Risk Management Plan

for

LOQTORZI

RMP version number: 1.5

Date: 12 July 2024

Administrative Information

RMP version to be assessed as part of this application: 1.5

RMP Version number: 1.5

Data lock point for this RMP: 16 Dec 2022

Date of final sign-off: 15 July 2024

Rationale for submitting an updated RMP:

Addressing multiple comments and requests for revisions to the RMP in the D195 document.

Summary of significant changes in this RMP:

- In response to Q2 of D195 document, the key messages for the patient alert card have been moved from V.2 to Annex 6.
- In response to Q3 of D195 document, the full patient alert card has been removed from Annex 6, and the missing template language from the *Guidance on the format of the risk management plan (RMP) in the EU – in integrated format Rev. 2.0.1 (31 October 2018)* has been added to Annex 6.
- The invented name in the European Economic Area (EEA) in Table Part I.1 has been updated.

Other RMP versions under evaluation: Not applicable

Details of the currently approved RMP: Not applicable

Note: This RMP is developed in accordance with the European Medicines Agency (EMA) European Union (EU) - RMP template

QPPV Name[1]: Amy Tanti

QPPV signature: PD [redacted]

[1] QPPV name will not be redacted in case of an access to documents request; see HMA/EMA Guidance document on the identification of commercially confidential information and personal data within the structure of the marketing-authorisation application; available on EMA website http://www.ema.europa.eu

Table of content

List of Abbreviations

Abbreviation	Definition/Description
ASR	Age-standard rate
CDR	Complementarity-determining regions
CHO	Chinese Hamster Ovary
COPD	Chronic obstructive pulmonary disease
CVD	Cardiovascular diseases
DNA	Deoxyribonucleic acid
EEA	European Economic Area
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EU	European Union
GVHD	Graft-versus-host-disease
HCP	Healthcare professionals
HNSCC	Head and neck squamous cell cancer
HLA	Human leukocyte antigen
INN	International non-proprietary name
IV	Intravenous
MAH	Marketing authorization holder
NCI	National Cancer Institute
NPC	Nasopharyngeal carcinoma
NSCLC	Non-small cell lung cancer

OSCC	Oesophageal squamous cell carcinoma
PD-1	Programmed death receptor 1
PI	Product Information
PL	Package leaflet
QPPV	Qualified Person Responsible For Pharmacovigilance
RMP	Risk Management Plan
SEER	Surveillance, Epidemiology, and End Results
SmPC	Summary of product characteristics
TNBC	Triple negative breast cancer
TKI	Tyrosine kinase inhibitor
VEGF	Vascular endothelial growth factor

Part I: Product(s) Overview

Table Part I.1 – Product(s) Overview

Active substance(s) (INN or common name)	Toripalimab
Pharmacotherapeutic group(s) (ATC Code)	L01FF13
Marketing Authorisation Applicant	TMC Pharma
Medicinal products to which this RMP refers	LOQTORZI
Invented name(s) in the European Economic Area (EEA)	LOQTORZI.
Marketing authorization procedure	Centralised
Brief description of the product including: • chemical class • summary of mode of action • important information about its composition (e.g., origin of active substance of biological products, relevant adjuvants or residues for vaccines)	LOQTORZI drug substance is a humanized modified $IgG_4\kappa$ mAb specific against human PD-1. LOQTORZI contains the complementarity-determining regions (CDR) of a murine antibody that binds to human PD-1 and human framework regions (FR) with limited back-mutations to the parental murine sequence. A serine to proline substitution was introduced at amino acid 233 (S233P) to minimize Fab arm exchange. LOQTORZI is produced by recombinant deoxyribonucleic acid (DNA) technology in a Chinese Hamster Ovary (CHO) mammalian cell expression system (LONZA).

	LOQTORZI has a predicted molecular weight of approximately 147 kDa, and it is composed of two 452 amino acid heavy chains and two 219 amino acid light chains. LOQTORZI contains an N-linked glycosylation site at heavy chain amino acid 302 (N302). The isoelectric point of LOQTORZI is between 6.4 to 7.4.
Hyperlink to the Product Information	Refer to proposed PI
Indication(s) in the EEA	- LOQTORZI, in combination with cisplatin and gemcitabine, is indicated for the first-line treatment of adult patients with metastatic or recurrent, locally advanced nasopharyngeal carcinoma not amenable to curative therapy. - 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.
Posology and route of administration in the EEA	The recommended dosing regimen of LOQTORZI is administered at 240 mg every 3 weeks (Q3W) as an intravenous (IV) infusion over 60 minutes for the first infusion and over 30 minutes for subsequent infusions. Treatment should continue until disease progression, unacceptable toxicity or up to a maximum duration of 24 months.
Pharmaceutical form(s) and strengths	LOQTORZI is supplied as a sterile liquid containing 240 mg toripalimab. It is formulated at a nominal

	concentration of 40 mg/mL in 20 mM Sodium Citrate, 2.5% (w/v) Mannitol, 50 mM NaCl, 0.02% (w/v) Polysorbate 80, pH 6.0. Each vial contains 6 mL of available volume.
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Brand names of concerned products (with this indication): LOQTORZI

Note: This RMP focuses primarily on nasopharyngeal carcinoma (NPC) and oesophageal squamous cell carcinoma (OSCC). The indications approved elsewhere are not described here.

Epidemiology of the Disease

a) Incidence and Prevalence

Nasopharyngeal carcinoma

Nasopharyngeal carcinoma is rare in the West with an age-standardized rate (ASR) of 0.44 in Europe. In China and other parts of Southeast Asia, NPC is relatively common with ASRs of 3.0 in China as a whole and 9.69 in South China [1][2].

In European regions, the annual age-adjusted incidence rate for nasopharyngeal carcinoma is 0.65 and 0.23/100,000 in males and females respectively. The incidence of NPC increases with age with incidence of 0.027/100,000 among individuals ages 0-14 years that increases to 0.897/100,000 among individuals aged 65 years and above.

Based on data from International Agency for Research on Cancer, there were 1901, 1304, 1584, and 415 new cases of NPC in countries of Central and Eastern Europe, Western Europe, Southern Europe, and Northern Europe, respectively in 2020. Cancer Research UK reported that there are around 260 cases diagnosed each year in UK [3].

According to the data from Globocan (International Agency for Research on Cancer (IARC)), there were nearly 130,000 new cases of NPC worldwide in 2018, of which China had the highest number of new cases, more than 60000. The annual incidence

rate of nasopharyngeal carcinoma in China (3.0/100,000) was significantly higher than the world average (1.5/100,000), and the incidence rate in men (4.3/100,000) was significantly higher than that in women (1.7/100,000). It is estimated that in 2018, the death toll of NPC in the world is about 73000, with a mortality rate of 0.84/100,000 and in China there were 31,000 deaths, with a mortality rate of 1.5/100,000 [3].

Nasopharyngeal carcinoma is one of the high incidence tumours in China, accounting for the first incidence rate of head and neck tumours. Nasopharyngeal carcinoma "is also commonly known as" Guangdong cancer "in China. It has a high incidence in southeast coastal areas such as Guangdong, Guangxi and Fujian, especially in the Pearl River Delta. Compared with the entire country, the highest incidence rate of nasopharyngeal carcinoma in Guangdong Province in 2013 was 10.5/100,000 and the incidence in males was 15.3/100,000, much higher than the national figures for nasopharyngeal carcinoma. [4].

Squamous cell carcinoma of the oesophagus

Oesophageal cancer, both adenocarcinoma and squamous cell carcinoma of the oesophagus, is uncommon in Europe with an ASR of 3.3/100,000. Further, in Europe, the majority of patients are diagnosed with adenocarcinoma, further decreasing the incidence of OSCC. In China, oesophageal cancer is relatively common; the ASR is 13.8/100,000 with the vast majority of patients (~ 90%) developing OSCC [1][5].

Based on National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results Program (SEER), the rate of new cases of oesophageal cancer was 4.2 per 100,000 men and women per year in the U.S. The age standardized incidence of oesophageal squamous carcinoma is 1.8 and 0.7/100,000 in males and females, respectively, in the US. The mortality rate was 3.9 per 100,000 men and women per year. These rates are age-adjusted and based on 2015–2019 cases and deaths [6].

Approximately 0.5 percent of men and women will be diagnosed with oesophageal cancer at some point during their lifetime, based on 2017–2019 data in the US [6].

In 2019, there were an estimated 49,084 people living with oesophageal cancer in the United States [6].

b) Demographics of the Target Population

Nasopharyngeal carcinoma

Age

Nasopharyngeal carcinoma is normally observed in middle-aged adults, over the age range from 40 to 50 years, although, individuals across a wide age range may be affected (including children).

Gender

Worldwide, nasopharyngeal carcinoma incidence is higher in males than in females with a male to female ratio between 2:1 to 3:1.

Race

Nasopharyngeal carcinoma occurs most frequently in Asians (including people currently residing in Southeast Asia, China, Mongolia, and Innuits of Alaska and Canada). Blacks have the second highest incidence, followed by Caucasians.

Risk Factors

Infection with the EBV is closely associated with the development of NPC. Persistent EBV infection is necessary for tumorigenesis [7][8]. Additional risk factors include carcinogenic nitrosamines and their precursors, certain fungi and their toxins, high-risk human leukocyte antigen (HLA) heteromorphism (mainly HLA- A * 11:01 and HLA-A * 02:27), and population and environmental factors [9][10][11].

Squamous cell carcinoma of the oesophagus

Age

Squamous cell carcinoma of the oesophagus is normally observed in middle-aged and older adults, age over 50 years, although, individuals of a wide age range may be affected (including children) [12].

Gender

Worldwide, the incidence of OSCC is higher in males than in females with a male to female ratio between 2:1 to 10:1.

Race

All races and ethnic groups are at risk for OSCC, but the geographical distribution varies from certain high-incidence areas (including parts of east China, north Iran, and Kazakhstan) to low-incidence areas (U.S. and Scandinavian countries) [12].

Risk Factors

Cigarette smoking, alcohol consumption, caustic injury, poor oral hygiene, ingestion of caustic agents, and nutritional deficiencies [13].

c) Main Treatment Options

For NPC, radiotherapy is the main treatment and radiotherapy can be alone or with chemotherapy (chemoradiotherapy) when the tumour is localized. Surgery is usually only considered if the cancer comes back after the original treatment (recurrence) [14]. For patients who present with metastatic disease or who recur after surgical resection or chemoradiotherapy, standard treatment consists of a gemcitabine/cisplatin chemotherapy regimen.

The standard of care for treatment of resectable OSCC involves surgical debulking of all visible or gross disease followed by adjuvant combination chemotherapy with a platinum agent and taxane [15][16]. For patients who present with metastatic disease or who recur after surgical resection or chemoradiotherapy, standard treatment includes a platinum and fluoropyrimidine in patients with PD-L1 low or

negative tumours and the same chemotherapy with nivolumab or pembrolizumab in PD-L1 expressing (TPS ≥1%) or PD-L1-high (CPS ≥10%) tumours.

d) Mortality and Morbidity (Natural History)

Nasopharyngeal carcinoma

In 2012 the highest NPC mortality rates were in Hong Kong (4.51/100,000 men and1.15/100,000 women), followed by selected Eastern European countries (Moldova and Romania). The lowest rates were in Northern Europe and Latin American countries. EU rates were 0.27/100,000 men and 0.09/100,000 women, US rates were 0.20/100,000 men and 0.08/100,000 women and Japanese rates were 0.16/100,000 men and 0.04/100,000 women. It is estimated that in 2018, the death toll of nasopharyngeal carcinoma in the world is about 73,000, with a mortality rate of 0.84/100,000, and that in China is about 31,000, with a mortality rate of 1.5/100,000. Based on data from IARC, there were 1091, 502, 746, and 247 deaths due to NPC in countries of Central and Eastern Europe, Western Europe, Southern Europe, and Northern Europe, respectively in 2020.

The 5-year survival rate of patients with nasopharyngeal carcinoma is 85%; 15% of patients have distant metastasis at the time of initial diagnosis. The effectiveness of treatment for recurrent and metastatic nasopharyngeal carcinoma is poor, and the median survival time is 20 months [17] [18] [19]. The 5-year overall survival rate of patients with advanced diseases is less than 10% [20].

Squamous cell carcinoma of the oesophagus

Globally, there were an estimated 544,100 deaths from oesophageal cancer in 2020, corresponding to age-standardized mortality rates of 5.6 per 100,000. Most cases were squamous cell carcinomas SCCs (85%). Mortality rates were 2- to 3-fold higher in males (8.2) compared with females (3.2). Global variations in mortality were observed across countries and world regions; the highest rates occurred in Eastern Asia and Southern and Eastern Africa and the lowest occurred in Western Africa and

Central America regions. If rates remain stable, 880,000 deaths from oesophageal cancer are expected in 2040.

Based on data from Cancer Research UK, there were 8043 deaths due to oesophageal cancer in 2017-2019 with a crude annual mortality rate of 12.7/100,000. The oesophageal cancer mortality rate was lower in females (7.2/100,000) than in males (16.9/100,000).

e) Concomitant Medication(s) in Target Population

Nasopharyngeal carcinoma

Radiotherapy is the first choice for the treatment of early nasopharyngeal carcinoma. In the treatment of locally advanced nasopharyngeal carcinoma, concurrent radiotherapy and chemotherapy is the standard treatment mode, in which cisplatin is the most commonly used chemotherapy drug. When using chemotherapy drugs, concomitant drugs that are often used: including antiemetics, painkillers, and drugs to prevent and treat haematopoietic toxicity. In addition, in China, traditional Chinese medicine preparations and liver protective drugs are often used in cancer treatment, which should also be considered in individual case safety report (ICSR) evaluation. For patients with recurrent, locally advanced or metastatic NPC, the standard of care is treatment with gemcitabine and cisplatin.

Possible complications of nasopharyngeal carcinoma include epistaxis or bloody nose, nasal congestion, exudative otitis media, headache, skull base invasion and eye symptoms. Side effects following radiotherapy include fatigue, dizziness, nausea, vomiting, insomnia, drowsiness and other systemic reactions, epistaxis, mucosal reaction in oral and nasal cavity, difficulty in opening mouth, radiation otitis media, skin radiation reactions (such as dry skin exfoliation or wet dermatitis), radiation lung injury (including cough, fever and dyspnoea), radiation esophagitis (including dysphagia, swallowing pain, post sternal pain and burning sensation), and radiation sinusitis [21]. Chemotherapy with a platinum-containing regimen may cause bone

marrow suppression, nephrotoxicity, ototoxicity, digestive system toxicity, neurotoxicity and other adverse reactions.

According to epidemiological studies of nasopharyngeal carcinoma, the incidence of bleeding events after radiotherapy is 78% and the incidence of bleeding in recurrent or metastatic advanced nasopharyngeal carcinoma is 3.2% ~ 10% [22]. Bleeding results from tumour progression that infiltrates local blood vessels. Infiltration of local arteries, leading to arterial rupture and fatal epistaxis can occur.

Squamous cell carcinoma of the oesophagus

Locally advanced, resectable, OSCC is generally treated with surgery, radiotherapy and chemotherapy [23]. Surgical treatment of early oesophageal cancer has a high remission rate, while comprehensive treatment is the main treatment for advanced oesophageal cancer. First-line treatment for patients with advanced, unresectable OSCC is usually radical concurrent chemoradiotherapy. Commonly used chemotherapy drugs for include 5-fluorouracil, platinum and taxanes [16]. Programmed death receptor 1 (PD-1) is also recommended as second-line therapy for patients with PD-L1-expressing, recurrent, locally advanced or metastatic OSCC [24]. Clinical studies have shown inconsistent results for the safety and efficacy of targeted therapy (e.g., epidermal growth factor receptor (EGFR) inhibitor [e.g., cetuximab, tyrosinase inhibitor (TKI)] and vascular endothelial growth factor (VEGF) inhibitor [e.g., bevacizumab, TKI]), with standard chemotherapy and further clinical exploration and application are needed [25][26]. In addition, in China, traditional Chinese medicine preparations are often used as cancer treatment, which should also be considered in ICSR evaluation.

The most common complications of OSCC include dysphagia caused by obstruction (more than 90%) and aspiration pneumonia [27]. Complications of advanced OSCC also include vocal cord and diaphragm paralysis, dry cough, tachycardia, paraesthesia and Horner syndrome caused by nerve invasion (about 15%) and perineural tissue (up to 47%) [28][29]. Death is caused by bleeding from primary

cancers, hematemesis caused by tumour invasion of thoracic vessels, and massive gastrointestinal bleeding (incidence: 5.8-7%) [30][31]; Oesophageal tracheal fistula caused by cancer erosion and ulceration (incidence of about 5-10%) [32], oesophageal perforation (incidence of about 2.6-4.4%) [33][34] and severe dysphagia resulting in malnutrition, dehydration and electrolyte disorders (incidence of about 2.8%) are also reported [35].

f) Important Co-morbidities Found in Target Population

Comorbid chronic diseases are common in individuals with cancer. In one analysis, 36% of cancer cases reported 1 chronic comorbid disease, 22% reported 2 chronic diseases, and 10.5% reported ≥3 chronic comorbid conditions.

The incidence of co-morbidity in over two thousand patients with newly-diagnosed, non-metastatic NPC showed that gastrointestinal disorders (19.4%), substance abuse (16.1%), and cardiovascular disease (7.1%) were the most common [36]. The incidence of co-morbidity in elderly patients with NPC ranged from 22.4% to 58% [37]. For NPC and OSCC, major co-morbidities include chronic obstructive pulmonary disease (COPD), cardiovascular disease, renal impairment, gastrointestinal disorders, and metabolic syndrome, which are common comorbidities in the elderly [38][39]. Dolan et al. reported that cardiac, peripheral vascular, chronic pulmonary disease and diabetes were major contributors to co-morbidity, which are also commonly seen in the elderly general population [40].

Chronic obstructive pulmonary disease (COPD)

Data for the incidence of COPD among NPC/oesophageal cancer patients were unavailable from literature. Data for COPD among NPC/oesophageal cancer patients were unavailable.

Cardiovascular Diseases (CVD)

In one study in NPC, diseases of the cardiovascular system were the most comorbidities (27%) [41] Comprehensive studies describing the incidence of CVD

not resulting from chemotherapy among patients with NPC or OSCC were unavailable. Data for CVD-specific mortality among patients with NPC or OSCC were unavailable.

Gastrointestinal Disorders

Guo et al. demonstrated that 44.2% patients with NPC in southern China had comorbidities, with the most common comorbidity being gastrointestinal disorders [36].

Comprehensive studies describing the incidence of gastrointestinal disorders not resulting from chemotherapy among patients with NPC or OSCC were unavailable.

Data for GI disorder-specific mortality among patients with NPC or OSCC were unavailable.

Renal Impairment

Data for the incidence of renal impairment among patients with NPC or OSCC were unavailable from literature. Data for renal impairment-specific mortality among patients with NPC or OSCC were unavailable.

Diabetes Mellitus

Data for the incidence of diabetes mellitus among patients with NPC or OSCC were unavailable from literature. Data for diabetes-specific mortality among patients with NPC or OSCC were unavailable.

Substance abuse

Data for the incidence of substance abuse specific mortality among patients with NPC were unavailable from literature.

Part II: Module SII - Non-clinical part of the safety specification

Safety Pharmacology

Cardiovascular parameters (electrocardiogram, heart rate and blood pressure) were evaluated within the context of the non-GLP single-dose toxicity study (2352-13085) as well as the GLP-compliant, 4-week, repeat-dose toxicity study (2352-13086) in cynomolgus monkeys. There were no abnormal findings attributable to LOQTORZI. Safety Pharmacology studies were incorporated into the GLP-toxicity study.

Toxicology

Key Issues Identified from Acute or Repeat-Dose Toxicity Studies

A single dose, exploratory dose range finding and toxicokinetic (TK) study in cynomolgus monkeys was conducted to assess the acute toxicity and tolerability of LOQTORZI. In this study, four (2/sex) cynomolgus monkeys were randomly assigned to two groups (1 animal/sex/group). Animals were administered LOQTORZI at 1 or 203 mg/kg (maximum feasible dose [MFD] of LOQTORZI) once via 30 minutes IV infusion at the dose volume of 5 mL/kg. In the 4-week observation period, there were no LOQTORZI-related effects in the in-life parameters (clinical observation, body weights and weight change, food consumption and clinical pathology), safety pharmacology (respiratory, circulatory, autonomic and central nervous systems) and the immunophenotyping of peripheral T, B, NK cells. The maximum tolerable dose of LOQTORZI in this study is 203 mg/kg when administered once via 30-minute IV infusion to male and female cynomolgus monkeys.

Four-week and 26-week repeat-dose toxicity studies were conducted in naïve cynomolgus monkeys to assess the potential sub-chronic and chronic toxicity of LOQTORZI. Based on the absence of significant toxicological findings at the highest dose administered in each study, 100 mg/kg is considered the NOAEL for both studies. A similar panel of parameters were evaluated in both studies, included in-

life parameters (daily clinical observations, body weight, weight changes, food consumption and clinical chemistry, haematology, coagulation, and urinalysis), ophthalmology, injection site, cardiology (electrocardiogram evaluations (ECG), heart rate, blood pressure), clinical pathology (clinical chemistry, haematology, coagulation, and urinalysis), gross and microscopic pathology, as well as ADA and TK analysis. In addition, special attention was paid on potential immunotoxicity / immunophenotyping of peripheral blood cells and monitoring of PD-1 receptor occupancy were included in both studies; cytokine analysis was conducted in the 4-week study; immune complex deposition in kidney and testosterone levels were evaluated in the 26-week study. Evaluations of the respiratory, circulatory, autonomic and central nervous systems, and of somatomotor and behavioural patterns were included in the weekly physical examinations in the 4-week toxicity study.

No morbidity or mortality attributed to the test article occurred during these studies. All animals survived to the planned necropsy date in the 4-week repeat-dose study. In the 26-week study, one female in the dose group of 100 mg/kg was found rectocele on SD98 and was euthanized on SD 104 due to persistence of the disease. However, no system toxicity related to the test article was noted in the comprehensive clinical pathology, immune function, macroscopic and microscopic examinations of this animal. Therefore, this death was due to progressive rectocele without faeces and was considered not related to the test article. In addition, incidental, minor and transient changes were noted in clinical pathology, ECG measurement, frequency of T and B subsets and organ weight changes. However, such differences in values between LOQTORZI -administered animals and vehicle control animals, including those that were statistically significant, were considered spurious because they had a pattern consistent with random variation, lacked a dosage-related pattern, and because there was overlap in magnitude relative to pre-dosing values and/or absolute value with vehicle control animals. In conclusion, there was no test-article related

significant toxicological findings in both studies. LOQTORZI was tolerated well in both male and female animals up to 100 mg/kg once a week for 26 weeks.

Taken together, following IV infusions once two weeks over 4 weeks (total of 3 doses), or weekly for 26 weeks (total of 27 doses) of LOQTORZI at dose range of 1-100 mg/kg to male and female cynomolgus monkeys, there was no LOQTORZI -related adverse effects on in-life parameters, ophthalmic examination findings, safety pharmacology, clinical pathology, immune function parameters (lymphocytes immunophenotyping, cytokine release, immune complex formation), hormone analysis (testosterone/free testosterone), macroscopic or microscopic findings.

Reproductive/Developmental Toxicity and Genotoxicity

It has been demonstrated in several non-clinical studies that the PD-1/PD-L1 signalling pathway was critical for maintaining foetal tissue tolerance and embryo-foetal survival through maternal immunity. No developmental or reproductive toxicity study was conducted for toripalimab and non are planned. Based on the critical effect of the PD-1/PD-L1 pathway on the maintenance of foetal tissue tolerance through maternal immunity, possible adverse effects on the developing foetus are expected.

In conclusion, no important safety findings were found for non-clinical studies.

Part II: Module SIII - Clinical trial exposure

Brief Overview of Development

Table below provides a brief overview of the clinical studies that form the human safety dataset to support the indications of NPC and OSCC.

Table SIII: Ongoing and completed clinical studies.

Cancer type/ study number	Phase	Population	Number of Patients Enrolled	Study Status
Advanced malignancies of multiple types				
CT1	I	Advanced tumours	36[a]	completed
CT2	I	Advanced tumours[1]	25[a]	completed
CT3	I	Advanced tumours[2]	33[a]	completed
Advanced malignancies of multiple types; study in the US				
TAB001-01	I	Advanced solid tumour[3]	184 [a]	completed
Lymphoma				
CT6	I	Relapsed/refractory malignant lymphoma	13[a]	completed
Neuroendocrine tumour				
CT14	I	Advanced neuroendocrine tumour after standard therapy failure	40[a]	completed
Advanced malignancies; multi-cancer cohorts				

Cancer type/ study number	Phase	Population	Number of Patients Enrolled	Study Status
CT5	Ib/II	Patients with advanced gastric adenocarcinoma (GC), oesophageal squamous cell cancer (OSCC), nasopharyngeal cancer (NPC), and head and neck squamous cell cancer (HNSCC) progressed on prior lines of treatment	NPC monotherapy[a] (190) NPC chemo combination therapy (12) OSCC monotherapy[a] (59) OSCC chemo combination therapy (12) GC monotherapy[a] (58) GC chemo combination therapy (33) HNSCC monotherapy[a] (34) HNSCC chemo combination-therapy (3)	completed
Triple negative breast cancer (TNBC)				
CT9	I	Advanced TNBC	20 [a]	completed
Melanoma				
CT7-2	I	Pharmacokinetic similarity before and after process changes in patients with advanced melanoma	26 [a]	completed
CT4	II	Locally advanced or metastatic melanoma after standard therapy failure	128 [a]	completed

Cancer type/ study number	Phase	Population	Number of Patients Enrolled	Study Status
CT8	II	Adjuvant treatment of completely resected mucosal melanoma	145 (73 JS001[a]; 72 control)	completed
Urothelial Cancer				
CT12	II	Locally advanced or metastatic urothelial cancer after failure of standard therapy	151[a]	completed
Nasopharyngeal cancer				
CT15	III	Advanced nasopharyngeal carcinoma	289 (146 JS001/chemo[b]; 143 control)	enrolment completed; study ongoing
Oesophageal cancer				
CT21	III	Advanced or metastatic oesophageal squamous cell cancer without prior systemic chemotherapy	514 (257 JS001/chemo[b]; 257 control)	enrolment completed; study going
Non-small cell lung cancer (NSCLC)				
CT7-1	I	Pharmacokinetic similarity before and after process changes in patients with advanced NSCLC	41 [a]	completed

[a] Included in the pooled safety analysis of toripalimab monotherapy.

[b] Included in the pooled safety analysis of toripalimab in combination with platinum-containing chemotherapy as the first line treatment of NPC or OSCC.

[1] CT2 included 6 patients with NPC and 6 patients with OSCC who received toripalimab monotherapy in the later line setting, respectively

[2] CT3 included 1 patient with NPC who received toripalimab monotherapy as later line treatment.

[3] TAB001-01 included 2 patients with NPC and 12 patients with OSCC who received toripalimab monotherapy in the later line setting, respectively.

JS001=toripalimab; chemo=chemotherapy

As shown in the table above, the safety of toripalimab as monotherapy has been evaluated in a pooled analysis of 1,111 patients enrolled in 13 studies (one randomized, active-controlled and 12 open-label, non-randomized). The tumour types included nasopharyngeal carcinoma (n=199), oesophageal carcinoma (n=77), or other types of tumours (n=835). Of these 1,111 patients, 927 patients were treated in China and East China and 184 patients were treated in the United Stated. The safety of toripalimab in combination with platinum-containing chemotherapy has been evaluated in a pooled analysis of 403 patients with NPC or OSCC receiving 240 mg toripalimab as an intravenous infusion every 3 weeks in JUPITER-02 (CT15) or JUPITER-06 (CT21).

Clinical Trial Exposure

In the toripalimab monotherapy safety pool (N=1,111), the toripalimab dosage regimens evaluated were 3 mg/kg every two weeks (Q2W) (n=851), 240 mg every three weeks (Q3W) (n=166), 10 mg/kg Q2W (n=31), and other dosage regimens (n=63). In the monotherapy patient population, the median duration of toripalimab exposure of 3.3 months (range 0.03-35.9).

In the safety pool of toripalimab in combination with chemotherapy (N=403; CT15 and CT21), the median duration of treatment in these patients was 6.5 months (range 1 day to 2.1 years).

The tables below provide the gender and age breakdown for the toripalimab pooled safety analysis population (N=1514).

Table SIII.1: Age group and gender

Overall LOQTORZI exposure during clinical development by age and gender

Age	Male	Female	Total
< 65 years	794	357	1151
≥ 65 years	246	117	363
Total	**1040**	**474**	**1514**

Table SIII.2: Ethnic origin

Overall LOQTORZI exposure during clinical development by race and ethnicity

Race	Number of subjects
American Indian/Alaska Native	1
Black/African American	14
Asian	1339
White	151
Native Hawaiian or other Pacific Islander	1
Unknown	8
Total	**1514**

Table SIII.3 - LOQTORZI exposure during clinical development by indication

NASOPHARYNGEAL CARCINOMA

MONOTHERAPY	Male	166
	Female	33
	Age 18-64	188
	Age 65 and up	11
	Total	**199**
COMBO-THERAPY	Male	124
	Female	22
	Age 18-64	139
	Age 65 and up	7
	Total	**146**

OESOPHAGEAL SQUAMOUS CELL CARCINOMA

MONOTHERAPY	Male	68
	Female	9
	Age 18-64	58
	Age 65 and up	19
	Total	**77**
COMBO-THERAPY	Male	217
	Female	40
	Age 18-64	156
	Age 65 and up	101
	Total	**257**

Part II: Module SIV - Populations not studied in clinical trials

NPC is an orphan disease and the occurrence of OSCC is also low in EU/UK region. As discussed in the epidemiology section (Section SI), the population of patients with NPC/OSCC represents only a very small proportion of patients with cancer.

SIV.1. Exclusion criteria in pivotal clinical studies

Due to concerns about exacerbation of underlying autoimmune disease, patients with an active/history of underlying autoimmune disease (except controlled hypothyroidism, diabetes, or vitiligo) were excluded from toripalimab trials. In addition, patients who had active infections (active tuberculosis or hepatitis B or C or HIV infection), were immunocompromised (systemic corticosteroids > 10 mg prednisone daily of prednisone equivalents within 2 weeks of randomisation), active or untreated CNS metastases, ECOG PS ≥2, or a history of interstitial lung disease were excluded. The Summary of Product Characteristics (SmPC) will clearly state that such patients were excluded from clinical trials of toripalimab.

SIV.2. Limitations to detect adverse reactions in clinical trial development programmes

There are no data on the use of toripalimab in pregnant women. Animal studies have not been conducted with toripalimab; however, animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-related rejection of the developing foetus and result in foetal death. LOQTORZI should not be used during pregnancy or in women of childrearing potential not using effective contraception unless the clinical benefit outweighs the potential risk.

It is unknown whether toripalimab is secreted in human milk. It is known that antibodies (including IgG4) are secreted in human milk; a risk to the breast-feeding new-born/infant cannot be excluded.

SIV.3. Limitation in respect to populations typically under-represented in clinical trial development programmes

The safety and efficacy of LOQTORZI in pregnant and lactating women have not yet been established. No data are available.

Based on the metabolic pathways of monoclonal antibodies, absorption, distribution, metabolism, and excretion studies and formal organ impairment studies were not conducted and are not planned. In a population pharmacokinetics model, mild hepatic impairment or mild to moderate renal impairment did not affect the pharmacokinetics of toripalimab. Hence, no dose adjustment is needed in patients with mild to moderate renal impairment or in patients with mild hepatic impairment. LOQTORZI has not been studied in patients with moderate or severe hepatic impairment. The impact of severe renal impairment or moderate or severe hepatic impairment on pharmacokinetics of toripalimab is not known.

The youngest patients with NPC and OSCC in the Phase 3 studies were aged 19 and 20 years, respectively. However, the effect of toripalimab in juvenile patients has not been thoroughly evaluated. Given that NPC and OSCC generally affect people after middle-age and that very few children or adolescents develop NPC and OSCC, the absence of an evaluation of the effects of toripalimab in paediatric patients is not considered missing information, given the age profile of the current NPC and OSCC populations.

Part II: Module SV - Post-authorisation experience

The cumulative post-marketing patient exposure to LOQTORZI (3 mg/kg) as of 16 December 2022 was estimated to be approximately [redacted].

SV.1. Post-authorisation exposure

The standard method to calculate exposure based on the posology of the product and/or treatment cycles and sales and global exposure data presented in an aggregated form would not be deemed to be commercially confidential and thus would not be redacted in case of an access to document request (unless a detailed justification is provided which demonstrate how the release of the data would undermine the commercial interests or competitive position of the company). The redaction would be accepted for data pertaining to national exposure data, if proposed.

SV.1.1 Method Used to Calculate Exposure

The recommended dose of LOQTORZI in China is 3 mg/kg IV once every two weeks when administered as a single agent and once every 3 weeks when given in combination with standard chemotherapy.

Based on the average body weight of 65 kg of a Chinese, the recommended dose is 195 mg (65 kg x 3 mg/kg) every 2 weeks.

According to the dosing cycle which is once every 2 weeks for toripalimab monotherapy, the annual dosage based on 26 doses (52 weeks/2) is, therefore, 5,070 mg (195 mg x 26 times) per patient-year.

Two strengths of LOQTORZI are available in China marketing: 240 mg/vial and 80 mg/vial. Since the Development International Birth Date (DIBD) of 23 December 2015 to 16 December 2022, which is the data lock point (DLP) of the most recent

PBRER, [redacted]

The patient exposure to LOQTORZI (3 mg/kg) was estimated to be approximately [redacted] as of December 2022.

SV.1.2 Exposure

The cumulative post-marketing patient exposure to LOQTORZI (3 mg/kg) as of 16 December 2022 was estimated to be [redacted].

No data regarding accidental overdose are available for toripalimab.

Part II: Module SVI - Additional EU requirements for the safety specification

Not Applicable

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Table SVII. 1 Reason for Not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP

Reason	List of Risks
Risks with minimal clinical impact on patients (in relation to the severity of the indication treated	None
Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated	None
Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised	Infusion-related reactions
Known risks that do not impact the risk-benefit profile	None
Other reasons for considering the risks not important	None

<Infusion-related reactions>

Overall, infusion related reactions occurred in 28 (1.8%) of 1514 patients treated with toripalimab, including Grade 4 (0.07%) and Grade 3 (0.13%) reactions. Of the 403 patients who received toripalimab in combination with platinum containing chemotherapy in JUPITER-02 or JUPITER-06, infusion-related reactions occurred in 11 patients (2.7%), including Grade 4 (0.2%), Grade 3 (0.2%) and Grade 2 (0.5%) adverse reactions.

As with any other intravenous administered drugs, infusion-related reactions can occur with toripalimab. Although it was observed in clinical studies, is not considered an important risk of toripalimab as the low incidence and it is well known risk and well managed by HCP. The risk can be managed in clinical practice, through pre-medications with antipyretics and antihistamines to mitigate

the risk of subsequent infusion reactions, and treatment modifications based on severity grade if needed and will continue to be monitored via routine pharmacovigilance activities.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

<Important Identified Risk 1>: Immune related adverse reactions (including immune-related pneumonitis, colitis and diarrhoea, hepatitis, myocarditis, nephritis, endocrinopathies, pancreatitis, myositis, skin ARs, and other immune-related reactions).

Immune-related adverse reactions (including immune-related pneumonitis, colitis and diarrhoea, hepatitis, myocarditis, nephritis, endocrinopathies, pancreatitis, myositis, skin ARs, and other immune-related reactions), which may be severe or fatal/life-threatening, can occur in patients treated with antibodies blocking the programmed cell death protein-1/programmed death-ligand 1 (PD-1/PD-L1) pathway, including toripalimab. While immune-related adverse reactions usually occur during treatment with PD-1/PD-L1 blocking antibodies, symptoms can also manifest after discontinuation of treatment. Immune-related adverse reactions have been reported in patients with a variety of tumour types, and they may occur in any organ or tissue and may affect more than one body system simultaneously.

The majority of adverse reactions reported with toripalimab were of Grades 1 or 2 severity. The most serious adverse reactions were immune-related adverse reactions. The incidence of immune-related adverse reactions with toripalimab monotherapy was 26.3% all Grades and 6.0% for Grades 3-5, while the incidence of irAE with toripalimab in combination with platinum containing chemotherapy were 33.5% all Grades and 7.7% for Grades 3-5.

The detailed characterization of each risk, including severity and incidence can be found in Table SVII. 2. 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. Corticosteroid tapering should be initiated when symptoms improve to Grade 1 or less. For myocarditis, consider administration of other systemic immunosuppressants in patients whose immune-related adverse reactions are not controlled with corticosteroid therapy.

Risk-benefit impact:

While immune related adverse reactions are important identified risk from treatment with antibodies blocking the programmed cell death protein-1/programmed death-ligand 1 (PD-1/PD-L1) pathway, including toripalimab, the benefit of toripalimab treatment for patients with NPC and OSCC, fatal conditions, outweighs this risk which can be managed in clinical practice through healthcare professional awareness of this type of reactions with oncology therapeutic agents, patient monitoring, dose modification, corticosteroid/immunosuppressive therapy, and hormone replacement.

The toripalimab SmPC instructs healthcare professionals on the timely identification and management of immune-related adverse reactions, including detailed dose modification instructions for toripalimab and use of concomitant therapy. The risk of these immune related adverse reactions is identifiable and can be managed.

<Important Identified Risk 2>: Solid organ transplant rejection

Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with PD-1 inhibitors. No reports of solid organ transplant rejection were from clinical trials of toripalimab. Two literature cases of solid organ transplant rejection have occurred following toripalimab in donor organ recipients from post-marketing surveillance; both were reported as “liver transplant rejection.” Follow patients closely for evidence of transplant-related complications and intervene promptly.

Risk-benefit impact:

Treatment with toripalimab may increase the risk of rejection in solid organ transplant recipients. The incidence of solid organ transplant rejection is low and risk can be effectively controlled through withholding or discontinuing toripalimab and prompt intervention. In consideration of the possibility of death caused by disease progression of NPC and OSCC patients, the benefits of using toripalimab are greater than related risks.

<Important Potential Risk 1>: Graft Versus Host Disease (GVHD) with toripalimab after allogeneic hematopoietic stem cell transplantation (HSCT)

Fatal and other serious complications can occur in patients who received an allogeneic haematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/PD-L1 blocking antibody. Transplant-related complications include hyperacute graft-versus-host-disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease after reduced intensity conditioning, and steroid-requiring febrile syndrome without an identified infectious cause. These complications may occur despite intervening therapy between PD-1/PD-L1 blockade and the allogeneic HSCT. Follow patients closely for evidence of

transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1/PD-L1 blocking antibody prior to or after an allogeneic HSCT.

Risk-benefit impact:

There are no available data on GVHD with the use of toripalimab. The rate of these adverse reactions with other PD(L)1 inhibitor was low. It can be well controlled and comprehensively evaluated through early diagnosis and intervention. Until further data become available, careful consideration to the potential benefits of HSCT and the possible increased risk of transplant-related complications should be made case by case.

<Important Potential Risk 2>: Embryotoxicities

There are no data on the use of toripalimab in pregnant women. Animal studies have not been conducted with toripalimab; however, animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-related rejection of the developing foetus and result in foetal death. Human immunoglobulin G4 (IgG4) is known to cross the placental barrier; therefore, toripalimab can potentially be transmitted from the mother to the developing foetus. Toripalimab should not be used during pregnancy or in women of childbearing potential not using effective contraception unless the clinical benefit outweighs the potential risk.

Risk-benefit impact:

The benefit of toripalimab treatment for patients with NPC and OSCC, life-threatening conditions, outweighs the important potential risk of embryotoxicities that has yet to be confirmed in humans and can be managed in clinical practice through healthcare professional awareness of the precautions to take with oncology therapeutic agents and adhering to the guidance in the SmPC.

Healthcare professionals are advised to verify the pregnancy status of women of reproductive potential prior to use and that women of reproductive potential should use effective contraception during treatment with toripalimab and at least 4 months after the last dose.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Table SVII. 2 - Important Identified Risks

Immune related adverse reactions (including immune-related pneumonitis, colitis and diarrhoea, hepatitis, myocarditis, nephritis, endocrinopathies, pancreatitis, myositis, skin ARs, and other immune-related reactions).

Immune-related Pneumonitis

Characterization of the risk	Immune-related pneumonitis occurred in 2.3% (26/1,111) of patients receiving toripalimab as monotherapy, including fatal (0.2%), Grade 3 (0.7%), and Grade 2 (0.9%) adverse reactions. The median time to onset of pneumonitis was 3.7 months (range 0.6 to16.7 months). The median duration was 1.0 months (range 1.0 to 4.24+ months). Systemic corticosteroids were required in 85% (22/26) of patients with pneumonitis. Pneumonitis led to permanent discontinuation of toripalimab in 1.0% (11/1,111) and interruption in 0.6% (7/1,111) of patients. Pneumonitis resolved in 31% (8/26) of these patients. Immune-related pneumonitis occurred 13/403 (3.2%) patients with toripalimab in combination with chemotherapy, including 2 (0.5%) Grade 3 and 7 (1.7%) Grade 2 events in JUPITER-02 and JUPITER-06. The median time to onset of pneumonitis was 5.4 months (range 1.3 to16.6 months). The median duration was 2.8 months (range 0.8 to 20.9 months). Corticosteroids were

	administered to 9/13 (69.2%) patients. Permanent discontinuation occurred in 3 (0.7%) and withholding of toripalimab in 5 (1.2%) patients. Immune-related pneumonitis resolved in 31.0% (4/13) patients.
Background incidence/prevalence	Immune-related pneumonitis is specific to immune checkpoint inhibitors such as toripalimab and its background incidence and prevalence in general cancer patient population has not been reported in the literature.
Risk groups or risk factors	Patients with a history of pneumonitis were excluded from the clinical trials. According to the literature, risk factors include history of interstitial lung disease or previous treatment including radiotherapy, previous or combined use of drugs with known pulmonary toxicity such as antibiotics, chemotherapy, antiarrhythmic; immunosuppression leading to pneumonia (bacteria, viruses, fungi, or protozoa), allergic pulmonary disease, autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis, etc.), occupational exposure (smoke, dust, siloxane, asbestos), smoking, and older age.
Potential mechanisms	Toripalimab is an immune checkpoint inhibitor of PD-1 pathway. By blocking PD-1 pathway and activating T cell immune surveillance, it leads to programmed death of tumour cells and changes of immune system, which can lead to immune related

	inflammatory reaction or autoimmune reaction in corresponding tissues and organs.
Preventability	The signs and symptoms of potential lung disease should be evaluated during treatment. At each tumour evaluation, or when severe dry cough and dyspnoea occur, the patients should be scanned with chest CT and attention should be paid to whether there are interstitial ground glass changes on CT. All pulmonary adverse events should be comprehensively evaluated for other common causes, such as pneumonia/ infection, lymphatic metastasis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease or pulmonary hypertension.
Potential public health impact of safety concern	Some patients may develop immune-related pneumonitis after exposure to toripalimab. It can be well controlled through early diagnosis and intervention, and the potential public health impact is small.
MedDRA terms	pneumonitis, interstitial lung disease, immune-related lung disease

Immune-related Colitis and Diarrhoea

Characterization of the risk	Immune-related colitis occurred in 0.4% (4/1,111) of patients receiving toripalimab as monotherapy, including Grade 3 (0.2%) and Grade 2 (0.2%) adverse reactions. The median time to onset of colitis

	was 2.9 months (range 0.4 to 12.6 months). The median duration was 0.8 month (range 0.1 to 1.87+ months). One patient received corticosteroid therapy for colitis. Colitis resolved in 3 (75%) of these 4 patients. Immune-related colitis occurred in 3/403 (0.7%) patients receiving toripalimab in combination with chemotherapy, including 2 (0.5%) Grade 3 and 1 (0.2%) Grade 2 events in JUPITER-02 and JUPITER-06. The median time to onset of colitis was 3.7 months (range 1.5 to 5.1 months). The median duration was 1.3 months (range 1.3 to 1.3 months). Corticosteroids were administered to 2 of the 3 (66.7%) patients. Permanent discontinuation occurred in 2 (0.5%) patients and withholding of toripalimab in 1 (0.2%) patient. Immune-related colitis resolved in 1 of the 3 patients.
Background incidence/prevalence	Immune-related colitis is specific to immune checkpoint inhibitors such as toripalimab and its background incidence and prevalence in general cancer patient population has not been reported in the literature.
Risk groups or risk factors	No specific risk factors for colitis and diarrhoea associated with toripalimab were identified.
Potential mechanisms	Toripalimab is an immune checkpoint inhibitor of PD-1 pathway. By blocking PD-1 pathway and activating T cell immune surveillance, it leads to programmed death of tumour cells and changes of

	immune system, which can lead to immune related inflammatory reaction or autoimmune reaction in corresponding tissues and organs.
Preventability	Colitis may occur in patients treated with toripalimab and the specific risk population for colitis is still unclear. If persistent or severe diarrhoea occurs during treatment or signs of systemic inflammation or acute phase reactions (such as increase of C-reactive protein or platelet count or bandaemia) are present, it is recommended that the following measures should be taken: perform sigmoidoscopy (or colonoscopy, if applicable) and colon biopsy to confirm diagnostic results of colitis. If possible, 1-2 biopsy specimens should be quick-frozen. Laboratory tests should be performed to exclude other aetiology.
Potential public health impact of safety concern	Due to low incidence and serious gastrointestinal toxicity in advanced tumour arising from diseases or other alternative therapies, the product has minimal potential public health impact.
MedDRA terms	colitis, colitis ulcerative, diarrhoea, and immune-related enterocolitis

Immune-related Hepatitis

Characterization of the risk	Immune-related hepatitis occurred in 3.2% (36/1,111) of patients receiving toripalimab as monotherapy, including Grade 4 (0.6%), Grade 3 (2.2%), and Grade 2 (0.4%) adverse reactions. The

	median time to onset of hepatitis was 1.4 months (range 0.1 to 9.0 months). The median duration was 0.9 month (range 0.1 to 5.26+ months). Hepatitis led to permanent discontinuation of toripalimab in 1.0% of patients and withholding of toripalimab in 0.8% of patients. Hepatitis resolved in 20 (55.5%) of the 36 patients. Immune-related hepatitis occurred in 8/403 (2.0%) patients receiving toripalimab in combination with chemotherapy, including 2 (0.5 %) Grade 4, 5 (1.2 %) Grade 3, and 1 (0.2%) Grade 2 events in JUPITER-02 and JUPITER-06. The median time to onset of hepatitis was 4.0 months (range 0.7 to 22.7 months). The median duration was 0.6 months (range 0.4 to 3.2 months). Corticosteroids were administered to 7 of the 8 (87.5%) patients. Permanent discontinuation occurred in 5 (1.2%) and withholding of toripalimab in 2 (0.5 %) patients. Immune-related hepatitis resolved in 7 (87.5%) of the 8 patients.
Background incidence/prevalence	Immune-related hepatitis is specific to immune checkpoint inhibitors such as toripalimab and its background incidence and prevalence in general cancer patient population has not been reported in the literature.
Risk groups or risk factors	The population with increased risk of immune related liver dysfunction after the use of toripalimab is unknown. Patients with moderate or severe

	hepatic impairment were excluded from clinical studies with toripalimab. According to the literature, the risk factors of liver dysfunction are history of viral hepatitis, excessive drinking, obesity, hepatotoxic drugs, genetic defects, and biliary obstruction.
Potential mechanisms	Toripalimab is an immune checkpoint inhibitor of PD-1 pathway. By blocking PD-1 pathway and activating T cell immune surveillance, it leads to programmed death of tumour cells and changes of immune system, which can lead to immune related inflammatory reaction or autoimmune reaction in corresponding tissues and organs.
Preventability	The liver function, assessed by total bilirubin and transaminases, should be checked before treatment. During treatment the liver function should be closely monitored. During treatment, if the patient develops pain in the right upper abdomen and / or unexplained nausea or vomiting, liver function tests (LFT) should be performed immediately, and the test results should be reviewed before the next study drug administration.
Potential public health impact of safety concern	A small number of patients treated with toripalimab will develop immune related liver dysfunction and can be effectively treated with corticosteroid. Potential public health impact is very small.

MedDRA terms	Liver injury, hepatitis, liver function abnormal

Immune-related Myocarditis

Characterization of the risk	Immune-related myocarditis occurred in 0.4% (4/1,111) of patients receiving toripalimab as monotherapy, including 2 Grade 3 (0.2%) and 2 Grade 2 (0.2%) adverse reactions. The median time to onset of immune-related skin adverse reactions was 1.0 month (range 0.7 to 1.3 months). The median duration was 1.3 months (range 1.2 to 1.5+ months). All four patients received corticosteroids and permanently discontinued toripalimab. Immune-related myocarditis resolved in 2/4 (50.0%) patients. Immune-related myocarditis occurred in 0.7% (3/403) of patients receiving toripalimab in combination with chemotherapy, including 2 (0.5%) Grade 4 and 1 (0.2%) Grade 3 events in JUPITER-02 and JUPITER-06. The median time to onset of immune-related myocarditis was 1.7 months (range 1.4 to 4.1 months). The median duration was 1.3 months (range 1.0 to 1.6 months). All three patients with immune-related myositis received corticosteroids. Two patients permanently discontinued toripalimab and no patients interrupted dosing. Immune-related myocarditis resolved in 1 of 3 patients.

Background incidence/prevalence	Immune-related myocarditis is specific to immune checkpoint inhibitors such as LOQTORZI and its background incidence and prevalence in general cancer patient population has not been reported in the literature.
Risk groups or risk factors	No specific risk groups were identified that increased the risk of immune related myocarditis when treated with toripalimab. According to the literature, viral infection, bacterial infection, autoimmune diseases, history of chest radiotherapy, combined or previous use of chemotherapy drugs with myocardial damage, such as anthracycline, chemotherapy or HER-2 inhibitors, and some antibiotics with myocardial damage are risk factors for myocarditis.
Potential mechanisms	Toripalimab is an immune checkpoint inhibitor of PD-1 pathway. By blocking PD-1 pathway and activating T cell immune surveillance, it leads to programmed death of tumour cells and changes of immune system, which can lead to immune related inflammatory reaction or autoimmune reaction in corresponding tissues and organs.
Preventability	When patients treated with toripalimab have symptoms such as dyspnoea, chest pain, palpitation, fatigue, decreased exercise tolerance, syncope, etc., special attention should be paid to immune related myocarditis. Other manifestation includes heart failure, cardiac arrhythmias, myocardial pericarditis,

	and cardiomyopathy. ECG, echocardiography, myocardial enzymes and other relevant examinations should be carried out. Consult a cardiologist if necessary to distinguish infectious myocarditis (usually viral infection), ischemic events, potential arrhythmias, deterioration of previous heart disease and tumour progression.
Potential public health impact of safety concern	The incidence rate of immune related myocarditis in patients using immune checkpoint inhibitor is low but the mortality is high. Therefore, early detection, early intervention and active treatment should be carried out. Usually, the treatment is effective and the outcome is good and the impact on public health is small.
MedDRA terms	Myocarditis

Immune-related Skin Adverse Reactions

Characterization of the risk	Immune-related skin adverse reactions occurred in 3.9% (43/1,111) of patients receiving toripalimab as monotherapy, including Grade 3 (0.5%) and Grade 2 (1.3%) adverse reactions. The median time to onset of immune-related skin reactions was 1.2 months (range 0.1 to 12.2 months). The median duration was 1.9 months (range 0.1 to 17.6+ months). Immune-related skin adverse reactions led to withholding of toripalimab in 0.3% (3) of the patients. Systemic corticosteroids were required in

	14.0% (6/43) of the patients with immune-related skin adverse reactions. Immune-related skin adverse reactions resolved in 62.8% (27/43) of these patients. Immune-related skin adverse reactions occurred in 9.4% (38/403) of patients receiving toripalimab in combination with chemotherapy, including 12 Grade 3 (3.0%) and 8 Grade 2 (2.0%) adverse reactions in JUPITER-02 and JUPITER-06. The median time to onset of immune-related skin adverse reactions was 1.0 month (range 0.1 to 23.1 months). The median duration was 1.2 months (range 0.1 to 13.1 months). Systemic corticosteroids were required in 18.4% (7/38) of the patients with immune-related skin adverse reactions. Immune-related skin adverse reactions led to permanent discontinuation or interruption of toripalimab in 1.5% (6) of patients. Immune-related skin adverse reactions resolved in 73.7% (28/38) of these patients. Stevens-Johnson syndrome/toxic epidermal necrolysis has been identified from post-marketing, but the incidence is rare (≥ 1/10,000 to < 1/1000). The majority of these severe adverse events responded to high-dose corticosteroids and discontinuation of toripalimab. The outcome of these events is often associated with early identification and immediate treatment.

Background incidence/prevalence	Immune-related skin adverse reactions is specific to immune checkpoint inhibitors such as toripalimab and its background incidence and prevalence in general cancer patient population has not been reported in the literature. However, adverse skin reactions of other aetiology(es) are relatively common in cancer patients.
Risk groups or risk factors	No specific risk groups were identified that increased the risk of immune related adverse skin reactions when treated with toripalimab.
Potential mechanisms	Toripalimab is an immune checkpoint inhibitor of PD-1 pathway. By blocking PD-1 pathway and activating T cell immune surveillance, it leads to programmed death of tumour cells and changes of immune system, which can lead to immune related inflammatory reaction or autoimmune reaction in corresponding tissues and organs.
Preventability	Serious skin toxicity may occur with toripalimab use and specific risk population for skin toxicity is still unclear. When a patient treated with toripalimab presents with a skin adverse event, a thorough evaluation of the severity of the skin AE should be performed. If serious and persistent rash or pruritus or excoriation occurs during treatment, dermatologists should be invited for consultation and further evaluation (including skin biopsy), and

	initiate timely and appropriate treatments depending on severity of the skin adverse reaction.
Potential public health impact of safety concern	Severe skin adverse reactions were observed in the use of similar products. Most of the adverse skin reactions in patients treated with toripalimab can be improved by symptomatic treatment or corticosteroid treatment, with little impact on public health.
MedDRA terms	Dermatitis, dermatitis acneiform, dermatitis allergic, drug eruption, erythema, erythema multiforme, hand dermatitis, palmar-plantar erythrodysaesthesia syndrome, rash, rash maculo-papular, rash pruritic, rash vesicular, urticaria, Stevens-Johnson syndrome, toxic epidermal necrolysis, skin exfoliation, dermatitis exfoliative, exfoliative rash, acquired epidermolysis bullosa.

Immune-related Hypothyroidism

Characterization of the risk	Hypothyroidism occurred in 14.0% (154/1,111) of patients receiving toripalimab as monotherapy, including Grade 3 (0.1%) and Grade 2 (7.5%) adverse reactions. The median time to onset of hypothyroidism was 2.8 months (range 0.26 to 20.3 months). The median duration was 1.9 months (range 0.3 to 13.8+ months). Thyroid hormone replacement therapy was required in 63.6% (98/154) of the patients. Toripalimab was discontinued in

	0.1% (1/1,111) and withheld in 0.5% (6/1,111) of patients. Hypothyroidism occurred in 17.1% (69/403) of patients receiving toripalimab in combination with chemotherapy, with 46 Grade 2 (11.4%) and 23 Grade 1 (5.7%) adverse reactions in JUPITER-02 and JUPITER-06. The median time to onset of hypothyroidism was 5.9 months (range 1.2 to 20.7 months). The median duration was 3.2 months (range 0.4 to 30.6 months). Thyroid hormone replacement therapy was required in 72.5% (50/69) of patients. Corticosteroids were administered to 1/69 (1.4%) patients. No patients permanently discontinued and 1.2% (5/403) of the patients interrupted toripalimab.
Background incidence/prevalence	Immune-related hypothyroidism is specific to immune checkpoint inhibitors such as toripalimab and its background incidence and prevalence in general cancer patient population has not been reported in the literature.
Risk groups or risk factors	There is no known risk group for immune related hypothyroidism among patients receiving toripalimab. According to the literature, patients who have received previous thyroid surgery are at risk for hypothyroidism.
Potential mechanisms	Toripalimab is an immune checkpoint inhibitor of PD-1 pathway. By blocking PD-1 pathway and activating T cell immune surveillance, it leads to

	programmed death of tumour cells and changes of immune system, which can lead to immune related inflammatory reaction or autoimmune reaction in corresponding tissues and organs.
Preventability	In case of symptoms of unknown causes (such as fatigue, myalgia, impotence, change of mental state or constipation), check whether there is hypothyroidism, ask an endocrinologist for consultation, and collect thyroid stimulating hormone (TSH) and free thyroxine (T4) levels to determine whether there is abnormal thyroid function.
Potential public health impact of safety concern	Patients treated with toripalimab may develop immune related hypothyroidism. Hypothyroidism is easy to be controlled by taking drugs, with little potential public health impact.
MedDRA terms	hypothyroidism

Immune-related Hyperthyroidism

Characterization of the risk	Hyperthyroidism occurred in 6% (70/1,111) of patients receiving toripalimab as monotherapy, including Grade 3 (0.1%) and Grade 2 (1.7 %) adverse reactions. Hyperthyroidism resolved in 52.9% (37/70) of the patients. In patients receiving toripalimab in combination with chemotherapy, hyperthyroidism occurred in 8/403 (2.0%) patients with no Grade 2-5 adverse

	reactions in JUPITER-02 and JUPITER-06. The median time to onset of hyperthyroidism was 1.3 months (range 0.5 to 17.6 months). The median duration was 1.2 months (range 0.4 to 7.5+ months). One (1.4%) patient received corticosteroids. Three patients (0.3%) interrupted toripalimab and none permanently discontinued toripalimab.
Background incidence/prevalence	Immune-related hyperthyroidism is specific to immune checkpoint inhibitors such as toripalimab and its background incidence and prevalence in general cancer patient population has not been reported in the literature.
Risk groups or risk factors	Among patients receiving toripalimab, there is no known risk group for immune related hyperthyroidism. Family history of hyperthyroidism, history of radiation, excessive or insufficient iodine intake and metabolic diseases are the risk factors for hyperthyroidism.
Potential mechanisms	Toripalimab is an immune checkpoint inhibitor of PD-1 pathway. By blocking PD-1 pathway and activating T cell immune surveillance, it leads to programmed death of tumour cells and changes of immune system, which can lead to immune related inflammatory reaction or autoimmune reaction in corresponding tissues and organs.
Preventability	When the patient has symptoms of unknown causes, check whether there is hyperthyroidism, ask an

	endocrinologist for consultation, and collect TSH and T4 levels to determine whether there is hyperthyroidism
Potential public health impact of safety concern	Patients treated with toripalimab may develop immune related hyperthyroidism. Hyperthyroidism is easy to be controlled by taking drugs, with little potential public health impact.
MedDRA terms	Hyperthyroidism

Immune-related Hypophysitis

Characterization of the risk	Hypophysitis occurred in 0.5% (5/1,111) of patients receiving toripalimab as monotherapy, including Grade 3 (0.2%) and Grade 2 (0.3%) adverse reactions. The median time to onset of hypophysitis was 8.4 months (range 6.9 to 24.9 months). The median duration was 2.5 months (range 0.9 to 4.1+ months). All five patients received systemic corticosteroids. Hypophysitis led to permanent discontinuation of toripalimab in 0.1% (1/1,111) of patients and withholding of toripalimab in 0.3% (3/1,111) of patients. In patients receiving toripalimab in combination with chemotherapy, hypophysitis occurred in 1/403 (0.2%) patient with 1 (0.2%) Grade 2 adverse reaction in JUPITER-02 and JUPITER-06. The time to onset of hypophysitis was 23.7 month. Corticosteroids were administered and the patient did not permanently discontinue toripalimab or interrupt dosing.
Background incidence/prevalence	Immune-related hypophysitis is specific to immune checkpoint inhibitors such as toripalimab and its background incidence and prevalence in general cancer patient population has not been reported in the literature.
Risk groups or risk factors	The specific risk population or risk factors that may cause immune-related hypophysitis associated with toripalimab treatment have not been identified.

Potential mechanisms	Toripalimab is an immune checkpoint inhibitor of PD-1 pathway. By blocking PD-1 pathway and activating T cell immune surveillance, it leads to programmed death of tumour cells and changes of immune system, which can lead to immune related inflammatory reaction or autoimmune reaction in corresponding tissues and organs.
Preventability	Hypophysitis may occur with toripalimab use and the specific risk population is still unclear. Pituitary hormone level and function tests (such as TSH, growth hormone, luteal hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotrophic hormone [ACTH], and cortisol levels and ACTH stimulation tests) are helpful. Head MRI may help diagnose pituitary insufficiency.
Potential public health impact of safety concern	The occurrence of hypophysitis in patient received LOQTORZI is uncommon, and can be well controlled by following recommended treatment modifications in SmPC or clinical guidelines of irAE management. There is minimal potential public health impact.
MedDRA terms	hypophysitis

Immune-related Adrenal Insufficiency

Characterization of the risk	Adrenal insufficiency occurred in 0.6% (7/1,111) of the patients receiving toripalimab as monotherapy,

	including 5 Grade 2 (0.5%) and 2 Grade 1 (0.2%) adverse reactions. The median time to onset of adrenal insufficiency was 4.8 months (range 1.1 to 16.1 months). The median duration was 0.7 month (range 0.2 to 11.3+ months). Systemic corticosteroids were required in 83% (5/6) of the patients with adrenal insufficiency. Adrenal insufficiency led to withholding of toripalimab in 0.1% (1/1,111) of patients. In the one patient in whom treatment was withheld, toripalimab was reinitiated after symptom improvement. Immune-related adrenal insufficiency occurred in 1/403 (0.2%) patients receiving toripalimab in combination with chemotherapy, including 1 (0.2%) Grade 3adverse reaction in JUPITER-02 and JUPITER-06. The time to onset of the event was 2.0 months. Corticosteroids were administered to this patient and toripalimab was permanently discontinued.
Background incidence/prevalence	Immune-related adrenal insufficiency is specific to immune checkpoint inhibitors such as toripalimab and its background incidence and prevalence in general cancer patient population has not been reported in the literature.
Risk groups or risk factors	The population at increased risk of immune-related adrenal insufficiency after being treated with toripalimab remains unknown. Hypopituitarism, long-term increase in blood concentration of

	glucocorticoid steroid or other steroid drugs resulting in hypothalamus and pituitary gland suppression are the causes of adrenal insufficiency.
Potential mechanisms	Toripalimab is an immune checkpoint inhibitor of PD-1 pathway. By blocking PD-1 pathway and activating T cell immune surveillance, it leads to programmed death of tumour cells and changes of immune system, which can lead to immune related inflammatory reaction or autoimmune reaction in corresponding tissues and organs.
Preventability	For patients with profound weakness, fatigue, weight loss, loss of appetite, nausea and vomiting, abdominal distension and diarrhoea, loss of fat storage and muscle wasting, hyperpigmentation, somnolence, indifference, abnormal laboratory examinations such as hypoglycaemia, hyponatremia, or abnormal laboratory indicators of adrenocortical function and/or radiological examination after being treated with toripalimab, doctors should be aware of adrenal insufficiency among the differential diagnoses to be evaluated (for example, examining prolactin and cortisol level in the morning can help distinguish primary adrenal insufficiency from primary pituitary insufficiency). When necessary, endocrinology should be consulted. ACTH and cortisol levels should be monitored in symptomatic patients.

Potential public health impact of safety concern	A small number of patients treated with toripalimab will develop immune-related adrenal insufficiency which can be controlled by replacement therapy of corticosteroid, with minimal potential public health impact.
MedDRA terms	Adrenal insufficiency

Immune-related Type-1 Diabetes Mellitus and Hyperglycaemia

Characterization of the risk	Diabetes mellitus occurred in 0.7% (8/1,111) of patients receiving toripalimab as monotherapy, including Grade 4 (0.1%), Grade 3 (0.5%), and Grade 2 (0.1%) adverse reactions. The median time to onset of diabetes mellitus was 1.2 months (range 0.5 to 11.4 months). The median duration was 0.4 months (range 0.3 to 0.6+ months). Diabetes mellitus led to permanent discontinuation in 0.3% of patients. Six of the 8 (75.0%) patients with diabetes mellitus required long-term insulin therapy. In patients receiving toripalimab in combination with chemotherapy, diabetes mellitus occurred in 1/403 (0.2%) patients, including 1 (0.2%) Grade 3 adverse reaction in JUPITER-02 and JUPITER-06. The time to onset of diabetes mellitus was 0.7 months. The patient did not receive corticosteroids, but was treated with insulin. The patient did not permanently discontinue or interrupt toripalimab.

Background incidence/prevalence	Immune-related diabetes mellitus is specific to immune checkpoint inhibitors such as toripalimab and its background incidence and prevalence in general cancer patient population has not been reported in the literature.
Risk groups or risk factors	The population with increased risk in immune-related hyperglycaemia and diabetes mellitus after the use of toripalimab is still unknown. High risk factors of type I diabetes mellitus include family medical history, obesity, hyperlipidaemia, lack of exercise, smoking, high stress level and hypertension.
Potential mechanisms	LOQTORZI is an immune checkpoint inhibitor of PD-1 pathway. By blocking PD-1 pathway and activating T cell immune surveillance, it leads to programmed death of tumour cells and changes of immune system, which can lead to immune related inflammatory reaction or autoimmune reaction in corresponding tissues and organs.
Preventability	If the patients have history of diabetes mellitus, it is required to control their blood glucose before toripalimab use. During the entire treatment period, the blood glucose of all patients shall be closely monitored by monitoring glycosylated haemoglobin and blood glucose.
Potential public health impact of safety concern	A small number of patients treated with toripalimab may develop immune-related hyperglycaemia and

	type-1 diabetes mellitus which can be controlled by insulin therapy, with minimal potential public health impact.
MedDRA terms	Type-1 diabetes mellitus, diabetes mellitus, hyperglycaemia

Immune-related Myositis

Characterization of the risk	Immune-related myositis occurred in 0.5% (5/1,111) of patients receiving toripalimab as monotherapy, including 1 Grade 4 (0.1%), 2 Grade 3 (0.2%) and 2 Grade 2 (0.2%) adverse reactions. The median time to onset of immune-related myositis was 0.9 month (range 0.4 to 6.8 months). The median duration was 1.1 months (range 0.2 to 2.1+ months). Four of these 5 (80.0%) patients received corticosteroids. Three patients (0.3%) permanently discontinued toripalimab and two patients (0.2%) interrupted dosing. Immune-related myositis resolved in 3/5 (60.0%) patients. Immune-related myositis occurred in 0.5% (2/403) of patients receiving toripalimab in combination with chemotherapy, including 1 (0.2%) Grade 4, 1 (0.2%) Grade 3, and no Grade 2 adverse reactions in JUPITER-02 and JUPITER-06. The median time to onset of immune-related myositis was 2.5 month (range 1.2 to 3.9 months). The two patients with immune-related myositis received corticosteroids

	and both patients permanently discontinued toripalimab.
Background incidence/prevalence	Immune-related myositis is specific to immune checkpoint inhibitors such as toripalimab and its background incidence and prevalence in general cancer patient population has not been reported in the literature.
Risk groups or risk factors	Risk population or risk factors for myositis/creatine kinase increased after therapy of toripalimab have not been identified.
Potential mechanisms	Toripalimab is an immune checkpoint inhibitor of PD-1 pathway. By blocking PD-1 pathway and activating T cell immune surveillance, it leads to programmed death of tumour cells and changes of immune system, which can lead to immune related inflammatory reaction or autoimmune reaction in corresponding tissues and organs.
Preventability	Immune-related myositis may occur among patients treated with toripalimab and the specific risk population is unclear. In case of abnormal elevation in creatine phosphokinase or myalgia, myasthenia etc., toripalimab can be suspended/discontinued based on clinical diagnosis and in accordance with severity. When necessary, experts should be invited for consultation. Use of glucocorticoid can effectively improve the adverse reaction and prevent its deterioration.

Potential public health impact of safety concern	Myositis can lead to myasthenia which can affect quality of life. But in general, the incidence of immune-related myositis is low and risk can be effectively controlled through withholding or discontinuing toripalimab and prompt hormonotherapy. In consideration of possibility of death caused by disease progression of terminal cancer patients, benefit of using toripalimab is greater than related risks. It has minimum impact on public health.
MedDRA terms	myositis

Immune-related Nephritis

Characterization of the risk	Immune-related nephritis occurred in 0.5% (6/1,111) of patients receiving toripalimab as monotherapy, including Grade 3 (0.4%) and Grade 2 (0.1%) adverse reactions. The median time to onset of immune-related nephritis was 3.4 months (range 0.7 to 10.6 months). The median duration was 0.5 month (range 0.2 to 1.0+ months). Corticosteroid therapy was administered to 1 of these 6(16.7%) patients with immune-related nephritis. Nephritis resolved in 66.7% (4/6) of these patients. Immune-related nephritis occurred in 0.2% (1/403) of patients receiving toripalimab in combination with chemotherapy in JUPITER-02 and JUPITER-06. The time to onset of immune-related nephritis

	was 18.2 months and the duration was 3.3 months. The one patient with immune-related nephritis (Grade 4) required systemic corticosteroids and nephritis led to discontinuation of toripalimab. Nephritis resolved in this patient.
Background incidence/prevalence	Immune-related nephritis is specific to immune checkpoint inhibitors such as toripalimab and its background incidence and prevalence in general cancer patient population has not been reported in the literature.
Risk groups or risk factors	Patients with severe renal impairment were excluded from clinical studies with toripalimab. The population at increased risk of immune-related nephritis after being treated with toripalimab remains unknown. According to the literature, risks factors of nephritis include autoimmune disorder, severe basal renal function injury, viral or bacterial infection, use of concomitant medications with renal toxicity and genetic factors.
Potential mechanisms	Toripalimab is an immune checkpoint inhibitor of PD-1 pathway. By blocking PD-1 pathway and activating T cell immune surveillance, it leads to programmed death of tumour cells and changes of immune system, which can lead to immune related inflammatory reaction or autoimmune reaction in corresponding tissues and organs.

Preventability	The renal functions should be tested before using toripalimab, and should be routinely monitored throughout the treatment period. If immune-related nephritis is suspected, other causes of renal impairment should be ruled out. Moreover, signs and symptoms of kidney problems should be closely monitored and guidelines for toxicity management of immune-related nephritis should be implemented while being treated with the product. If necessary, physicians of nephrology department should be invited for consultation.
Potential public health impact of safety concern	Corticosteroid therapy is effective in immune-related nephritis, and its benefits outweigh its risks given the disease control needs of patients with advanced tumours. A small number of patients treated with toripalimab may develop immune-related nephritis with minimal potential public health impact.
MedDRA terms	chronic kidney disease, renal failure, renal impairment, and renal injury

Immune-related Pancreatitis

Characterization of the risk	Immune-related pancreatitis occurred in 0.6% (7/1,111) of patients receiving toripalimab as monotherapy, with 1 (0.1%) Grade 4, 4 (0.4%) Grade 2 and 1 (0.1%) Grade 1 adverse reactions. While increases in amylase or lipase without any

	signs or symptoms of pancreatitis were observed during treatment with toripalimab, all but 1 of these cases was not adjudicated as pancreatitis or as an irAE. In one patient, a Grade 1 event of lipase increased (preferred term) was adjudicated by the investigator as an irAE and is included among the aforementioned 7 cases of immune-related pancreatitis. The median time to onset was 1.4 months (range; 13 days-5.6 months). Corticosteroids were administered to 1 (14.3%) of the 7 patients. Permanent discontinuation of toripalimab occurred in 4 (0.4%) and dose interruption in 1 (0.1%) patient. There was no report of immune-related pancreatitis in patients receiving toripalimab in combination with chemotherapy in JUPITER-02 and JUPITER-06 as of the DLP for this RMP.
Background incidence/prevalence	Immune-related pancreatitis is specific to immune checkpoint inhibitors such as toripalimab and its background incidence and prevalence in general cancer patient population has not been reported in the literature.
Risk groups or risk factors	the population with increased risk in immune-related pancreatitis after the use of toripalimab is still unknown. Risk factors of acute pancreatitis include cholelithiasis, biliary tract disorder, drinking and overeating, obstruction of the pancreatic duct by compression, endocrine and metabolic disorders,

	infection, and known use of some drugs (such as thiazide diuretics, azathioprine, glucocorticoid, tetracycline and sulphonamides) that may directly damage pancreatic tissue, and increase the secretion or viscosity of pancreatic juice.
Potential mechanisms	Toripalimab is an immune checkpoint inhibitor of PD-1 pathway. By blocking PD-1 pathway and activating T cell immune surveillance, it leads to programmed death of tumour cells and changes of immune system, which can lead to immune related inflammatory reaction or autoimmune reaction in corresponding tissues and organs.
Preventability	As for patients with abdominal pain and elevated levels of amylase and lipase after the use of toripalimab, pancreatitis or acute pancreatitis shall be considered during differential diagnosis. Appropriate examination items include: assessment of obstruction and detection of serum amylase and lipase.
Potential public health impact of safety concern	A small number of patients treated with toripalimab will develop immune-related pancreatitis. However, corticosteroid therapy is effective to most patients with minimal potential public health impact.
MedDRA terms	Pancreatitis, pancreatitis acute or lipase increased

Other Immune-related Reactions

Characterization of the risk	Given the mechanism of action of toripalimab, other immune-related adverse reactions may occur. Clinically significant immune-related adverse reactions reported in less than 1% of patients treated with toripalimab in the clinical studies include iritis, uveitis, immune-related cystitis, immune-related inflammatory arthritis. In the toripalimab monotherapy safety database, two adverse reactions of ocular toxicity (Grade 3 uveitis and Grade 2 iritis) occurred in the same patient. The patient developed Grade 2 iritis on toripalimab. Iritis, treated with corticosteroid eye drops, improved to Grade 1, and toripalimab was continued. The patient later developed disease progression which led to permanent discontinuation of toripalimab and started another anti-cancer agent, vemurafenib, which is also associated with ocular toxicity. While taking vemurafenib, the patient developed immune related uveitis which was treated with administration of corticosteroids and vemurafenib was interrupted and dose reduced. This patient recovered from uveitis. There was no report of immune-related ocular toxicity in patients receiving toripalimab in combination with chemotherapy in JUPITER-02 and JUPITER-06 as of the DLP for this RMP. In the toripalimab monotherapy safety database, immune-related inflammatory arthralgia/arthritis occurred in 2 patients with a Grade 3 and a Grade 2 adverse reaction, respectively. Corticosteroids were

	administered to 1 of the 2 patients. Permanent discontinuation of toripalimab occurred in 1 patient and dose interruption in the other patient. Among the patients who received toripalimab in combination with chemotherapy in JUPITER-02 and JUPITER-06, immune-related inflammatory arthralgia /arthritis occurred in one patient with a grade 3 adverse reaction, Corticosteroids were administered and toripalimab was permanently discontinued. There was no report of immune-related cystitis in patients receiving toripalimab monotherapy as of the DLP for this RMP. Immune-related cystitis occurred in 2 patients who received toripalimab in combination with chemotherapy in JUPITER-02 and JUPITER-06. These 2 adverse reactions were reported under the preferred terms of non-infectious cystitis and haemorrhagic cystitis, respectively. For Grade 3 haemorrhagic cystitis, corticosteroids were administered, toripalimab was permanently discontinued, and the cystitis resolved. The patient with Grade 1 non-infectious cystitis remained on toripalimab treatment with no change in dosing; as of the data cut-off, the event was ongoing.
Background incidence/prevalence	Other immune-related reaction is specific to immune checkpoint inhibitors such as toripalimab and its background incidence and prevalence in general cancer

	patient population has not been reported in the literature.
Risk groups or risk factors	Risk population or risk factors for other immune-related reactions after therapy of toripalimab have not been identified.
Potential mechanisms	Toripalimab is an immune checkpoint inhibitor of PD-1 pathway. By blocking PD-1 pathway and activating T cell immune surveillance, it leads to programmed death of tumour cells and changes of immune system, which can lead to immune related inflammatory reaction or autoimmune reaction in corresponding tissues and organs.
Preventability	Other immune-related reactions may occur among patients treated with toripalimab and the specific risk population is unclear. For suspected immune-related reactions, appropriate testing should be carried out to see if they may be related to treatment. Toripalimab can be suspended/discontinued based on clinical diagnosis and in accordance with severity. When necessary, experts should be invited for consultation. Use of glucocorticoid can effectively improve the adverse reaction and prevent its deterioration.
Potential public health impact of safety concern	Immune related ocular toxicity, if left untreated can lead to visual loss can affect quality of life. Immune-related arthritis, accompanied by pain and inflammatory, may lead to loss of activities of daily living. But in general, the incidence of other immune-

	related reactions, is low and risk can be effectively controlled through withholding or discontinuing toripalimab and prompt hormonotherapy. In consideration of possibility of death caused by disease progression of terminal cancer patients, benefit of using toripalimab is greater than related risks. It has minimum impact on public health.
MedDRA terms	Iritis, uveitis, arthralgia, arthritis, cystitis, immune-mediated uveitis, immune-mediated arthritis, immune-mediated cystitis.

Solid organ transplant rejection

Characterization of the risk	No reports from clinical trial. Two literature cases of solid organ transplant rejection have occurred following toripalimab in donor organ recipients from post-marketing surveillance; both were reported as “liver transplant rejection.”
Background incidence/prevalence	Solid organ transplant rejection is specific to immune checkpoint inhibitors such as toripalimab and its background incidence and prevalence in general cancer patient population has not been reported in the literature.
Risk groups or risk factors	Patients with history of solid organ transplantation who were previously treated with a PD-1 inhibitor.
Potential mechanisms	Toripalimab is an immune checkpoint inhibitor of PD-1 pathway. By blocking PD-1 pathway and activating T cell immune surveillance, it leads to programmed death

	of tumour cells and changes of immune system, which can lead to immune related inflammatory reaction or autoimmune reaction in corresponding tissues and organs. Treatment with toripalimab may increase the risk of rejection in solid organ transplant recipients.
Preventability	Solid organ transplant rejection may occur among patients treated with toripalimab and the specific risk population is unclear. Transplant organ loss may be an outcome of treatment with cancer with immunotherapy including toripalimab, should be discussed with patient and the organ transplant team. The benefit of treatment with this product should be weighed against the potential risk of organ rejection in these patients, who should be monitored closely for signs of symptoms of organs transplant rejection and transplant rejection-related complications. In patients with suspected transplant rejection, initiate appropriate treatment. Toripalimab can be withheld or discontinued based on clinical diagnosis and in accordance with severity. When necessary, experts should be invited for consultation.
Potential public health impact of safety concern	But in general, the incidence of solid organ transplant, is low and risk can be effectively controlled through withholding or discontinuing toripalimab and prompt hormonotherapy. In consideration of possibility of death caused by disease progression of terminal cancer patients, benefit of using toripalimab is greater than related risks. It has minimum impact on public health.

MedDRA terms	Solid organ transplant rejection, Liver transplant rejection.

Table SVII. 3 - Important Potential Risks

Graft Versus Host Disease (GVHD) with toripalimab after allogeneic hematopoietic stem cell transplantation (HSCT)

characterization of the risk	Given the mechanism of action of toripalimab, GVHD after HSCT have been reported with other PD(L)1 inhibitor may occur, including potentially serious events.
Background incidence/prevalence	There are no available data on the use of toripalimab.
Risk groups or risk factors	The risk groups are patients who have previously undergone allogeneic HSCT prior to toripalimab therapy.
Potential mechanisms	Toripalimab is an immune checkpoint inhibitor of PD-1 pathway. By blocking PD-1 pathway and activating T cell immune surveillance, it leads to programmed death of tumour cells and changes of immune system, which can lead to immune related inflammatory reaction or autoimmune reaction in corresponding tissues and organs.
Preventability	It can be well controlled and comprehensively evaluated through early diagnosis and intervention. All the important immune-related adverse reactions not included in the list above should be sufficiently evaluated as to identify the cause and exclude other

	causes. For first occurrence of grade 2-3 adverse reactions, this product should be interrupted and corticosteroid should be given. If the condition is improved, dose of this product can be resumed after dose reduction of corticosteroid. For other grade 4 adverse reactions or recurrent grade 3 adverse reactions, this product should be discontinued permanently.
Potential public health impact of safety concern	The rate of these adverse reactions with other PD(L)1 inhibitor was low. It can be well controlled and comprehensively evaluated through early diagnosis and intervention and the potential public health impact is small.
MedDRA terms	Allogeneic haematopoietic stem cell transplantation complications, include hyperacute graft-versus-host-disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease.

Embryotoxicities

characterization of the risk	There are no data on the use of toripalimab in pregnant women. No developmental or reproductive toxicity study was conducted for toripalimab and none are planned. A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the foetus. In murine models of pregnancy, blockade of PD-L1 signalling has been

	shown to disrupt tolerance to the foetus and to result in an increase in foetal loss; therefore, potential risks of administering toripalimab during pregnancy could include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-1/PD-L1 signalling in the offspring of these animals; however, immune-related disorders occurred in PD-1 and PD-L1 knockout mice. Based on its mechanism of action, foetal exposure to toripalimab may increase the risk of developing immune-related disorders or altering the normal immune response.
Background incidence/prevalence	There are no available data on the use of toripalimab.
Risk groups or risk factors	Exposure during pregnancy.
Potential mechanisms	It is known that human IgG4 can go through placental barrier, while toripalimab is a kind of IgG4. Therefore, toripalimab is likely to be transmitted from the mother to the developing foetus. It is still unclear whether toripalimab is secreted in human breast milk. As many products (including antibody) may be secreted in human breast milk, risks to new-borns/infants cannot be excluded.
Preventability	The risk related with reproductive toxicity can be minimized through use of appropriate contraceptive

	measures. Dosing during pregnancy is not recommended. Women of childbearing potential should use effective contraception during treatment with toripalimab and for at least 4 months after the last dose of toripalimab.
Potential public health impact of safety concern	As cancer patients of childbearing age who use toripalimab are informed of the risk of reproductive toxicity through SmPC, impact on public health is limited.
MedDRA terms	Birth defect

SVII.3.2 Presentation of the Missing Information

Not applicable.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1 - Summary of Safety Concerns

Important identified risks	• Immune related adverse reactions (including immune-related pneumonitis, colitis and diarrhoea, hepatitis, myocarditis, nephritis, endocrinopathies, pancreatitis, myositis, skin ARs, and other immune-related reactions). • Solid organ transplant rejection
Important potential risks	• GVHD with toripalimab after allogeneic HSCT • Embryotoxicities
Missing Information:	• None

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance practices include the collection and assessment of reports for regulatory authorities such as expedited adverse drug reactions (ADR) reports, signal detection reports and PSURs. All newly acquired safety information will be actively monitored in accordance with Good Pharmacovigilance Practices and signal detection and evaluation process including review and evaluation of cumulative data as triggered by new information. Communication with regulatory agencies will occur through submission of individual expedited reports, following minutes of EU fora, PSURs and updates of the product information as required. The effectiveness of any additional risk minimisation measures will also be measured by these routine pharmacovigilance activities and be presented in future PSURs.

Routine Pharmacovigilance activities beyond adverse reaction reporting and signal detection:

Specific adverse reaction follow-up questionnaires:
There is no plan to use specific adverse reaction follow-up questionnaires for Toripalimab.

Other forms of routine pharmacovigilance activities:
There are no other planned forms of routine pharmacovigilance activities for LOQTORZI.

III.2 Additional Pharmacovigilance Activities

There is no ongoing or planned additional Pharmacovigilance activities.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable.

Part IV: Plans for post-authorisation efficacy studies

There is no ongoing or planned post-authorisation efficacy studies.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimization measures by safety concern

Risk	Risk minimization measures
Immune related adverse reactions (including immune-related pneumonitis, colitis and diarrhoea, hepatitis, myocarditis, nephritis, endocrinopathies, pancreatitis, myositis, skin ARs, and other immune-related reactions)	Routine risk communication: • Adverse reactions in SmPC section 4.8. • Side effects in Package leaflet (PL) section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: • Guidance for toripalimab treatment modification and additional concomitant medical management based on the occurrence and severity of immune related adverse reactions are included in SmPC section 4.2, *Posology and method of administration.* • Guidance that patients should be monitored for signs and symptoms of immune-related adverse reactions for early identification and treatment recommendations of corticosteroids is included in SmPC section 4.4, *Special Warning and Precautions*. • Information for the patient on how to detect signs and symptoms of immune related adverse reactions is included in PL sections 4, *Possible Side Effects.* • Information for the patient on seeking medical attention if they develop signs and symptoms of immune related adverse reactions is included in PL

	section 2, *What you need to know before you are given LOQTORZI*. Other routine risk minimisation measures beyond the Product Information: • Restricted medical prescription.
Solid organ transplant rejection	Routine risk minimization communication: • Information that solid organ transplant rejection has been reported in the post-marketing setting in patients treated with PD-1 inhibitors in SmPC section 4.4. • Side effects in PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: • Guidance for the increase the risk of rejection in solid organ transplant recipients and the benefit of treatment with toripalimab versus the risk of possible organ rejection should be considered in these patients in SmPC section 4.4, *Special Warning and Precautions*. • Information for the patient to talk to their doctor if they have had a solid organ transplant in PL section 2, *What you need to know before you are given LOQTORZI* and section 4, *Possible side effects*. Other routine risk minimisation measures beyond the Product Information: • Restricted medical prescription.
Embryotoxicities	Routine risk minimization communication: In SmPC 5.3 • Information that in murine models of pregnancy, blockade of PD-L1 signalling has been shown to

	disrupt tolerance to the foetus and to result in an increase in foetal loss in SmPC 5.3. Routine risk minimisation activities recommending specific clinical measures to address the risk: • Guidance that toripalimab can potentially be transmitted from the mother to the developing foetus and a risk to the breast-feeding new-born/infant cannot be excluded because of antibodies (including IgG4) are secreted in human milk in SmPC section 4.6, *Fertility, pregnancy and lactation*. • Recommendation for women of childbearing potential to use effective contraception during treatment with toripalimab and for at least 4 months after the last dose in SmPC section 4.6, *Fertility, pregnancy and lactation*. • Recommendation that if a woman chooses to be treated with toripalimab, she should be instructed not to breast-feed while receiving toripalimab and for at least 4 months after the last dose in SmPC section 4.6, *Fertility, pregnancy and lactation*. • Information for the patient to talk to their doctor before they are given toripalimab if they are pregnant, think may be pregnant or are planning to have a baby in PL section 2, *What you need to know before you are given LOQTORZI*. • Information for women to use effective contraception during treatment with toripalimab and for at least 4

	months after the last dose in PL section 2, *What you need to know before you are given LOQTORZI*. Other routine risk minimisation measures beyond the Product Information (pack size and legal status): • Restricted medical prescription.
GVHD with toripalimab after allogeneic HSCT	Routine risk minimization communication: • Information that fatal and other serious complications (GVHD) can occur in patients who received an allogeneic haematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/PD-L1 blocking antibody in SmPC section 4.2. • Side effects in PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendations of following patients closely and promptly for evidence of transplant-related complications and intervene are included in SmPC sections 4.4, *Special Warning and Precautions*. • Information for the patient to talk to their doctor if they have had a bone marrow (stem cell) transplant that used donor stem cells (allogeneic) in PL section 2, *What you need to know before you are given LOQTORZI*. Other routine risk minimisation measures beyond the Product Information (pack size and legal status): • Restricted medical prescription.

V.2. Additional Risk Minimisation Measures

Details of proposed additional risk minimisation measures are provided in Annex 6. Patient Alert Card.

Table Part V.2: Additional Risk Minimisation Measures

Patient Alert Card	**Objectives:** To further raise awareness of patients on signs and symptoms of important risks for toripalimab: • Immune related adverse reactions (including immune-related pneumonitis, colitis and diarrhoea, hepatitis, myocarditis, nephritis, endocrinopathies, pancreatitis, myositis, skin ARs, and other immune-related reactions). **Rationale for the additional risk minimisation measure:** This communication tool will provide the opportunity for reinforcing the key messages to ensure early recognition and appropriate management of important identified risks to maintain favourable benefit/risk of LOQTORZI in market use. **Target audience and planned distribution path:** Patient alert card will be distributed to the patients via healthcare professionals at each visit. Distribution of the patient alert card will follow distribution of the product. Before product launch, the MAH will arrange for training of the distribution Representative Person in order to explain the delivery system. The delivery

	system will work along the lines outlined below, after consulting with any marketing partners: 1. The manufacturer will prepare hard copy distribution packs which consist of a patient alert card. From the manufacturer, the distributor will receive as many packs as product ordered. 2. After releasing the product, the Representative Person will dispatch the patient material to the pharmacy. 3. At the pharmacy, orders for Toripalimab will need to be dispensed with the associated materials addressed to the prescribing physicians, for the particular patient in the prescription. 4. The physician will then give out the materials to patients with an explanation of the scope and correct use. 5. When the pharmacy requires more product orders from the distributor, the pharmacist must (i) check whether the new patient is a new or repeat patient and order products together with the correct number of distribution packs. 6. The distributor to orders more packs from the manufacturer per request.

	7. The manufacturer fulfils the order, and sends all the materials to the distributor together with the products. Training material to be provided to the manufacturer, distributor Representative Person and pharmacy by the MAH and training records will be presented at any regulatory inspection per request. The manufacturer will be responsible for providing initial and yearly refresher training to the distributor, and keep training records. The distributor will be responsible for providing initial and yearly refresher training to its customer pharmacies. The above distribution plan will be submitted for agreement to each national competent authority before the launch of a product, to get a country specific approval. **Plans to evaluate the effectiveness of the interventions and criteria for success:** Routine PV activities will provide information on any changes in the occurrence, severity, and outcome of important identified risks as it relates to the established safety profile, and will be reported in future regulatory safety reports (e.g., PBRERs/PSURs).

The distribution flow of the Patient alert card will be further developed and updated when the product is approved.

V.3. Summary of Risk Minimisation Measures

Please refer to section V.1 and V.2 for routine risk minimisation measures and additional risk minimisation measures.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Immune related adverse reactions (including immune-related pneumonitis, colitis and diarrhoea, hepatitis, myocarditis, nephritis, endocrinopathies, pancreatitis, myositis, skin ARs, and other immune-related reactions)	Routine risk minimisation measures: SmPC section 4.2, 4.4 and 4.8. PL section 2 and 4. Additional risk minimisation measures: Patient alert card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Solid organ transplant rejection	Routine risk minimisation measures: SmPC section 4.4 PL section 2 and 4. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Embryotoxicities	Routine risk minimisation measures: SmPC section 4.6, 5.3. PL section 2. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
GVHD with Toripalimab after allogeneic HSCT	Routine risk minimisation measures: SmPC section 4.2, 4.4 PL section 2 and 4. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Part VI: Summary of the risk management plan

This is a summary of the Risk Management Plan (RMP) for LOQTORZI. The RMP details important risks of LOQTORZI, how these risks can be minimised, and how more information will be obtained about LOQTORZI`s risks and uncertainties.
LOQTORZI`s summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how LOQTORZI should be used.
Important new concerns or changes to the current ones will be included in updates of LOQTORZI's RMP.

I. The medicine and what it is used for

LOQTORZI, in combination with cisplatin and gemcitabine, is indicated for the first-line treatment of adult patients with metastatic or recurrent, locally advanced nasopharyngeal carcinoma.

LOQTORZI, in combination with platinum-based chemotherapy, is indicated for the first-line treatment of adult patients with recurrent or metastatic oesophageal squamous cell carcinoma

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of LOQTORZI, together with measures to minimise such risks and the proposed studies for learning more about LOQTORZI`s risks, are outlined below.
Measure to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals.
- Important advice on the medicine`s packaging.

- The authorised pack size – the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.
- The medicine`s legal status – the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of important risks and missing information

Important risks of LOQTORZI are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine);

List of important risks and missing information

Important identified risks	Immune related adverse reactions (including immune-related pneumonitis, colitis and diarrhoea, hepatitis, myocarditis, nephritis, endocrinopathies, pancreatitis, myositis, skin ARs, and other immune-related reactions). Solid organ transplant rejection
Important potential risks	GVHD with toripalimab after allogeneic HSCT Embryotoxicities

Missing information	None

II.B Summary of important risks

Important identified risks:

Immune related adverse reactions (including immune-related pneumonitis, colitis and diarrhoea, hepatitis, myocarditis, nephritis, endocrinopathies, pancreatitis, myositis, skin ARs, and other immune-related reactions).	
Evidence for linking the risk to the medicine	Review of toripalimab clinical trials data regarding Immune related adverse reactions (including immune-related pneumonitis, colitis and diarrhoea, hepatitis, myocarditis, nephritis, endocrinopathies, pancreatitis, myositis, skin ARs, and other immune-related reactions) represent sufficient evidence of a causal association with toripalimab exposure.
Risk factors and risk groups	**Immune-related pneumonitis** According to published literature, risk factors include history of interstitial lung disease or previous treatment including radiotherapy, previous or combined use of drugs with known pulmonary toxicity such as antibiotics, chemotherapy, antiarrhythmic; immunosuppression leading to pneumonia (bacteria, viruses, fungi, or protozoa), allergic pulmonary disease, autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis, etc.), occupational exposure (smoke, dust, siloxane, asbestos), smoking, and older age. **Immune-related Colitis and Diarrhoea**

	No specific risk factors for colitis and diarrhoea associated with toripalimab were identified. **Immune-related Hepatitis** According to the literature, the risk factors of liver dysfunction are history of viral hepatitis, excessive drinking, obesity, hepatotoxic drugs, genetic defects, biliary obstruction and other factors. **Immune-related Myocarditis** According to the literature, viral infection, bacterial infection, autoimmune diseases, history of chest radiotherapy, exposure to of chemotherapy drugs that may cause myocardial damage, such as anthracyclines, HER-2 inhibitors, or some antibiotics, are risk factors for myocarditis. **Immune-related Skin Adverse Reactions** No specific risk groups were identified that increased the risk of immune related adverse skin reactions when treated with toripalimab. **Immune-related Hypothyroidism** There is no known risk group for immune related hypothyroidism among patients receiving toripalimab. According to the literature, patients who have received previous thyroid surgery are risk factors for hypothyroidism. **Immune-related Hyperthyroidism** Among patients receiving toripalimab, there is no known risk group for immune related hyperthyroidism. Family history of

	hyperthyroidism, history of radiation, excessive or insufficient iodine intake and metabolic diseases are the risk factors for hyperthyroidism. **Immune-related Hypophysitis** The specific risk population or risk factors that may cause immune-related hypophysitis associated with toripalimab treatment have not been identified. **Immune-related Adrenal Insufficiency** The population at increased risk of immune-related adrenal insufficiency after being treated with toripalimab remains unknown. Hypopituitarism, long-term increase in blood concentration of glucocorticoid steroid or other steroid drugs resulting in hypothalamus and pituitary gland suppression are the causes of adrenal insufficiency. **Immune-related Type-1 Diabetes Mellitus and Hyperglycaemia** The population with increased risk in immune-related hyperglycaemia and diabetes mellitus after the use of toripalimab is still unknown. High risk factors of type I diabetes mellitus include family medical history, obesity, hyperlipidaemia, lack of exercise, smoking, high stress level and hypertension. **Immune-related Myositis** Risk population or risk factors for myositis/creatine kinase increased after therapy of toripalimab have not been identified.

	Immune-related Nephritis The population at increased risk of immune-related nephritis after being treated with toripalimab remains unknown. Risks factors of nephritis include autoimmune disorder, severe basal renal function injury, viral or bacterial infection, use of concomitant medications with renal toxicity and genetic factors. **Immune-related Pancreatitis** The population with increased risk in immune-related pancreatitis after the use of toripalimab is still unknown. Risk factors of acute pancreatitis include cholelithiasis, biliary tract disorder, drinking and overeating, obstruction of the pancreatic duct by compression, endocrine and metabolic disorders, infection, and known use of some drugs (such as thiazide diuretics, azathioprine, glucocorticoid, tetracycline and sulphonamides) that may directly damage pancreatic tissue, and increase the secretion or viscosity of pancreatic juice. **other immune-related reactions** Risk population or risk factors for other immune-related reactions after therapy of toripalimab have not been identified.
Risk minimisation measures	Routine risk minimisation measures • Dose modifications based on severity and occurrence in SmPC section 4.2

	• Warnings in SmPC section 4.4 • Adverse reaction in SmPC section 4.8 • Warning in PL section 2. • Side effect in PL section 4. • Restricted medical prescription Additional risk minimization measure: • Patient Alert Card
Additional Pharmacovigilance activities	None

Solid organ transplant rejection	
Evidence for linking the risk to the medicine	Review of toripalimab literature regarding solid organ transplant rejection represent scientific evidence of a causal association with toripalimab exposure.
Risk factors and risk groups	Patients with history of solid organ transplantation who were previously treated with a PD-1 inhibitor.
Risk minimisation measures	Routine risk minimisation measures • Warnings in SmPC section 4.4 • Warning in PL section 2. • Side effect in PL section 4. • Restricted medical prescription Additional risk minimization measure: • None
Additional Pharmacovigilance activities	None

Important potential risks

Embryotoxicities	
Evidence for linking the risk to the medicine	Preclinical safety data
Risk factors and risk groups	Unknown
Risk minimisation measures	Routine risk minimisation measures • Preclinical safety data in SmPC section 5.3 • Fertility, pregnancy and lactation in SmPC section 4.6 • Pregnancy and Breast-feeding in PL section 2. • Restricted medical prescription Additional risk minimization measure: • None
Additional Pharmacovigilance activities	None

GVHD with toripalimab after allogeneic HSCT	
Evidence for linking the risk to the medicine	Published literature Post marketing data with other PD-1 inhibitors.
Risk factors and risk groups	There are no available data on the use of toripalimab. The risk groups are patients a history of allogeneic HSCT treated with a PD-1 inhibitor.
Risk minimisation measures	Routine risk minimisation measures • Warnings in SmPC section 4.4 • Warning in PL section 2. • Side effect in PL section 4. • Restricted medical prescription

	Additional risk minimization measure: • None
Additional Pharmacovigilance activities	None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

NA

II.C.2 Other studies in post-authorisation development plan

There are no studies required for LOQTORZI

Part VII: Annexes

Table of content

Annex 1: EudraVigilance interface

Not Applicable

Annex 2: Tabulated summary of planned, on-going and completed pharmacovigilance study

Not Applicable

Annex 3: Protocols for proposed, on-going, and completed pharmacovigilance study programs

Not Applicable

Annex 4: Specific adverse drug reaction follow-up form

Not Applicable

Annex 5: Protocols for proposed and on-going studies in RMP part IV

Not Applicable

Annex 6: Details of proposed additional risk minimization*f* activities

Prior to the launch of LOQTORZI in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at educating the patients/caregivers about the risk of immune-mediated adverse reactions and the importance of reporting the symptoms immediately to healthcare providers.

Marketing Authorization Holder (MAH) shall ensure that in each Member State where LOQTORZI is marketed, all healthcare professionals (HCPs) and patients/caregivers who are expected to prescribe and use LOQTORZI have access to/are provided with the patient alert card.

Patient Alert Card

The Patient Alert Card shall contain the following key messages:

- That LOQTORZI treatment may increase the risk of:
    - Immune related adverse reactions (including immune-related pneumonitis, colitis and diarrhoea, hepatitis, myocarditis, nephritis, endocrinopathies, pancreatitis, myositis, skin ARs, and other immune-related reactions)
- Signs or symptoms of the safety concern and when to seek attention from an HCP.
- Contact details of the LOQTORZI prescriber
- The importance of carrying the patient alert card at all times and to show it at all medical visits to healthcare professionals other than the prescriber (e.g., emergency healthcare professionals).

Annex 7: References

[1] Cancer Today: International Agency for Research on Cancer [Internet]. Globocan 2020, [Cited 2022 July 6] Available from https://gco.iarc.fr/today/fact-sheets-populations.

[2] Wei KR, Zheng RS, Zhang SW, Liang ZH, Li ZM, Chen WQ. Nasopharyngeal carcinoma incidence and mortality in China, 2013.Chin J Cancer, 2017;36:90

[3] Globocan 2018 IARC (http://gco.iarc.fr/today) World Health Organization

[4] Xia L, Meng RL, XU YJ. Cancer Incidence and Mortality in Cancer Registration Areas of Guangdong Province, 2013. China Cancer. 2017(11):4-12.

[5] Li J, Xu JG, Zheng YD, Gao Y, He SY, Li H, Zou KY, Li N, Iian JH, Chen WQ, He J. Esophageal cancer: Epidemiology, risk factors and screening. Chin J Cancer Res. 2021 Oct 31; 33(5): 535–547.

[6] National Cancer Institute (https://seer.cancer.gov/statfacts/html/esoph.html)

[7] Tatlı Doğan H, Kılıçarslan A, Doğan M, Süngü N, Güler Tezel G, Güler G. Retrospective analysis of oncogenic human papilloma virus and Epstein-Barr virus prevalence in Turkish nasopharyngeal cancer patients. Pathol Res Pract. 2016 Nov;212(11):1021-1026.

[8] Zhang J, Huang T, Zhou Y, Cheng ASL, Yu J, To KF, Kang W. The oncogenic role of Epstein-Barr virus-encoded microRNAs in Epstein-Barr virus-associated gastric carcinoma. J Cell Mol Med. 2018 Jan;22(1):38-45.

[9] Jain A, Chia WK, Toh HC. Immunotherapy for nasopharyngeal cancer-a review. Chin Clin Oncol 2016;5(2):22.

[10] Chin YM, Mushiroda T, Takahashi A, et al. HLA-A SNPs and amino acid variants are associated with nasopharyngeal carcinoma in Malaysian Chinese. Int J Cancer 2015;136:678-87.

[11] Tian W, Zhu FM, Wang WY, et al. Sequence-based typing of HLA-A gene in 930 patients with nasopharyngeal carcinoma in Hunan province, southern China. Tissue Antigens 2015;86:15-20.

[12] Squamous Cell Carcinoma of Esophagus (dovemed.com)

[13] Wong MCS, Hamilton W, Whiteman DC, Jiang JY, Qiao Y, Fung FDH, Wang HHX, Chiu PWY, Ng EKW, Wu JCY, Yu J, Chan FKL, Sung JJY. Global Incidence and mortality of oesophageal cancer and their correlation with socioeconomic indicators temporal patterns and trends in 41 countries. Sci Rep. 2018 Mar 14;8(1):4522.

[14] Blanchard P, Lee A, Marguet S, et al. Chemotherapy and radiotherapy in nasopharyngeal carcinoma: an update of the MAC-NPC meta-analysis. Lancet Oncol 2015;16:645-55.

[15] Smyth E C , Lagergren J , Fitzgerald R C , et al. Oesophageal cancer[J]. Nature Reviews Disease Primers, 2017, 3:17048.

[16] Guidelines for the diagnosis and treatment of esophageal cancer 2020.Chinese Society of Clinical Oncology (CSCO).

[17] Chemotherapy and radiotherapy in nasopharyngeal carcinoma: an update of the MAC- nasopharyngeal carcinoma meta-analysis. Lancet Oncol 2015; 16: 645–55.

[18] Yang L, Hong S, Wang Y, et al. Development and External Validation of Nomograms for Predicting Survival in Nasopharyngeal Carcinoma Patients after Definitive Radiotherapy[J]. Scientific Reports, 2015, 5:15638.

[19] Wei W, Sham J. Nasopharyngeal carcinoma[J]. Lancet, 2005, 365(9476):2041-2054.

[20] Jin Y, Shi YX, Cai XY, et al. Comparison of five cisplatin based regimens frequently used as the first-line protocols in metastatic nasopharyngeal carcinoma. J Cancer Res Clin Oncol 2012;138:1717-25.

[21] Peng YC. Prevention and treatment of complications of nasopharyngeal carcinoma and rehabilitation after treatment [J]. Chinese General Practice.2002(4):267-269.

[22] Jose Pereira, Tien Phan. Management of bleeding in patients with advanced cancer. Oncologist. 2004;9(5):561-70.

[23] Smyth E C, Lagergren J, Fitzgerald R C, et al. Oesophageal cancer[J]. Nature Reviews Disease Primers, 2017, 3:17048.

[24] Kojima T, Doi T. Immunotherapy for Esophageal Squamous Cell Carcinoma. Curr Oncol Rep. 2017; 19(5): 33.

[25] WU SX, WANG LH, LUO HL, et al. Randomised phase III trial of concurrent chemoradiotherapy with extended nodal irradiation and erlotinib in patients with inoperable oesophageal squamous cell cancer. Euro J Cancer, 2018, 93: 99-107.

[26] CROSBY T, HURT CN, FALK S, et al. Chemoradiotherapy with or without cetuximab in patients with oesophageal cancer (SCOPE-1): a multicentre, phase 2/3 randomised trial. Lancet Oncol, 2013, 14: 627-637.

[27] Zhou N , Rajaram R , Hofstetter W L . Management of Locally Advanced Esophageal Cancer[J]. Surgical Oncology Clinics of North America, 2020, 29(4).

[28] Gao ZA, Xian MS. A pathomorphological study of the relationship between perineural and vascular invasion and prognosis in patients with ductal squamous cell carcinoma[J].Cancer Research on Prevention and Treatment.1992, 19(004):208-210.

[29] Chen J W , Xie J D , Ling Y H , et al. The prognostic effect of perineural invasion in esophageal squamous cell carcinoma[J]. BMC Cancer, 2014, 14(1):313.

[30] Liu RH, Li CQ, Ma MH, et al. Clinical X-ray analysis of 72 cases of esophageal cancer bleeding death [J]. Cancer Research on Prevention and Treatment. 1993(3):208-209.

[31] Yamada, Shogo. Fatal Hemorrhage in Irradiated Esophageal Cancer Patients.[J]. Acta Oncologica, 1998.

[32] A Giménez, Franquet T, Erasmus JJ, et al. Thoracic complications of esophageal disorders.[J]. Radiographics A Review Publication of the Radiological Society of North America Inc, 2002, 22 Spec No(suppl_1): S247.

[33] Xiao ZF. Analysis of prognostic factors in patients with esophageal perforation treated with radiotherapy [J],1997, Chinese Journal of Radiation Oncology.

[34] Lu QH. Analysis of the causes of esophageal perforation during radiotherapy for esophageal cancer[J]. China Journal of Modern Medicine.2004, 14(007):141-142.

[35] Crosby, T., Brewster, A., Borley, A. et al. Definitive chemoradiation in patients with inoperable oesophageal carcinoma. Br J Cancer 90, 70–75 (2004).

[36] Guo R, Chen XZ, Chen L, Jiang F, Tang LL, Mao YP, Zhou GQ, Li WF, Liu LZ, Tian L, Lin AH, Ma J. Comorbidity predicts poor prognosis in nasopharyngeal carcinoma: development and validation of a predictive score model. Radiother Oncol. 2015 Feb;114(2):249-56.

[37] Huang Y, Chen W, Haque W, Verma V, Xing Y, Teh BS, Brian Butler E. The impact of comorbidity on overall survival in elderly nasopharyngeal carcinoma patients: a National Cancer Data Base analysis. Cancer Med. 2018 Apr;7(4):1093-1101.

[38] Chan WL, Chow JCH, Xu ZY, Li J, Kwong WTG, Ng WT, Lee AWM. Management of Nasopharyngeal Carcinoma in Elderly Patients. Front Oncol. 2022 Feb 1;12:810690.

[39] Elfriede Bollschweilera, Patrick Pluma, Stefan P. Mönig, Arnulf H. Hölschera. Current and future treatment options for esophageal cancer in the elderly. EXPERT OPINION ON PHARMACOTHERAPY, 2017;18;10:1001–1010.

[40] Dolan JP, Kaur T, Diggs BS, Luna RA, Schipper PH, Tieu BH, Sheppard BC, Hunter JG. Impact of comorbidity on outcomes and overall survival after open and minimally invasive esophagectomy for locally advanced esophageal cancer. Surg Endosc. 2013 Nov;27(11):4094-103.

[41] Ramakrishnan Y, Paleri V, Shah R, Steen IN, Wight RG, Kelly CG. Comorbidity in nasopharyngeal carcinoma: a preliminary communication on the prevalence, descriptive distribution and impact on outcome. Clin Otolaryngol. 2007 Dec;32(6):484-8.

Annex 8: Summary of changes to the risk management plan over time

Not Applicable