Toripalimab (Loqtorzi®) in combination with cisplatin and gemcitabine for the first-line treatment of recurrent, not amenable to surgery or radiotherapy, or metastatic nasopharyngeal carcinoma (NPC)

General information [1]

Drug description

The active substance of Loqtorzi® (JS001) is toripalimab, an antineoplastic agent. Toripalimab is a humanised IgG4 kappa monoclonal antibody that binds to programmed death receptor-1 (PD-1). It blocks the binding of programmed death ligand-1 (PD-L1) and PD-L2 to PD-1, thereby preventing the inhibition of immune responses via the PD-1 pathway, including anti-tumour immune responses.

Indication

Loqtorzi®, in combination with cisplatin and gemcitabine, is indicated for the first-line treatment of adult patients with recurrent, not amenable to surgery, radiotherapy, or metastatic NPC.

Incidence [2]

In 2022, NPC's worldwide age-standardised incidence rate was 1.3/100,000. The 5-year prevalence was 83.5% in Asia, compared to 4.4% in Europe.
The number of total cases was 120,434, with 83.3% of cases in Asia and 3.7% of cases in Europe.

Current treatment [3]

The ESMO treatment recommendation for the treatment of recurrent and/or metastatic NPC is displayed in Figure 1 of the Appendix.

Regulatory status

EMA [1]	FDA [4, 5]
Approval status for this indication: On 25 July 2024, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for Loqtorzi® for the following indication: ❖ Loqtorzi®, in combination with cisplatin and gemcitabine, is indicated for the first-line treatment of adult patients with recurrent, not amenable to surgery, radiotherapy, or metastatic NPC. **Other indications**: ❖ 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.	**Approval status for this indication**: On 27 October 2023, the FDA approved toripalimab-tpzi (Loqtorzi®) with cisplatin and gemcitabine for the first-line treatment of adults with metastatic or recurrent, locally advanced NPC. **Other indications**: Loqtorzi® is indicated ❖ as a single agent for the treatment of adults with recurrent unresectable or metastatic NPC with disease progression on or after platinum-containing chemotherapy.

Manufacturer

Loqtorzi® is manufactured by Coherus BioSciences, Inc.

Costs

Currently, no cost information is available for Loqtorzi®.

Warnings and precautions

Currently, no EMA EPAR is available for Loqtorzi®.

Study characteristics [6, 7]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Median follow-up (PFS)	Characteristics	Biomarker	Funding	Publication(s)
JUPITER-02 NCT03581786	289 (1:1)	toripalimab (240 mg) + gemcitabine-cisplatin for up to 6 cycles, followed	placebo + gemcitabine-cisplatin for up to 6 cycles, followed by	PFS by BICR	NR	international, multi-centre, randomised, double-blind phase 3 study conducted in NPC-endemic	-	Shanghai Junshi Biosciences and	JUPITER-02 trial [6]

		by maintenance with toripalimab[1]	maintenance with placebo[2]			regions, including mainland China, Taiwan, and Singapore		Coherus Biosciences	

Inclusion criteria[3]	Exclusion criteria	Patient characteristics at baseline (n=146 vs. n=143)
❖ 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 to local regional treatment or curative treatment. ❖ At least one measurable lesion according to RECIST version 1.1. ❖ Life expectancy ≥ 3 months	❖ History of severe hypersensitivity reactions to other 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 procedures other than for the diagnosis of NPC within 28 days prior to randomisation or anticipation of the need for a major surgical procedure during the study. ❖ History of hypersensitivity to gemcitabine or cisplatin or any of the excipients. ❖ Female patients who are pregnant or lactation.	❖ Median age: 46 years vs. 51 years • ≤50 years: 66% vs. 48% • >50 years: 34% vs. 52% ❖ Male sex: 85% vs. 81% ❖ Asian: 100% vs. 100% ❖ Disease status: • Recurrent: 58% vs. 61% o Locally advanced: 22% vs. 23% o With distal metastasis: 78% vs. 77% • Primary metastatic: 42% vs. 39% ❖ ECOG PS score: • 0: 57% vs. 57% • 1: 43% vs. 43% ❖ Histology: • Nonkeratinising squamous cell carcinoma: 88% vs. 98% • Keratinising squamous cell carcinoma: 1% vs. 1% • Other: 0% vs. 1% ❖ Metastatic sites at baseline (ITT population): • Liver: 42% vs. 40% • Bone: 41% vs. 39% • Lung: 40% vs. 39% ❖ Current or former smoker: 52% vs. 41% ❖ Current or former alcohol use: 21% vs. 13% ❖ Prior treatment: • Radiation therapy: 58% vs. 61% • Concurrent chemotherapy to radiation: 45% vs. 48% • Neoadjuvant therapy: 37% vs. 34% • Surgery: 26% vs. 30% • Adjuvant therapy: 16% vs. 15% ❖ Disease-free interval • ≤2 years: 64% vs. 57% • >2 years: 36% vs. 43% ❖ PD-L1 status positive: 84% vs. 82% ❖ Baseline plasma EBV DNY copy No., IU/mL:

[1] Until disease progression, intolerable toxicity, or completion of 2 years of treatment.
[2] Until disease progression, intolerable toxicity, or completion of 2 years of treatment.
[3] For detailed in-and exclusion criteria, please see trial protocol.

		• <2000: 37% vs. 38% • ≥2000: 63% vs. 62%

Efficacy (I vs. C)	**Safety** (I vs. C)
PFS; cutoff date 8 June 2021: **Median PFS**: 21.4 vs 8.2 months; HR 0.52 (95% CI, 0.37-0.73; nominal p<0.001) **1-year PFS rates**: 59.0% vs. 32.9% and **2-year PFS rates**: 44.8% vs. 25.4% **OS; cutoff date 18 November 2022; median survival follow-up: 36.0 months:** **Median OS**: was not reached vs. 33.7 months; HR, 0.63 (95% CI, 0.45-0.89); 2-sided p=0.008, crossing the prespecified efficacy boundary) **OS rates at 1 year**: 90.9% vs. 87.1% **OS rates at 2 years**: 78.0% vs. 65.1% **OS rates at 3 years:** 64.5% vs. 49.2%. **Tumour Response; cutoff date 8 June 2021** **ORR by BICR**: 78.8% vs. 67.1% in the two groups **CR rates by BICR**: 26.7% vs. 13.3% **Median DoR by BICR**: 18.0 months (95% CI, 10.5-not estimable) vs. 6.0 months (95% CI, 5.6-8.3); HR 0.49 (95% CI, 0.33-0.72) **EBV DNA Copy Number** ❖ Dynamic plasma EBV DNA copy number was monitored for correlation with clinical response. ❖ Among patients with detectable EBV DNA copy number at baseline and at least one posttreatment EBV result, 107 of 107 patients in the toripalimab group and 99 of 103 (96.1%) in the placebo group experienced EBV DNA copy number reduction after the study treatments, including 96.3% in the toripalimab group and 84.5% in the placebo group who had EBV DNA copy number decreased to undetectable level. ❖ After the initial reduction, 36.5% in the toripalimab group and 57.4% in the placebo group experienced EBV DNA copy number rebound. ❖ The median time from the lowest EBV DNA copy number to the rebound was 20.5 vs. 6.0 months. ❖ The rebound also preceded investigator-assessed disease progression by a median of 1.9 months in the toripalimab group.	**Safety cutoff date 8 May 2022** **Any TEAE of any grade:** 100% vs. 100% **Any TRAE grade≥3:** 89.7% vs. 90.2% **Fatal TEAEs:** 3.4% vs. 2.8% **SAEs:** 43.8% vs. 43.4% **Infusion reactions:** 4.1% vs. 4.2% **Immune-related AEs:** 54.1% vs. 21.7% **Immune-related AEs grade ≥3:** 9.6% vs. 1.4%

Patient-reported outcomes

According to the trial protocol, assessment of disease-related symptoms and HRQoL in patients treated with toripalimab plus chemotherapy compared with placebo plus chemotherapy using the EORTC QLQ-C30, EORTC QLQ-H&N35 and ECOG PS assessments are planes. Results are not available (yet).

ESMO-MCBS version 1.1 [8]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2B	>6 months	PFS: +12.3 months	0.52 (0.37-0.73)	HR≤0.65 AND gain ≥3 months	3	-	NA	-	3
Adapted	NC	2B	>6 months	PFS: +12.3 months	0.52 (0.37-0.73)	HR≤0.65 AND gain ≥3 months	3	+32.4% immune-related AEs	NA	-1[4]	2

Risk of bias (RCT) [9]

[4] Toxicity adjustment.

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes low risk	yes low risk	yes low risk	unclear[5] unclear risk	yes[6] high risk	unclear

Ongoing trials [10]

NCT number/trial name	Description	Estimated study completion date
NCT04907370	Toripalimab combined with induction chemotherapy followed by radiotherapy alone or concurrent chemoradiotherapy in locoregionally advanced NPC: A phase 3, multi-centre RCT.	05/2027
NCT04453813	A multi-center randomised clinical phase 3 trial of toripalimab plus concurrent chemoradiotherapy vs. concurrent chemoradiotherapy alone for unresectable locally recurrent NPC.	07/2027
NCT03907826	PD-1 antibody combined with chemoradiotherapy vs. chemoradiotherapy in recurrent NPC patients: a multi-centre, randomised controlled, phase III clinical trial.	12/2027
NCT05340491	Chemoradiotherapy combined with PD- 1 antibody in recurrent NPC: A Multi-center, open-label, randomised, controlled, phase III trial.	12/2027
NCT04376866	Toripalimab in combination with concurrent chemoradiotherapy for local-regional recurrent NPC: a phase 3, multi-centre RCT	04/2028
NCT05869227	Maintenance therapy with toripalimab combined with capecitabine/placebo for recurrent and metastatic NPC.	04/2029
NCT04778956	Toripalimab plus surgery vs. surgery alone for resectable recurrent NPC: a prospective, parallel, multi-centre, phase 3 RCT.	03/2033

Available assessments

- In March 2023, NIHR published a Health Technology Briefing "Toripalimab with chemotherapy for previously untreated recurrent or metastatic nasopharyngeal carcinoma" [11].
- No assessments were identified via NICE, CDA-AMC, ICER and G-BA.

Other aspects and conclusions

- In July 2024, the **CHMP adopted a positive opinion**, recommending the granting of a marketing authorisation for Loqtorzi® in combination with cisplatin and gemcitabine for the first-line treatment of adult patients with recurrent, not amenable to surgery or radiotherapy, or metastatic NPC. In October 2023, the **FDA approved** Loqtorzi® with cisplatin and gemcitabine for the first-line treatment of adults with metastatic or recurrent, locally advanced NPC.
- **JUPITER-02** (**NCT03581786) i**s an international, multi-centre, randomised, double-blind **phase 3 study** conducted in NPC-endemic regions, aiming to assess toripalimab plus chemotherapy for recurrent or metastatic NPC. Eligible patients were aged between 18 and 75 years and were required to have histologically or cytologically confirmed primary recurrent or metastatic NPC, which was not amenable to local-regional or curative treatment, and must have received no prior systemic chemotherapy in the recurrent or metastatic setting.
- According to the trial protocol, an assessment of **patient-reported outcomes** is planned. However, results are not available (yet).
- The **original and adapted ESMO-MCBS** were applied, resulting in a final adjusted magnitude of clinical benefit grade of **3 and 2**, respectively.
- Since not all of the predefined endpoint results have been reported yet, the **risk of bias was considered unclear**. However, it is increased by the industry-funded background.
- Several RCTs assessing toripalimab in different settings and combinations were identified via ClinicalTrials.gov.
- Final analysis results and patient-reported outcome data are required to determine the future role of toripalimab treatment of adult patients with recurrent, not amenable to surgery, radiotherapy, or metastatic NPC.

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Abbreviations: AE=adverse event, AJ=adjustment, BICR=blinded independent committee review, C=comparator, CDA-AMC=Canada´s Drug Agency, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CR=complete response, DoR=duration of response, EBV=Epstein-Barr virus, ECOG PS=ECOG Eastern Cooperative Oncology Group, EMA=European Medicines Agency, EPAR=European Public Assessment Report, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, G-BA=Gemeinsamer Bundesausschuss, HR=hazard ratio, I=intervention, ICER=Institute for Clinical and Economic Review, Int.=intention, MG=median gain, n=number of patients, NICE=National Institute for Health Care Excellence, NPC=Nasopharyngeal carcinoma, ORR=objective

[5] Results for the predefined endpoints "disease control rate" and "HRQoL" are missing.
[6] Industry-funded.

response rate, OS=overall survival, PD-L1=Programmed cell death-ligand 1, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, RECIST=Response Evaluation Criteria In Solid Tumors, SAE=serious adverse event, ST=standard treatment, TEAE=treatment-emergent adverse event

References:

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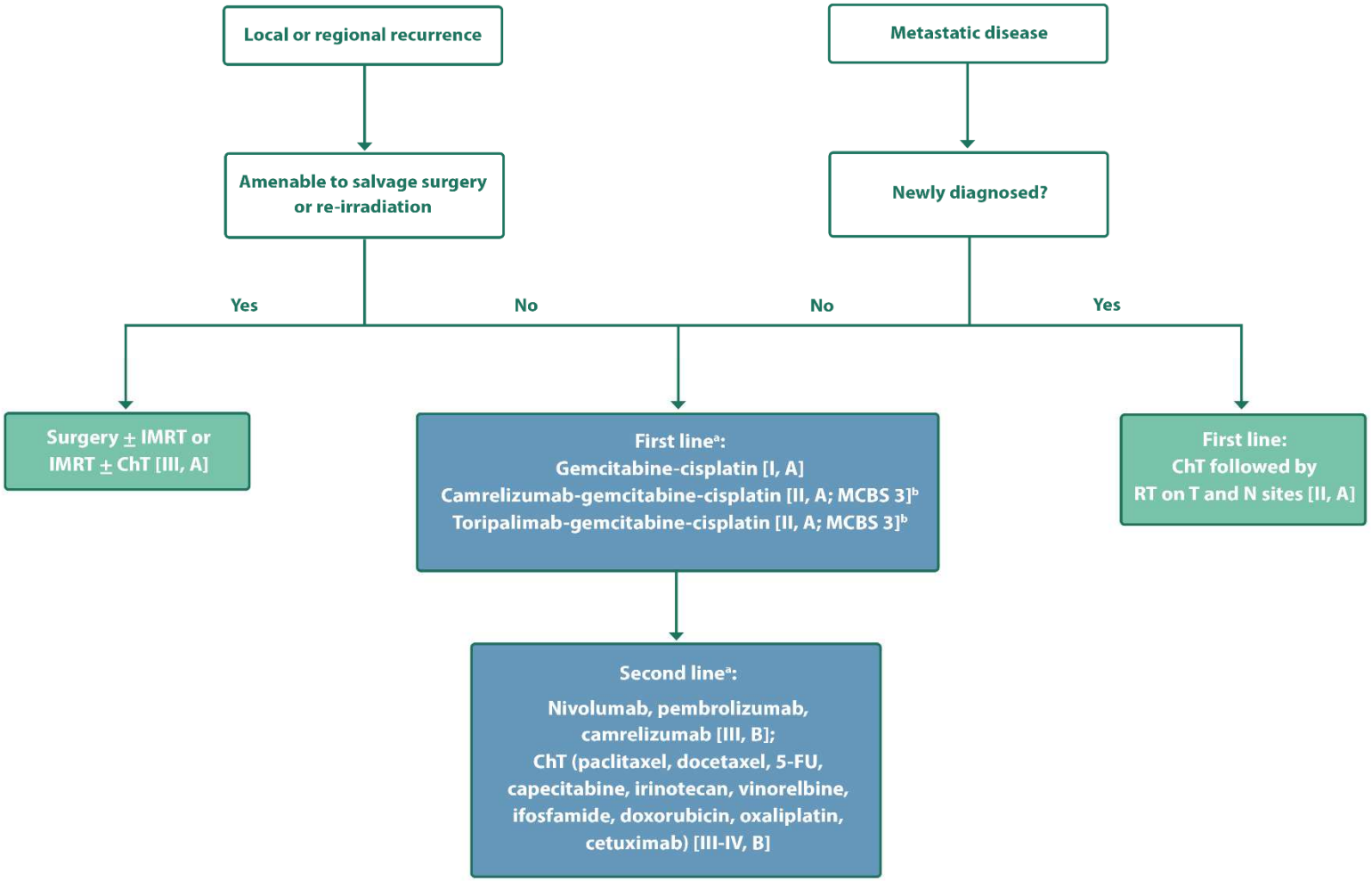
Appendix – Figure 1:



5-FU, 5-fluorouracil; ChT, chemotherapy; EMA, European Medicines Agency; FDA, US Food and Drug Administration; IMRT, intensity-modulated radiotherapy; MCBS, Magnitude of Clinical Benefit; N, node; NPC, nasopharyngeal carcinoma; RT, radiotherapy; T, tumour.

[a]Consider RT [III, B] or surgery [IV, C] on metastatic sites.

[b]ESMO-MCBS v1.1 was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).