Yu 2025	Yu Z, Hong S, Yu H, Zhang X, Li Z, Chen P, Zhou Y. Efficacy and safety of immune checkpoint inhibitors in the treatment of recurrent or metastatic nasopharyngeal carcinoma: A systematic review and meta-analysis. Chinese Medical Journal 138(5):p 531-539	Study type
U#GL6 Qiu 2025	Qiu L, Wei Q, Hu Y, Yuan J, Wu M, Li Y, Xu Y, Guan X, Cao Y, Pu J, Ding Z, Fei Y, Xu W and Zhou S. Efficacy, safety and cost-effectiveness of chemo-immunotherapy combinations for recurrent or metastatic nasopharyngeal carcinoma: an updated systematic review and cost-effectiveness analysis. Translational cancer research. 2025;14(10):7102-7118.	Study type
#1384 Xu 2024	Xu R, Wong CHL, Chan KSK, Chiang CL. PD-L1 expression as a potential predictor of immune checkpoint inhibitor efficacy and survival in patients with recurrent or metastatic nasopharyngeal cancer: a systematic review and meta-analysis of prospective trials. Frontiers in Oncology. 2024;14:1386381.	Study type
#1141 Polintan 2022	Polintan ET, Canicula SK, Catahay JA, Lo KB, Villalona-Calero M, Loong HHF. Adjunctive PD-1 inhibitor versus standard chemotherapy in recurrent or metastatic nasopharyngeal carcinoma: a systematic review and meta-analysis. Therapeutic Advances in Medical Oncology. 2022;14()1-14.	Study type
#1533 Zhu 2022	Zhu Y, Liu K, Ding D, Wang K, Liu X, Tan X. Chemo-immunotherapy regimes for recurrent or metastatic nasopharyngeal carcinoma: a network meta-analysis and cost-effectiveness analysis. Frontiers in Pharmacology. 2022;13:858207.	Study type
U#79 Zhang 2025	Zhang J, Mao Y, Zhang Y, Wang X, Yin W, Ding L. Efficacy and safety of PD-1/PD-L1 inhibitors for relapsed/metastatic nasopharyngeal carcinoma: A systematic review and meta-analysis. Letters in Drug Design & Discovery. 2025;22(8):100128.	Study type
#973 Ma 2018	Ma SX, Zhou T, Huang Y, Yang YP, Zhan JH, Zhang YX et al. The efficacy of first-line chemotherapy in recurrent or metastatic nasopharyngeal carcinoma: a systematic review and meta-analysis. Annals of translational medicine. 2018;6(11):201.	Study type
#1397 Yan 2022	Yan L, Zheng H, Ren B, Zhang H, Gou H, Dai L. Comparison efficacy and safety of gemcitabine plus cisplatin and 5-fluorouracil plus cisplatin for metastatic nasopharyngeal carcinoma: a meta-analysis and systematic review. Journal of Oncology. 2022(1):7233559	Study type

H.1.4 Quality assessment

Strengths of the literature search included that methods followed were in line with the guidance provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and National Institute for Health and Care Excellence (NICE) guidelines. Therefore, it can be considered that a standard approach was followed - for example, the use of independent reviewers, standard template tables and use of recommended risk of bias checklists.

Further, search terms were carefully developed following our standard approach. The population terms were developed using the subject headings 'Exp nasopharynx tumor/' for Embase and 'Exp Nasopharyngeal Neoplasms/' for Medline, plus free text terms were developed from these subject headings and the relevant narrower subject headings' scope notes (for Embase 'nasopharynx cancer', 'nasopharynx carcinoma', 'lymphoepithelioma' and 'nasopharynx squamous cell carcinoma', and for Medline 'nasopharyngeal carcinoma'). For the clinical review, filters for interventions/comparators and study designs were added. For the economic review, an economic filter based on the SIGN economic filter was added.

One limitation was that the population of "untreated recurrent and/or metastatic NPC" was found to be not specific enough for decision making at the full text review stage. To manage this, after some test reviewing, a clearer description of the criteria was added, of:

Recurrent and/or metastatic NPC was assessed at full text review by either one of the following criteria:

- Histologically or cytologically confirmed primary RM-NPC
- Not amenable for radiotherapy or surgery
- No prior systemic chemotherapy in the RM setting
- For the recurrent NPC after curative treatment (including radiotherapy and/or induction, concurrent or adjuvant chemotherapy), the interval between recurrence and the last dose of previous radiotherapy or chemotherapy must be more than 6 months

H.1.5 Unpublished data

This application only uses the Clinical Study Report of the Jupiter-02 study and the related addendums.

Appendix I. Literature searches for health-related quality of life N/A

I.1 Health-related quality-of-life search

N/A

Table 63 Bibliographic databases included in the literature search N/A

Abbreviations:

Table 64 Other sources included in the literature search N/A

Table 65 Conference material included in the literature search N/A

I.1.1 Search strategies

(((N/A

Table 66 Search strategy for [name of database] N/A

#1
#2
#3
#4
#5
#6

#7

#8

#9

#10

Literature search results included in the model/analysis:

N/A

I.1.2 Quality assessment and generalizability of estimates

N/A

I.1.3 Unpublished data

N/A

Appendix J. Literature searches for input to the health economic model N/A

J.1 External literature for input to the health economic model

(N/A

J.1.1 Example: Systematic search for […]

N/A

Table 67 Sources included in the search N/A

Abbreviations:

N/A

J.1.2 Example: Targeted literature search for [estimates] N/A

N/A

Table 68 Sources included in the targeted literature search N/A

Abbreviations:

N/A

Appendix K. Assessment of proportional hazards for overall survival

Tests for proportional hazards (log–log plots and Schoenfeld residuals) were performed for overall survival to assess the validity of the hazard ratio over time. A corresponding test was not conducted for progression-free survival, as PFS was evaluated at an earlier data cut-off with limited follow-up, showed early and sustained separation of Kaplan–Meier curves, and was not used for extrapolation or modelling purposes. Furthermore, proportional hazards testing for PFS was not pre-specified in the statistical analysis plan.

The proportional hazards assumption for overall survival (OS) was evaluated using standard graphical and residual-based diagnostic methods. As shown in the log cumulative hazard plot (Figure 18), the curves for the two treatment arms are not parallel over time, indicating that the relative treatment effect is not constant. Schoenfeld residuals for the treatment effect (Figure 19) demonstrate a time-dependent pattern, further supporting deviation from proportional hazards. In addition, the quantile–quantile (Q–Q) plot of residuals (Figure 20) shows departures from linearity, consistent with variation in the hazard ratio over time. Collectively, these diagnostic assessments indicate that the proportional hazards assumption is not met for overall survival in the JUPITER-02 trial.

Figure 18 Log cumulative hazards plot for overall survival (Source: Data on file)

Figure 19 Schoenfeld residual plots for overall survival (Source: Data on file)

Figure 20 Quantile-quantile plots for overall survival (Source: Data on file)

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